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Progress Toward the Total Syntheses of Vinigrol and Hibarimicin B

A thesis presented

by

Benjamin Charles Milgram

to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

October 2013

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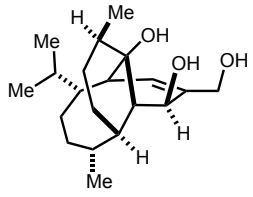
Thesis Advisor: Professor Matthew D. Shair Benjamin Charles Milgram

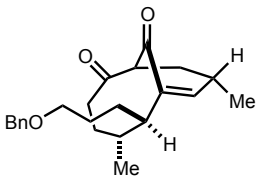
Progress Toward the Total Syntheses of Vinigrol and Hibarimicin B

Abstract

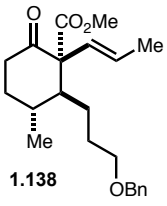
Vinigrol (**1.1**) is a structurally unique diterpenoid natural product featuring a tricyclo[4.4.4.0.^{4a,8a}]tetradecene carbon skeleton containing eight contiguous stereocenters and a challenging oxygenation pattern. **1.1** has been demonstrated to possess a wide array of biological activities including tumor necrosis factor (TNF) antagonism, antihypertensive activity, and platelet aggregation inhibitory activity. Our first-generation plan for the synthesis of **1.1** utilized a cascade reaction sequence involving: (1) diastereoselective alkylation of α-alkenyl-β-ketoester **1.138**, (2) retro-aldol-aldol equilibration (3) anion-accelerated oxy-Cope rearrangement, and (4) transannular Dieckmann condensation to afford the bicyclo[5.3.1]undecene ring system of diketone **1.182** in a single operation. Discoveries concerning the limitations of this process are disclosed. Our second-generation approach to **1.1** employed *cis*-decalin **1.217** in an alternative cascade reaction sequence, which was expected to deliver the complete tricyclo[4.4.4.0.^{4a,8a}]tetradecene carbon skeleton of **1.1** in one step. An unexpected deviation from the envisioned reaction pathway instead afforded tricyclic enol silane **1.230**.



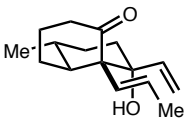
Vinigrol (**1.1**)



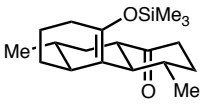
1.182



1.138



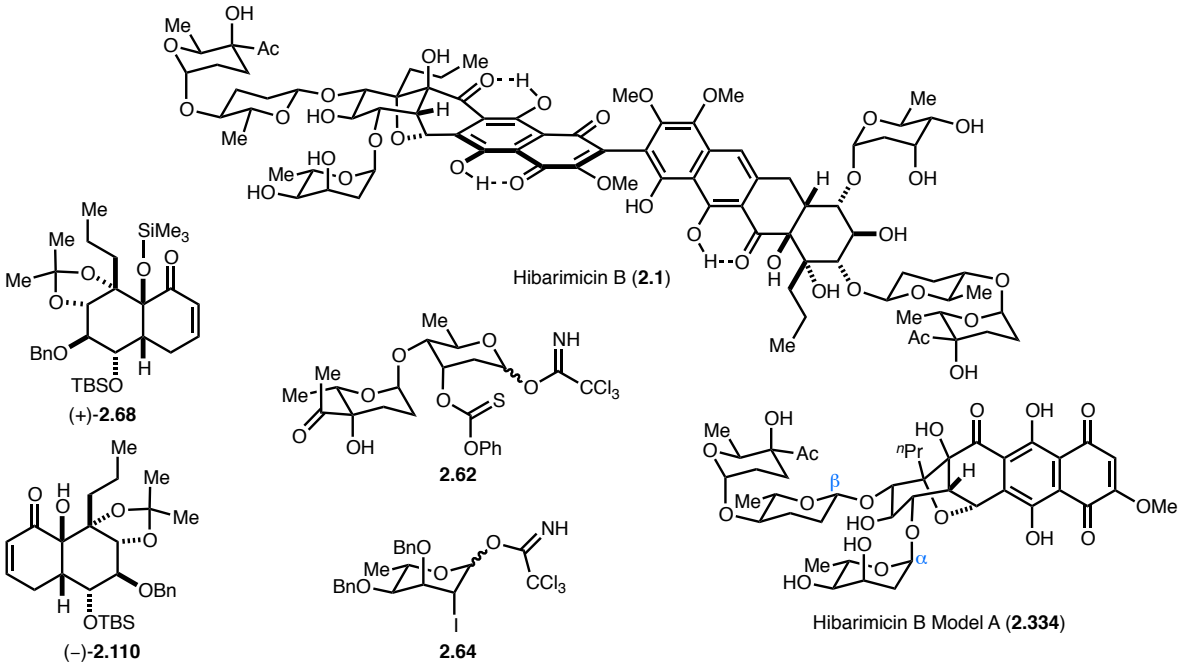
1.217



1.230

Hibarimicin B (**2.1**) is a member of the hibarimicin family of natural products, which are amongst the most complex and largest type-II polyketides known. They share a common nonacyclic pseudo-C_2-symmetric aglycon decorated with a variety of deoxy sugars. **2.1** has been demonstrated to potently inhibit the proliferation and induce the differentiation of numerous cancer cell lines. We envisioned that **2.1** or its analogs could be used as molecular probes for determining a potentially unknown biological

target for anticancer therapy. The biosynthesis of hibarimicin B and related natural products inspired our synthesis plan involving a two-directional unsymmetrical double annulation strategy and a biomimetic etherification reaction to construct the polycyclic skeleton of the hibarimicin B aglycon (hibarimicinone). As the absolute stereochemistry of hibarimicinone was unknown at the outset of our work, enantiomeric enones (+)-**2.68** and (–)-**2.110** were prepared on multi-gram scale starting from methyl-α-D-glucopyranoside. Enone (+)-**2.68** was used to accomplish the total syntheses of HMP-Y1, atrop-HMP-Y1, hibarimicinone, atrop-hibarimicinone, and HMP-P1. With a synthesis route to the aglycon of **2.1** established, we developed novel glycosylation methods for the synthesis of hibarimicin B model A (**2.334**). Specifically, the 3-thionocarbonate directing group of disaccharide trichloroacetimidate glycosyl donor **2.62** was demonstrated to be a useful control element for the stereoselective formation of 2-deoxy-β-glycosides. Reductive removal of the 3-thionocarbonate group from the product provided access to 2,3-dideoxy-β-glycosides. Additionally, the 2-iodo directing group of trichloroacetimidate glycosyl donor **2.64** was used for the first time to induce α-selectivity in the formation of digitoxosides. Progress has been made toward applying the glycosylation methods developed for the synthesis of model **2.334** to the total synthesis of **2.1**.



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For my Grandparents, Jack and Irene Budkowski

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I would like to thank my advisor, Professor Matthew Shair, for being so supportive over the last six years. Matt has inspired me to work hard and stay curious. Under his guidance I have grown both as a scientist and as a person.

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I would never have had the opportunity to come to Harvard and pursue my interest in organic chemistry if it had not been for Prof. Karl Scheidt. Karl has been an advocate of mine throughout the years and for that I am extremely grateful.

List of Abbreviations

°C	degrees celcius
Δ	reflux
Å	angstrom (1×10^{-10} meters)
1,4-BQ	1,4-benzoquinone
18-C-6	18-crown-6
4-DMAP	4-dimethylamino pyridine
AcOH	acetic acid
ADP	adenosine diphosphate
AIDS	acquired immunodeficiency syndrome
aq	aqueous
Ar	aryl
atrop	atropisomer
AZT	azidothymidine
Bn	benzyl
BzCl	benzoyl chloride
CDMP	2-chloro-4,6-dimethoxy-1,3,5-triazine
cis	*L.*, on the same side
CSA	camphorsulfonic acid
CSAID	cytokine-suppressing anti-inflammatory drug
DA	Diels–Alder
DB18-C-6	dibenzo-18-crown-6
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEPT	distortionless enhancement by polarization transfer

DIAD	diisopropyl azodicarboxylate
DIB	(diacetoxyiodo)benzene
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
dppf	1,1'-bis(diphenylphosphino)ferrocene
DQF-COSY	double quantum filtered-correlated spectroscopy
d.r.	diastereomeric ratio
DTBBP	di(*tert*-butyl)phosphane
DTBC	3,5-di-tert-butylcatechol
E	*Ger.*, *entgegen*
EC_{50}	half maximal effective concentration
ESI	electrospray ionization
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
equiv	equivalent
FMO	frontier molecular orbital
FTIR	Fourier transform infrared
g	gram
GGPP	geranyl geranyl pyrophosphate
HDDA	hydroxyl-directed Diels–Alder reaction

HIV	human immunodeficiency virus
HL-60	human promyelocytic leukemia cells
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high-pressure liquid chromatography
IBX	*ortho*-iodobenzoic acid
IC_{50}	half maximal inhibitory concentration
IMDA	intramolecular Diels–Alder reaction
$(^{d}Ipc)_2BH$	diisopinocampheylborane
J	coupling constant
kcal	kilocalorie
kg	kilogram
KHMDS	potassium bis(trimethylsilyl)amide
KOH	potassium hydroxide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LiTMP	lithium tetramethylpiperidide
M	molar
m/z	mass to charge ratio
^{m}CPBA	*meta*-chloroperbenzoic acide
MeCN	acetonitrile
MEK	methyl ethyl ketone
mg	milligram

MHz	megahertz
min	minute
mL	milliliter
µL	microliter
mM	millimolar
mmol	millimole
µmol	micromole
MOM	methoxymethyl
MoOPH	MoO_5•pyr•HMPA
MsCl	methanesulfonyl chloride
MS	molecular sieves
MVK	methyl vinyl ketone
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NBSH	2-nitrobenzenesulfonylhydrazide
NHS	*N*-hydroxysuccinimide
NMM	4-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
N-phenyl triflimide	*N*-phenyl-bis(trifluoromethanesulfonimide)
NTG	*N*-methyl-*N*′-nitro-*N*-nitrosoguanidine
o-DCB	1,2-dichlorobenzene
Oxone	potassium peroxymonosulfate

PAF	platelet activating factor
PBBz	*para*-nitrobenzoyl
Pd/C	palladium on carbon
Ph	phenyl
PhH	benzene
PivCl	Pivaloyl chloride
PPTS	pyridinium *para*-toluenesulfonate
psi	pounds per square inch
PTK	protein tyrosine kinase
PTSA	*para*-toluenesulfonic acid
Py	pyridine
R	rectus (Cahn–Ingold–Prelog system)
RCM	ring-closing metathesis
RCEM	ring closing enyne metathesis
R_f	retention factor
ROSEY	rotating-frame nuclear Overhauser effect correlation spectroscopy
RT	room temperature
S	sinister (Cahn–Ingold–Prelog system)
TASF	tris(dimethylamino)sulfonium dofluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldimethylphenylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
^{t}Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

TESCl	triethylsilyl chloride
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
Thexyl	2,3-dimethyl-2-butyl
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMU	tetramethylurea
TNF	tumor necrosis factor
TOCSY	total correlation spectroscopy
TPAP	tetrapropylammonium perruthenate
trans	*L.*, across
$TrisNHNH_2$	2,4,6-triisopropylbenzenesulfonyl hydrazide
Triton B	benzyltrimethylammonium hydroxide
TsCl	4-toluenesulfonyl chloride
TsNa	sodium 4-toluenesulfonate
TsOH	4-toluenesulfonic acid
Z	*Ger.*, zusammen

Chapter 1

Progress Toward a Synthesis of Vinigrol

1.1 Isolation and Structural Characterization of Vinigrol

Hashimoto and co-workers reported the isolation of vinigrol (**1.1**, Figure 1.1) in 1987 from the fungal strain *Vigaria nigra* F-5408.[1] Vinigrol was isolated for its antihypertensive and platelet aggregation inhibitory activity.[2] Structurally, **1.1** exhibits an unprecedented diterpenoid tricyclo[4.4.4.0.^{4a,8a}]tetradecene[3] carbon skeleton containing eight contiguous stereocenters and multiple sites of oxygenation. The compact nature of vinigrol's unusual structure necessitates its depiction from multiple viewpoints.

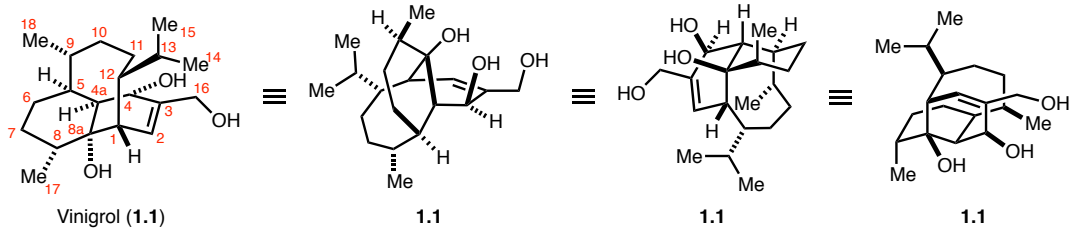


Figure 1.1 Structure of vinigrol.[4]

Vinigrol (**1.1**) was isolated from the F-5408 mycelium fermentation broth through acetone extraction. Purification of the organic extract by repeated silica gel chromatography followed by recrystallization from a mixture of heptane and ethyl acetate provided pure **1.1** as colorless prisms (mp 108 °C, $[\alpha]_D$ = –96.2°) (*c* = 1.05, $CHCl_3$)). However, the structure of **1.1** could not be completely elucidated through the combined application of IR, MS, ^{1}H, and ^{13}C NMR spectroscopy. Ultimately, chemical derivitazation of **1.1** was required to reveal its complete structure (Scheme 1.1). Jones' oxidation of **1.1** provided three compounds: **1.2**, **1.3**, and **1.4**, of which **1.4** gave optimal X-ray crystal data.

---

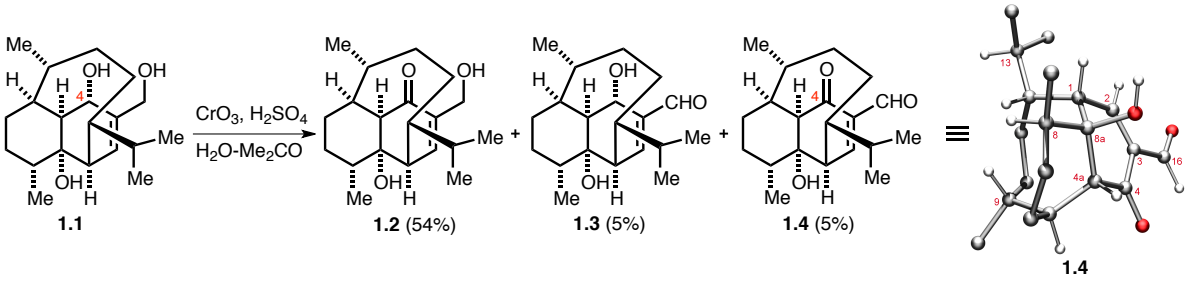
[1] Uchida, I.; Ando, T., Fukami; N., Yoshida, K., Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. *J. Org. Chem.* **1987**, *52*, 5292–5293.

[2] (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot*. **1988**, *41*, 25–30. (b) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.* **1988**, *41*, 31–35.

[3] Vinigrol's carbon framework can also been described as a decahydro-1,5-butanonaphthalene skeleton or a *cis*-fused [4.4.0] ring system bridged by an 8-membered ring.

[4] The numbering convention used in Figure 1.1 will be referred to through out this document.

Scheme 1.1 Oxidative derivatization of vinigrol and X-ray crystal structure of vinigrol derivative **1.4**.



Structure **1.4** defined the relative stereochemistry of **1.1** except for the C4 stereocenter, which was assigned based on (1) a lack of a $^{1}J_{H4,H4a}$ coupling, indicating a dihedral angle close to 90°, and (2) NOESY correlations depicted in Figure 1.2.

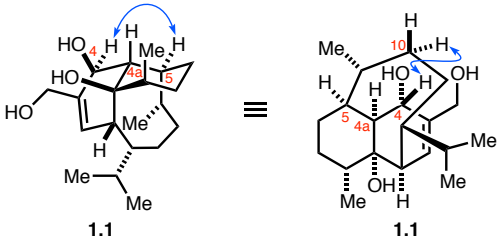
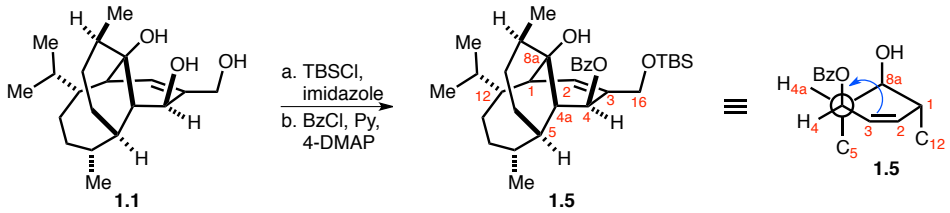


Figure 1.2 NOESY correlations confirming the C4 stereochemistry of vinigrol.

The absolute stereochemistry of **1.1** was established based on a negative Cotton effect[5] in the CD spectrum of allylic benzoate derivative **1.5** (Scheme 1.2) ($\Delta\varepsilon$ = –14.0 at 230 nm (MeOH)), which indicates a counterclockwise relationship between the C4 benzoate and C2–C3 olefin chromophores.

[5] (a) Harada, N.; Nakanishi. K. *Circular Dichroic Spectroscopy: Exiton Coupling in Organic Spectrometry*; University Science Books: Mill Valley, CA, 1983. (b) Harada, H.; Iwabuchi. J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103,* 5590–5591.

Scheme 1.2 Determination of vinigrol's absolute stereochemistry through CD spectroscopic analysis of allylic benzoate derivative **1.5**.



1.2 Biological Activity of Vinigrol

Interest in **1.1** originated in the discovery of its antihypertensive and platelet aggregation inhibitory activity.[2] Since blood pressure control is an important modern therapeutic area,[6] it was anticipated that **1.1** might be useful tool for the discovery of new protein targets for the treatment of hypertension. Intravenous injection of **1.1** in spontaneously hypertensive rats, produced a dose-dependant decrease in mean arterial blood pressure. Studies on the contraction of rat aortic smooth muscle strips demonstrated **1.1** to be a potent Ca^{2+} agonist; however, the precise mechanism by which **1.1** induces antihypertensive activity in humans remains to be determined. Uchida and coworkers showed that **1.1** inhibited human platelet aggregation induced by epinephrine or platelet activating factor (PAF) with IC_{50} values of 52 nM and 33 nM, respectively. However, **1.1** did not demonstrate inhibitory activity on adenosine diphosphate (ADP), thrombin, or collagen-induced platelet aggregation.

Vinigrol was later identified by Norris and coworkers to be a tumor necrosis factor (TNF) antagonist[7] and was therefore investigated as a potential treatment for endotoxic shock, inflammation, infection, and cachexia. In an *in vitro* binding assay on HL-60 cells, **1.1** (310 μM) showed 100% inhibition of [I^{125}]-TNF at 2.1 nM. TNF is known to cause lysis of the sensitive L929 cell line at low concentrations. At 15.5 μM, **1.1** completely inhibited TNF-induced cytotoxicity yet produced no cytotoxic effects in the absence of TNF. These findings prompted the Fujisawa Pharmaceutical Company Limited to patent **1.1** as a potential treatment for human immunodeficiency virus (HIV). However, when

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[6] Krum, H.; Gilbert, R. E. *J. Hypertens.* **2007**, *25*, 25–35.

[7] Norris, D. B.; Depledge, P.; Jackson, A. P. Tumor Necrosis Factor Antagonist. PCT Int. Appl. WO9107953, November 22, 1991.

they compared **1.1** to the current standard of care (azidothymidine (AZT)), **1.1** showed only modest activity (EC_{50} for **1.1** = 0.092 mM, EC_{50} for AZT = 0.2 nM).[8] In 1997, building upon the work of Norris, patents claiming **1.1** could be used as a cytokine-suppressing anti-inflammatory drug (CSAID) to treat various autoimmune diseases including rheumatoid arthritis and type 1 diabetes were filed.[9]

1.3 Proposed Biosynthesis of Vinigrol

Corey and Goodman proposed a possible biosynthesis for **1.1** based on the established biosynthesis of similar terpenoid natural products including lanosterol, arteannuin B, and pseudopterosin K–L (Scheme 1.3).[10] Specifically, they envisioned **1.1** and the pseudopterosin K–L aglycon (**1.11**) could share a common biosynthetic intermediate, erogorgiaene (**1.9**). Their proposed biosynthesis begins with intramolecular cyclization of diterpenoid building block geranyl geranyl pyrophosphate (GGPP, **1.6**), to afford 10-membered ring intermediate **1**.**7**. A series of hydride shifts and a transannular cyclization is belived to deliver erogorgiaene (**1.9**). Oxidation of **1.9** likely generates a cationic intermediate **1.10** en route to the pseudopterosin K–L aglycon (**1.11**). In contrast, an alternative series of aromatic oxidations could potentially yield phenoxide radical **1.13**. Transannular cyclization of the carbon-based radical tautomer **1.14** onto the pendant propenyl group could generate the unprecedented decahydro-1,5-butanonaphthalene carbon skeleton exhibited by postulated intermediate **1.15**. Finally, a series of enzymatically-controlled oxidations could deliver **1.1**. Maimone and Baran have identified several other diterpene natural product families isolated subsequent to Corey and Goodman's initial proposal, which

---

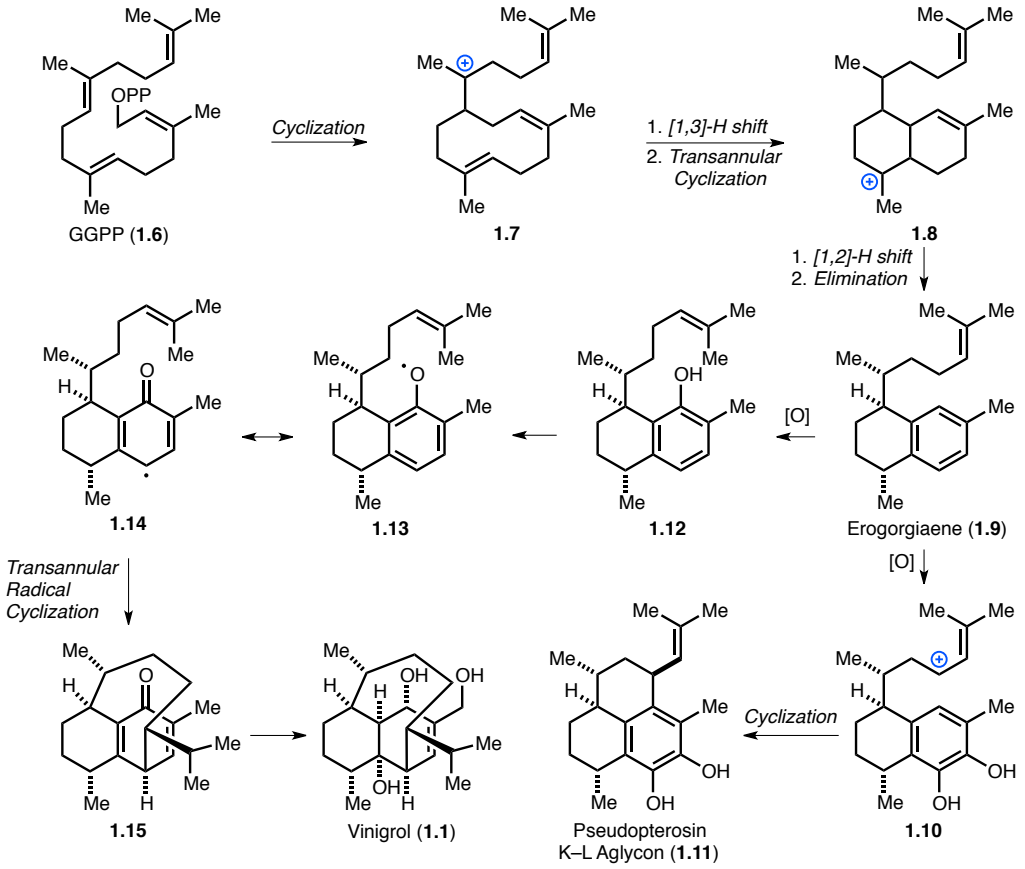
[8] Nakajima, H.; Yamamoto, N.; Kaizu, T.; Kino, T. Therapeautic Agent for Human Immune Deficiency Virus Infectious Disease. Japan Patent 07206668, January 11, 1994.

[9] (a) A. Guglielmotti, A.; Dionisio, P. A Pharmaceutical Composition for the Treatment of Autoimmune Diseases. PCT Int. Appl. WO9716185, October, 26, 1996. (b) Keane, J. T. Combination of Tumor Necrocis Factor (TNF) Antagonists and COX-2 Inhibitors for the Treatment of Inflammation. PCT Int. Appl. WO2001000229, June 26, 2000.

[10] (a) Goodman, S. N. Ph.D. Thesis, Harvard University, 2000 and references therein. (b) Ferns, T.; Kerr, R. G. *Tetrahedron* **2005**, *61*, 12358–12365. (c) Berrué, F.; McCulloch, M. W. B.; Kerr, R. G. *Bioorg. Med. Chem.* **2011**, *19*, 6702–6719.

are believed to be formed through transannular oxidative phenoxyl radical-based cyclization, including the colombiasin and the elisapterosin natural product families.[11]

Scheme 1.3 Corey and Goodman's proposed biosynthesis of vinigrol.



1.4 Previous Synthesis Efforts Directed Toward Vinigrol

Since its original isolation and structural assignment in 1987, **1.1** has been a highly sought after synthesis target due to its interesting biological activity and unusual structure. Numerous groups have attempted to synthesize **1.1** including Corey,[10] Paquette,[12] Hanna,[13] Barriault[14] Mehta,[15] Matsuda,[16]

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[11] Maimone, T. J. Ph.D. Thesis, Scripps Research Institute, 2009.

[12] (a) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096–6107. (b) Guevel, R. Ph.D. Thesis, The Ohio State University, 1994. (c) Efremov, I. V. Ph.D. Thesis, The Ohio State University, 2001. (d) Paquette, L. A.; Efremov, I.; Liu, Z. S. *J. Org. Chem.* **2005**, *70*, 505–509. (e) Paquette, L. A.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 510–513. (f) Paquette, L. A.; Liu, Z. S.; Efremov, I. *J. Org. Chem.* **2005**, *70*, 514–518.

[13] (a) Devaux, J.-F.; Hanna, I.; Lallemand, J. Y. *J. Org. Chem.* **1993**, *58*, 2349–2350. (b) Devaux, J.-F.; Hanna, I.;

Fallis,[17] Doyle,[18] Njardarson[19], and Baran.[20] During the course of our studies directed toward the total synthesis of **1.1**, the Baran group reported the first racemic total synthesis of **1.1** in 23 steps.[20b] This work was followed by a formal synthesis by Barriault and coworkers[14f] that intercepts one of Baran's intermediates. More recently, the Njardarson group has disclosed a racemic total synthesis of **1.1**, which was accomplished in 38 steps.[19d] The synthesis approaches toward **1.1** have been recently reviewed;[21] therefore, only a selection of the chemistry highlighting the intriguing structural challenges **1.1** presents as a synthesis target will be discussed.

1.4.A Hanna's Synthesis of Vinigrol's Tricyclic Carbon Skeleton

Hanna and coworkers were the first to report the synthesis of vinigrol's tricyclic carbon skeleton in 1993.[13a] Their synthesis began with an intermolecular Diels-Alder (IMDA) reaction between 2-

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Fraisse, P.; Lallemand, J.-Y. *Tetrahedron Lett.* **1995**, *36*, 9471–9474. (c) Devaux, J. F.; Hanna, I.; Lallemand, J. Y.; Prange, T. *J. Chem. Res. Synth.* **1996**, 32–33. (d) Devaux, J. F.; Hanna, I.; Lallemand, J. Y. *J. Org. Chem*. **1997**, *62*, 5062–5068. (e) Gentric, L.; Hanna, I.; Ricard, L. *Org. Lett.* **2003**, *5*, 1139–1142. (f) Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. *Org. Lett.* **2003**, *5*, 3631–3634. (g) Gentric, L.; Le Goff, X.; Ricard, L.; Hanna, I. *J. Org. Chem*. **2009**, *74,* 9337–9344.

[14] (a) Morency, L.; Barriault, L. *Tetrahedron Lett.* **2004**, *45*, 6105–6107. (b) Morency, L.; Barriault, L. *J. Org. Chem*. **2005**, *70*, 8841–8853. (c) Morency, L., Ph.D. Thesis, University of Ottawa, 2006. (d) Grise, C. M.; Tessier, G.; Barriault, L. *Org. Lett.* **2007**, *9*, 1545–1548. (e) Tessier, G.; Barriault, L. *Org. Prep. Proc. Int.* **2007**, *37*, 313–353. (f) Poulin, J.; Grise-Bard, C. M.; Barriault, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2111–2114.

[15] Mehta, G.; Reddy, K. S. *Synlett* **1996**, 625–627.

[16] (a) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 1057–1060. (b) Kito, M.; Sakai, T.; Shirahama, H.; Miyashita, M.; Matsuda, F. *Synlett* **1997**, 219–220. (c) Matsuda, F.; Sakai, T.; Okada, N.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 863–864. (d) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369–14380.

[17] Souweha, M. S.; Enright, G. D.; Fallis, A. G. *Org. Lett.* **2007**, *9*, 5163–5166.

[18] Brekan, J. A. Ph.D. Thesis, State University of New York, 2008.

[19] (a) Morton, J. G. M.; Kwon, L. D.; Freeman, J. D.; Njardarson, J. T. *Tetrahedron Lett.* **2009**, *50*, 1684–1686. (b) Morton, J. G. M.; Kwon, L. D.; Freeman, J. D.; Njardarson, J. T. *Synlett*. **2009**, 23–27. (c) Morton, J. G. M.; Draghici, C.; Kwon, L.; Njardarson, J. T. *Org. Lett.* **2009**, *11*, 4492–4495. (d) Yang, Q.; Njardarson, J. T.; Draghici, C.; Li, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 1–5.

[20] (a) Maimone, T. J.; Voica, A.-F.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3054–3056. (b) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 17066–17067.

[21] (a) Tessier, G.; Barriault, L. *Org. Prep. Proced. Int.* **2007**, *37*, 313–353. (b) Harmata, M.; Calkins, N. L. *Chemtracts* **2009**, *22*, 205–209. (c) Lu, J.-Y.; Hall, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2286–2288. (d) Huters, A. D.; Garg, N. K. *Chem. Eur. J.* **2010**, *16*, 8586–8595.

(trimethylsilyl)oxy-1,3-cyclohexadiene (**1.16**) and 1,4-benzoquinone (1,4-BQ) followed by Luche reduction resulting in tetracycle **1.17** (Scheme 1.4). The secondary carbinol was MOM protected and the silyl ether deprotected with BF_3•OEt_2 to afford hemiacetal **1.18** and ketone **1.19**. Dehydration of the product mixture with $POCl_3$ gave diene **1.20**. Chemoselective hydrogenation of the disubstituted olefin was accomplished under a hydrogen atmosphere with Wilkinson's catalyst[22] to provide ketone **1.21**. Exposure of **1.21** to vinylmagnesium chloride yielded allylic alcohol **1.23**, which was a result of stereoselective attack of the organometallic reagent on the more sterically hidered *endo* face of **1.21**. Hanna rationalized this result by invoking remote chelation-control of the organometallic reagent by the C4 alkoxy substituent depicted in **1.22**.[23] Interestingly, when the C4–OH was protected as the corresponding MOM ether, nucleophilic attack occurred with high selectivity from the opposite *exo* face of the molecule. Heating a mixture of the resultant allylic alcohol **1.23** and potassium hydride with 18-crown-6 promoted anion-accelerated oxy-Cope rearrangement to supply tricycle **1.24**. Unfortunately, Hanna and co-workers were never able to complete a total synthesis of **1.1** based on this strategy despite the relative ease by which they were able to access its decahydro-1,5-butanonaphthalene skeleton.

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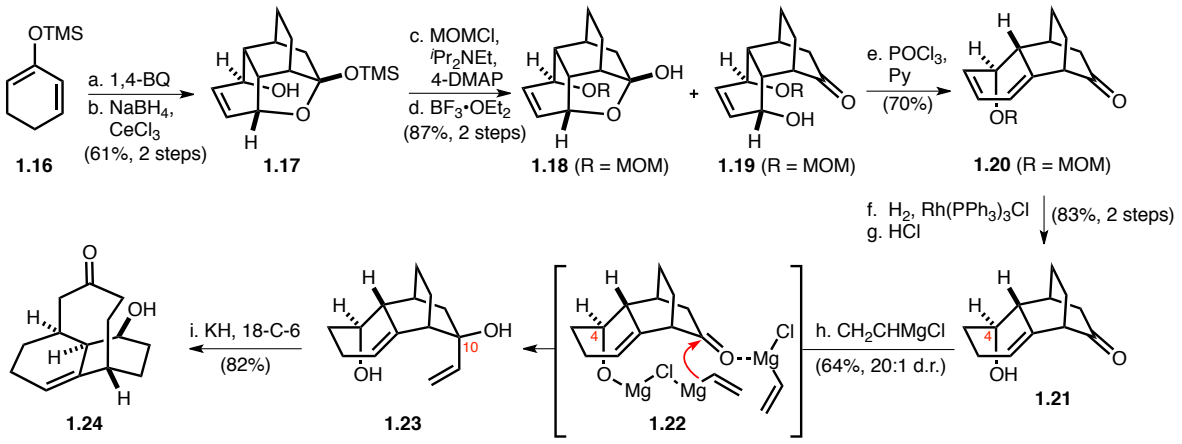
[22] Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A,* **1966**, 1711–1732.

[23] For a review on chelation-controlled reactions, see: Reetz, M. T. *Angew. Chem. Int. Ed.* **1984**, *23*, 556–569.

Scheme 1.4 Hanna's synthesis of vinigrol's tricyclic carbon skeleton.



Reagents and conditions: (a) 1,4-benzoquinone, PhH, reflux; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 61% (two steps); (c) MOMCl, $^{i}Pr_2NEt$, 4-DMAP, CH_2Cl_2, 0 °C → RT, 94%; (d) BF_3•OEt_2, THF, –78 °C → RT, 93% (mixture of **1.18** and **1.19**); (e) $POCl_3$, Py, 70%; (f) H_2, $Rh(PPh_3)_3Cl$, PhH, 87%; (g) 4.0 N HCl, THF, 65 °C, 95%; (h) vinylmagnesium chloride, THF, 0 °C, 64%, 20:1 d.r.; (i) KH, 18-crown-6, THF, 0 °C → 65 °C, 82%.[24]

1.4.B Paquette's Attempt to Construct Vinigrol's 8-Membered Ring

The Paquette group investigated several iterations of a common strategy for the synthesis of vinigrol's decahydro-1,5-butanonaphthalene carbon skeleton. A representative example of his approach is illustrated in Scheme 1.5.[12] The synthesis commenced with chiral aldehyde **1.25**, accessed in four steps from (*S*)-oxazolidinone. Modified Stork enamine alkylation[25] of **1.25** with methyl vinyl ketone (MVK) provided 2-cyclohexenone **1.26** as a mixture of C1 diastereomers. Methylation of **1.26** followed by exposure to LiHMDS in the presence of phenyl vinyl sulfoxide promoted a double-Michael reaction to give an intermediate, which when warmed with calcium carbonate underwent an extrusion of benzene sulfenic acid to provide bicyclo[2.2.2]octenone **1.27** in 22% overall yield as a mixture of separable C1 diastereomers. Carbonyl addition of a vinyl organometallic reagent derived from methyl (*R*)-2-(hydroxymethyl)propionate occurred with modest diastereoselectivity for the desired *endo* allylic alcohol

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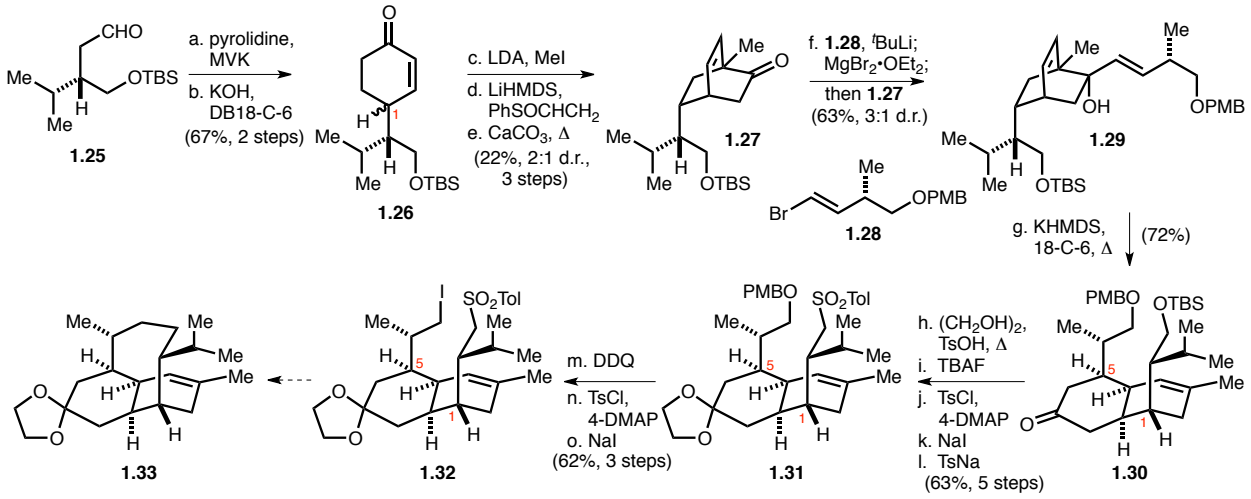
[24] Yield based on Hanna's note stating **1.24** was "almost pure."

[25] (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222. (b) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

product **1.29**. Deprotonation of **1.29** with KHMDS followed by heating to 120 °C facilitated an anion-accelerated oxy-Cope rearrangement to construct *cis*-decalin **1.30**. Next, the alkyl substituents at C1 and C5 were elaborated to the corresponding tolyl sulfone and alkyl iodide, respectively. Unfortunately, attempted formation of vinigrol's 8-membered ansa bridge via a S_N2 reaction of the resultant intermediate **1.32** failed under various conditions.

Scheme 1.5 Paquette's attempted synthesis of vinigrol's tricyclic carbon skeleton.



Reagents and conditions: (a) pyrolidine, MVK, PhH, reflux, 84%; (b) KOH, dibenzo-18-crown-6, PhH, 80%, 1.7:1.0 PhMe, reflux, 27%, 2:1 d.r. (two steps); (f) ^{t}BuLi, **1.28**, Et_2O, –78 → 0 °C; $MgBr_2$•OEt_2; then **1.27**, THF, 0 °C, 63%, 3:1 d.r.; (g) KHMDS, 18-crown-6, THF, 0 → 120 °C, 72%; (h) 1,2-ethanediol, TsOH, PhH, reflux, 84%; (i) TBAF, THF, 100%; (j) TsCl, 4-DMAP, CH_2Cl_2, 91%; (k) NaI, MEK, reflux; (l) TsNa, DMF, 110 °C 82% (two steps); (m) DDQ, CH_2Cl_2-H_2O (18:1), 94%; (n) TsCl, 4-DMAP, CH_2Cl_2, 81%; (o) NaI, MEK, reflux, 82%.

Paquette explored several other transannular cyclization strategies to form vinigrol's 8-membered ring including ring-closing metathesis (RCM), carbonyl addition, and Ramburg–Bäcklund ring contraction (Figure 1.3); however, none proved successful.

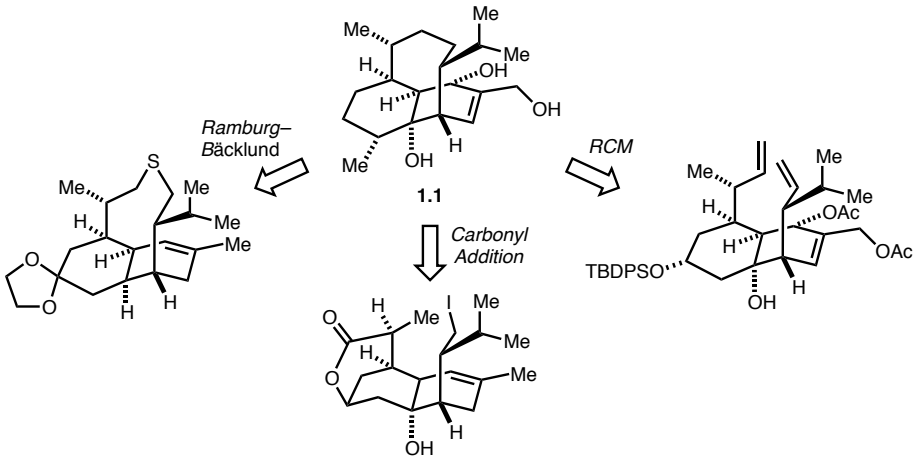


Figure 1.3 Paquette's transannular cyclization strategies.

MM2 transition structures **1.34** and **1.35**, based on *ab initio* calculations, help explain the failure of a transannular cyclization strategy to form the 8-membered ring of the decahydro-1,5-butanonaphthalene carbon skeleton (Figure 1.4). The pseudo-diaxial substituted *cis*-decalin conformer **1.35**, which might allow transannular C–C bond formation, is thermodynamically disfavored by 12.5 kcal/mol relative to the more stable pseudo-diequatorial conformer **1.34**.

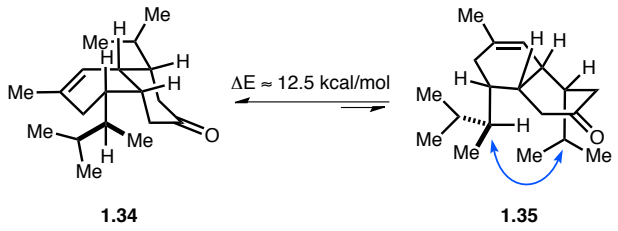


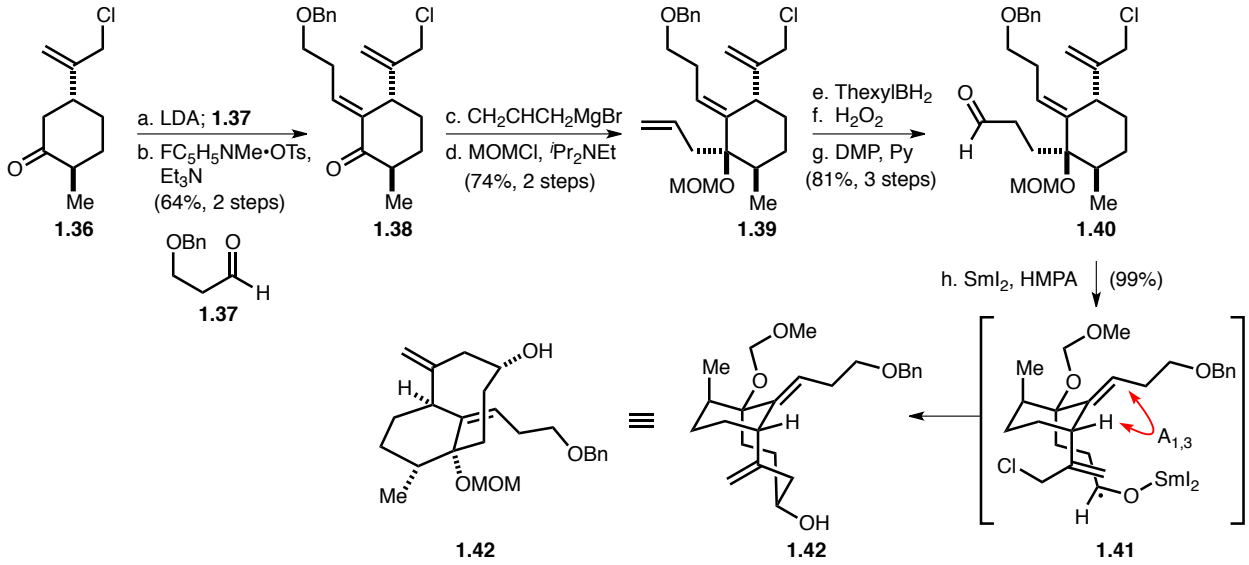
Figure 1.4 MM2 transition structures calculated by Paquette.

1.4.C Matsuda's Approach to the Synthesis of Vinigrol's 8-Membered Ring

Matsuda and co-workers have shown that the formation of a similar 8-membered ring contained within the bicyclo[5.4.1]undecene portion of vinigrol's carbon skeleton was possible through a transannular SmI_2-promoted Barbier coupling reaction (Scheme 1.6).[16d] Their synthesis began with an aldol/dehydration sequence between chlorodihydrocarvone **1.36** and aldehyde **1.37** to give cyclohexenone **1.38**. Treatment of **1.38** with allylmagnesium bromide provided a 5:1 diasteriomeric mixture of tertiary carbinols. The desired α-epimer was protected as its corresponding MOM ether. A regioselective hydroboration/oxidation sequence then afforded cyclization substrate **1.40**. Remarkably, exposure of **1.40**

to SmI_2 promoted an intramolecular Barbier-coupling reaction to construct the bicyclo[5.4.1]undecene ring system exhibited by **1.42** in quantitative yield. This reaction was facilitated by the conformational rigidification of the cyclohexane intermediate **1.41** and reinforced by $A_{1,3}$ strain minimization[26], which placed the intermediate samarium ketyl radical anion and allylic chloride coupling partners in close proximity. In contrast to Paquette's strategy, Matsuda's approach was not subject to the conformational constraints engendered by the *cis*-decalin core of vinigrol's carbon skeleton.

Scheme 1.6 Matsuda's transannular Barbier coupling strategy.



Reagents and conditions: (a) LDA, THF, –78 °C; then **1.37**, 75%; (b) $FC_5H_5NMe•OTs$, Et_3N, CH_2Cl_2, reflux, 85%; (c) allylmagnesium bromide, Et_2O, –78 °C, 5:1 d.r.; (d) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 74% (two steps); (e) $ThexylBH_2$, THF, 0 °C; (f) 30% H_2O_2, 90% (two steps); (g) DMP, Py, CH_2Cl_2, 90%; (h) SmI_2, HMPA, THF, 99%.

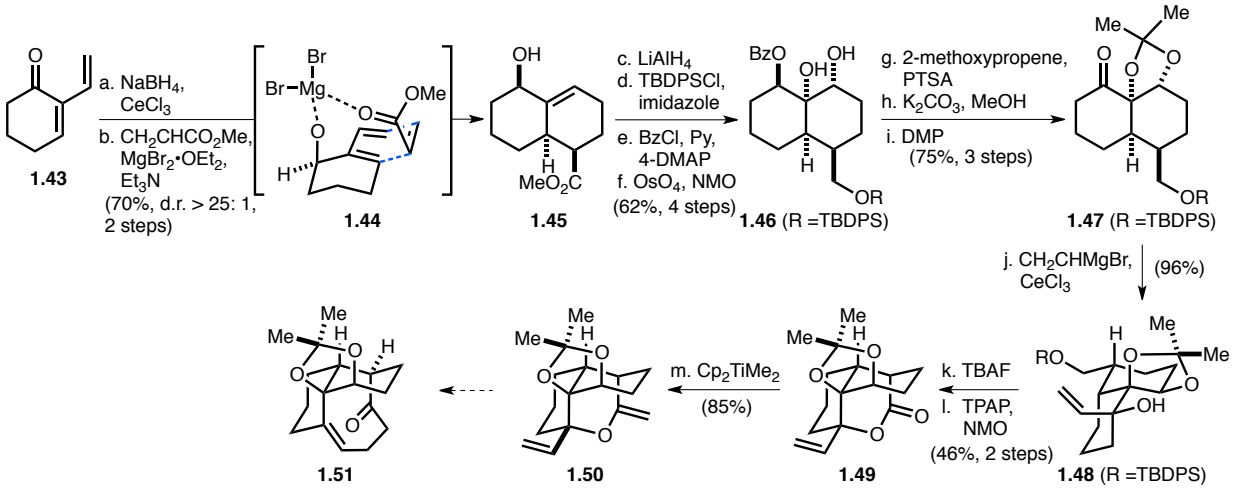
1.4.D Barriault's Synthesis of Vinigrol's Carbon Skeleton

Barriault and coworkers explored several distinct strategies toward vinigrol's tricyclic carbon skeleton. The first to be discussed involved late-stage Claisen rearrangement to form vinigrol's 8-membered ring (Scheme 1.7).[14b] The synthesis began with a Luche reduction of enone **1.43** followed by hydroxyl-directed Diels–Alder reaction (HDDA) with methyl acrylate promoted by $MgBr_2•OEt_2/NEt_3$ to

[26] For a review of $A_{1,3}$ strain minimization as a control element in organic synthesis, see: Hoffmann, R. *Chem. Rev.* **1989**, *89*, 1841–1860.

afford cycloadduct **1.45** as a single diastereomer. Allylic alcohol **1.45** was converted to ketone **1.47** in seven steps through a series of oxidation state manipulations and protecting group introductions. Treatment of **1.47** with an organocerium reagent derived from vinylmagnesium bromide resulted in organometallic addition from the convex face of the molecule to yield allylic alcohol **1.48**. Silyl ether deprotection and Ley oxidation provided tetracyclic ester **1.49**. Exposure of **1.49** to Petasis' reagent furnished exocyclic enol ether **1.50**. Unfortunately, all attempts to promote ring expansion of **1.50** through a Claisen rearrangement were unsuccessful, possibly due to poor orbital overlap of the olefinic substituents.

Scheme 1.7 Barriault's attempt to construct vinigrol's octalin belt via Claisen rearrangement.

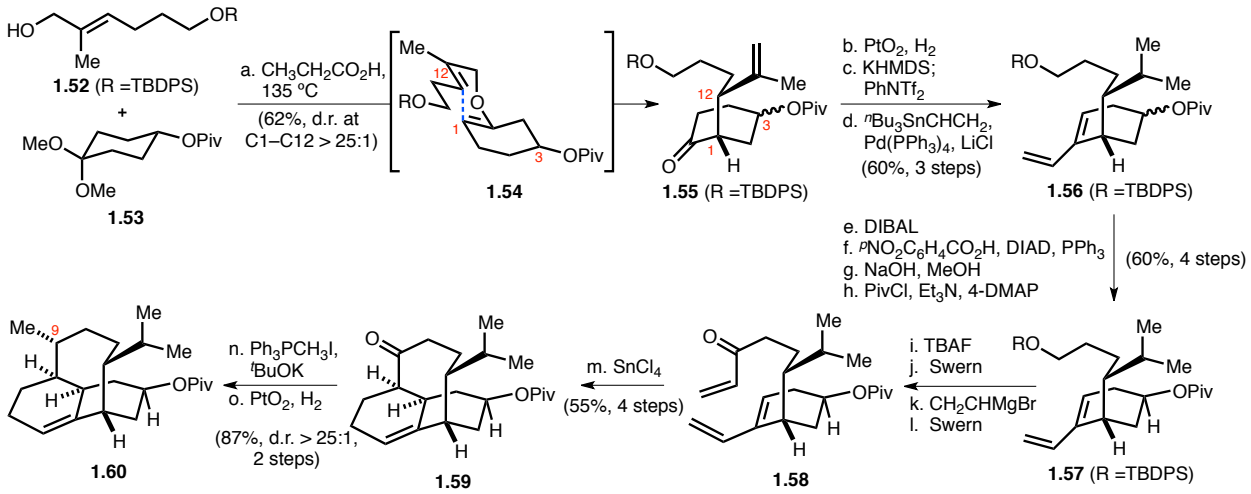


Reagents and conditions: (a) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, 90%; (b) methyl acrylate, $MgBr_2$•OEt_2, Et_3N, CH_2Cl_2, 78%, >25:1 d.r.; (c) $LiAlH_4$, THF, –78 °C; (d) TBDPSCl, imidazole, DMF, 78% (two steps); (e) BzCl, Py, 4-DMAP, CH_2Cl_2, 97%; (f) OsO_4 (4 mol%), NMO, THF-H_2O (5:1), reflux, 82%; (g) 2-methoxypropene, PTSA, CH_2Cl_2, 100%; (h) K_2CO_3, MeOH, PhMe, reflux, 75%; (i) DMP, CH_2Cl_2, 100%; (j) $CH_2CHMgBr$, $CeCl_3$, THF, –78 °C, 96%; (k) TBAF, THF, 90%. (l) TPAP, NMO, 4 Å MS, CH_2Cl_2, 51%; (l) Cp_2TiMe_2, PhMe, 80 °C, 85%.

Barriault's next approach focused on the use of an intramolecular Diels–Alder reaction (IMDA) to form the 8-membered ring and one of the six-membered rings of vinigrol's tricyclic carbon skeleton in a single operation (Scheme 1.8). Their synthesis began with propionic acid promoted enol ether formation between alcohol **1.52** and dimethylketal **1.53**. Thermal Claisen rearrangement of the intermediate enol

ether provided ketone **1.55** with excellent diastereoselectivity for C1–C12 bond formation. The isopropenyl group was then reduced through hydrogenation and the ketone was converted to diene **1.56** via a Stille coupling of the corresponding vinyl triflate. At this point, the undesired C3 α-pivaloyl ester epimer could be recycled to the β-epimer **1.57** through a Mitsunobu inversion process. Next, the primary alcohol was deprotected and converted into enone **1.58**. Exposure of **1.58** to $SnCl_4$ facilitated a key transannular IMDA reaction to form vinigrol's tricyclic carbon framework. The C9 methyl stereocenter was then introduced through a highly stereoselective Wittig/hydrogenation sequence to give tricycle **1.60**, which was used to complete a formal total synthesis of **1.1** based on the work of Baran and coworkers (*vide infra*). [20b] However, it should be noted that Barriault's IMDA strategy, disclosed in 2007,[14d] preceded a very similar disconnection published by Baran in 2008. [20a]

Scheme 1.8 Barriault's synthesis of vinigrol's tricyclic carbon framework.



Reagents and conditions: (a) propionic acid, neat, 135 °C, 62%, >25:1 d.r. at C1–C12, 1:1 d.r. at C3; (b) PtO_2, H_2, EtOAc, 76%; (c) KHMDS, THF, –78 °C; then $PhNTf_2$, 99%; (d) $^nBu_3SnCHCH_2$, $Pd(PPh_3)_4$ (10 mol%), LiCl, THF, 60 °C, 80%; (e) DIBAL, CH_2Cl_2, –78 °C; (f) $^pNO_2C_5H_4CO_2H$, DIAD, PPh_3, THF, 0 °C; (g) NaOH, MeOH; (h) PivCl, Et_3N, 4-DMAP, CH_2Cl_2, 60% (four steps); (i) TBAF, THF, 84%; (j) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –78 → 0 °C; (k) $CH_2CHMgBr$, PhMe, –78 °C; (l) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –78 → 0 °C; (m) $SnCl_4$, CH_2Cl_2, –78 °C, 65% (four steps); (n) Ph_3PCH_3I, ^tBuOK, THF-PhMe (1:1), 88%; (o) PtO_2, H_2, EtOAc, 0 °C, 99%, >25:1 d.r..

1.4.E Corey's Approaches Toward the Total Synthesis of Vinigrol

Corey and coworkers investigated two conceptually dissimilar approaches toward the total synthesis of **1.1**. Their first strategy sought to take advantage of their biosynthesis hypothesis through the use of an intramolecular Friedel–Crafts reaction to form vinigrol's 8-membered ring (Scheme 1.9).[27] The synthesis began with conversion of (*S*)-citronellal (**1.61**)[28] to diol **1.62** in three steps including: (1) intramolecular ene reaction promoted by $ZnBr_2$, (2) directed hydroboration, and (3) oxidation. The C9 methyl stereocenter was inverted through a lactone formation/epimerization sequence to give hemiactal **1.64** after lactone reduction with DIBAL. Wittig olefination and Ley oxidation of the resultant secondary carbinol gave ketone **1.65**. Exocyclic enone **1.66** was then prepared in fours steps including: (1) regioselective enol silane formation, (2) $TiCl_4$ promoted alkylation with thiophenylchloromethane, (3) sulfide oxidation, and (4) sulfoxide elimation. Treatment of **1.66** with lithiated 1-methoxy-3-phenylsulfanyl-propan-2-one (**1.67**) gave decalin **1.68** via a Michael-aldol annulation sequence. Oxidative elimination of the thiophenyl substituent and dehydration provided phenol **1.69**, which was converted to the Friedel–Craft cyclization substrate **1.72** in a straightforward manner. Activation of α,β-unsaturated aldehyde **1.72** under a variety of Lewis acidic conditions was unable to facilitate transannular cyclization, likely due to the strain imparted by the *trans*-olefin. Consequently, this strategy was abandoned.

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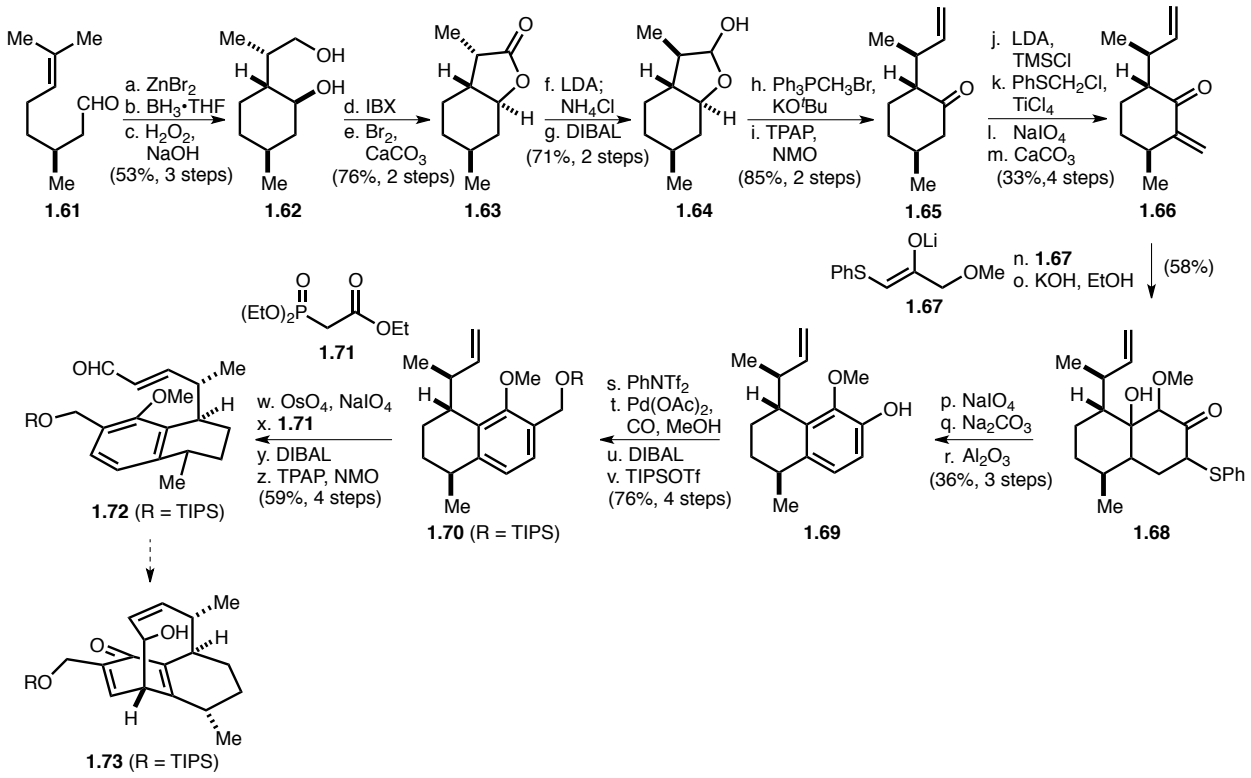
[27] A. Palani, Harvard University, unpublished results reported by S. N. Goodman in his Ph.D. Dissertation, Harvard University, 2000.

[28] The chemistry conducted in this scheme was directed toward *ent*-vinigrol due to some confusion regarding the published ORTEP drawing in Ref. 1.

Scheme 1.9 Corey's unsuccessful Biomimetic Friedel–Craft appoach.[29]



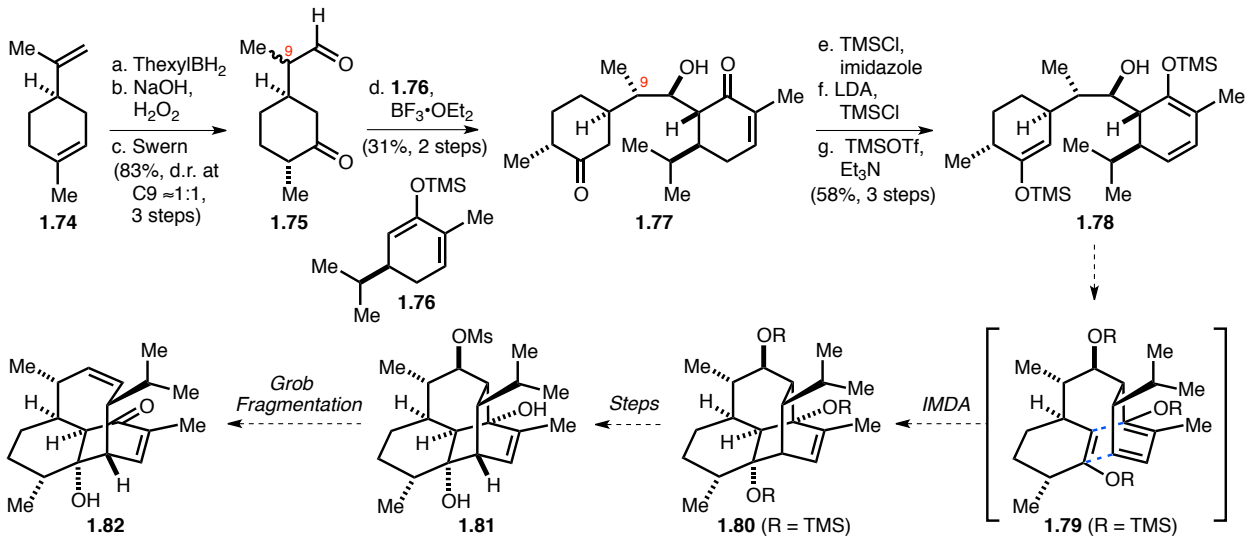
Corey and Goodman's strategy to build vinigrol's unusual decahydro-1,5-butanonaphthalene tricyclic carbon skeleton involved a IMDA reaction/Grob fragmentation sequence (Scheme 1.10).[30] The Baran group later utilized a variation on this strategy to complete the first total synthesis of **1.1** (*vida infra*). Corey's second-generation synthesis commenced with hydroboration/oxidation of (*R*)-limonene (**1.74**) to yield aldehyde **1.75** as 1:1 mixture of C9 diastereomers. Since, resolution of the diastereomeric aldehydes at this stage proved to be problematic, the product mixture was submitted to a Mukiayama aldol reaction with (*R*)-carvone derived silyl enol ether **1.76** to provide two diastereomeric products, one of which possessed the desired C9 stereochemistry. The Felkin-Ahn-Eisenstein model can be invoked to

[29] Reaction conditions were not provided.

[30] (a) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594–610; (b) Wharton, P.S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254–3257. (c) C. A. Grob, *Angew. Chem. Int. Ed.* **1969**, *8*, 535–546. (d) Grob, C. A. *Chimia* **1971**, *25*, 87. (e) Grob, C. A. *Angew. Chem. Int. Ed.* **1976**, *15*, 569–575. (f) Grob, C. A. *Helv. Chim. Acta* **1985**, *68*, 882–886. (g) Grob, C. A. *Angew. Chem. Int. Ed.* **1982**, *21*, 87–96. (h) Ho, T.-L. *Heterolytic Fragmentation of Organic Molecules*; Wiley: New York, 1993.

explain the observed facial selectivity for nucleophilic carbonyl addition in this reaction.[31] Next, sequential silyl protection and enol silane formation gave IMDA substrate **1.78**. Unfortunately, the proposed IMDA reaction to form **1.80** was unsuccessful under a variety of conditions, ostensibly due to the poor frontier molecular orbital (FMO) overlap between the silyl enol ether and the pendant 1-silyloxydiene subunit in transition state **1.79**. Attempts were undertaken to modify the electronic nature of the substrate for this reaction, but to no avail. Lack of success in this key transformation prevented the Corey group from assessing the viability of a Grob fragmentation strategy for the synthesis of vinigrol's tricyclic carbon skeleton illustrated below.

Scheme 1.10. Corey's IMDA/Grob fragmentaion strategy.



Reagents and conditions: (a) ThexylBH$_2$, THF, 0 °C; (b) NaOH, H_2O_2, EtOH, 0 °C → RT, 91%, 1:1 d.r. at C1; (c) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then Et_3N, –60 → –30 °C, 91%; (d) **1.76**, BF_3•OEt_2, CH_2Cl_2, –78 °C, 31%, 1.1:1.0 d.r.; (e) TMSCl, imidazole, THF, –78 °C, 85%; (f) LDA, TMSCl, THF, –78 °C, 90%; (g) TMSOTf, Et_3N, CH_2Cl_2, –78→ –10 °C, 76%.

[31] (a) Anh, N. T. in *Topics in Current Chemistry*; Boschke, F. L., Ed. Springer-Verlag: New York, 1980; Vol. 88, p 145. (b) Anh, N. T.; Eisenstein, O. *Nouveau J. Chem.* **1977**, *1*, 61. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

1.4.F Baran's Racemic Total Synthesis of Vinigrol

Learning from other's past mistakes and successes, the Baran group developed the first racemic total synthesis of **1.1** in 2009 utilizing an IMDA reaction/Grob fragmentation sequence to construct vinigrol's tricyclic carbon skeleton (Scheme 1.11). Their synthesis began with a Lewis acid promoted intermolecular *endo*-selective Diels–Alder reaction between silyloxy diene **1.83** and α,β-unsaturated ester **1.84** to provide bicyclo[2.2.2]octane **1.85**. The cycloadduct **1.85** was then transformed to the corresponding vinyl triflate, which underwent Stille cross-coupling with tributylstannylethylene to give diene **1.86**. Next, the methyl ester was treated with DIBAL and the resultant aldehyde was exposed to allylmagnesium chloride to furnish triene intermediate **1.87**. Warming the reaction mixture to reflux promoted a facile IMDA reaction to yield tetracycle **1.88**. Next, the C9 methyl stereocenter was introduced through oxidation of the C10–OH to the ketone followed by enolate alkylation from the convex face of the molecule. The C10 mesylate **1.89**, required for Grob fragmentation, was accessed in three steps via: (1) silyl ether deprotection, (2) C4–OH directed reduction of the C10 ketone with $Me_4NBH(OAc)_3$, and (3) mesylation. It should be noted that the depicted C10 stereochemistry was specifically prepared to optimize orbital overlap during the impending Grob fragmentation process. Gratifyingly, treatment of tertiary carbinol **1.89** with KHMDS provided decahydro-1,5-butanonaphthalene **1.90**. The next synthesis challenge was the introduction of the C8 methyl group and the C8a tertiary carbinol. Many strategies for *syn* introduction of these substitents were attempted including epoxide opening with bromide or cyanide nucleophiles, however none were successful. This obstacle was overcome though the use of a [3+2] dipolar bromonitrile oxide cycloaddition. Exposure of **1.90** to in situ generated bromonitrile oxide promoted chemoselective formation of the corresponding C8–C8a cycloadduct. Next, the C10–C11 olefin was found to be resistant to hydrogentation under a variety of conditions. It was discovered that reduction of the C4 carbonyl was necessary to facilitate hydrogentation of the C10–C11 olefin via C4–OH direction. Accordingly, the intermediate cycloadduct was treated with DIBAL to reduce the C4 carbonyl group and a solution of the resultant alcohol was stirred under a

hydrogen atmosphere with Crabtree's catalyst to afford intermediate **1.92**.[32] The C4 alcohol was then dehydrated via xanthate formation and Chugauv elimination[33] to give cyclohexene **1.93**. Sequential reduction of the bromoisoxazole subunit to deliver intermediate **1.94** exhibiting the requisite C8–Me and C8a–OH substituents, was accomplished in four steps including: (1) reduction with $LiAlH_4$, (2) formylation of the resultant amine, (3) dehydration to the primary isonitrile, and (4) C–N bond reduction with $^{n}Bu_3SnH$ and AIBN.[34] The C3–C4 olefin was then dihydroxylated and the resultant C3–OH was chemoselectively oxidized with NaOCl to an α-hydroxy ketone intermediate, which underwent hydrazone formation with trisylhydrazide to give compound **1.95**. Finally, simultaneous installation of the C2–C3 olefin and the C16 hydroxymethyl group was accomplished via a Shapiro reaction, thereby completing the first total synthesis of **1.1** in 23 steps and 3% overall yield.[35]

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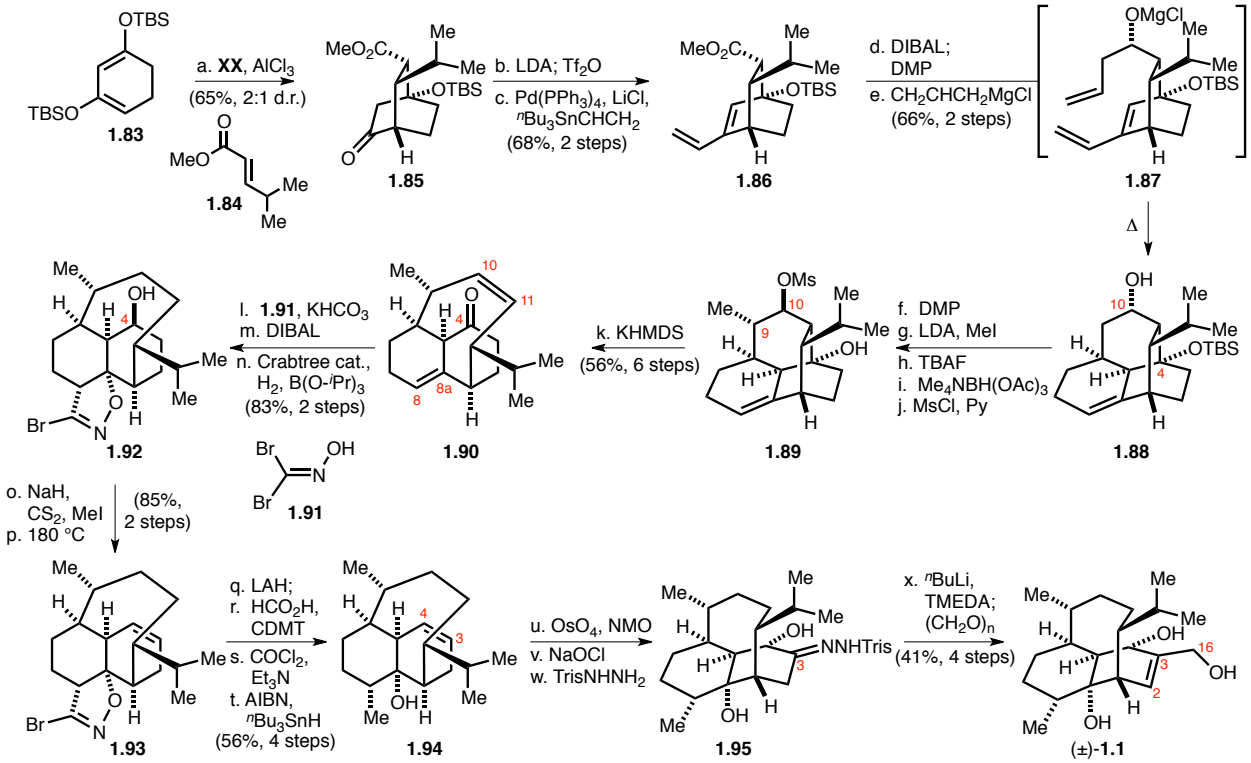
[32] Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.

[33] DePuy, C. H.; King, R. W. *Chem. Rev*. **1960**, *60*, 431–457.

[34] Saegusa, T.; Kobayashi, S.; Ito, Y.; Yasuda, N. *J. Am. Chem. Soc.* **1968**, *90*, 4182.

[35] Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734–5735.

Scheme 1.11 Baran's strategy for the first racemic total synthesis of vinigrol.



Reagents and conditions: (a) **1.84**, $AlCl_3$, CH_2Cl_2, –78 → –45 °C, 65%, 2:1 d.r.; (b) LDA, Tf_2O, THF, –78 °C → RT, 76%; (c) $^nBu_3SnCHCH_2$, LiCl, $Pd(PPh_3)_4$, THF, reflux, 90%; (d) DIBAL, CH_2Cl_2, –78 °C; then DMP, CH_2Cl_2, 81% (two steps); (e) allylmagnesium chloride, PhMe, –78 → 105 °C, 81%; (f) DMP, CH_2Cl_2, 92%; (g) LDA, MeI, THF, –78 → 0 °C; (h) TBAF, THF, 50 °C; (i) $Me_4NBH(OAc)_3$, HOAc-MeOH-THF (1:1:1), 72% (three steps); (j) MsCl, Py, 0 °C; (k) KHMDS, THF, 0 °C → RT, 85% (two steps); (l) **1.91**, $KHCO_3$, EtOAc, 88%; (m) DIBAL, CH_2Cl_2, –78 °C → RT, 95%; (n) Crabtree's catalyst (20 mol%), $B(O\text{-}^iPr)_3$, H_2, $ClCH_2CH_2Cl$, 80 °C, 87%; (o) NaH, CS_2, MeI, THF, 70 °C → RT, 88%; (p) *o*-DCB, 180 °C, 96%; (q) $LiAlH_4$, THF, 0 °C → RT; (r) HCO_2H, CDMT, NMM, 4-DMAP (10 mol%), CH_2Cl_2, 81%, (two steps); (s) $COCl_2$, Et_3N, CH_2Cl_2, –20 °C, 76%; (t) AIBN, $^nBu_3SnH$, PhMe, 100 °C, 91%; (u) OsO_4 (10 mol%), NMO, Me_2CO-H_2O (3:1), 95%; (v) NaOCl, TEMPO (10 mol%), KBr, (10 mol%), 5% aq $NaHCO_3$-CH_2Cl_2 (2:5), 0 °C, 85%; (w) $TrisNHNH_2$, CH_2Cl_2; (x) ^nBuLi, $(CH_2O)_n$, TMEDA-THF (2:1), –78 °C → RT, 51% (two steps).

1.4.G Njardarson's Racemic Total Synthesis of Vinigrol

Njardarson and coworkers recently published the second racemic total synthesis of **1.1** (Scheme 1.12).[19d] Their synthesis employed several key chemical transformations including an oxidative dearomatization/Diels–Alder cycloaddition, a Heck reaction cascade, and a Wharton/Grob fragmentation sequence[36] to construct vinigrol's carbocyclic core. Unfortunately, a lengthy series of oxidation state manipulations and one-carbon homologations were required to complete the total synthesis. Despite these drawbacks the synthesis illustrates a great deal of ingenuity and a number of intriguing reactions. The synthesis began with 3-(trimethylsilyl)propargyl alcohol, which was elaborated to cyclization substrate **1.96** in 11 steps (not depicted). Exposure of phenol **1.96** to iodobenzene diacetate in MeOH promoted an oxidative dearomatization reaction to give an intermediatate mixted acetal. The intermediate was heated to facilitate an IMDA reaction and afford cycloadduct **1.97**, exhibiting the requisite C8a, C1, and C12 stereochemistry. It should be noted that the use of a trifluoroethyl phenol protecting group was necessary to electronically deactivate the aromatic ring and thus guide the oxidative dearomatization reaction to the more hindered site of the molecule. Synthesis of pentacycle **1.98** was accomplished through a tandem Heck reaction cascade in which the C4a and C5 stereocenters of **1.1** were introduced. Next, the C9 methyl stereocenter was set through hydrogenation of the corresponding exocyclic olefin and the intermediate ketone was converted to alternative exocyclic olefin **1.99** via carbonyl addition with methylmagnesium bromide and dehydration of the resultant tertiary carbinol. Hydrogenation of **1.99** with Pfaltz catalyst **1.100**[37] introduced the C8 methyl stereocenter. Presumably the high facial selectivity for hydrogen transfer in this reaction was due to coordination of the furan oxygen to the iridium catalyst. Wharton/Grob fragmentation substrate **1.102** was then prepared through a series of oxidation state manipulations. Treatment of **1.102** with ^{t}BuOK stimulated C6–C12 bond fragmentation and ring expansion to yield ketone **1.103**. The C12 isopropyl substituent was then introduced and the methyl ether at C16 deprotected

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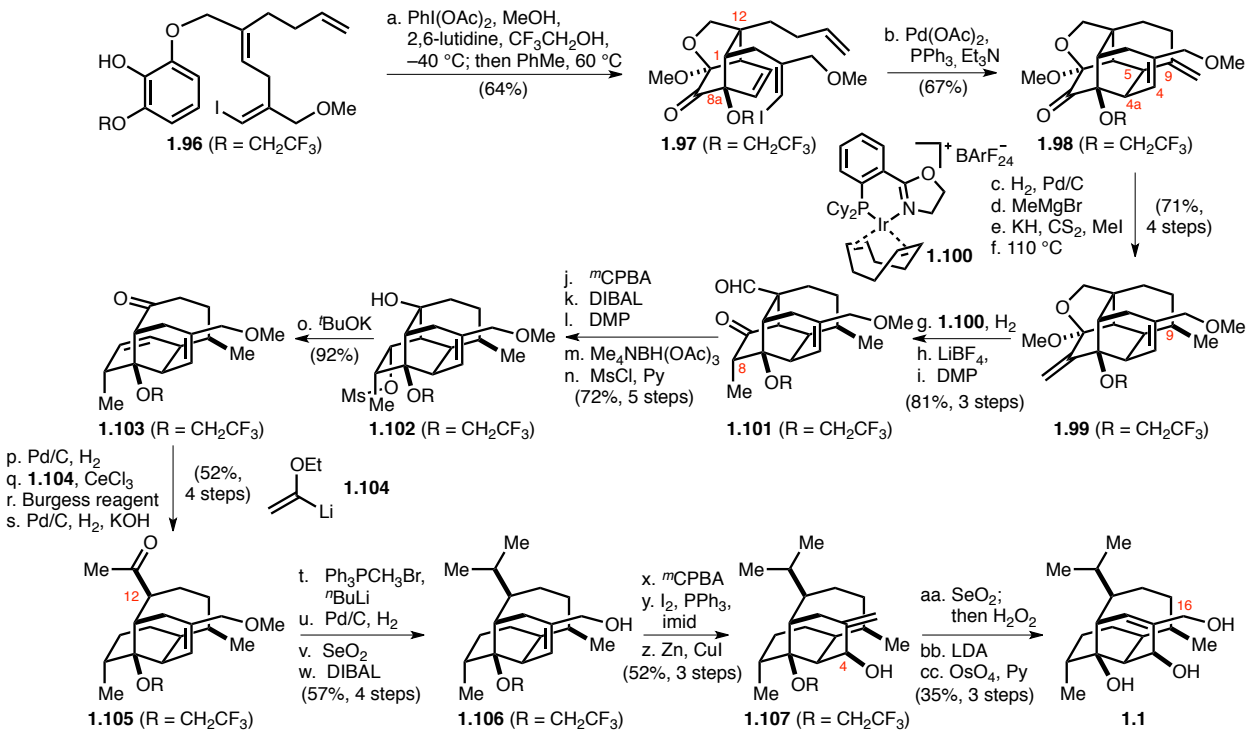
[36] Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781–4782.

[37] Stenberg, B. W.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174–178.

to provide allylic alcohol **1.106**. Epoxidation of **1.106** followed by iodination of the primary alcohol and reductive fragmentation via sonication with activated zinc metal afforded transposed allylic alcohol **1.107**. Next, the C3–C16 exocyclic olefin was oxidized with concomitant 1,3-transposition by exposure to SeO_2. Finally, the second racemic total synthesis of of **1.1** was completed through deprotection of the trifluoroethyl protecting group via a novel fluoride elimination/oxidation sequence.

Scheme 1.12 Njardarson's total synthesis of vinigrol.



Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 2,6-lutidine, CF_3CH_2OH, –40 °C; then PhMe, 60 °C, 64%; (b) $Pd(OAc)_2$, PPh_3, Et_3N, $PhCF_3$, 150 °C, 67%; (c) Pd/C (10 mol%), H_2 (1000 psi), EtOAc, 92%; (d) MeMgBr, $MgBr_2$•OEt_2, Et_2O, 0 °C → RT, 98%; (e) KH, CS_2, MeI, THF, 0 °C → RT; (f) PhMe, 110 °C, 79% (two steps); (g) **1.100** (1 mol%), H_2, CH_2Cl_2, 94%; (h) $LiBF_4$, H_2O-MeCN (2:98), 83 °C; (i) DMP, CH_2Cl_2, 86% (two steps); (j) ^{m}CPBA, CH_2Cl_2, 91%; (k) DIBAL, CH_2Cl_2, –78 °C, 91%; (l) DMP, CH_2Cl_2, 94%; (m) $Me_4NBH(OAc)_3$, AcOH, MeCN, 95%; (n) MsCl, Py, 0 °C, 97%; (o) ^{t}BuOK, ^{t}BuOH, THF, 92%; (p) Pd/C (5 mol%), H_2, EtOAc, 98%; (q) **1.104**, $CeCl_3$, THF, –78 °C, 79%; (r) Burgess's reagent, PhH, 80 °C, 71%; (s) Pd/C (10 mol%), KOH, H_2, EtOH, 94%; (t) Ph_3PCH_3Br, ^{n}BuLi, PhMe, –80 °C, 81%; (u) Pd/C (10 mol%), H_2, EtOAc, 98%; (v) SeO_2, PhH, 80 °C, 73%; (w) DIBAL, PhMe, –78 °C, 98%; (x) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2; (y) I_2, PPh_3, imidazole, THF, 65 °C, 68%

Reagents and conditions for Scheme 1.12 continued: (two steps); (z) Zn, CuI, EtOH, H_2O, sonication, 77%; (aa) SeO_2, CH_2Cl_2; then 30% aq H_2O_2, 50%; (bb) LDA, THF, –78 °C; (cc) OsO_4, ^tBuOH, Py, 70% (two steps).

1.5 First-Generation Synthesis Plan and Retrosynthesis Analysis

When planning our first-generation synthesis of **1.1** in 2007, we sought to apply a disconnection strategy that differed from many of the previously published approaches. Specifically we were interested in forming the 6-membered ring highlighted in structures **1.110** and **1.111** (Figure 1.5) at a late-stage in the synthesis rather than the 8-membered ring highlighted in structures **1.108** and **1.109**, due to the problems associated with 8-membered ring closure encountered by Paquette.[12]

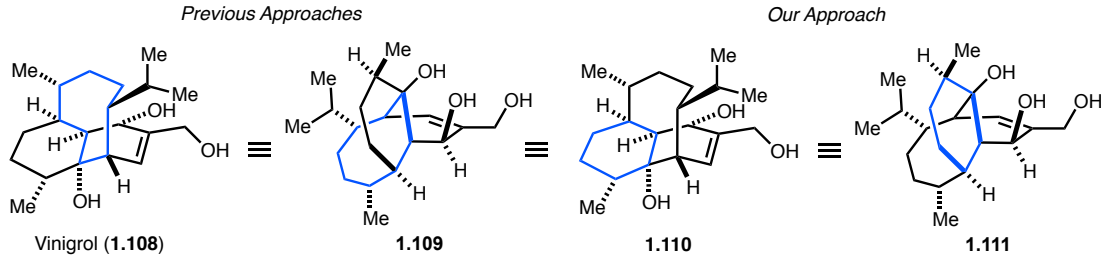


Figure 1.5 Disconnection strategy for vinigrol.

Our initial approach to **1.1** therefore focused on formation of the embedded bicyclo[5.3.1]undecene ring system, highlighted in structure **1.112** of Figure 1.6, common to the taxane family of natural products.[38] We were inspired to target this bicyclic architecture by previous work conducted in the Shair laboratory on the total synthesis of the natural product (+)-CP-263,114 (**1.113**)[39] and on the synthesis of bridgehead enone-containing polycyclic ring systems.[40,41]

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[38] (a) Woods, M. C.; Chiang, H.-C.; Nakadaira, Y.; Nakanishi, K. *J. Am. Chem. Soc*. **1968**, *90*, 522–523. (b) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425–437. (c) Guéritte-Voegelein, F.; Guénard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9–18. (d) Appendino, G.; Tagliapietra, S.; Çetin Özen, H.; Gariboldi, P.; Gabetta, B.; Bombardelli, E. *J. Nat. Prod.* **1993**, *56*, 514–520. (e) Hanson, J. R. *Nat. Prod. Rep.* **1993**, *10*, 159–174. (f) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448–1472. (g) Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 245–256. (f) Shi, Q.-W.; Kiyota, H. *Chem. Biodiversity* **2005**, *2*, 1597–1623.

[39] (a) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424–7425. (b) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784–10785. (c) Chen, C. Ph.D. Thesis, Harvard University, 2001. (d) Layton, M. Ph.D. Thesis, Harvard University, 2002.

[40] Sheehan, S. M.; Lalic, G.; Chen, J.; Shair, M. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 2714–2715.

[41] Oyelaran, O. O. Ph.D. Thesis, Harvard University, 1995.

Juxtaposition of (+)-CP-263,114 (**1.113**) with vinigrol (**1.112**, depicted in an orientation beneficial for comparison) illustrates their structural similarities (Figure 1.6). The total synthesis of **1.113** was accomplished in 12 steps from intermediate **1.114**, which exhibits a similar bicyclo[4.3.1]-deca-1(9)-ene ring system. **1.114** was constructed via a fragment coupling/tandem cyclization reaction of vinyl Grignard **1.117** and β-ketoester **1.118**, comprising: (1) chelation-controlled alkylation, (2) anion accelerated oxy-Cope rearrangement, and (3) transannular acylation.

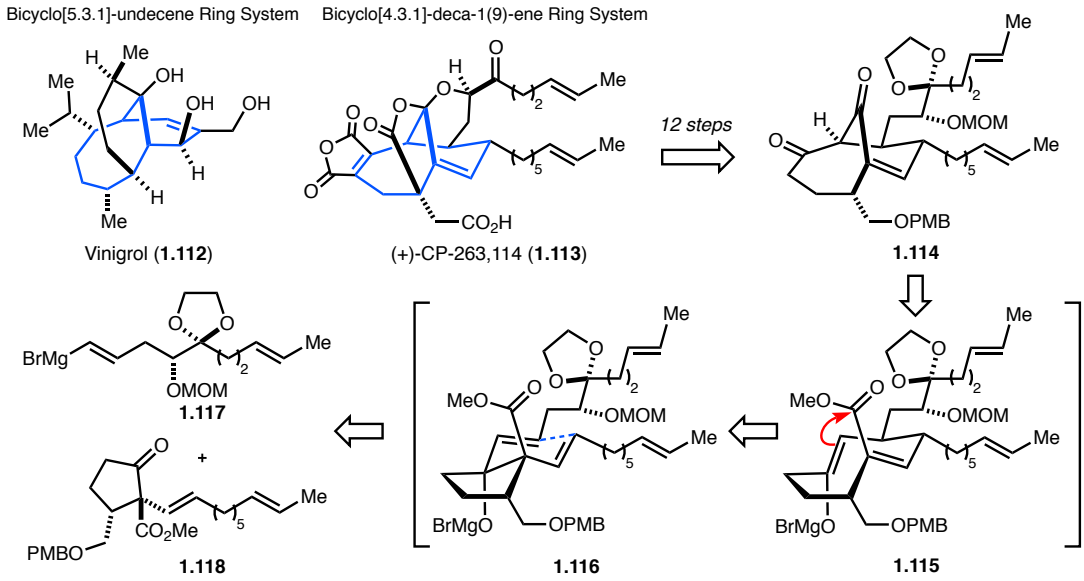

Figure 1.6 Structural comparison of vinigrol with (+)-CP-263,114.

Based on these initial considerations, our synthesis plan for **1.1** is illustrated in Figure 1.7. In a retrosynthetic sense, we anticipated that the C8–C8a bond of the tricyclo[4.4.4.0.^{4a,8a}]tetradecene skeleton could be constructed through a diastereoselective 6-exo-trig cyclization of a ketyl radical derived from the bridgehead ketone of compound **1.119** on to a pendant terminal olefin.[42] The 6-membered ring embedded in **1.119** could then be functionalized, following olefin isomerization, through a precedented series of oxidations.[12d] Introduction of the isopropyl subunit at C12 in **1.119** could then be accomplished in a stereoselective manner utilizing a cross-coupling/hydrogenation sequence. These simplifications reveal compound **1.120**, exhibiting the requisite bicyclo[5.3.1]undecene skeleton of vinigrol. We anticipated that

[42] For a review of samarium(II) iodide-mediated cyclizations in natural product synthesis, see: Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403.

a tandem alkylation/retro-aldol-aldol equilibration/anion-accelerated oxy-Cope rearrangement/transannular acylation cascade reaction of cyclohexanone **1.121** with vinylmagnesium bromide could yield intermediate **1.120**.[43] Finally, cyclohexanone **1.121** could potentially be accessed from chiral enone **1.122** via a three-component coupling protocol. A total synthesis based on this strategy would be enantiospecific in nature, wherein the stereochemical information contained in **1.122** could be propagated to set all the other stereocenters in the molecule diastereoselectively.

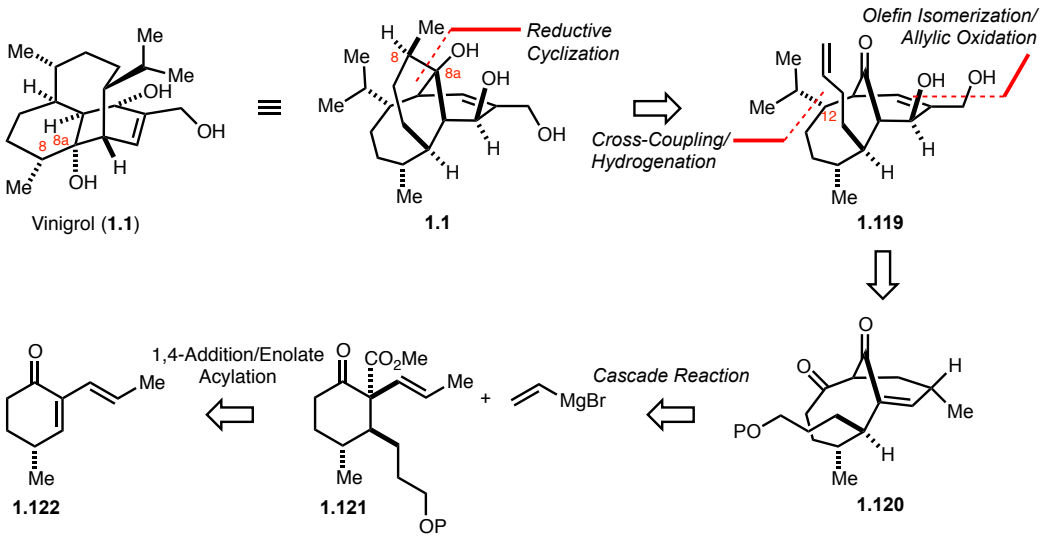

Figure 1.7 Retrosynthetic analysis of vinigrol.

A brief discussion of our proposed first-generation cascade reaction sequence will help clarify several of the reaction design elements (Scheme 1.13). We anticipated that the tandem reaction sequence would begin with chelation-controlled diastereoselective vinylmagnesium bromide addition to β-ketoester **1.121** from the axial face of the depicted chair conformer **1.123**[44,45] furnishing tertiary allylic alkoxide **1.124**, which notably contains *trans*-1,2-diaxial alkenyl substituents. We proposed that in order for these alkene groups to become geometrically capable of participating in an anion-accelerated oxy-Cope

[43] For a review on cascade reactions in natural product total synthesis, see: (a) Tietze, L. F. *Chem. Rev.,* **1996**, *96*, 115–136. (b) Nicolaou, K. C. Edmonds, D. J. Bulger, P. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[44] (a) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944–2956. (b) Eicher, T.; Servet, F.; Speicher, A. *Synthesis* **1996**, 863–870. (c) Molander, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 3705–3716.

[45] For a review on the stereochemistry of organometallic addition to ketones, see: Ashby, E. C.; Laemmle, J. T. *Chem. Rev.,* **1975**, *75*, 521–546.

rearrangement,[46,47,48] a retro-aldol-aldol equilibration step must first take place. This equilibration event would avoid two 1,3-diaxial interactions in chair conformer **1.125**, which orients the alkenyl substituents in *trans*-1,2-diequitorial positions.[49] The push-pull arrangement of the alkoxide and the α-ester was expected to promote fragmentation via a retro-aldol reaction[50] and facilitate the subsequent anion-accelerated oxy-Cope rearrangement.[51] The dynamic retro-aldol-aldol process would allow for the generation of several products, all of which are theoretically capable of undergoing oxy-Cope rearrangement. However, since anion accelerated oxy-Cope rearrangement will likely be the rate-determining step,[49] only the retro-aldol-aldol product with the lowest activation barrier was expected to proceed through the transannular acylation step of the cascade sequence. In this way, the success of the cascade sequence completely relies on the Curtin─Hammett principle;[52] the retro-aldol-aldol product with the lowest activation barrier to anion-accelerated oxy-Cope rearrangement will most likely have a chair-

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[46] For the discovery of the anionic oxy-Cope rearrangement, see: Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.

[47] For recent reviews on the oxy-Cope rearrangement, see: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971–14020. (b) Paquette, L. A. *Angew. Chem., Int. Ed.* **1990**, *29,* 609–626. (c) Hill, R. K. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; vol. 5, ch. 7.1. (d) Wilson, S. R. *Org. React.* **1993**, *43,* 93–250.

[48] For recent applications of the oxy-Cope rearrangement in medium-ring syntheses, see: (a) Yang, J.; Long, Y. O.; Paquette, L. A. *J. Am. Chem. Soc.* **2003**, *125,* 1567–1574. (b) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. *New J. Chem.* **2003**, *27,* 50–60. (c) Hashimoto, H.; Jin, T.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43,* 3633–3636. (d) Banwell, M. G.; McRae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2194–2203. (e) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3,* 2431–2434. (f) Chu, Y.; White, J. B.; Duclos, B. A. *Tetrahedron Lett.* **2001**, *42,* 3815–3818. (g) Jansma, M. J.; Hoye, T. R. *Org. Lett.*, **2012**, *14*, 4738–4741. (h) Hu, D. X.; Clift, M. D.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc*. **2011**, *133*, 1799–1804.

[49] Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D.; *Angew. Chem. Int. Ed.* **2005**, *44*, 2259–2261.

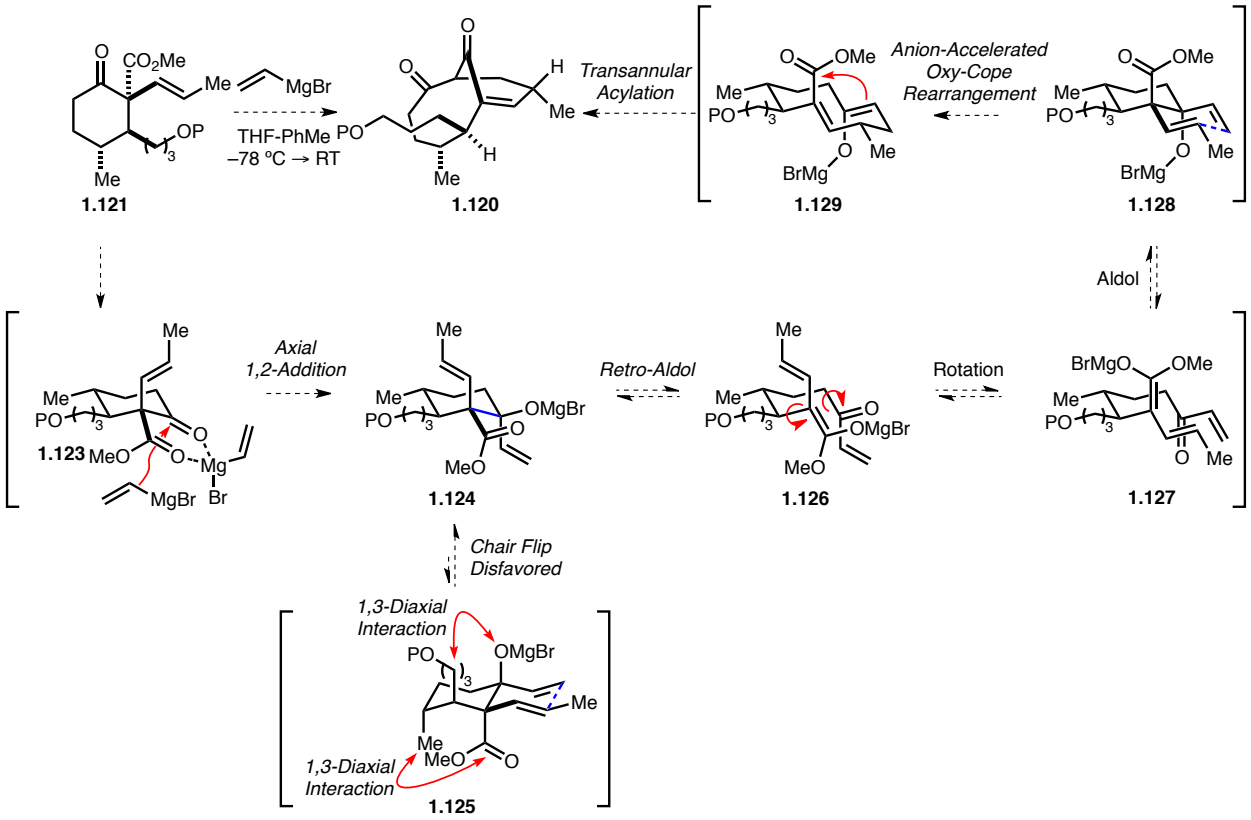
[50] (a) Tomooka, K.; Nagasawa, A. Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1996**, *37,* 8899–8900. (b) Black, W. C.; Giroux, A.; Greidanus, G. *Tetrahedron Lett.* **1996**, *37,* 4471–4474. (c) Schneider, C.; Rehfeuter, M.; *Synlett* **1996***,* 212–214.

[51] Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242–2244.

[52] (a) Curtin, D. Y. *Rec. Chem. Prog*. **1954**, *15*, 111–118; (b) Winstein S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578; (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962. (d) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1970; ch 5; (e) Seeman, J. I. *Chem. Rev*. **1983**, *83*, 83–134; (f) Seeman, J. I. *J. Chem. Educ*. **1986**, *63*, 42–48.

chair-chair-like transition state.[53] For this reason, we anticipated that intermediate **1.128**, which possesses alkene substituents positioned in a *trans*-1,2-diequatorial orientation, should outcompete all other retro-aldol-aldol pathways for anion-accelerated oxy-Cope rearrangement to give intermediate **1.129**. Stereodefined 10-membered ring enolate **1.129**, can then participate in transannular acylation reaction with the pendant methyl ester, liberating an equivalent of methoxide, to yield bicyclo[5.3.1]undecene **1.120**.

Scheme 1.13 Proposed first-generation cascade reaction sequence.



[53] For previous examples of oxy-Cope rearrangements which proceed through boat or chair transition states, see: (a) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102,* 774–782. (b) Paquette, L. A.; Guevel, R.; Sauer, D. R. *Tetrahedron Lett.* **1992**, *33,* 923–926. (c) Chu, Y.; Colclough, D.; Hotchkin, D.; Tuazon, M.; White, J. B. *Tetrahedron* **1997**, *53,* 14235–14246. (c) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901–14904.

1.6 Synthesis of First-Generation Cascade Reaction Precursor

In order assess the viability of our proposed tandem reaction sequence we undertook a synthesis of the cascade precursor (±)-**1.138** (Scheme 1.14). Our initial forays into the synthesis of (±)-**1.138** targeted the cascade substrate as a racemic mixture. Accordingly, commercially available cyclohexane-1,3-dione (**1.130**) was converted to racemic 4-methyl-2-cyclohexen-1-one ((±)-**1.132**) on multi-gram scale through a precedented series of transformations based on the work of Stork and Danheiser.[54] While we elected to utilize racemic (±)-**1.132** in the developmental stages of the project, enantiomerically pure 4-methyl-2-cyclohexene-1-one ((+)-**1.132**) is available on multi-gram scale through a catalytic enantioselective *meso*-epoxide opening procedure developed by Feringa[55] or from (*R*)-pulegone in six steps.[56] Treatment of (±)-**1.132** with iodine and pyridine resulted in the formation of α-iodoenone (±)-**1.133** through a modification of Johnson's procedure in 53% yield over three steps.[57] Suzuki-Miyaura cross-coupling[58] between (±)-**1.133** and (*E*)-propenylboronic acid (**1.134**)[59] resulted in a 74% yield of α-propenyl cyclohexenone (±)-**1.122**. Addition of higher order cuprate **1.135**[60] to (±)-**1.122** in the presence of TMSCl[61] furnished enol silane (±)-**1.136**[62] with high levels of diastereoselectivity. While (±)-**1.136** was

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[54] (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38,* 1775–1776. (b) Kende, A. S.; Fludzinski, P. *Org. Synth.* **1986**, *64*, 68–71. (c) Trost, B. M. Bream, R. N.; Xu, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.

[55] Bertozzi, F.; Crotti, P.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Synthesis* **2001**, 483–486.

[56] Lee, H. W.; Ji, S. K.; Lee, I.-Y. C.; Lee, J. H. *J. Org. Chem.* **1996**, *61,* 2542–2543.

[57] (a) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovich, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918. (b) Scott, T. L.; Burke, N.; Carrero-Martínez, G.; Söderberg, B. C. G. *Tetrahedron*, **2007**, *63*, 1183–1190.

[58] (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc*. **1985**, *107*, 972–980. (b) Urdaneta, N.; Ruíz, J.; Zapata, A. J. *J. Organomet. Chem.* **1994**, *464*, C33–C34.

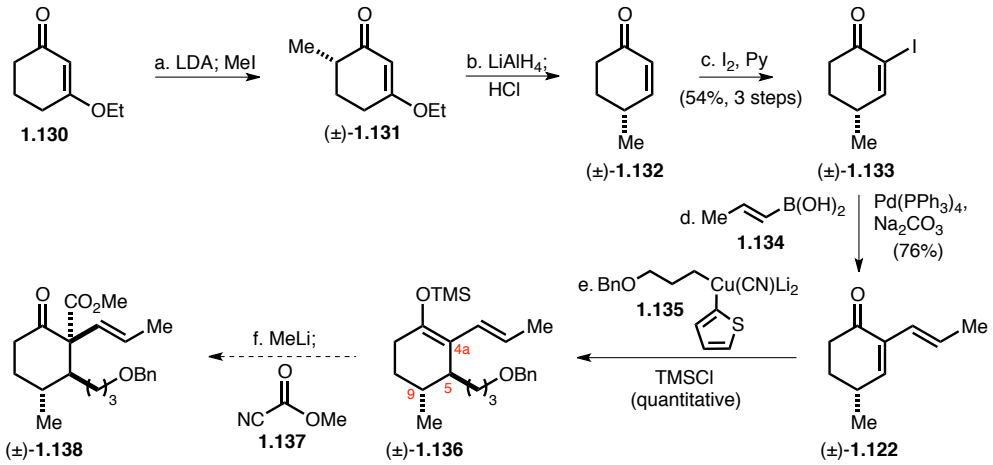
[59] Braun, J.; Normant, H. *Bulletin de la Société Chimique de France* **1966***, 8*, 2557–2564.

[60] (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron*, **1984**, *40*, 5005–5038.

[61] (a) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288–3295. (b) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283–9284. (c) Gooding, O. W. *J. Org. Chem*. **1990**, *55*, 4209–4211. (d) Nakamura, E.; *In Organocopper Reagents: A Practical Approach*, Tayler, R. J. K., Ed; Oxford University Press: Oxford, 1994; pp 129–142. (e) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349–362. (f) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930–4939. (g) Linderman, R. J.;

unstable to purification, it could be treated directly with methyl lithium in THF at –78 °C to regenerate the lithium enolate[63] for the proposed *C*-acylation reaction with methyl cyanoformate.[64] Unfortunately, efforts to affect this transformation were unsuccessful in both Et_2O and THF and in the presence of various additives such as HMPA.

Scheme 1.14 Attempted synthesis of cascade substrate (±)-**1.138**.



Reagents and conditions: (a) LDA, THF, –78 °C; then MeI, –78 °C → RT; (b) $LiAlH_4$, Et_2O; then HCl; (c) I_2, Py, Et_2O, 0 °C → RT, 54% (three steps); (d) **1.134**, 2.0 M Na_2CO_3, $Pd(PPh_3)_4$ (10 mol%), THF, 60 °C, 76%; (e) thiophene, ^{n}BuLi, THF, –78 °C; CuCN, –78 → 0 °C; $BnO(CH_2)_3I$, ^{t}BuLi, Et_2O-pentane, –78 °C → RT; TMSCl, –78 °C; (±)-**1.122**, –78 °C; (f) MeLi, Et_2O, –78 → 0 °C; $CH_3OC(O)CN$ (**1.137**), –78 → 0 °C.

The three-component coupling of a cyclic enone with an organometallic reagent and an electrophile generally results in *trans* relative stereochemistry of the incorporated nucleophile and electrophile.[65] Two potential low energy cyclohexene half-chair conformations exist for the intermediate lithium enolate (Figure 1.8). Putative enolate conformer **1.139** places the C5 and C9 alkyl substituents in

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Godfrey, A. *Tetrahedron Lett.* **1986**, *27*, 4553–4556. (h) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029–4032. (i) Corey, E.J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26,* 6015–6018.

[62] Cyclohexane numbering based on vinigrol's numbering, Scheme 1.1.

[63] Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465.

[64] Crabtree, S. R.; Chu, W. L. A.; Mander L. N. *Synlett* **1990**, *3*, 169–170.

[65] For a review on the application of the three component coupling strategy to prostaglandin syntheses, see: Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed.* **1984**, *23,* 847–876.

a pseudoequitorial orientation, but in doing so engenders steric congestion between the C4a-propenyl substituent and the C5-alkyl side chain. This interaction likely pushes the conformational equilibrium towards half-chair **1.40**. The substrate's overall lack of reactivity may be attributed to the pseudoaxial C9 methyl substituent in **1.140**, which hinders the *Si* face of the lithium enolate and disfavors substitution by methyl cyanoformate.

1.139 **1.140**

Figure 1.8 Rationalization for failed C-acylation.

Due to these difficulties, an alternative strategy to construct the C4a quaternary carbon stereocenter of the first-generation cascade reaction substrate was developed (Scheme 1.15). Specifically, we anticipated that a Claisen rearrangement[66] could be applied to address this issue. The revised synthesis of (±)-**1.138** began with commercially available racemic methyl 2-hydroxy-5-methylcyclohex-1-enecarboxylate ((±)-**1.141**). α-Phenylselenation of (±)-**1.141** followed by oxidation and selenoxide elimination gave α,β-unsaturated β-ketoester (±)-**1.142**. Conjugate addition of alkyl Grignard **1.144**, promoted by catalytic CuBr•SMe_2, occurred *anti* to the C9 methyl substituent to the provide β-ketoester (±)-**1.144** in a 10:1 diastereomeric ratio for the newly formed C5 stererocenter. The enol tautomer of (±)-**1.144** was then selectively *O*-allylated by treatment with NaH and allyl bromide to provide *O*-allyl-β-ketoester (±)-**1.145** in 42% over four steps on multi-gram scale. Allylation of cyclic β-ketoester sodium or potassium enolates generally provides a mixture of *C*-allylated and *O*-allylated products, favoring the former.[67] The exclusive *O*-allylation observed in this reaction can be explained by a steric interaction

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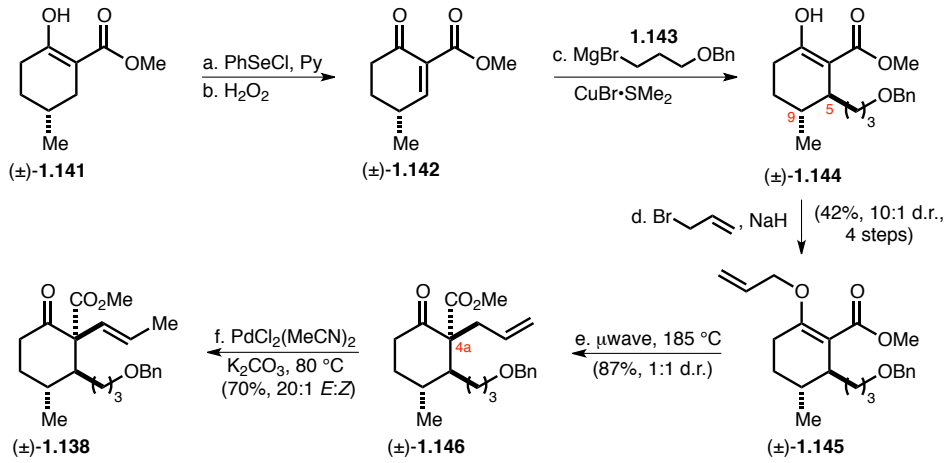
[66] For reviews on the Claisen rearangement, see: (a) Wipf, P. *Comprehensive Organic Synthesis;* Trost, B. M. Ed.; Pergamon: Oxford, 1991; vol 5; pp 827–873. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939−3002. (c) Hiersemann, M.; Nubbemeyer. U. Eds. *The Claisen Rearrangement*; Wiley-VCH: Weinheim, 2007.

[67] (a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228–9229. (b) Uyeda, C.; Rötheli, A. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 9753–9756.

between the incoming allyl electrophile and an axially disposed C9 methyl substituent of a half-chair enolate conformer analogous to **1.140** (Figure 1.8). Next, microwave irradiation of neat allyl vinyl ether (±)-**1.145** for 15 min at 185 °C afforded *C*-allyl-β-ketoester (±)-**1.146** in 87% yield, in which the C4a quaternary center was formed as a 1:1 mixture of diastereomers. Finally, exposure of the desired *C*-allyl-β-ketoester diasteomer (±)-**1.146** to catalytic $PdCl_2(MeCN)_2$ and K_2CO_3 in warm PhMe promoted olefin isomerization to give cascade substrate (±)-**1.138** in 70% yield. Notaly, the Pd(II) catalyzed olefin isomerization process preferentially gave the thermodynamically favored internal *trans* olefin isomer.[68,69]

Scheme 1.15 First-generation cascade substrate synthesis via Claisen rearrangement.



Reagents and conditions: (a) PhSeCl, CH_2Cl_2, 0 °C → RT; (b) 30% aq H_2O_2, CH_2Cl_2, 0 °C; (c) $BnO(CH_2)_3Br$, Mg(0), THF, reflux; then $CuBr•SMe_2$, –78 °C; then (±)-**1.144**; (d) allyl bromide, NaH, DMF, 0 °C, 42%, 10:1 d.r. (four steps); (e) neat, μwave, 185 °C, 87%, 1:1 d.r.; (f) $PdCl_2(MeCN)_2$ (5 mol%), K_2CO_3, PhMe, 80 °C, 70%, 20:1 *E*:*Z*.

1.7 First-Generation Cascade Reaction Sequence

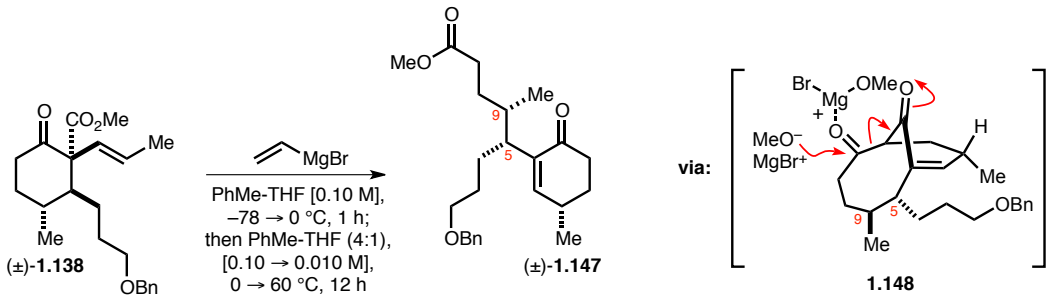
With cascade substrate (±)-**1.138** in hand, we investigated the proposed alkylation/retro aldol-aldol/anion-accelerated oxy-Cope rearrangement/transannular acylation cascade reaction sequence. *C*-propenyl-β-ketoester (±)-**1.138** was exposed to reaction conditions previously developed for a similar

[68] For mechanism, see: Sen, A; Lai, T. W. *Inorg. Chem.*, **1984**, *23*, 3257–3258.

[69] For a review, see: (a) Herrmann, W. A.; Prinz, M. *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B.; Herrmann, W. A. Eds.; Wiley-VCH: Weimheim, 2nd ed., 2002; vol 3; p. 1119. (b) Donohoe, T. J.; O'Riordan, T. J. C. Rosa, C. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1014–1017.

tandem reaction sequence (Scheme 1.16).[39,40,41] A freshly prepared solution of vinylmagnesium bromide in THF was added to a 0.10 M solution (±)-**1.138** in PhMe at –78 °C and warmed to 0 °C over 1 h; after 1,2-addition had taken place,[70] the resultant reaction mixture was transferred via cannula into a solution of PhMe and THF (4:1 by volume) to generate a 0.010 M solution of the intermediate allylic alkoxide. The reaction vessel was then sealed and heated to 60 °C for 12 h. Unfortunately, the only product observed upon work-up was 2-cyclohexenone (±)-**1.147**, formed through a retro-Dieckmann condensation of bicycle **1.148**. Methoxide liberated during the final transannular acylation step of the cascade sequence underwent irreversible 1,2-addition into the non-bridgehead carbonyl group of **1.148**. The dilution process employed in the cascade reaction sequence had been shown in previous examples to suppress the bimolecular retro-Dieckmann condensation process. One possible explanation for the observed reactivity difference could be ascribed to the elevated temperatures (i.e. 60 °C) required to encourage the key anion-accelerated oxy-Cope rearrangement step of this particular cascade reaction. In contrast, previous examples of the anion-accelerated oxy-Cope rearrangement proceeded at ambient temperature. Additionally, compared to the structure of the expected casade reaction product (**1.120**, Scheme 1.13), the alkyl substituentents at C5 and C9 of the putative bicyclic intermediate **1.148** were inverted relative to the bridgehead carbonyl group. This issue will be addressed in a subsequent section of the document.

Scheme 1.16 Cascade reaction under standard conditions.



We speculated whether application of a $ZnBr^+$ rather than a $MgBr^+$ counter ion to the tandem reaction sequence might mitigate the retro-Dieckmann condensation process since Mg^{2+} can be considered

[70] Reaction progress monitored by TLC.

a hard metal while Zn^{2+} is often considered to be soft.[71] Interestingly, the reactivity of magnesium alkoxide catalysts for ring-opening polymerization of L-lactide has been shown to exceed the analogous zinc alkoxide in a head-to-head comparison.[72] Other counter ions such as Li^+, Na^+, or K^+ had previously been demonstrated to be incapable of promoting the transannular acylation step of the tandem reaction sequence;[39d] $MgBr^+$ was considered to be unique in its ability to facilitate both the oxy-Cope rearrangement and the transannular acylation steps of the cascade reaction sequence. Generally, the anion-accelerated oxy-Cope rearrangement of unstrained systems requires elevated temperatures and a highly dissociated counterion (e.g. K^+ with 18-crown-6).[47] The relatively mild conditions under which $MgBr^+$ has been shown to facilitate oxy-Cope rearrangement was attributed to two effects: (1) ground state destabilization by the bromomagnesium alkoxide (highly dissociated counterions accentuate this effect); and (2) transition state stabilization by the α-ester substituent.[51] We anticipated that application of a $ZnBr^+$ counterion to the oxy-Cope rearrangement could replicate these effects.

To test this hypothesis, (±)-**1.138** was exposed to vinylmagnesium bromide at –78 °C and the initial chelation-controlled 1,2-carbonyl addition adduct (±)-**1.149** was isolated in 89% yield as a single C12 diasteomer (Scheme 1.17). The relative stereochemistry of (±)-**1.149** was established though NOESY.[73] The resultant allylic alcohol was then deprotonated through exposure to *tert*-butylzinc bromide at –78 °C and warmed to 0 °C to ensure deprotonation. Following the dilution procedure, the intermediate zinc alkoxide was transferred to a solution of PhMe and THF, sealed, and heated to 50 °C. After only 1 h, the reaction had reached completion. Unfortunately, the only product observed in this transformation again was 2-cyclohexenone (±)-**1.147**, isolated in 53% yield.

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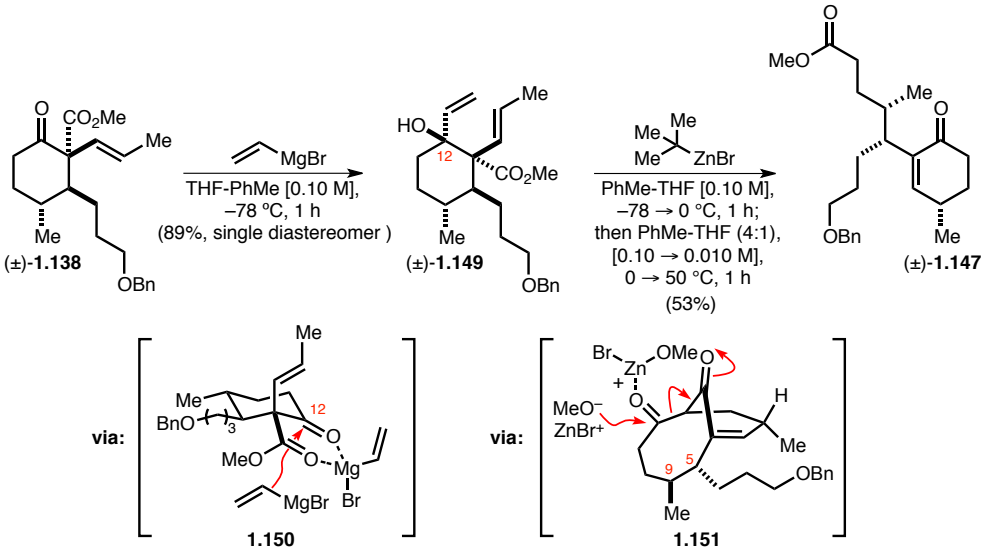
[71] (a) Huheey, J. E.; Keiter, E. A.; Keiter, R. L. *Inorganic Chemistry: Principles of Structure and Reactivity,* 4th ed.; Harper Collins College Publishers: New York, 1993; pp 344–348.

[72] Chisholm, M. H.; Eilerts, N. W.; Huffman, J. C.; Iyer, S. S.; Pacold, M.; Phomphrai, K. *J. Am. Chem. Soc.* **2000**, *122,* 11845–11854.

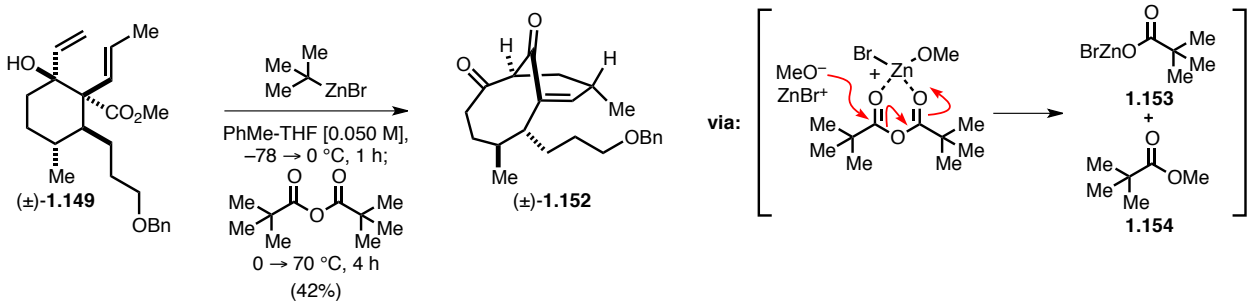
[73] See compound (±)-**1.149** experimental section.

Scheme 1.17 Unsuccessful application of a zinc counter ion toward suppression of retro-Dieckmann condensation.



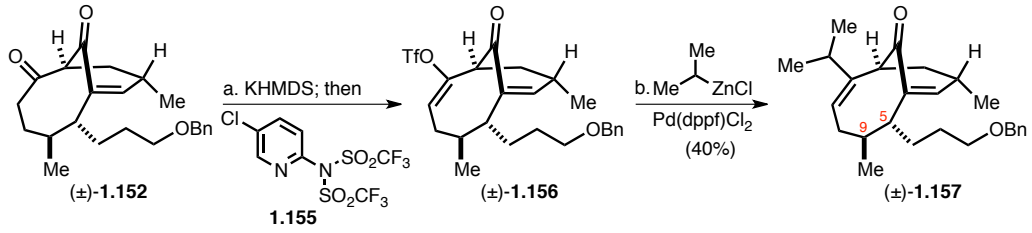
Our next strategy to suppress the retro-Dieckmann reaction was to scavenge the methoxide nucleophile liberated in the tranannular acylation step of the cascade sequence. A variety of electrophilic reagents were investigated including TIPSCl, ethyl β-iodoacrylate, bromodiphenylmethane, and di-*tert*-butyl dicarbonate. Gratifyingly, addition of five equivalents of pivalic anhydride after deprotonation of allylic alcohol (±)-**1.149** with *tert*-butylzinc bromide at 0 °C followed by heating the sealed reaction mixture to 70 °C for 4 h provided bicyclo[5.3.1]undecene (±)-**1.152** in 42% yield (Scheme 1.18). Three attributes of pivalic anhydride underlie its ability to scavange methoxide in this reaction: (1) it is more electrophilic than the non-bridgehead ketone of bicycle (±)-**1.152**, (2) the zinc pivalate byproduct **1.153** is less nucleophilic than zinc methoxide, and (3) its hindered nature prevents pivalation of either the initial tertiary zinc alkoxide or the 10-membered zinc enolate intermediates.

Scheme 1.18 Successful use of pivalic anhydride to suppress of retro-Dieckmann condensation.



The next challenge in the synthesis of **1.1** was the installation of the C12 isopropyl substituent. Kinetic enolization of bicyclic diketone (±)-**1.152** with KHMDS followed by addition of Comins' reagent (**1.155**) provided alkenyl triflate (±)-**1.156** (Scheme 1.19). Negishi sp^2-sp^3 cross-coupling with isopropylzinc chloride afforded crystalline product (±)-**1.157** in 40% yield over two steps, which appeared to have the correct bond connectivity by NMR analysis. However, X-ray crystallographic analysis of (±)-**1.157**[74] surprisingly revealed that we had formed an undesired bicyclic diastereomer, in which the alkyl substituents at C5 and C9 were opposite relative to the bridgehead carbonyl group when compared to the desired diastereomer (exemplified by **1.120**, Figure 1.7). Regrettably, a synthesis intermediate derived from bicycle (±)-**1.157** would be geometrically incapable of participating in a reductive ketone/olefin coupling reaction at a later-stage of the total synthesis.

Scheme 1.19 Determination of undesired bicyclic stereochemistry.



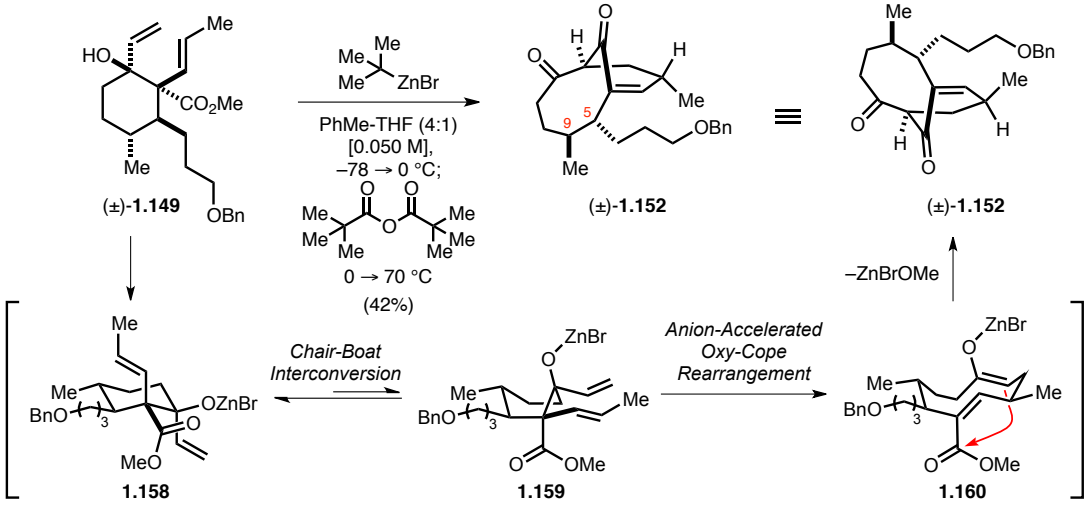
Reagents and conditions: (a) KHMDS, THF, –78 °C; then **1.155**; (b) $Pd(dppf)Cl_2$, LiCl, isopropylmagnesium bromide, $ZnCl_2$, THF, 40 °C.

Based on these findings, the cascade sequence was reevaluated. Formation of bicycle (±)-**1.152**

[74] See experimental section for X-ray crystal structure of (±)-**1.157**.

with the observed relative stereochemistry can be explained if one removes the predicted dynamic retro-aldol-aldol equilibration step from the proposed cascade reaction sequence (Scheme 1.20). An alternative cascade reaction that explains the formation of bicycle (±)-**1.152** involves: (1) deprotonation of allylic alcohol (±)-**1.149** with *tert*-butylzinc bromide to provide zinc alkoxide **1.158**, (2) an unexpected chair-boat interconversion that places the *trans*-1,2-dialkenyl substituents in a pseudoequitorial orientation (i.e. **1.159**), (3) anion-accelerated oxy-Cope rearrangement to afford 10-membered zinc enolate **1.160**, and (4) transannular acylation with concomitant expulsion of ZnBrOMe.

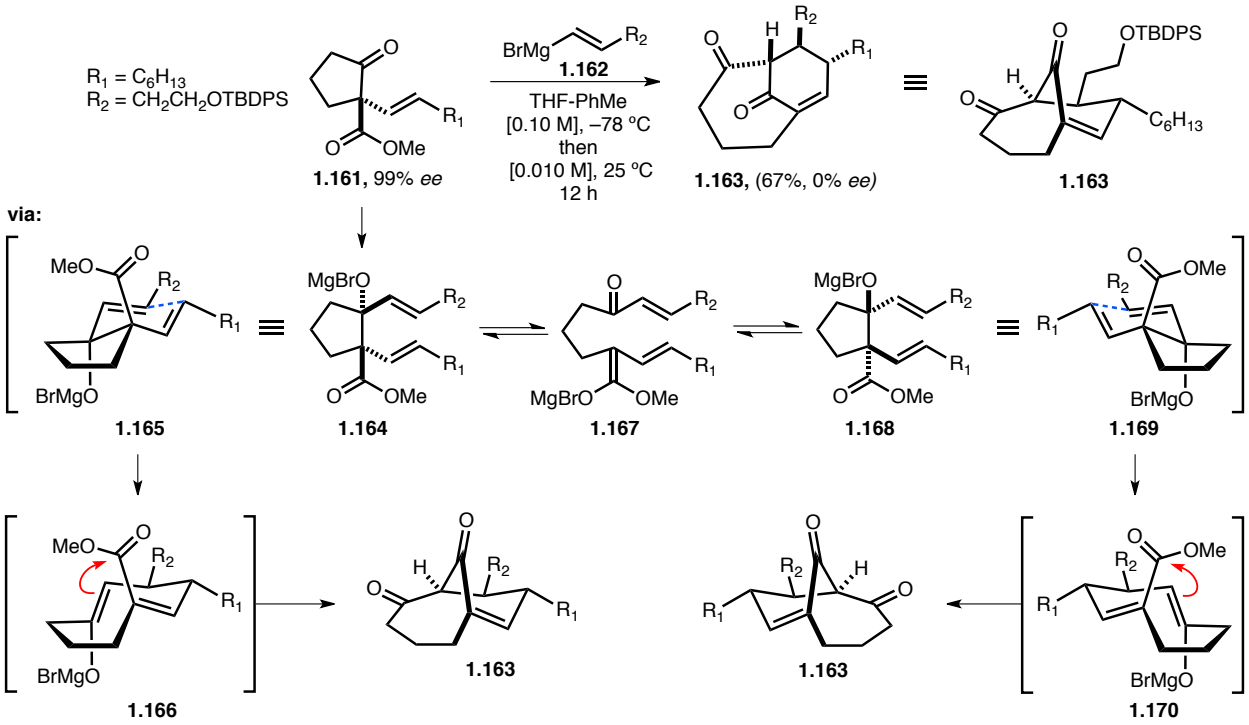
Scheme 1.20 Explanation for undesired relative stereochemistry of (±)-**1.152**: hypothetical cascade reaction sequence.



A brief comparison of two previously studied cascade reaction sequences will help elucidate the substrate requirements for retro-aldol-aldol equilibration. A typical substrate known to be capable of retro-aldol-aldol equilibration during the tandem reaction sequence is illustrated in Scheme 1.21.[49] In this example, the use of enantiopure β-ketoester **1.161** and alkenyl Grignard **1.162** for the cascade reaction sequence resulted in racemic bicyclic **1.163** via a retro-aldol-aldol equilibration mechanism. Chelation controlled 1,2-addition of Grignard **1.162** to α-alkenyl-β-ketoester **1.161** provided a *trans*-1,2-dialkenyl adduct **1.164**. The push-pull arrangement of the alkoxide and the α-ester in **1.164** both facilitated the subsequent anion-accelerated oxy-Cope rearrangement and promoted fragmentation via a retro-aldol reaction to generate acyclic intermediate **1.167**. An intramolecular aldol reaction then produced *trans*-1,2-

dialkenyl alkoxides **1.164** and **1.168** as a racemic mixture. Procession of **1.164** and **1.168** through the anion-accelerated oxy-Cope and transannular Dieckmann steps of the cascade reaction sequence afforded a racemic mixture of bicycle-[4.3.1]deca-1(9)-ene product **1.163**. This fragmentation/recombination pathway was later exploited in a dynamic kinetic resolution of racemic α-alkenyl-β-ketoesters with enantiopure alkenyl Grignard reagents.[49]

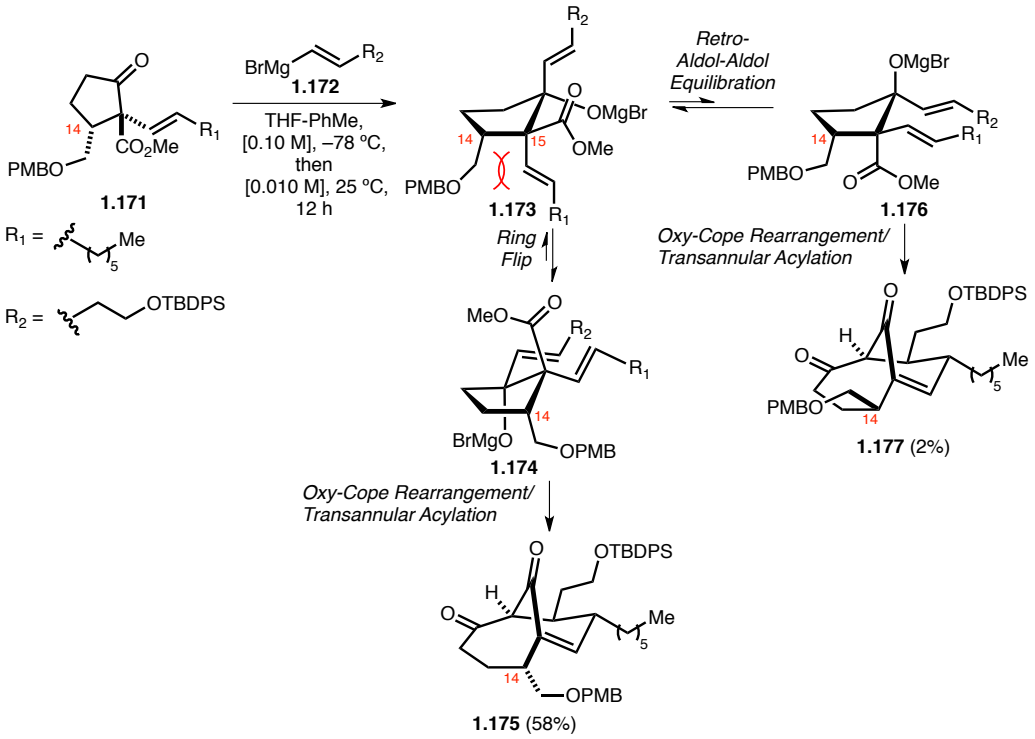
Scheme 1.21 Previously reported cascade reaction sequence involving a retro-aldol-aldol equilibration step.



In contrast, if the cyclic α-alkenyl-β-ketoester substrate was substituted at the 3- or 4-positions, the retro-aldol-aldol equilibration step of the cascade reaction sequence was found to be drastically suppressed. For example, when α-alkenyl-β-ketoester **1.171**, substituted with a C14 alkyl sidechain, was submitted to the cascade reaction conditions, bicycles **1.175** and **1.177** were formed in 58% and 2% yield, respectively (Scheme 1.22). These structures were isomeric in respect to the C14 stereocenter. A mechanism that can account for the observed product distribution begins with chelation-controlled addition of (*E*)-alkenylmagnesium bromide **1.172** to α-alkenyl-β-ketoester **1.171** to generate alkoxide **1.173**, possessing pseudoaxial *trans*-1,2-dialkenyl substituents, which are not geometrically capable of

undergoing oxy-Cope rearrangement. Instead, it is likely that a ring flip took place to alleviate steric congestion between the C15 and C14 substituents. This conformational adjustment then allowed for oxy-Cope rearrangement to proceed through the energetically favored chair transition state **1.174** and eventually provide the major isomeric product **1.175**. Alternatively, retro-aldol-aldol equilibration of alkoxide intermediate **1.173** could generate intermediate **1.176** possessing equatorial *trans*-1,2-dialkenyl substituents. Advancement of **1.176** through the anion-accelerated oxy-Cope rearrangement/transannular acylation steps of cascade reaction sequence then furnished the minor isomeric product **1.177**. The observed product ratio implies that only a small percentage of the intermediate *trans*-1,2-dialkenyl alkoxide **1.173** participated in retro-aldol-aldol equilibration. It is therefore not surprising that our tandem reaction sequence, described in Scheme 1.20, did not include a retro-aldol-aldol equilibration step.

Scheme 1.22 β-Ketoester substitution impedes retro-aldol-aldol equilibration.

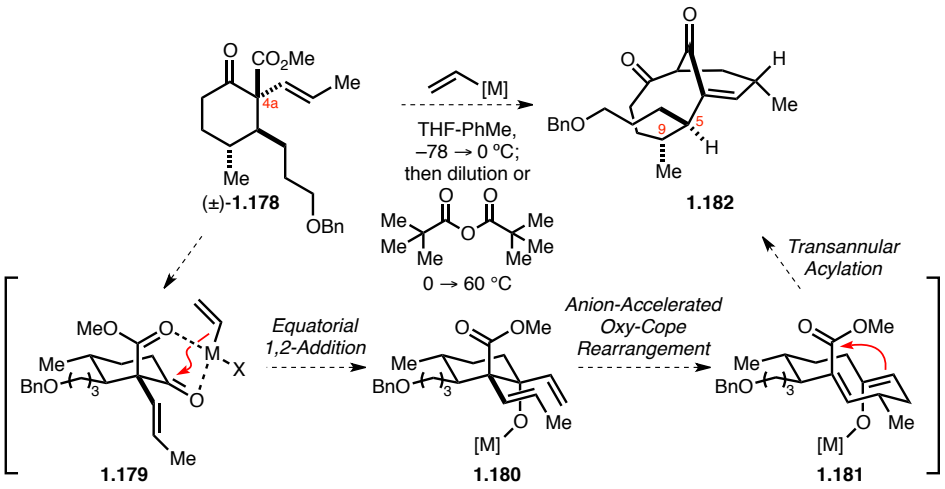


1.8 Revised First-Generation Cascade Reaction Sequence

Based on the aforementioned results, we continued to pursue the synthesis of bicycle **1.182**, depicted in Scheme 1.23, exhibiting the desired stereochemistry at C9 and C15 relative to the bridgehead

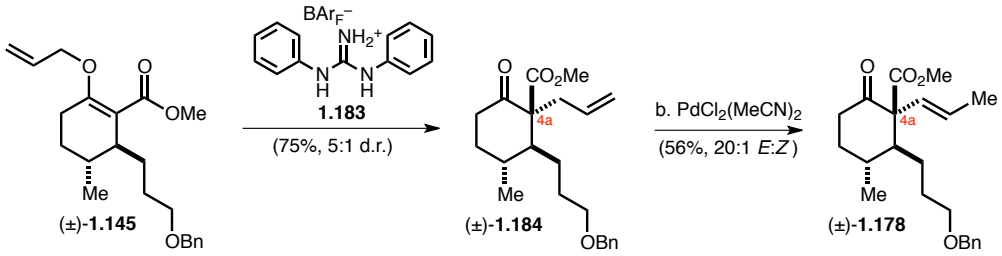
carbonyl group. We envisaged an alternative cascade reaction sequence that omitted a retro-aldol-aldol equilibration step. The first step in the amended reaction sequence involved diastereoselective 1,2-addition of a vinyl organometallic reagent on the *Re* face of α-alkenyl-β-ketoester (±)-**1.178** to yield alkoxide **1.180**, which possesses *trans*-1,2-dialkenyl equatorial substituents. Intermediate **1.180** was expected to undergo a direct anion-accelerated oxy-Cope rearrangement/transannular acylation sequence without the necessity for retro-aldol-aldol equilibration.

Scheme 1.23 Revised first-generation cascade reaction sequence.



Cascade substrate (±)-**1.178** was accessed from previously prepared *O*-allyl β-ketoester (±)-**1.145** through a modified Claisen rearrangement (Scheme 1.24). Exposure of (±)-**1.145** to achiral *N*,*N*'-diphenylguanidinium catalyst **1.183**, developed by Jacoben and Uyeda,[67] promoted Claisen rearrangement at 85 °C to deliver *C*-allyl β-ketoester (±)-**1.184** in 75% yield as a 5:1 mixture of diastereomers at C4a, favoring the stereochemistry necessary for the revised cascade reaction sequence. This reaction could be performed on gram-scale and the catalyst could be isolated and recycled through column chromatography. Isomerization of the allyl group to the *trans*-propenyl substituent was accomplished by exposure of (±)-**1.184** to $PdCl_2(MeCN)_2$ in 56% yield. Interestingly, while the opposite C4a diastereomer required only 5 mol% catalyst loading to complete isomerization, (±)-**1.184** required an equivalent of Pd(II) to reach full conversion.

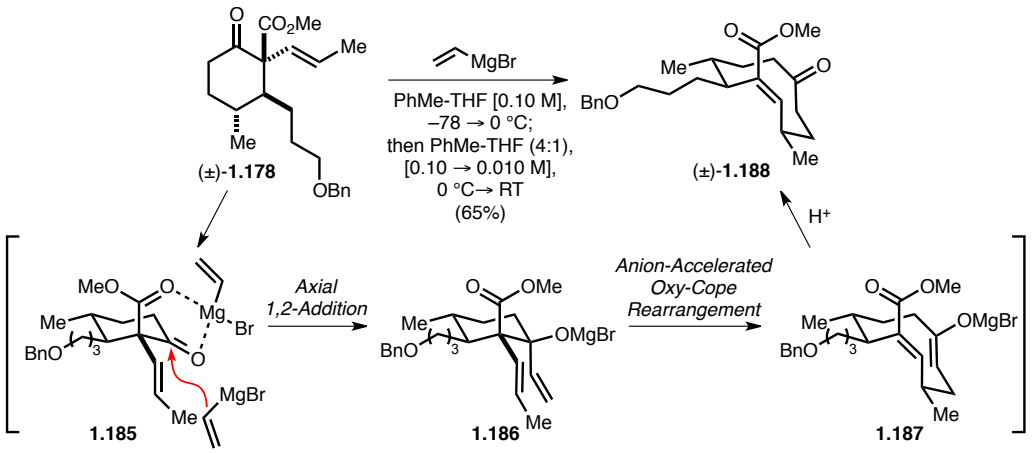
Scheme 1.24 Synthesis of revised first-generation cascade reaction substrate via *N*,*N*'-diphenylguanidinium-catalyzed Claisen rearrangement of *O*-allyl β-ketoester (±)-**1.145**.



Reagents and conditions: (a) **1.183** (30 mol%), heptane, 85 °C, 75%, 5:1 d.r.; (b) $PdCl_2(MeCN)_2$ (1.0 equiv), K_2CO_3, PhMe, 90 °C, 56%, 20:1 *E*:*Z*.

Next, α-alkenyl-β-ketoester (±)-**1.178** was submitted to the previously optimized reaction conditions to test the revised cascade reaction sequence (Scheme 1.25). Addition of vinylmagnesium bromide to a cold solution of (±)-**1.178** in PhMe (0.10 M) resulted in 1,2-addition, as discerned by TLC analysis. The resultant alkoxide was then diluted to suppress retro-Dieckmann condensation and the reaction vessel was sealed and stirred at ambient temperature for 12 h to give *cis*-cyclodecene (±)-**1.188** in 65% yield. The *cis*-olefin geometry of (±)-**1.188** was confirmed by NOESY. Based on our understanding of the cascade reaction sequence, the events leading to (±)-**1.188** were as follows: (1) diastereoselective 1,2-addition to the *Si* face of α-alkenyl-β-ketoester (±)-**1.178** to give magnesium alkoxide **1.186**, which notably possesses *cis*-1,2-dialkenyl substituents, (2) anion-accelerated oxy-Cope rearrangement through a chair-boat-chair transition state, and (3) protonation of the intermediate macrocyclic bromomagnesium enolate upon work-up with HOAc.

Scheme 1.25 Synthesis of *cis*-cyclodecene (±)-**1.188**.



Several important facets of this reaction sequence are important to note. First, given that axial attack on cyclohexanones by relatively small nucleophiles is generally favored,[45,75] it was not surprising that vinylmagnesium bromide preferentially underwent axial carbonyl addition on the lowest energy chair conformer of α-alkenyl-β-ketoester (±)-**1.178**. This hypothesis was confirmed through isolation and characterization of the initial carbonyl addition adduct corresponding to **1.186**.[76] Second, it was interesting to note that anion-accelerated oxy-Cope rearrangement of this particular substrate occurred at ambient temperature, whereas the previous substrate required temperatures as high as 70 °C to undergo [3,3] sigmatropic rearrangement. The *cis*-orientation of the 1,2-dialkenyl substituents of **1.186**, which presumably resulted in a low energy chair-boat-chair transition state, is likely responsible for this reactivity difference. Finally, the inability of the intermediate 10-membered ring enolate **1.187** to undergo transannular acylation reaction is likely a result of geometric constraints placed on the macrocycle by the *cis*-olefin. Even when this reaction was conducted at elevated temperatures, the only product isolated was (±)-**1.188**.

Confident in our analysis of the reaction mechanism, we questioned whether an appropriate vinyl organometallic reagent or Lewis acid additive might favor equatorial attack on α-alkenyl-β-ketoester (±)-

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[75] Trost, B. M.; Florez, F.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109,* 613–615.

[76] See experimental section for full details (compound (±)-**S1.2**).

1.178. Two main factors generally dictate the course of organometallic addition to cyclohexanones: (1) the steric interaction of the incoming nucleophile with the 3- or 5-diaxial substituents and (2) the torsional strain engendered by the nucleophile with the 2- or 6-diaxial substituents.[45] Equatorial attack by bulky nucleophiles is favored, as steric interactions encountered with the 3- or 5-diaxial substituents out-compete torsional effects. Additionally, bulky Lewis acids are also known to favor equatorial approach of organometallic nucleophiles on cyclohexanones. In this case, the steric interactions of the Lewis acid with the 3- or 5-diaxial substituents dominate and control the trajectory of carbonyl addition. A variety of metals and Lewis acids were investigated for vinyl organometallic addition including: $Yb(OTf)_3$,[77] CuI,[78] $(^iPrO)_3TiCl$,[79] $CeCl_3$,[80] $LiClO_4$,[81] $Mn(OCO^tBu)_2$,[82] SmI_2[83] and MAD.[84] After extensive experimentation, it was discovered that addition of freshly prepared vinyl lithium in dibutylether to a solution of α-alkenyl-β-ketoester (±)-**1.178** in dibutyl ether at –78 °C afforded cascade substrate (±)-**1.189** in 57% yield as a 1:1 mixture of diastereomers with respect to C12 (Scheme 1.26). Exposure of the revised cascade substrate (±)-**1.189** possessing equatorial *trans*-1,2-dialkenyl substituents to *tert*-butylzinc bromide at 0 °C, followed by addition of pivalic anhydride and warming the reaction mixture to 50 °C in a sealed vessel

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[77] Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990***, 55*, 4990–4991.

[78] (a) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280–5281. (b) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *Tetrahedron Lett.* **1977**, *18*, 1709–1711.

[79] (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis;* Springer-Verlag: Berlin, 1986. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441–1454. (c) Reetz, M. T. *Tetrahedron* **1986**, *42*, 2931–2935. (d) Weidmann, B.; Seebach, D. *Angew. Chem. Int. Ed.* **1983**, *12,* 31–45.

[80] (a) Imamoto,T.; Kusumoto,T.; Tawarayama,Y.; Sugiura,Y.; Mite, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904–3912. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.*, **1989**, *111*, 4392–4398.

[81] Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371–4377.

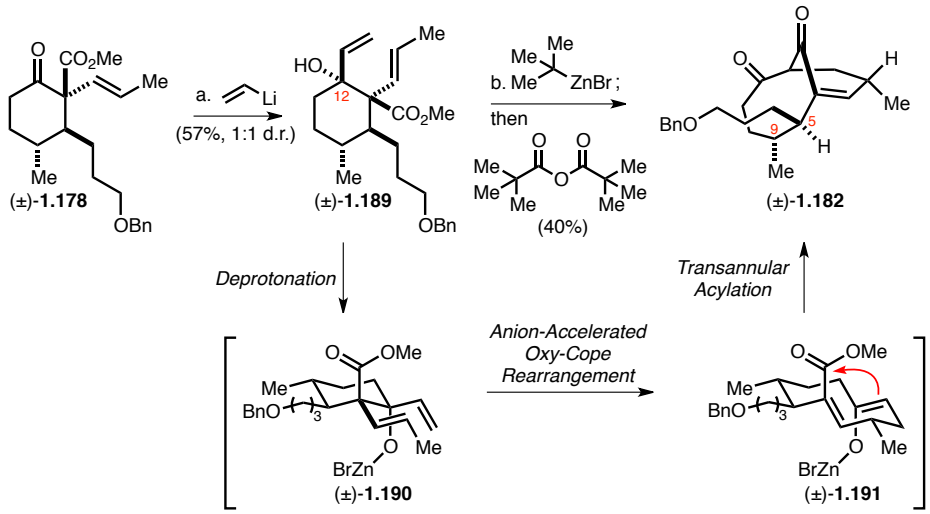
[82] Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **1992**, *33*, 6963–6966.

[83] Evans, W. J.; Allen, N. T. *J. Am. Chem. Soc.* **2000**, *122*, 2118–2119.

[84] Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588–3597.

gratifyingly resulted in the desired bicyclo[5.3.1]undecene (±)-**1.152** in a modest 40% yield. The relative stereochemistry of the byciclic product was confirmed by NOESY.

Scheme 1.26 Synthesis of allylic alcohol (±)-**1.189** and a successful cascade reaction sequence.



Reagents and conditions: (a) tetravinyltin, C_6H_5Li, $^nBu_2O$; then (±)-**1.178**, –78 °C, 57%, 1:1 d.r.; (b) *tert*-butylzinc bromide, PhMe-THF (4:1), [0.050 M], –78 → 0 °C; pivalic anhydride, 40 °C, 40%.

Although it was possible to access bicyclo[5.3.1]undecene (±)-**1.182** for additional studies toward the total synthesis of **1.1**, the poor yields in the final two steps of the synthesis (i.e. 29% and 40%) made us reevaluate our synthesis route to this point. Additionally, computational studies indicated that the proposed late-stage ketone/olefin reductive cyclization reaction to complete the decahydro-1,5-butanonaphthalene tricyclic carbon skeleton of **1.1** would be extremely challenging. These considerations accompanied by a desire to increase the complexity that our cascade reaction sequence could potentially generate, prompted us to develop an alternative strategy for the total synthesis of **1.1**.

1.9 Second-Generation Synthesis Plan and Retrosynthetic Analysis

Our second-generation retrosynthesis plan for **1.1** is outlined below in Figure 1.9. In devising a revised synthesis of **1.1** we hoped to make use of the knowledge gleaned from our previous route. We envisioned introduction of hydroxyl substituents at C4 and C16 could be realized following bridgehead olefin isomerization of a tricyclic precursor **1.192**, through a precedented series of oxidations.[12d] Introduction of the isopropyl subunit at C12 could then be accomplished in a stereoselective manner via a

cross-coupling/hydrogenation strategy. These transformations simplify the synthesis of **1.1** to the construction of tricycle **1.193**, which notably possesses vinigrol's tricyclo[4.4.4.0.^{4a,8a}]tetradecene carbon framework. We anticipated that an alternative cascade reaction sequence involving anion-accelerated oxy-Cope rearrangement of tertiary allylic alcohol **1.194** followed by a transannular aldol cyclization would provide **1.193** in a single operation. We expected that the requisite stereochemistry at C12 of allylic alcohol cascade substrate **1.194** could be set through an alkylation/C12-isomerization protocol. Finally, conjugate addition of an alkyl cuprate derived from **1.197** on to chiral enone **1.196** followed by intramolecular Mukaiyama aldol cyclization could potentially afford *cis*-decalin **1.195** after olefin isomerization.

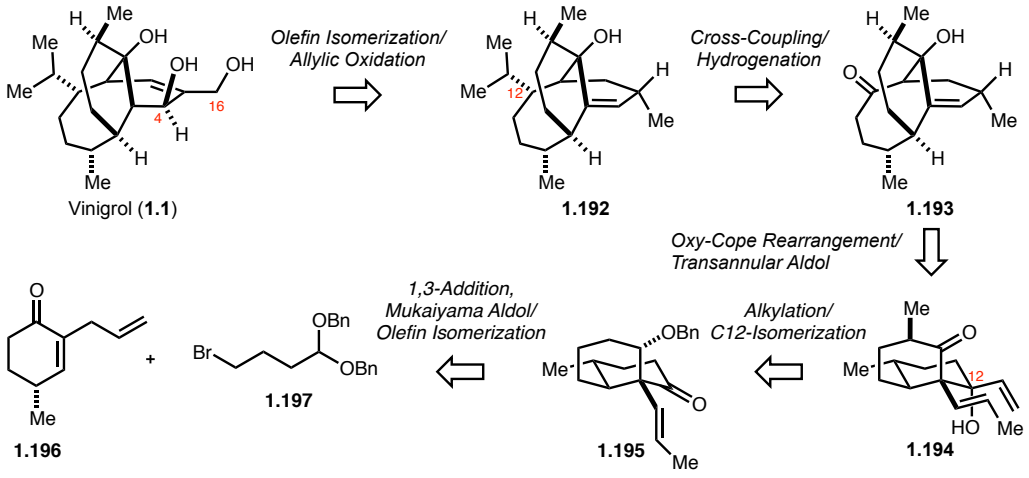
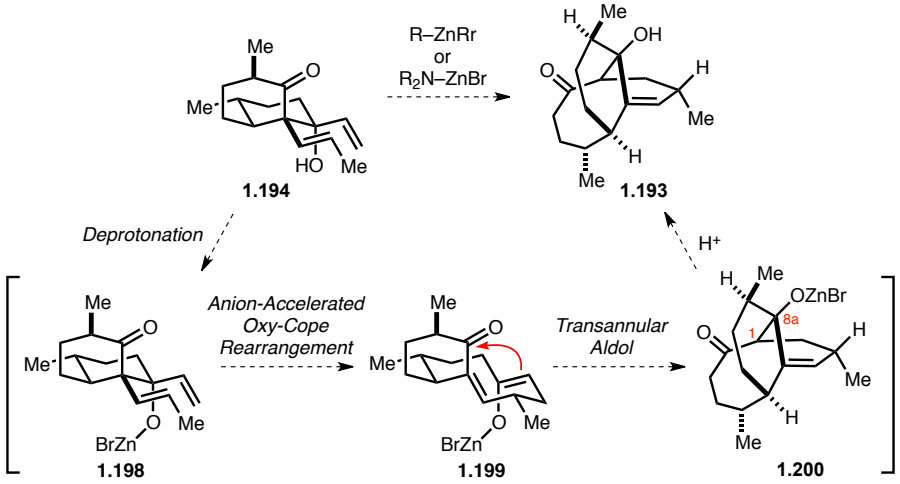


Figure 1.9. Second-generation synthesis plan for vinigrol.

The proposed second-generation cascade reaction sequence is outlined in Scheme 1.27. We anticipated deprotonation of tertiary allylic alcohol **1.194**, which was expected to be several orders of magnitude more acidic than the α-position of the carbonyl group, could be accomplished by exposure to a suitable organometallic base. Following deprotonation, alkoxide **1.198** could undergo an anion-accelerated oxy-Cope rearrangement to regiospecifically generate macrocyclic enolate intermediate **1.199**. The efficiency of this rearrangement was expected to benefit from the polarizing capacity of the carbonyl functionality vicinal to the C–C bond broken during the oxy-Cope process. However, we were apprehensive that the same push-pull arrangement of the alkoxide and the α-ketone, which was expected

to facilitate the anion-accelerated oxy-Cope rearrangement, might also promote undesired fragmentation via a retro-aldol reaction. Nevertheless, we predicted 10-membered enolate **1.199** would participate in a transannular aldol cyclization to furnish tricyclic alkoxide **1.200**. While it is well known that the equilibrium developed during aldol cyclization of an enolate onto a ketone generally favors the reactants,[85] we hoped that a judicious choice of metal counterion or silylating reagent would allow us to favor the formation of the desired tricycle **1.193**.

Scheme 1.27 Proposed second-generation cascade reaction sequence.



1.10 Synthesis of Second-Generation Cascade Reaction Precursor and Attempted Cascade Reaction

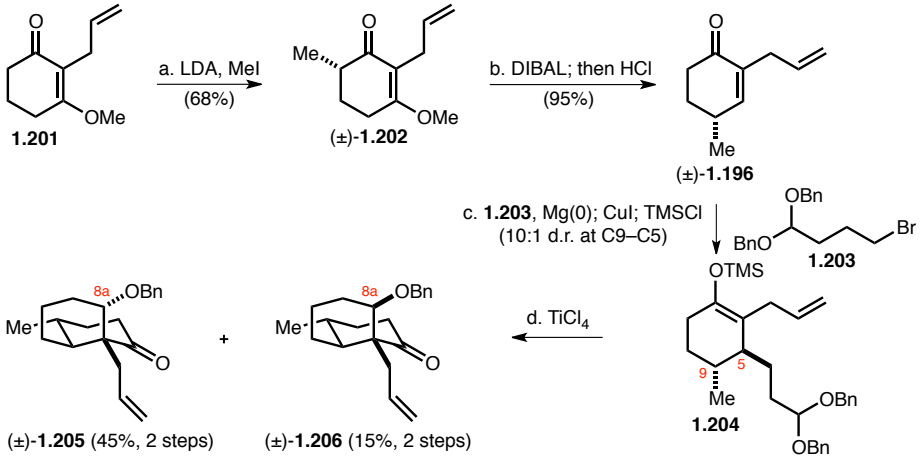
The synthesis of cascade precursor **1.194** began with Stork–Danheiser alkylation followed by reduction and hydrolysis of readily available 2-allyl-3-methoxycyclohex-2-enone (**1.201**)[86] to give racemic enone (±)-**1.196** on multi-gram scale (Scheme 1.28). Alkyl bromide **1.203** was converted to the corresponding Grignard reagent, which underwent CuI promoted 1,3-addition with (±)-**1.196** in the presence of TMSCl. The resultant enol silane **1.204** was formed as a 10:1 diastereomeric mixture with respect to the C9 and C5 stereocenters. Exposure of **1.204** to $TiCl_4$ facilitated an intramolecular

[85] (a) Bartroli, J.; Turmo, E. Belloc, J. Forn, J. *J. Org. Chem.* **1995**, *60*, 3000–3012. (b) Iseki, K.; Oishi, S.; Taguchi,T.; Kobayashi, Y. *Tetrahedron Lett*. **1993**, *34*, 8147–8150.

[86] 2-allyl-3-methoxycyclohex-2-enone (**1.194**) was prepared according to the literature procedure: Mphahlele, M. J.; Modro, T. A. *J. Org. Chem.* **1995**, *60*, 8236–8240.

Mukaiyama-aldol reaction to afford *cis*-decalin C8a diastereomers (±)-**1.205** and (±)-**1.206** in 45% and 15% yield, respectively. The C8a diastereomers were separated and carried through the subsequent steps of the cascade reaction substrate synthesis independently.

Scheme 1.28 Synthesis of *cis*-decalins (±)-**1.205** and (±)-**1.206**.

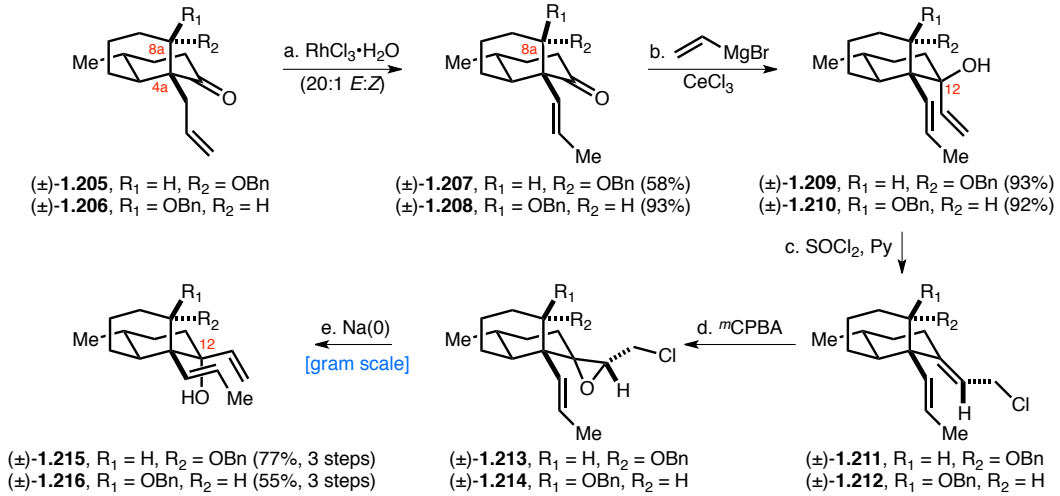


Reagents and conditions: (a) LDA, THF, –78 °C; MeI, –78 → 0 °C, 68%; (b) DIBAL, CH_2Cl_2, 0 °C; HCl, 0 °C → RT, 95%; (c) **1.203**, Mg(0), THF; CuI, –30 °C; (±)-**1.196**, TMSCl, –78 °C; (d) $TiCl_4$, CH_2Cl_2, –78 °C, 45% for (±)-**1.205** and 15% for (±)-**1.206** (two steps).

Exposure of (±)-**1.205**/(±)-**1.206** to catalytic rhodium trichloride in warm benzene promoted isomerization of the C4a allyl moiety to funish propenyl substituted *cis*-decalin (±)-**1.207**/(±)-**1.208** (Scheme 1.29). Interestingly, there was a notable difference in the relative reactivities of the C8a diastereomers towards olefin isomerization. Nevertheless, addition of (±)-**1.207**/(±)-**1.208** to a slurry of vinylcerium chloride in THF delivered (±)-**1.209**/(±)-**1.210** as a single diastereomer with respect to C12, where the organocerium reagent had added exclusively from the convex face of the *cis*-decalin core. The stereochemistry of C12 tertiary allylic alcohol was inverted at this point to generate a *trans*-relationship between the 1,2-dialkenyl substitutents required for the proposed cascade reaction sequence. Accordingly, treatment of (±)-**1.209**/(±)-**1.210** with thionyl chloride and pyridine provided primary allylic chloride (±)-**1.211**/(±)-**1.212**. Chemo- and diastereoselective epoxidation of (±)-**1.211**/(±)-**1.212**, again from the convex face of the cis-decalin skeleton, generated epoxy chloride (±)-**1.213**/(±)-**1.214**. Addition of (±)-**1.213**/(±)-**1.214** to a mixture of sodium metal in ether at ambient temperature facilitated reductive epoxide

opening to supply C12 inverted allylic alcohol (±)-**1.215**/(±)-**1.216** on multi-gram scale.

Scheme 1.29 Synthesis of allylic alcohols (±)-**1.215** and (±)-**1.216**.



Reagents and conditions for (±)-**1.215**: (a) $RhCl_3•H_2O$, K_2CO_3, EtOH, 85 °C, 4.5 h, 58% and 17% recovered (±)-**1.205**; (b) $CeCl_3$, $CH_2CHMgBr$, THF, –78 °C, 93%; (c) $SOCl_2$, Py, hexanes, 0 °C → RT; (d) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2, –60 → –30 °C; (e) Na(0), Et_2O, 77% (three steps).

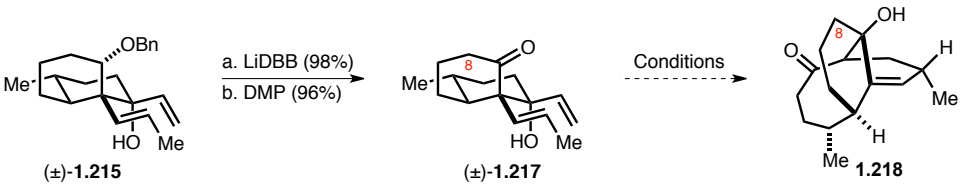
Reagents and conditions for (±)-**1.216**: (a) $RhCl_3•H_2O$, K_2CO_3, EtOH, 95 °C, 1.5 h, 93%; (b) $CeCl_3$, $CH_2CHMgBr$, THF, –78 °C, 92%; (c) $SOCl_2$, Py, hexanes, 0 °C → RT; (d) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2, –60 → –30 °C; (e) Na(0), Et_2O, 55% (three steps).

Next, (±)-**1.215** was treated with LiDBB to facilitate benzyl deprotection and the resultant alcohol was oxidized with DMP to afford model cascade reaction substrate (±)-**1.217** (lacking the C8 methyl substituent) (Scheme 1.30). The cascade reaction sequence was tested by exposing of (±)-**1.217** to a variety of bases, all of which caused immediate decomposition of (±)-**1.217** presumably through a retro-aldol pathway. The bases tested for this reaction included: TMPZnCl•LiCl,[87] TMPMgCl•LiCl,[88] *tert*-butylzinc bromide, 2-mesitylmagnesium bromide, LDA, LDA/$ZnCl_2$, NaHMDS, and KH.

[87] Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837–1840.

[88] Lrasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006,** *45,* 2958–2961.

Scheme 1.30 Preparation of a second-generation model cascade reaction substrate (±)-**1.217** and attempted cascade reaction.

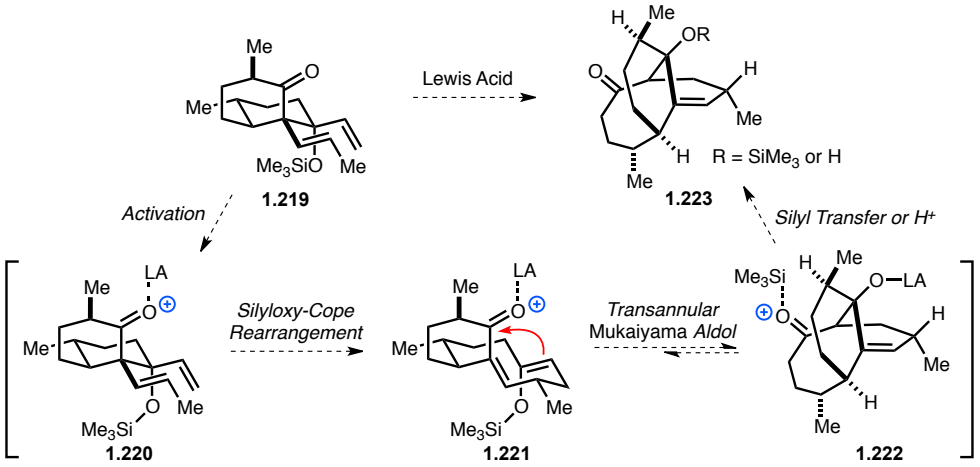


Reagents and conditions: (a) LiDBB, THF, 0 → –78 °C, 98%; (b) DMP, CH_2Cl_2, 96%.

1.11 Revised Second-Generation Cascade Reaction

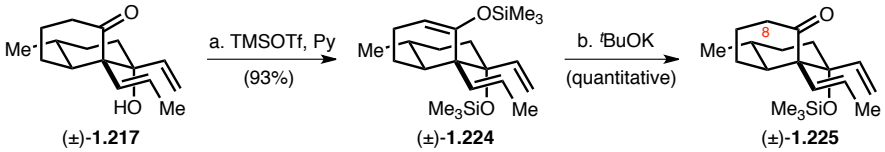
An alternative strategy for the construction of vinigrol's carbon skeleton was envisioned involving a Lewis acid-accelerated silyloxy-Cope rearrangement/transannular Mukaiyama aldol reaction sequence illustrated in Scheme 1.31. We wondered if exposure of silyl protected *cis*-decalin **1.219** to a Lewis acid might promote [3,3] sigmatropic rearrangement through coordination of the carbonyl substituent,[51] thereby weakening the C–C bond broken during the proposed Cope rearrangement to generate 10-membered enol silane **1.221** as a single regioisomer. At this point, we imagined that intermediate **1.221** might engage in a transannular Mukaiyama aldol reaction to form tricyclic intermediate **1.222**, which possesses vinigrol's decahydro-1,5-butanonaphthalene carbon skeleton. Finally, we expected that the corresponding tricyclic product (**1.223**) could potentially be isolated though either protonation or silyl transfer.

Scheme 1.31 Proposed Lewis acid-accelerated silyloxy-Cope rearrangement/transannular Mukaiyama aldol cascade reaction sequence.



A model substrate for the proposed Lewis acid-accelerated silyloxy-Cope rearrangement/transannular Mukaiyama aldol reaction sequence ((±)-**1.225)** was prepared in two steps from ketone (±)-**1.217** in 93% yield (Scheme 1.32). Adddition of TMSOTf to a solution of (±)-**1.217** in pyridine at ambient temperature resulted in bis-silylated product (±)-**1.224**. The enol silane moiety was then selectively cleaved by treatment of (±)-**1.224** with ^{t}BuOK to afford (±)-**1.225** in quantitative yield.[89]

Scheme 1.32 Preparation of Silyloxy-Cope rearrangement substrate (±)-**1.225**.



Reagents and conditions: (a) TMSOTf, Py, 93%; (b) ^{t}BuOK, THF, 0 °C, quantitative.

Ketone (±)-**1.225** was exposed to a variety of Lewis acids in order to promote the desired cascade reaction sequence (Scheme 1.33). Addition of BF_3•OEt_2 to a solution of (±)-**1.225** in CH_2Cl_2 at –78 °C exclusively provided *trans*-decalin (±)-**1.226** in 71% yield. Formation of (±)-**1.226** can be rationalized by a low energy *open synclinal* transition state **1.227**.[90] In contrast, use of $TiCl_4$ as a promotor afforded *trans*-decalin (±)-**1.228** in 83% yield, presumably through a closed *synclinal* transition state (**1.229**).

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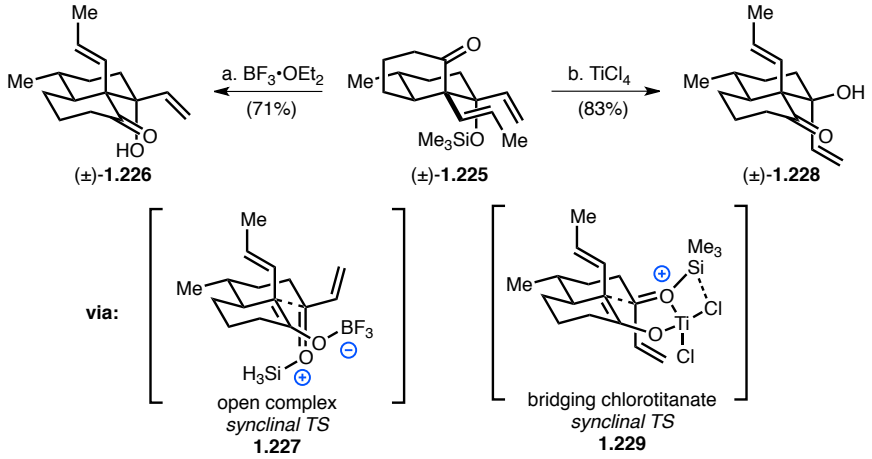
[89] Quesnel, Y.; Bidois-Sery, L.; Poirie, J.-M.; Duhamel, L. *Synlett* **1998**, 413–415.

[90] Denmark, S. E.; Wheeseong; L. *J. Org. Chem.* **1994**, *59*, 707–709.

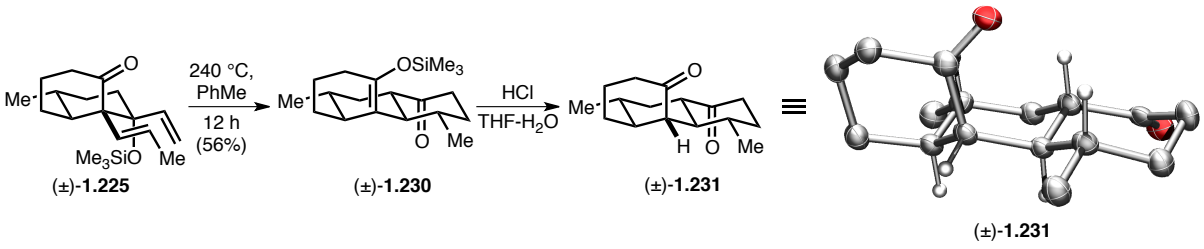
Scheme 1.33 Lewis acid-promoted retro-aldol-aldol reaction.



Reagents and conditions: (a) BF_3•OEt_2, CH_2Cl_2, –78 °C → RT, 71%; (b) $TiCl_4$, CH_2Cl_2, 0 °C→ RT, 83%.

Next, we attempted to promote each step of the reaction sequence independently in order to avoid the undesired Lewis acid-mediated retro-aldol-aldol reaction (Scheme 1.34). Therefore, thermal conditions for the silyloxy-Cope rearrangement were evaluated to synthesize a 10-membered enol silane analogous to intermediate **1.221** (Scheme 1.31). We then planned on treating resultant enol silane with a variety of Lewis acids to promote the desired transannular Mukaiyama aldol reaction. However, heating a solution of (±)-**1.225** in PhMe in a sealed vessel to 240 °C for 12 h afforded unexpected tricyclic enol silane (±)-**1.230** in 56% yield. The structure of (±)-**1.230** was elucidated through a comination of 2D NMR spectroscopy and X-ray crystallographic analysis of the enol silane hydrolysis product (±)-**1.231**.

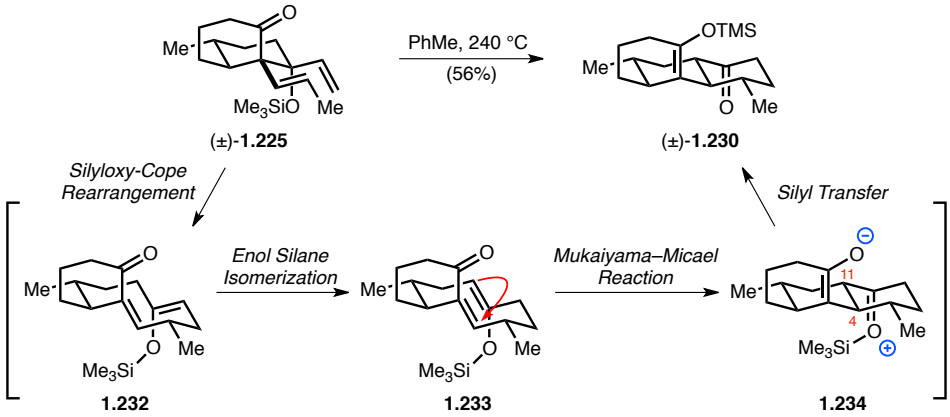
Scheme 1.34 Synthesis of tricycle (±)-**1.230** and X-ray crystal structure of enol silane hydrolysis product (±)-**1.230**.



One possible explanation for the formation (±)-**1.230** is based on a cascade reaction sequence illustrated in Scheme 1.35. It is likely that heating (±)-**1.225** to 240 °C promoted the desired silyloxy-Cope rearrangement to afford 10-membered enol silane **1.232**. Unfortunately, at 240 °C **1.232**

spontaneously isomerized to the regioisomeric enol silane **1.233**. This process was potentially catalyzed by an unknown source of acid.[63] Next, a facile transannular Mukaiyama–Michael reaction took place to construct the C4–C11 bond of zwitterionic intermediate **1.234**, which potentially provided the observed tricyclic product (±)-**1.230** after silyl transfer.[91] We hypothesized that the extreme temperatures necessitated by the silyloxy-Cope rearrangement caused the normally unfavorable enol silane isomerization to take place. This result prompted us to investigate a milder method for the formation of **1.233** or an analogous 10-membered enol silane, thereby avoiding the isomerization process.

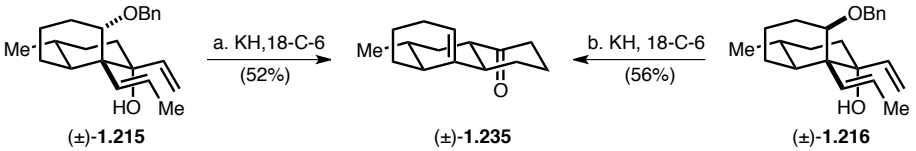
Scheme 1.35 Mechanism to account for the formation of tricycle (±)-**1.230**.



We chose to study the anion-accelerated oxy-Cope rearrangement of C8a benzyl ether diastereomers (±)-**1.215** and (±)-**1.216** since both (±)-**1.215** and (±)-**1.216** benefited from a functional group arrangement that rendered them incapable of retro-aldol fragmentation (Scheme 1.36). Independent subjection of (±)-**1.215** and (±)-**1.216** to standard anion-accelerated oxy-Cope rearrangement conditions with KH and 18-crown-6 in anhydrous THF at *room temperature* for only 10 min provided tricycle (±)-**1.235** as the only isolable product in 52% and 56% yields, respectively. The structure of (±)-**1.235** was elucidated by 2D NMR analysis.

[91] It is likely that the Mukaiyama–Michael reaction may also have been facilitated by acid.

Scheme 1.36 Synthesis of tricycle (±)-**1.235**.



(±)-**1.215** (±)-**1.235** (±)-**1.216**

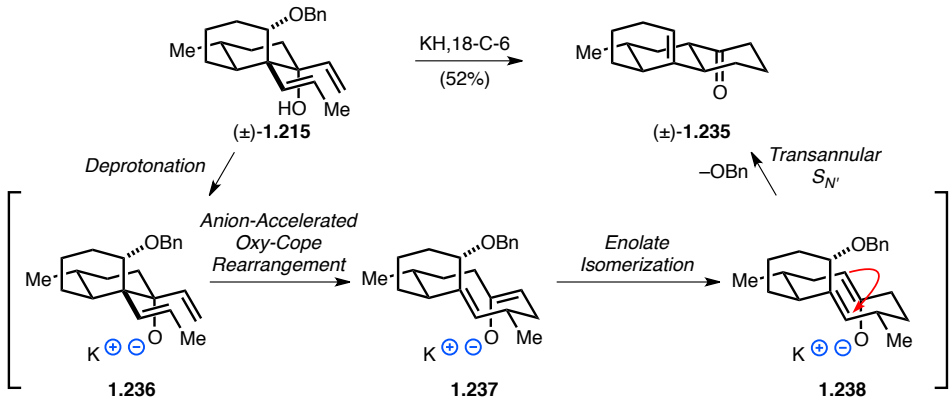
Reagents and conditions: (a) KH, I_2 (50 mol%),[92] 18-crown-6, THF, 52%; KH, I_2 (50 mol%), 18-crown-6, THF, 56%.

A potential pathway for the formation of tricycle (±)-**1.235** is depicted in Scheme 1.37. Deprotonation of the tertiary allylic alcohol (±)-**1.215** with KH facilitated an anion-accelerated oxy-Cope rearrangement through a chair-like transition state to generate 10-membered potassium enolate **1.237**. We had anticipated that it would be possible to trap this enolate and regenerate it at a later point in the synthesis; instead, it immediately underwent facile enolate isomerization to give regioisomeric enolate **1.238**. Next, we believe a transannular S_N' reaction of the intermediate enolate onto the opposing allylic benzyloxy group provided tricycle (±)-**1.235**. In retrospect, the observed reaction sequence might have been predicted based on the work of Paquette and Schreiber.[93]

[92] Treatment of KH with catalytic iodine is know to improve the yield and reproducibility of anion-accelerated oxy-Cope rearrangement by reducing trace potassium metal before the reaction, see: Macdonald, T. L.; Natalie, K. J.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1985**, *51*, 1124–1126.

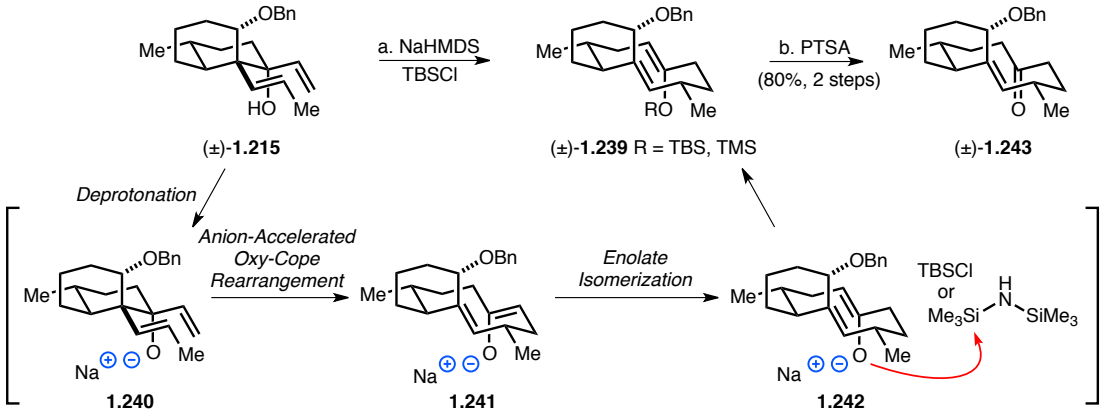
[93] (a) Paquette, L. A.; Oplinger J. A. *Tetrahedron* **1989**, *45*, 107–124. (b) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331–2332.

Scheme 1.37 Mechanism to account for the formation of tricycle (±)-**1.235**.



Screening conditions for the previous transformation yielded an interesting observation; the combined use of NaHMDS as a base and TBSCl as an in situ enolate trapping reagent was capable of fully suppressing transannular S_N' reaction (Scheme 1.38). Instead, a mixture of macrocyclic TMS and TBS enol silanes ((±)-**1.239**) were isolated. 1D TOCSY studies on the product mixture indicated that isomerization of the intermediate macrocyclic sodium enolate ((±)-**1.241**) had occurred before silyl trapping by HMDS or TBSCl could take place to yield an undesired olefin regioisomer. The enol silane product mixture could be hydrolyzed with PTSA to afford 10-membered bicyclic ketone (±)-**1.243** in 80% yield over two steps.

Scheme 1.38 Synthesis of bicycle (±)-**1.243** via anion-accelerated oxy-Cope rearrangement/enolate silylation.

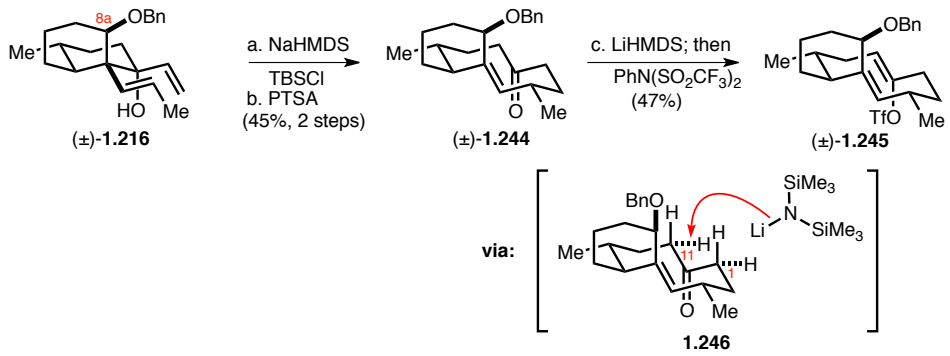


Reagents and conditions: (a) NaHMDS, TBSCl, THF; (b) PTSA, THF-H_2O, 80% (two steps).

The opposing C8a diastereomer ((±)-**1.216**) was converted to the corresponding 10-membered bicyclic ketone (±)-**1.244** under analogous conditions. Kinetic deprotonation of ketone (±)-**1.244** at

cryogenic temperatures was attempted in order to avoid thermodynamic equilibration of the 10-membered enolate intermediate (Scheme 1.39).[94] Accordingly, (±)-**1.244** was exposed to LiHMDS at –50 °C in THF for 45 minutes to promote enolate formation. The resultant enolate was treated with *N*-phenyl triflimide to yield a single regioisomeric alkenyl triflate (±)-**1.245** in 47% yield. Key TOCSY and NOESY correlations indicated that we had again obtained the undesired olefin regioisomer, which was a result of selective deprotonation of C11 over C1 followed by trapping with *N*-phenyl triflimide.

Scheme 1.39 Alkenyl triflate (±)-**1.245** formation via kinetic deprotonation.



Reagents and conditions: (a) NaHMDS, TBSCl, THF; (b) PTSA, THF-H_2O, 45% (two steps); (c) LiHMDS, THF, –78 → –50 °C; then $PhN(SO_2CF_3)_2$, –78 °C → RT, 47%.

Examination of the calculated ground state conformations (MMF) of model macrocyclic enols **1.247** and **1.248** help explained the observed trend for formation of the undesired regioisomeric 10-membered enolate (Figure 1.10).[95] Our calculations revealed that **1.248** is 15-20 kcal/mol lower in energy than **1.247**, indicating that there is a substantial thermodynamic benefit for enolate isomerization. The energy difference between conformation **1.247** and **1.248** is likely due to added ring strain engendered by placement of the olefins in a 1,5- vs. 1,6-relationship to one another. A top-down view of the molecular models illustrates the unfavorable strain placed on the 10-membered ring in model **1.247** relative to **1.248**.

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[94] Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038–4039.

[95] Single point calculations were performed using Spartan '02: DFT/6-31G*/MMFF.

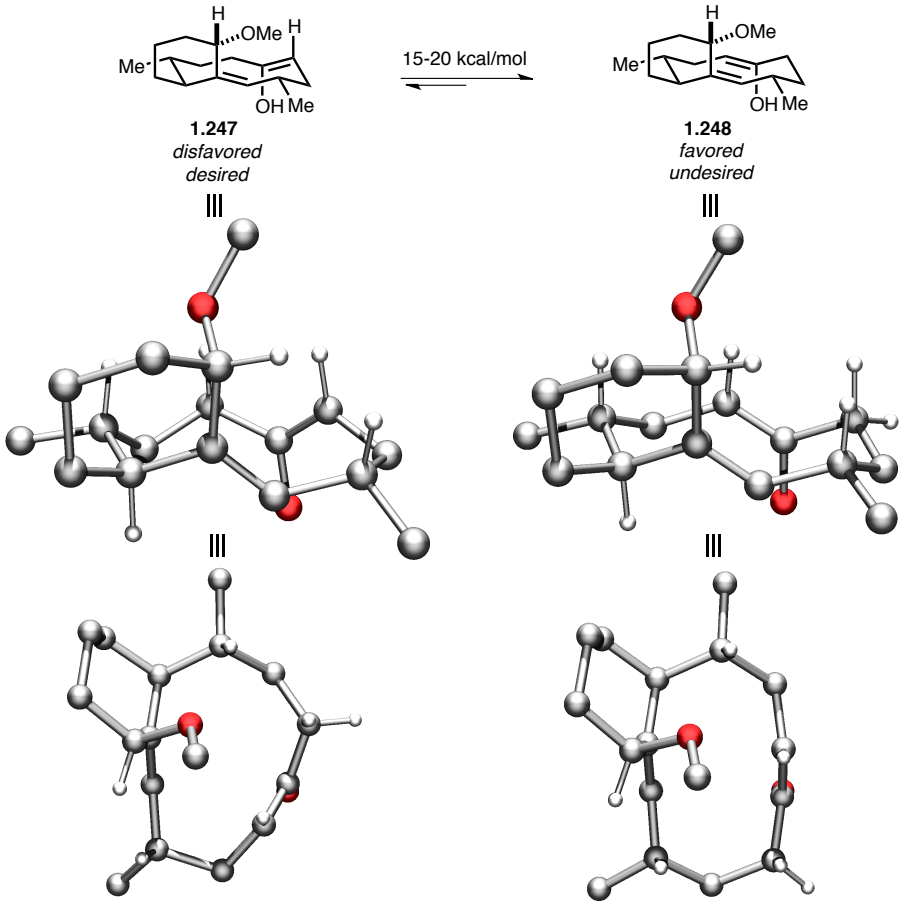
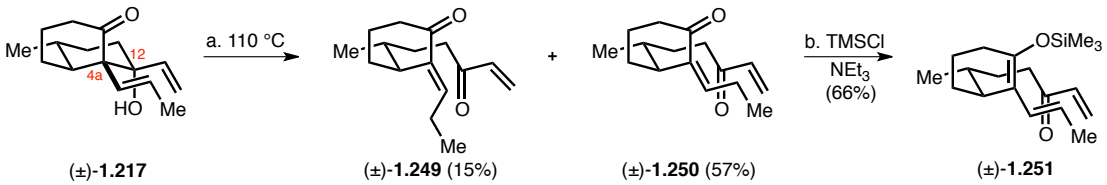


Figure 1.10 Model ground state energy conformations: rationale for enolate isomerization.

Finally, an interesting discovery was made during an attempt to understand the propensity the cascade reaction substrate (±)-**1.217** has for retro-aldol fragmentation. Heating (±)-**1.217** to 110 °C for 6 h resulted in rupture of the C4a–C12 bond and formation of two isomeric enones (±)-**1.249** and (±)-**1.250** in 15% and 57% yield, respectively (Scheme 1.40). Exposure of the major enone isomer ((±)-**1.250**) to TMSCl and Et_3N at 75 °C furnished enol silane (±)-**1.251** in 66% yield. Inspection of this product prompted us to consider an alternative IMDA disconnection strategy for the synthesis of vinigrol's tricyclo[4.4.4.0.^{4a,8a}]tetradecene carbon framework.

Scheme 1.40 Access to a potential IMDA reaction substrate via thermal-Cope rearrangement.



(±)-**1.217** (±)-**1.249** (15%) (±)-**1.250** (57%) (±)-**1.251**

Reagents and conditions: (a) PhMe, 110 °C, 15% for (±)-**1.249** and 57% for (±)-**1.250**; (b) TMSCl, NEt_3, THF, 75 °C, 66%.

Suggestive illustrations of the potential IMDA reaction are depicted in Figure 1.11a. It is conceivable that this reaction could be promoted thermally or by an appropriate Lewis acid since the *endo* transition state (**1.252**) has the proper electronic arrangement for a normal demand Diels–Alder reaction.[96] Unfortunately, concurrent with this analysis, the Baran group completed the first total synthesis of **1.1** through an IMDA reaction strategy.[20] Given the similarities of our IMDA disconnection and Barran and Barriault's disconnections (**1.254** and **1.255**, respectively), we abandoned this strategy.

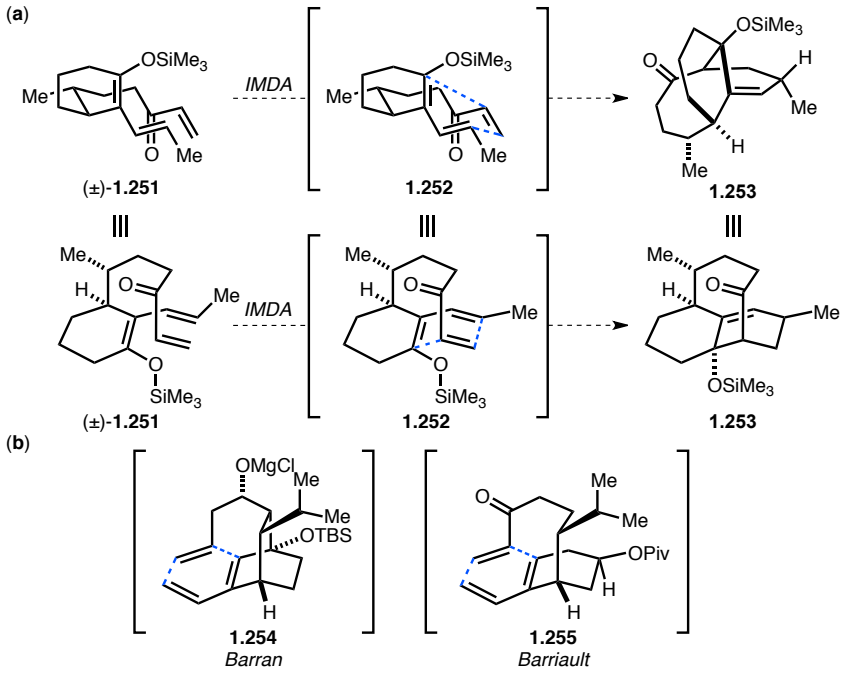


Figure 1.11 (a) Potential IMDA reaction disconnection for vinigrol. (b) Barriault and Barran's IMDA reaction disconnections.

[96] For a review on the Diels–Alder reaction in natural product total synthesis, see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

1.12 Conclusion

Progress toward a total synthesis of vinigrol (**1.1**) has been presented. In our first-generation synthesis approach we prepared cascade reaction substrates (±)-**1.149** and (±)-**1.189** in 7 steps and 21% and 4% yield, respectively. Pivalic anhydride was utilized as a methoxide sequestration reagent in the key anion-accelerated/oxy-Cope rearrangement/transannular acylation reaction sequence, which allowed for isolation of the corresponding bicyclo[5.3.1]undecene containing products (±)-**1.152** and (±)-**1.182** in 42% and 40% yield, respectively. An important discovery made during the development of this tandem reaction sequence was the observation that an expected retro-aldol-aldol equilibration step was non-operative.

Our second-generation approach toward **1.1** was anticipated to involve a key anion-accelerated oxy-Cope rearrangement/transannular aldol cyclization reaction sequence to form vinigrol's tricyclo[4.4.4.0.^{4a,8a}]tetradecene carbon framework in a single operation. In accordance with this plan, we prepared gram-quantities of a *cis*-decalin containing model cascade reaction precursor (±)-**1.217** in 10 steps and 15% overall yield. Unfortunately, the desired tandem reaction sequence was not observed. Alternatively, silyl protected cascade reaction substrate (±)-**1.225** underwent a silyloxy-Cope rearrangement/transannular Michael reaction sequence to form tricycle (±)-**1.230** in 56% yield. The observed deviation from the desired reaction pathway was attributed to a facile enol silane isomerization fostered by macrocyclic ring strain.

Chapter 2

Progress Toward the Synthesis of Hibarimicin B

2.1 Isolation and Biological Activity of Hibarimicin B (Angelmicin B)

Angelmicin B (**2.1**, Figure 2.1) was first isolated in 1993 by Uehara and coworkers from the culture broth extract of the rare actinomycete *Microbispora* subsp. AA9966 for its inhibitory activity against oncogenic Src signal transduction.[97] The hibarimicin family of natural products (hibarimcins A–K) were later isolated from the actinomycete *Microbispora rosea* subsp. *hibaria* TP-A0121.[97,99h] The structure of angelmicin B (**2.1**) was found to match that of hibarimicin B (**2.1**) and will be referred to as such henceforth.

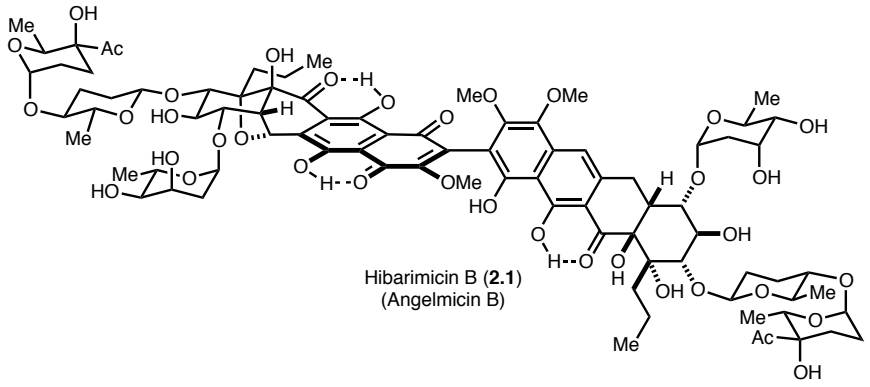


Figure 2.1 Structure of hibarimicin B (angelmicin B).

Hibarimicin B (**2.1**) was demonstrated to selectively inhibit *v*-Src protein tyrosine kinase (PTK) (IC_{50} = 1.8 μM) over protein kinase A and C.[97,99g] Additionally, **2.1** was found to possess the greatest anti-proliferative activity in human myeloid leukemia HL-60 cells (IC_{50} = 58 nM) amongst the hibarimicin family of natural products.[98,99g] Perhaps more importantly, **2.1** significantly induced the differentiation of

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[97] Uehara, Y.; Li, P. M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamoto, C.; Furumai, T.; Oki, T. *J. Antibiot.* **1993**, *46*, 1306–1308.

[98] Yokoyama, A.; Okabekado, J.; Uehara, Y.; Oki, T.; Tomoyasu, S.; Tsuruoka, N.; Honma, Y. *Leuk. Res*. **1996**, *20*, 491–497.

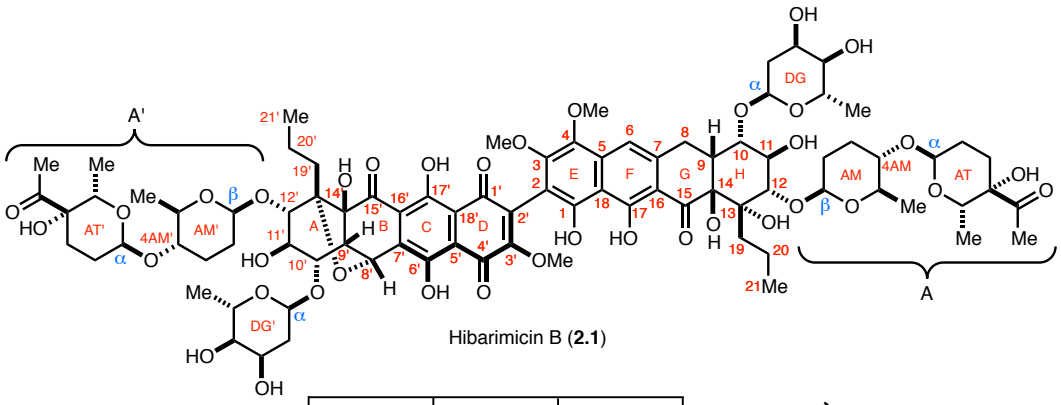
[99] (a) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett.* **1996**, *37*, 2785–2788. (b) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394–401. (c) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 402–417. (d) Hori, H.; Kajiura, T.; Igarashi, Y.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 46–52. (e) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 53–60. (f) Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 61–70. (g) Cho, S. I.; Fukazawa, H.; Honma, Y.; Kajiura, T.; Hori, H.; Igarashi, Y.; Furumai, T.;

HL-60 cells at a concentration of 174 nM. The discrepancy between hibarimicin B's effective concentration for kinase inhibition and anti-cancer activity suggests *v*-Src is not the target responsible for growth-inhibition or proliferation-inducition of HL-60 cells. To date, the cellular target and biological mechanism of action of **2.1** remain undetermined. It is interesting to note that the aglycon of **2.1**, hibarimicinone **2.2** (Figure 2.3), is a more potent inhibitor of PTK (IC_{50} = 1.2 μM), yet showed no anti-cancer activity.[99g] Furthermore, the differentiation-inducing and the growth-inhibitory actions of hibarimicins A–E (Figure 2.2) appear qualitatively similar. Therefore, the presence of the sugar componenets of **2.1** is critical for its anti-cancer activity, however the specific nature of those sugars does not appear to be as important.

2.2 Structural Determination of Hibarimicin B and Related Natural Products

The two-dimensional structure of hibarimicin B (**2.1**) was first elucidated by Hori and coworkers in 1996 through the combination of DEPT, DQF-COSY, TOCSY, HMQC, HMBC and ROESY NMR experiments.[99a] Subsequent isolation of hibarimicins C–K indicated they shared a common highly oxidized aglycon and differ in respect to their disaccharide components (A and A′, Figure 2.2).[99g]

Oki, T.; Uehara, Y. *J. Antibiot.* **2002**, *55*, 270–278. (h) Hori, H.; Igarashi, Y.; Kajiura, T.; Sato, S.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uehara, Y.; Oki, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2004**, *46*, 49–54.



Hibarimicin	A	A'
A	ATα–4AMβ–	ATβ–4AMβ–
B		ATα–4AMβ–
C		AMα–4AMβ–
D		AXα–4AMβ–
E		AMβ–
F	AMβ–4AMβ–	AXα–4AMβ–
G	AXα–4AMβ–	AXα–4AMβ–
H	AMβ–	AMβ–4AMβ–
I	AMβ–	AXα–4AMβ–
K	AMβ–4AMβ–	AMβ–4AMβ–

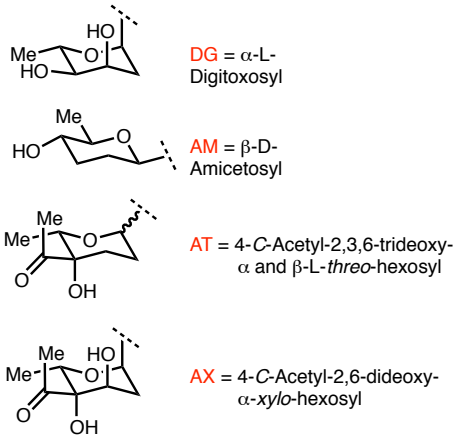


Figure 2.2 Positional numbering system for hibarimicin B and structures of hibarimicins A–K.

The hibarimicins are among the most complex and largest type-II polyketides known. Their common aglycon, hibarimicinone **2.2** (Figure 2.3), is pseudo-C_2-symmetric in nature; The C_2-symmetry of **2.2** is broken by oxidation of the B-, C-, and D-rings relative to the G-, F-, and E-rings, respectively. Specifically, the B-ring contains a cyclic ether bridging C8' and C13', the C-ring contains a hydroxyl group at C6', and the D-ring is a quinone. Additionally, the aglycon is decorated with six intriguing 2-deoxyglycosides including: two α-L-digitoxosyl (DG/DG') monosaccharide subunits and two disaccharide subunits comprised of a 4-*C*-acetyl-2,3,6-trideoxy-α-L-*threo*-hexoside (AT/AT') linked to the 4-postion of a β-D-amicetoside (AM/AM'). The absolute stereochemistry of the aforementioned 2-deoxyglycosides was determined by comparison of the optical rotations of the DG-, AM-, and AT-methyl glycosides, obtained from **2.1** through acid mediated methanolysis, to analogous known or synthetically accessible methyl glycosides.

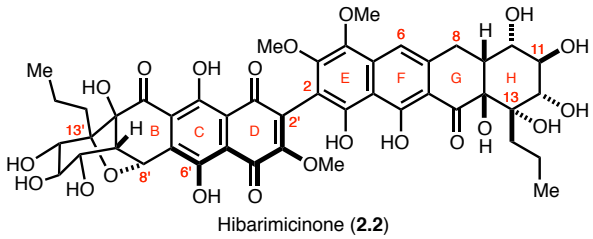


Figure 2.3 Structure of hibarimicinone.

However, many of the structural questions concerning **2.1** could not be addressed through NMR spectroscopy or chemical degradation, leaving several features of the molecule undetermined at the outset of our synthesis.[100] First, it was unkown whether **2.1** exhibited axial chirality about its highly congested C2–C2' bond. Second, the absolute stereochemistry of hibarimicinone (**2.2**) had yet to be established.

2.3 Biosysynthesis of Hibarimicin Related Natural Products

The biosynthesis of **2.1** was elucidated through the combination of feeding experiments with ^{13}C labeled sodium acetate and cosynthesis using blocked mutants. Fermentation of *Microbispora rosea* subsp. *hibaria* TP-A0121 with [1-^{13}C], [2-^{13}C], or [1,2-^{13}C] labeled sodium acetate provided differentially labeled hibarimicin B (**2.3**).[99d] An illustrative compilation of the data collected from this experiment is depicted in Figure 2.4.

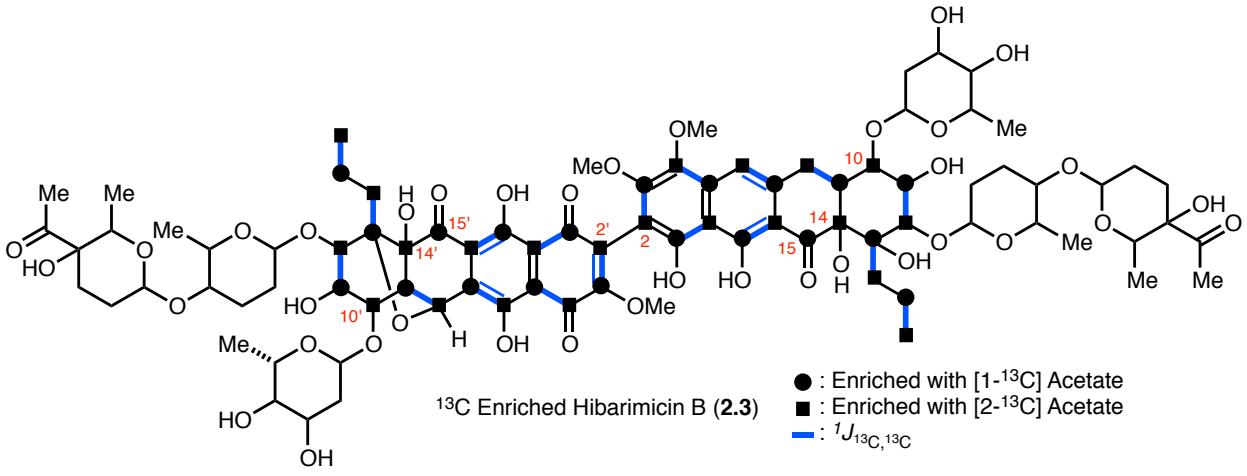


Figure 2.4 Incorporation pattern of ^{13}C-labeled sodium acetate.

[100] The absolute stereochemistry of **2.2** had been determined by the Mosher method and through CD spectroscopy in Ref. 99h. Unfortunately we were unaware of this work prior to the publication of Ref. 107.

Three important deductions were made from this experiment: (1) the alternation of isotopically enriched carbons provided by feeding experiments with either [1-^{13}C] or [2-^{13}C] sodium acetate demonstrated that the aglycon of **2.1** is polyketide derived; (2) the symmetric distribution of ^{13}C between the two halves of **2.1**, indicated that the C2–C2' bond was formed through the dimerization of a tetracyclic monomer; (3) unobserved $^{1}J_{13C,13C}$ coupling for C10/C10', C14/C14', and C15/C15' combined with observed long range $^{3}J_{13C,13C}$ (three bond) coupling between C10/C10' and C15/C15' provided insight in to the polyketide cyclization pathway illustrated in Figure 2.5. In this pathway, undecaketide precursor **2.4** cyclizes to form tetracycle **2.5** with concomitant skeletal rearrangement involving cleavage of the C10/C10'–C15/C15' bond. The derivation of C10/C10' and C15/C15' from a common acetate unit explains their long range $^{3}J_{13C,13C}$ coupling and their lack of $^{1}J_{13C,13C}$ coupling. Next, oxidative cleavage of an extra carbon atom from C14/C14' could install the C14/C14'–OH substituent and would explain the lack of $^{1}J_{13C,13C}$ coupling to C14/C14'. Finally, a dimerization/methylation/glycosylation sequence could provide hibarimicin B (**2.1**). The specific nature of this process was elucidated by cosynthesis using blocked mutants.

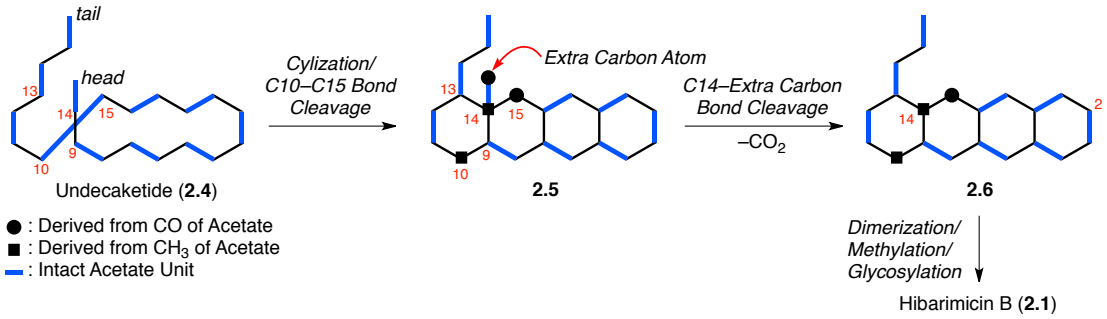


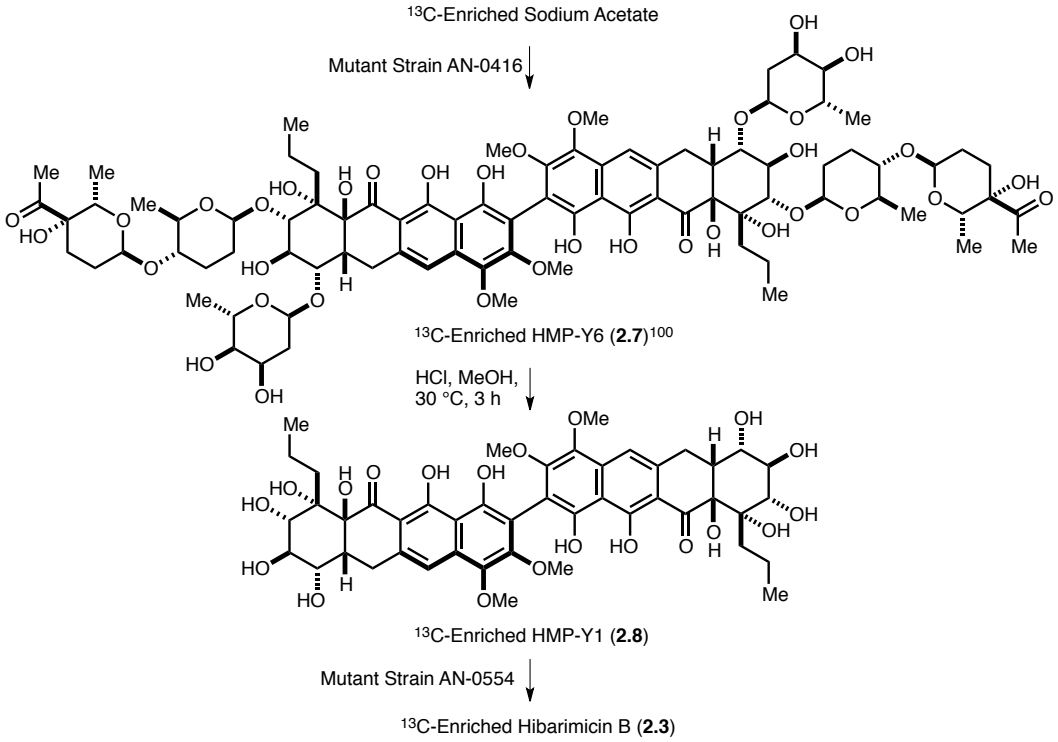
Figure 2.5 Partial proposed biosynthesis of hibarimicin B

Incubation of *Microbispora rosea* subsp. *hibaria* TP-A0121 with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (NTG) resulted in the production of a multitude of blocked mutant actinomycete strains. Five stable mutant strains (AN-0416, AN-0554, AN-0623, AN-0763, and AN-0772) were selected as

hibarimicin B non-producing strains based on their lack of red pigmentation.[101] Interestingly, incubation of mutant strain AN-0554 with ^{13}C enriched sodium acetate afforded isotopically labeled metabolite HMP-Y6 (**2.7**, Scheme 2.1), which is a fully symmetrical dimer of the western half of **2.1**. Exposure of **2.7** to HCl in MeOH at 30 °C for 3 h promoted methanolysis of the sugar subunits to deliver the ^{13}C-enriched symetrical aglycon HMP-Y1 (**2.8**). Incubation of mutant strain AN-0554 with ^{13}C enriched HMP-Y1 (**2.8**) afforded isotopically labeled hibarimicin B (**2.3**). In contrast, utilization of ^{13}C enriched HMP-Y6 (**2.7**) in the same experiment did not provide **2.3**. Additionally, in a separate experiment AN-0554 was able to convert hibarimicinone (**2.2**) to **2.1**. Taken together, these findings suggested that HMP-Y1 (**2.9**, Figure 2.6) and hibarimicinone (**2.2**) are biosynthetic precursor to hibarimicin B (**2.1**).

[101] The color of agar plates containing hibarimicin B was found to be pH-dependant, showing red under acidic and green under basic conditions.[99e]

Scheme 2.1 Cosynthesis experiments using blocked mutant strains AN-0416 and AN-0554.[102]



A plausible biosynthetic pathway for the conversion of C_2-symmetric precursor HMP-Y1 (**2.9**) to hibarimicione (**2.2**) is illustrated in Scheme 2.2. We envisioned that the C_2-symmetry of **2.9** could be broken via oxidation of the C-ring to hypothetical quinone **2.10**. Tautomerization of **2.10** to C8'-*ortho*-quinone methide **2.11** followed by oxy-Michael addition of the pendant C13'–OH could then install the B-ring cyclic ether bridge. Finally, re-oxidation of the C-ring to a quinone followed by transposition to the D-ring with concomitant demethylation could afford **2.2**. Enzymatic glycosylation of **2.2** could then provide acesss to hibarimins A-K.[103] Lastly, HMP-P1 (**2.12**), which is believed to be an artifact of isolation rather than a natural product, is presumed to arise from **2.2** via cyclization of C1–OH onto C3' of the D-ring quinone with subsequent expulsion of methanol.

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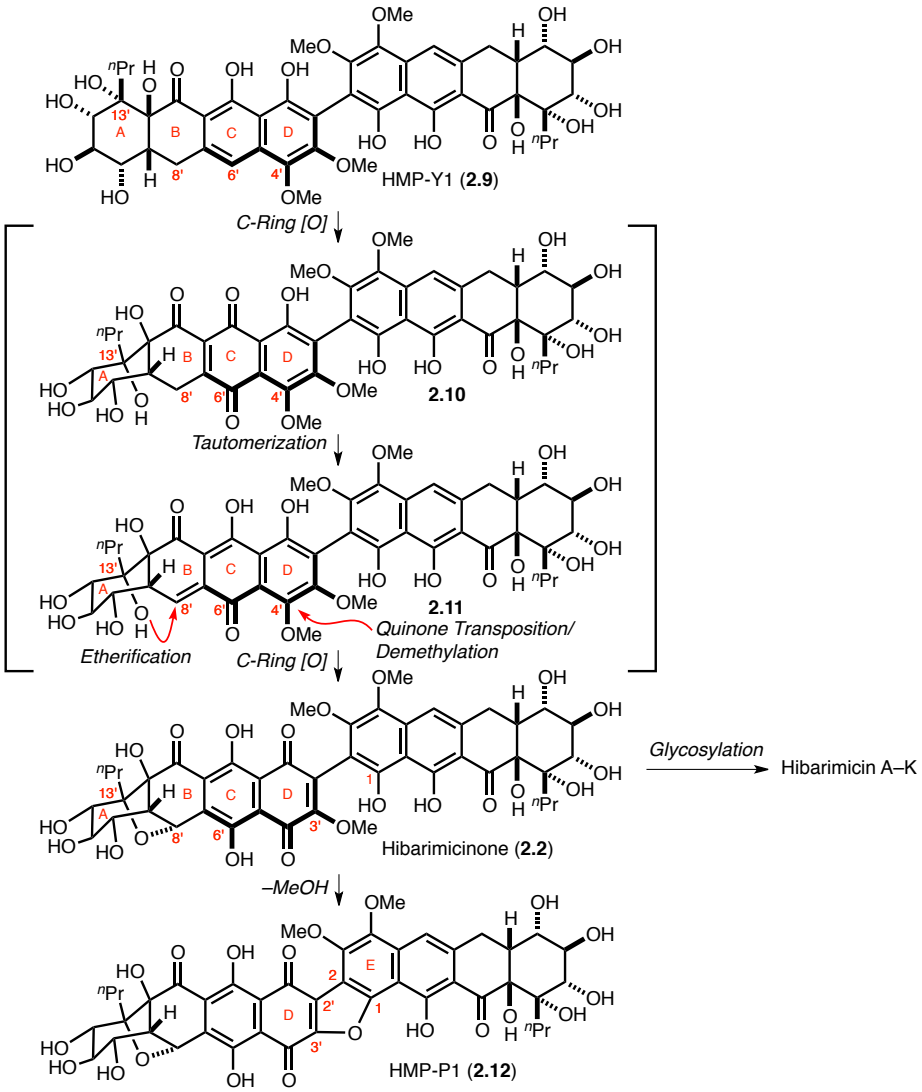
[102] The strereochemistry of the HMP-Y6 atropisomeric linkage was assigned based on analogy to HMP-Y1.

[103] For reviews on the biosynthesis of 2-deoxy sugars, see: (a) Thibodeaux, C. J.; Melançon III, C. E.; Liu, H.-W. *Nature*, **2007**, *446*, 1008–1016. (b) Thibodeaux, C. J.; Melançon III, C. E.; Liu, H.-W. *Angew. Chem. Int. Ed.* **2008**, *47*, 9814–9859.

Scheme 2.2 Proposed biosynthetic pathway for converstion of HMP-Y1 to hibarimicinone.



2.4 Previous Synthesis Efforts Toward Hibarimicin B

The potential importance of hibarimicin B's biological activity combined with its structural complexity and stereochemical ambiguities have made **2.1** an attractive target for total synthesis. Since its isolation in 1993, several groups have reported progress towards this goal including: Roush,[104]

[104] (a) Narayan, S.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3789–3792. (b) Lambert, W. T; Roush, W. R. *Org. Lett.* **2005**, *7*, 5501–5504. (c) Narayan, S. Ph.D. Thesis, The University of Michigan, 2003.

Sulikowski,[105] Mootoo,[106] and Tatsuda.[107] To date, a total synthesis of **2.1** has not been achieved.

2.4.A Roush's Synthesis of Model CD–E Arylnapthoquinone and AB-Subunit of Hibarimicin B

The Roush group's approach for the total synthesis of **2.1** focused on the central C2–C2' bond as a key strategic disconnection (Scheme 2.3).[104a] Model studies were directed toward formation of the *ortho*, *ortho'*-tetrasubstituted biaryl C2–C2' bond through known transition metal catalyzed processes. A Suzuki-Miyaura cross-coupling reaction between highly electron rich naphthol boronic acid CD-ring **2.13** and EF-ring naphthol triflate **2.14** was attempted, but yield only proto-deborylated product **2.15**. An analogous Stille reaction with aryl triflate **2.17** formed a product containing the desired C2–C2' bond (**2.18**), albeit in poor yield. In contrast, when electron poor bromonaphthoquinone CD-ring coupling partener **2.19** was employed in a Suzuki-Miyaura cross-coupling reaction with aryl boronic acid **2.20**, model CD–E arylnapthoquinone **2.21** was formed in 59% yield. Presumably the electron deficient nature of **2.19** facilitated oxidative addition of Pd(0). Unfortunately, when a more complex naphthol boronic ester cross-coupling partener **2.22** was employed in this transformation no reaction was observed.[104c]

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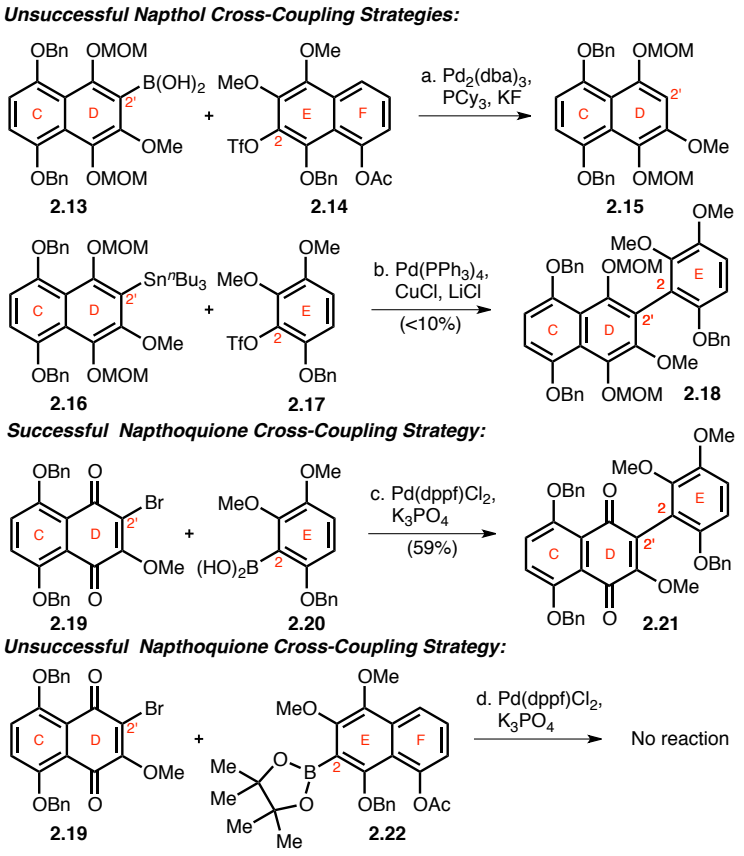
[105] (a) Lee, C.-S.; Audelo, M. Q.; Reibenpies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403–4409. (b) Maharoof, U. S.; Sulikowski, G. A. *Tetrahedron Lett.* **2003**, *44*, 9021–9023. (c) Kim, K.; Mahroof, U. S.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777–2780. (d) Lee, W. D.; Kim, K.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 1687–1689. (e) Romaine, I. M.; Hempel, J. E.; Shanmugam, G.; Hori H.; Igarashi, Y.; Polavarapu, P. L.; Sulikowski, G. A. *Org. Lett*. **2011**, *13*, 4538–4541.

[106] (a) Li, J.; Todaro, L. J.; Mootoo, D. R. *Org. Lett.* **2008**, *10*, 1337–1340. (b) Li, J.; Todaro, L.; Mootoo, D. R. *Eur. J. Org. Chem.* **2011**, 6281–6287. (c) Li, J. Ph.D. Thesis, The City University of New York.

[107] Tatsuta, K.; Fukuda, T.; Ishimori, T.; Yachi, R.; Yoshida, S.; Hashimoto, H.; Hosokawa, S. *Tetrahedron Lett.* **2012**, *53*, 422–425.

Scheme 2.3 Roush's Synthesis of Model CD–E Arylnapthoquinone.



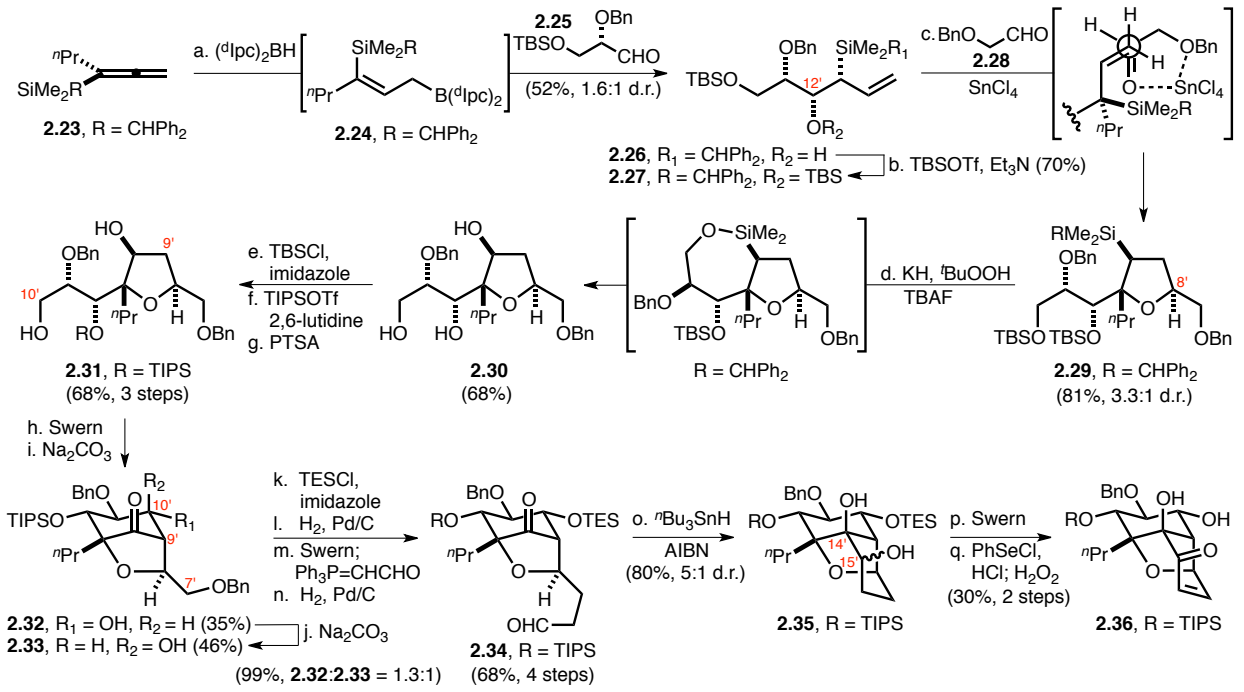
Reagents and conditions: (a) $Pd_2(dba)_3$, PCy_3, KF, THF; (b) $Pd(PPh_3)_4$, CuCl, LiCl, DMSO, 60 °C, <10%; (c) $Pd(dppf)Cl_2$, K_3PO_4, H_2O/DME, 60 °C, 59%; (d) $Pd(dppf)Cl_2$, K_3PO_4, DMSO, 80 °C.

Roush's synthesis of the AB-subunit of **2.1** took advantage of a γ-silylallylborane/aldehyde [3+2] annulation strategy to form the tetrahydrofuran ring found in **2.36** (Scheme 2.4).[104b] Their synthesis began with hydroboration of allene **2.23** with (^{d}Ipc)$_2$BH to furnish intermediate organoborane **2.24**. Addition of aldehyde **2.25** to a solution of **2.24** in THF afford allylsilane **2.26** with moderate diastereoselectivity. Next, **2.26** was silyl protected and exposed to aldehyde **2.28** in the presence of $SnCl_4$ to provide tetrahydrofuran **2.29** via a modestly diastereoselective [3+2] annulation. Tamao–Fleming oxidation[108] of alkylsilane **2.29** followed by protecting group manipulations gave diol **2.31**. Swern oxidation of **2.31** and exposure of the resultant keto-aldehyde to Na_2CO_3 promoted an aldol reaction to yield a mixture of isomeric bicycles **2.32**

[108] (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29–31.

and **2.33**. The undesired C10' diastereomer **2.32** was recycled to give sufficient quantities of **2.33**. Chemoselective hydrogenolysis of the C8' benzyl group and a two carbon homologation provided aldehyde **2.34**. Exposure of **2.34** to AIBN and $^{n}Bu_3SnH$ in refluxing benzene promoted a Pinacol cyclization to generate tricycle **2.35** as an epimeric mixture of C15' secondary carbinols. Finally, **2.35** was converted to the AB-subunit of hibarimicin B (**2.36**) through sequential Swern and Sharpless-Reich[109] oxidations. Overall **2.36** was prepared in 16 steps and 2% overall yield.

Scheme 2.4 Roush's Synthesis of the AB-subunit of hibarimicin B.



Reagents and conditions: (a) $(^{d}Ipc)_2BH$, THF –50 °C; THF, –78 °C → RT, 52%, 1.6:1 d.r.; (b) TBSOTf, Et_3N, CH_2Cl_2, –20 °C → RT, 70%; (c) **2.28**, $SnCl_4$, 4 Å MS CH_2Cl_2, –78 °C, 81%, 3.3:1 d.r.; (d) KH, $^{t}BuOOH$, TBAF, TBAF, NMP, 50 °C, 68%; (e) TBSCl, imidazole, DMF, 91%; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 99%; (g) PTSA, MeOH, 0°C → RT, 81%; (h) $(COCl)_2$, DMSO CH_2Cl_2, –50 °C; Et_3N, –50 °C → RT; (i) Na_2CO_3, MeOH-H_2O-THF (4:3:3), 35% for **2.32** and 46% for **2.33** (two steps); (j) Na_2CO_3, MeOH-H_2O-THF (4:3:3), 99%, **2.32**:**2.33** = 1.3:1; (k) TESCl, imidazole, CH_2Cl_2, 0 °C, 97%; (l) H_2, 10% Pd/C, EtOH, 99%; (m) $(COCl)_2$, DMSO, Et_3N,

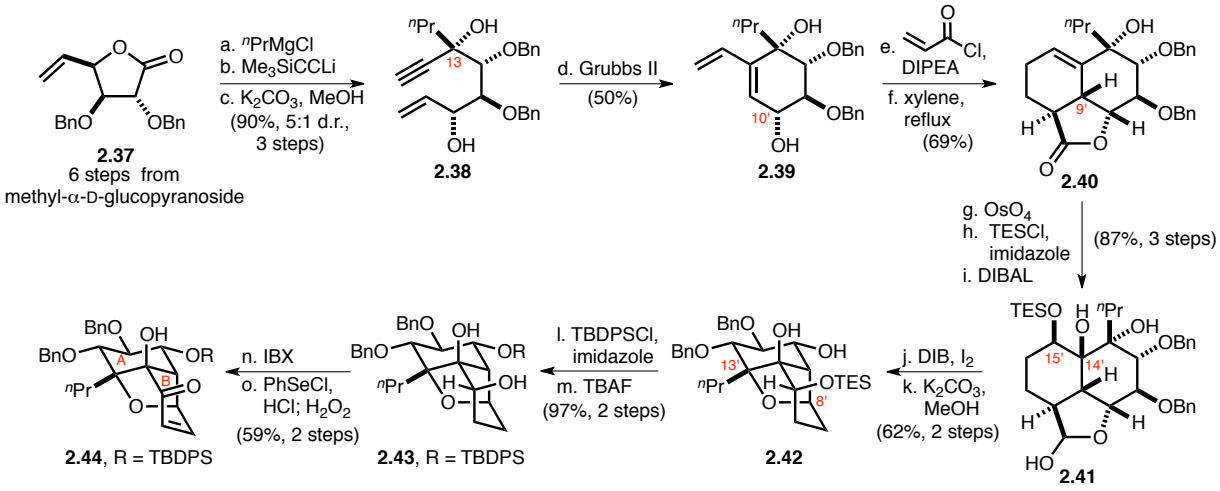
[109] (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

Reagents and conditions for Scheme 2.4 continued: CH_2Cl_2, –78 °C → RT; Ph_3P=CHCHO, 90% (n) H_2, 10% Pd/C, EtOAc-EtOH (10:1), 79%; (o) $^nBu_3SnH$, AIBN, PhH, reflux, 80 %, 5:1 d.r.; (p) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → RT, 74%; (q) PhSeCl, HCl, EtOAc; aq H_2O_2, 41%.

2.4.B Mootoo's Synthesis of the AB-Subunit of Hibarimicin B

The Mootoo group reported an efficient synthesis of the AB-subunit of **2.1** that utilized a ring closing enyne metathesis (RCEM)/IMDA reaction sequence to form the decalin ring system of **2.44** and set the challenging C9' stereocenter (Scheme 2.5).[106] Their synthesis commenced with known lactone **2.37**, which was available in 6 steps and 80% overall yield from methyl-α-D-glucopyranoside. A three step double alkylation sequence delivered propargylic alcohol RCEM substrate **2.38** in good yield. Exposure of **2.38** to Grubbs' second generation olefin metathesis catalyst under an ethylene atmosphere affected the desired annulation to provide diene **2.39**. Esterification of the C10' hydroxyl substituent with acroyl chloride and heating the resulting ester in xylene facilitated an *exo*-selective IMDA reaction to afford tricycle **2.40**. The use of the C10' carbinol to control the facial selectivity of the IMDA reaction was critical in setting the C9' stereocenter. The stereochemistry at C9' was then relayed to C14' through a diastereoselective OsO_4 catalyzed dihydroxylation reaction. TES protection of the resultant C15'–OH and reduction of the ester supplied lactol **2.41** in 87% overall yield. The C8'–C13' ether bridge was then formed by exposure of **2.41** to (diacetoxyiodo)benzene (DIB) and iodine in cyclohexane at ambient temperature. The precise mechanism of this transformation is unclear, however Mootoo suggests that **2.42** is formed though a radical-based iodination/displacement pathway. Finally, protecting group manipulation and oxidation of the B-ring, following a similar protocol to that employed by Roush, afforded the AB-subunit of hibarimicin B (**2.44**). Overall, Mootoo was able to prepare **2.44** in 15 steps and 9% yield from **2.37**.

Scheme 2.5 Mootoo's Synthesis of the AB-subunit of hibarimicin B.



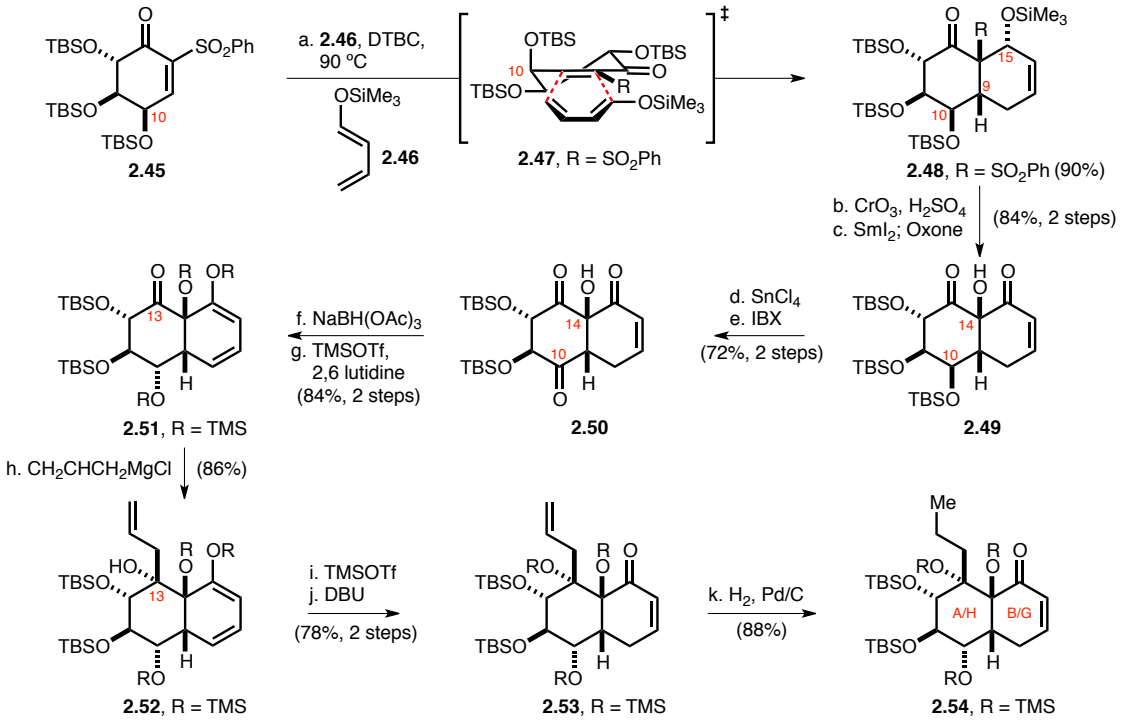
Reagents and conditions: (a) ^{n}PrMgCl, THF –78 °C, 95%; (b) Me_3SiCCH, ^{n}BuLi, THF –78 → 0 °C; (c) K_2CO_3, MeOH, 79% (two steps); (d) Grubbs II, CH_2Cl_2, 50%; (e) acroyl chloride, DIPEA, CH_2Cl_2, –78 °C, 81%; (f) xylene, reflux, 85%; (g) OsO_4, NMO, H_2O, Me_2CO, 0 °C, 95%; (h) TESCl, imidazole, DMF, quantitative; (i) DIBAL, CH_2Cl_2, –78 °C, 95%; (j) DIB, I_2, cyclohexane, 63%; (k) K_2CO_3, MeOH, CH_2Cl_2, 0 °C, quantitative; (l) TBDMSCl, TBAI, imidazole, DMF, 98%; (m) TBAF, THF, 0 °C, 99%; (n) IBX, DMSO, PhF, 75 °C, 90%; (o) PhSeCl, EtOAc, HCl; ^{m}CPBA, $NaHCO_3$, 66% (two steps).

2.4.C Tatsuda's Synthesis of Hibarimicinone

Tatsuta and coworkers completed the first total synthesis of hibarimicinone (**2.2**) in 2012.[107] Their synthesis of the AB/HG enone (**2.54**) is illustrated in Scheme 2.6. Their synthesis began with 1-phenylsulphonyl enone **2.45** which was available in 9 steps and 42% yield from D-arabinose. Thermal intermolecular Diels-Alder (DA) reaction of **2.45** with 1-silyloxydiene **2.46** gave a single *cis*-decalin diastereomer **2.48** in 90% yield. The observed relative stereochemistry of the product, specifically at C9 and C15, can be explained by approach of **2.46** opposite the bulky C10 silyloxy substituent through *exo* transition state **2.47**. Exposure of **2.48** to CrO_3 and H_2SO_4 resulted in hydrolysis of the C15 silyl ether and oxidation of the resultant allylic alcohol to provide a 1,3-diketone intermediate. Treatment of the product with SmI_2 promoted reduction of the phenylsulphonyl group to generate a Sm(III) enolate which was oxidized by in situ treatment with Oxone to furnish α-hydroxy-1,3-diketone **2.49**. The C10 secondary

carbinol, whose stereochemistry was required to induce the desired facial selectivity in the DA reaction, was inverted through a four step sequence involving: (1) chemoselective cleavage of the C10 silyl protecting group with $SnCl_4$, (2) oxidation of the resultant alcohol with IBX to give trione **2.50**, (3) chemo- and stereoselective C14–OH directed reduction of the C10 carbonyl with $NaBH(OAc)_3$, and (4) TMS protection of the C10–OH afforded 1,3-dienyl silane **2.51** in 61% overall yield. Protection of the C15 carbonyl through enol silane formation allowed for subsequent organometallic addition to the C13 carbonyl. Accordingly, treatment of **2.51** with allylmagnesium chloride provided homoallylic alcohol **2.52** as a single diastereomer, in which the nucleophile had approached from the convex face of the *cis*-decalin carbon framework. The resultant C13–OH was protected with TMSOTf and the dienolsilane functional group was hydrolyzed with DBU in warm ^{i}PrOH to supply enone **2.53**. Finally, chemoselective hydrogenation of the allyl moiety over the enone delivered AB/HG enone **2.54** for the total synthesis of **2.2** in 20 steps and 11% overall yield.

Scheme 2.6 Tatsuda's synthesis of AB/HG Enone.

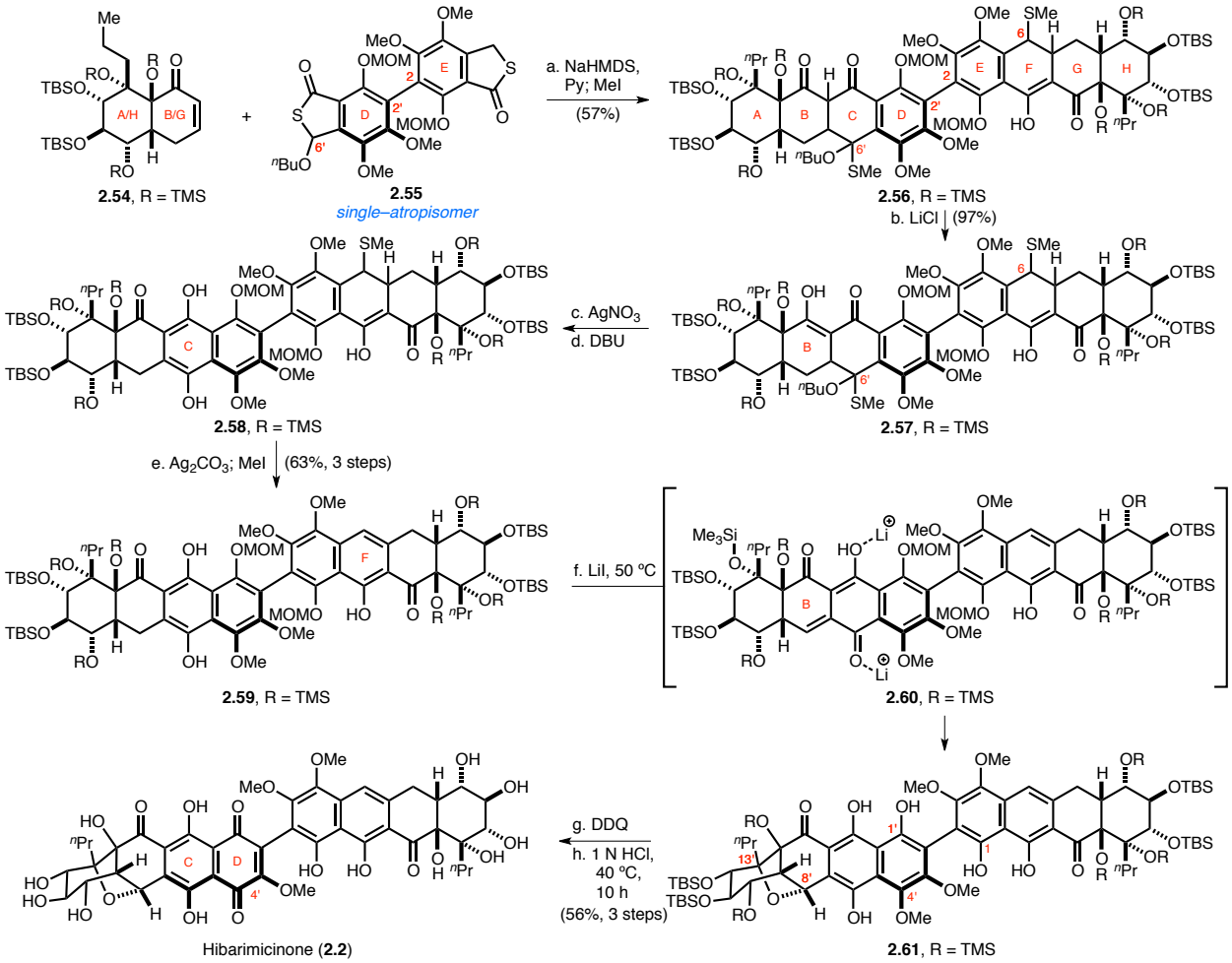


Reagents and conditions: (a) 1-trimethylsiloxy-1,3-butadiene (**2.46**), DTBC, PhMe, 90 °C, 4 d, 90%; (b) aq H_2SO_4, CrO_3, Me_2CO, 94%; (c) SmI_2, THF, –78 °C; then Oxone, –78 °C → RT; aq $NaHCO_3$, 89%; (d) $SnCl_4$, CH_2Cl_2,

Reagents and conditions for Scheme 2.6 continued: –30 °C, 83%; (e) IBX, PhMe-DMSO, 50 °C, 87%; (f) $NaBH(OAc)_3$, EtOH, 0 °C → RT, 96%; (g) TMSOTf, 2,6-lutidine, $ClCH_2CH_2Cl$, 80 °C, 88%; (h) allylmagnesium chloride, Et_2O, 0 °C, 86%; (i) TMSOTf, 2,6-lutidine, $ClCH_2CH_2Cl$, 80 °C, 87%; (j) DBU, ^{i}PrOH, PhMe, 80 °C, 90%; (k) H_2, 10% Pd/C, PhMe, 88%.

Tatsuda's synthesis of hibarimicinone (**2.2**) continued with a two-directional annulation reaction between AB/HG enone **2.54** and enantiopure unsymmetrical DE-biaryl bis-thiolactone **2.55** (Scheme 2.7), which was available from 2,4,5-trimethoxybenzoic acid in 12 steps and 3% overall yield. They discovered that exposure of **2.54** and **2.55** to NaHMDS in PhMe-THF-pyridine followed by in situ methylation facilitated a two-directional double annulation reaction to afford octacycle **2.56** and **2.57** as a mixture of keto and enol tautomers in 39% and 18% yield, respectively. Pyridine was found to be critical to suppress the formation of polymerization side products. The keto tautomer **2.56** was converted to enol **2.57** in the presence of LiCl. The hemithioacetal was then hydrolyzed by treatment with $AgNO_3$ in warm PhMe–acetone–H_2O and the product was enolized with DBU to provide C-ring hydroquinone **2.58**. Next, C-ring oxidation and F-Ring aromatization, to deliver octacycle **2.59**, were accomplished through sequential addition of Ag_2CO_3 and MeI to a solution of **2.58** in PhMe–acetone–H_2O. The C8'–C13' ether bridge was then formed by treatment of **2.59** with LiI via a two step process involving: (1) quinone tautomerization with simultaneous MOM deprotection to generate orthoquinone methide intermediate **2.60** and (2) cyclization of the pendant C13' silyl ether onto the electrophilic C8' position with concomitant cleavage of the silicon protecting group to yield hydroquionone **2.61**. Finally, The C-ring hydroquinone was reoxidized with DDQ and the resultant quinone stirred with 1 N HCl in MeOH at 40 °C for 10 h to promote tautomerization to the D-ring and cleavage of the C1' methyl ether to deliver hibarimicinone (**2.2**) as a single atropisomer in 56% yield over three steps. Coincidentally, Tatsuda's synthesis of **2.2** took advantage of similar disconnection strategy to our own and was published shortly before ours. However, their protecting group strategy is not likely to be amenable to the completion of hibarimicin B (**2.1**) due to the acid labile nature of its 2-deoxyglycosidic linkages.

Scheme 2.7 Tatsuda's synthesis of hibarimicinone.



Reagents and conditions: (a) NaHMDS, MeI, THF-PhMe-Py, –20 °C, 57% (39% for **2.56** and 18% for **2.57**); (b) LiCl, THF, 97%; (c) $AgNO_3$, PhMe-Me_2CO-H_2O, 40 °C; (d) DBU, PhMe, 0 °C; (e) Ag_2CO_3, PhMe-Me_2CO-H_2O, 40 °C; then MeI, 63% (three steps); (f) LiI, MeCN, $ClCH_2CH_2Cl$, 50 °C; (g) DDQ, THF-PhMe, 0 °C, 70% (two steps); (h) 1 N HCl, MeOH, 40 °C, 80%.

2.5 Hibarimicin B Retrosynthesis Plan

Our synthesis plan for **2.1** is outlined in Figure 2.6. We envisioned the AT-AM/AT'-AM' dissacharide and the DG/DG' monosaccharide subunits could be retrosynthetically disconnected from the aglycon to provide four potential synthesis precursors: disaccharide trichloroacetimidate glycosyl donor **2.62**, monosaccharide glycosyl donors **2.63** or **2.64**, and orthogonally protected aglycon **2.65**. In a forward sense, we anticipated that the two-directional stereocontrolled introduction of the β-glycosidic

linkages between the AM/AM' subunits and aglycon **2.65** could be accomplished through the functional group addition of a phenyl thionocarbonate directing group at AM3/AM3'. After protecting group manipulation, we envisioned that glycosyl donor **2.63** or **2.64** could be used to stereoselectively construct the α-glycosidic linkages between the DG/DG' subunits and the intermediate partially glycosylated aglycon. 2-Deoxy thiophenyl donors such as **2.63** generally rely on reagent control to induce α-selective glycosidic bond formation. Alternatively, we anticipated that the functional group addition of an axial iodo directing group at DG2/DG2' of **2.64** could be exploited to favor α-glycoside formation. Next, aglycon **2.65** was retrosynthetically simplified to pseudo-C_2-symmetric octacycle **2.66** through a series of biosynthetically inspired oxidations. The reaction sequence developed for **2.65** could potentially be modified to afford hibarimicinone (**2.2**). The C_2-symmetry of intermediate **2.66** is perturbed by the presence of the C4'–OBn group and the C6'–OH (highlighted in red). The use of a C4'–OBn rather than C4'–OMe (used by Tatsuda) was choosen to allow for late stage oxidation of the D-ring hydroquinone in the presence of the highly acid labile 2-deoxyglycosidic linkages. The addition of the C6'–OH was expected to facilitate chemoselective C-ring oxidation to a quinone, which could then undergo our proposed biomimetic relay oxidation sequence. Most importantly, the retrosynthetic excision of the B-ring cyclic ether bond makes the AB- and HG-ring systems identical. Consequently, we envisioned octacycle **2.66** could be assembled in one step via a two-directional double annulation reaction between the dianion of unsymmetrical DE-biaryl **2.67** and two equivalents of AB/HG-enone **2.68**.[110] In this process, the C-ring would be constructed through a Hauser annulation[111] and the F-ring would be built though a Michael–Claisen condensation.[112] This convergent strategy circumvents the need to form the hindered C2–C2' bond of **2.1** at a late stage in the synthesis, which was a transformation that we expected

[110] For other examples of two-directional double annulation reactions, see: (a) Hauser, F. M.; Gauuan, P. J. *Org. Lett.* **1999**, *1*, 671–672. (b) Ref. 105e. (c) Ref.107, and references therein.

[111] Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43,* 178–180.

[112] (a) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem Commun.* **1978**, 406–407. (b) Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *20*, 3593–3596. (c) For other uses of Michael–Dieckmann reaction sequences to construct naphthalene derivatives, see: Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–17927, and references therein.

would be problematic based on the efforts of Roush (*vide supra*). At the outset of our study, the absolute configuration of the C2–C2' axis of **2.1** and **2.2** was ambiguous.[99h] Consequently, we elected to proceed with racemic biaryl annulation donor (±)-**2.67** in order to prepare and characterize both atropisomers of **2.2**. Additionally, as the absolute stereochemistry of **2.2** was unknown,[99h] we designed a synthesis of both potential enantiomers of the AB/HG enone annulation acceptor **2.68**.

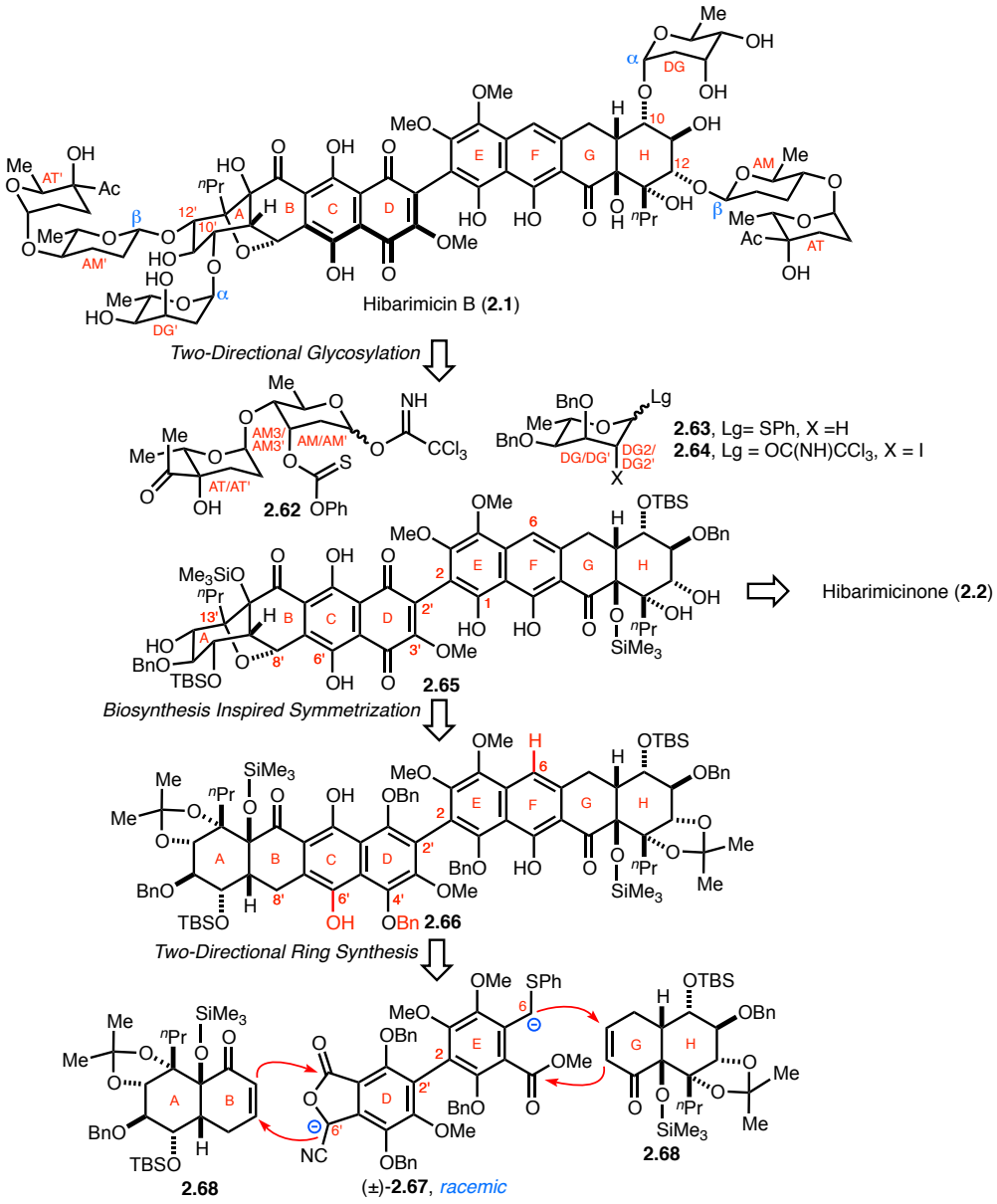


Figure 2.6 Retrosynthesis of hibarimicin B.

The total synthesis of hibarimicin B (**2.1**) was anticipated to be an extremely labor and time intensive endeavor due to its size and structural complexity. For this reason, Brian B. Liau joined me early on and we divided the labor necessary for the completion of this goal. My initial focus was the synthesis of both AB/HG-enone **2.68** and *ent*-AB/HG-enone **2.69** (Figure 2.7) annulation acceptors in order to determine the absolute stereochemistry of the aglycon of **2.2**. Brian's primary focus was the synthesis of the racemic DE-biaryl annulation donor (±)-**2.67** and the development of robust naphthol and hydroquinone annulation reactions necessary to complete a synthesis of the **2.2**. Once these goals had been met, my objective was to accomplish a synthesis of both the AM/AM'-AT/AT' dissacharide and the DG/DG' monosacharride glycosyl donors and to develop methods for their installation onto a suitably protected aglyon. Realization of these aims would potentially enable the first total synthesis of hibarimicin B (**2.1**).

2.6 AB/HG-Enone Synthesis

Without knowing the absolute stereochemistry of the hibarimicin B aglycon, we were forced to make an arbitrary decision regarding which AB/HG-enone enantiomer to target. Our first-generation retrosynthesis for what was later determined to be the *ent*-AB/HG-enone (**2.69**) is outlined in Figure 2.7. Our plan for the synthesis of **2.69** relied on a key Lewis acid-catalyzed contrasteric Diels–Alder reaction between cyclohexenone **2.71** and 1-alkoxy-1,3-butadiene **2.70** to set the challenging C9 stereochemistry and assemble the *cis*-decalin carbon framework **of 2.69** in a single operation. We anticipated that the C14–OH could be installed through the oxidative decarboxylation of the corresponding ester. We expected that diastereoselective introduction of the *n*-propyl substituent could be accomplished through a organometallic addition to a C13 carbonyl group from the convex face of the rigid *cis*-decalin carbon framework. Finally, cyclohexenone **2.71** could be constructed through a Robinson annulation of an orthogonally protected linear precursor **2.72** derived from readily available methyl α-D-glucopyranoside (**2.73**).

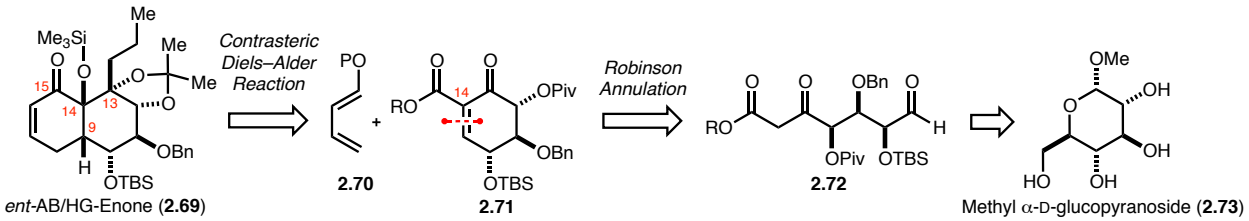
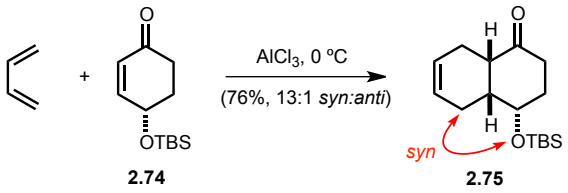


Figure 2.7 First-generation ent-AB/HG-enone retrosynthesis.

A reaction first reported by Danishefsky and coworkers in 1991[113] inspired us to take advantage of a Lewis acid-promoted contrasteric Diels–Alder reaction in our synthesis plan for **2.69** (Scheme 2.8). They demonstrated that 2-cyclohexenone **2.74**, bearing a γ-OTBS group, participated in a contrasteric intermolecular Diels–Alder reaction with 1,3-butadiene when catalyzed by $AlCl_3$ to afford *cis*-decalin **2.75** in 76% yield. In this transformation, the β-C–C bond was formed *syn* relative to the γ-OTBS group in high diastereoselectivity (13:1 *syn*:*anti*). We anticipated similar stereoselectivity in our proposed Diels–Alder reaction, despite the additional Lewis basic groups in our substrate (**2.71**).

Scheme 2.8 Danishefsky's Lewis acid-promoted contrasteric Diels–Alder reaction.



Reagents and conditions: (a) 1,3-butadiene (20 equiv), $AlCl_3$ (0.9 equiv), PhMe, 23 °C, 1 h, 76%, 13:1 *syn*:*anti*.

The first-generation synthesis of *ent*-AB/HG-enone (**2.69**) began with silylation of methyl α-D-glucopyranoside (**2.73**) followed by $FeCl_3$ catalyzed regioselective benzylation of the resultant triemethylsilyl protected glucopyranoside **2.76** according to a modified literature procedure (Scheme 2.9).[114] Recrystallization of the product mixture supplied benzylidene acetal (–)-**2.77** on multi-gram scale in 50% yield. Next, the C12 secondary carbinol was protected as a pivalate ester and the benzylidene acetal was hydrolyzed by treatment with HOAc to deliver diol (+)-**2.78** in 86% yield over two steps.

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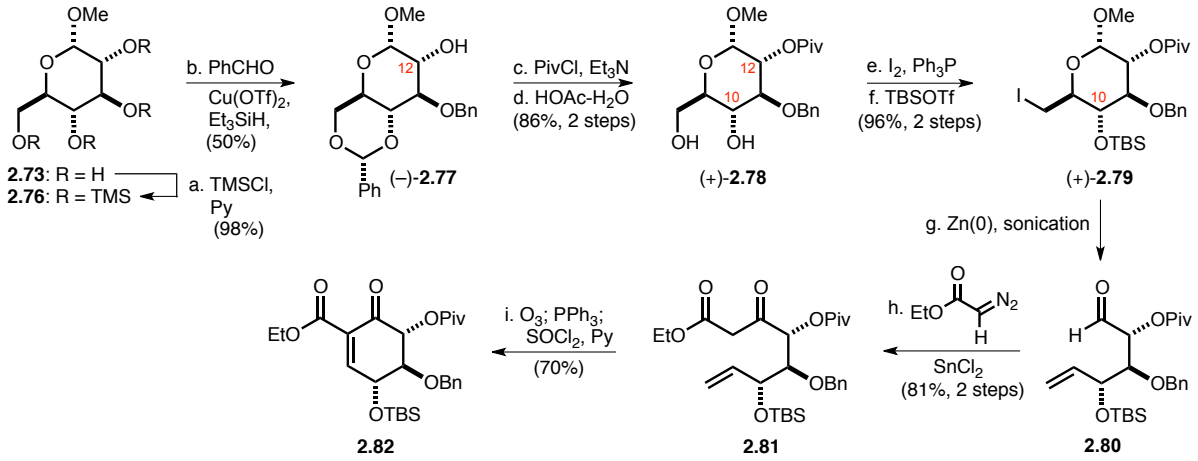
[113] Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J.; Shulte G. M. *J. Org. Chem.* **1991**, *56*, 387–395.

[114] Bourdreux, Y.; Lemétais, A. Urban, D.; Beau, J.-M. *Chem. Commun.*, **2011**, *47*, 2146–2148.

Formation of the primary iodide and protection of the C10 secondary carbinol as a silyl ether gave iodide (+)-**2.79** in excellent yield. Sonication of (+)-**2.79** with activated zinc powder promoted reductive fragmentation to generate an aldehyde intermediate (**2.80**),[115] which upon treatment with ethyl diazoacetate and $SnCl_2$ furnished β-ketoester **2.81**.[116] Finally, ozonolysis of **2.81** followed by reductive workup with PPh_3 gave another aldehyde intermediate. Exposure of this aldehyde to thionyl chloride and pyridine promoted a Robinson annulation to provide enone **2.82** in 56% yield over three steps.

Scheme 2.9 Synthesis of first-generation Diels–Alder substrate **2.82**.



Reagents and conditions: (a) TMSCl, Py, 45 °C, 98%; (b) PhCHO, $Cu(OTf)_2$, MeCN-CH_2Cl_2 (1:4), 0 °C; then Et_3SiH, 0 °C → RT, 50%; (c) PivCl, Et_3N, 4-DMAP, CH_2Cl_2, 0 °C → RT, 95%; (d) HOAc-H_2O (4:1), 80 °C, 94%; (e) PPh_3, imidazole, PhMe; then I_2; then (+)-**2.78**, RT → 45 °C, 97%; (f) TBSOTf, 2,6-lutidine, 0 °C → RT, 99%; (g) Zn(0), THF-H_2O (4:1), sonication, 40 °C; (h) ethyl diazoacetate, $SnCl_2$, CH_2Cl_2, 81% (two steps); (i) O_3, CH_2Cl_2, –78 °C; PPh_3; $SOCl_2$, Py, –78 °C → RT, 70%.

With a route to enone **2.82** established, we attempted the proposed Lewis acid-catalyzed contrasteric Diels–Alder reaction with 1-acetoxy-1,3-butadiene (**2.83**),[117] which was known to be stable in

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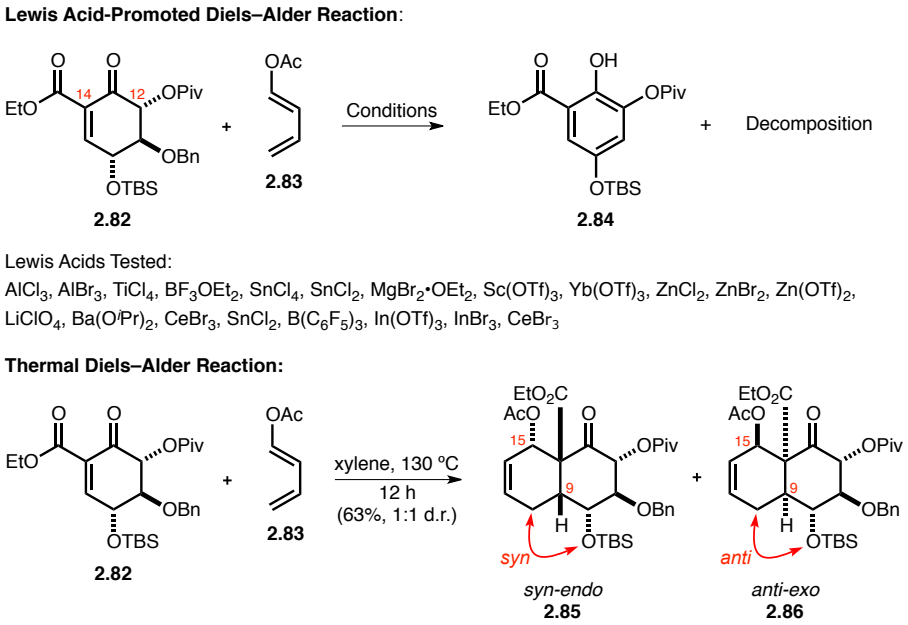
[115] (a) Skaanderup, P. R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467–472. (b) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444–8452. (c) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2411–2431. (c) Nakane, M.; Hutchinson, C. R.; Gollman, H. *Tetrahedron Lett.* **1980**, *21*, 1213–1216. (c) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem*. **1991**, *56*, 2213–2217.

[116] Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.

[117] Bailey, W. J.; Barclay, R. *J. Org. Chem.* **1956,** *21,* 328–331.

the presence of a variety of Lewis acids (Scheme 2.10).[118] Unfortunately, an extensive screen of potential reaction conditions and Lewis acids did not yield a Diels–Alder product. The major product formed under a variety of reaction conditions was phenol **2.84**, which was a result of β-elimination of the benzyloxy group and tautomerization of the resultant cyclohexadienone. In contrast, heating a solution of **2.82** and **2.83** in xylene to 130 °C for 12 h promoted a thermal Diels–Alder reaction to provide *cis*-decalin isomers **2.85** and **2.86**. Independent NOESY analysis of the cycloadducts indicated that we had produced a 1:1 mixture of the desired *syn* and undesired *anti* diasereomers. Additionally, the stereochemistry of the C15 acetoxy group indicated that the *syn* diastereomer (**2.85**) was presumably formed through an *endo* transition state. The lack of facial selectivity in the thermal Diels–Alder reaction prompted us to devise an alternative Lewis acid compatible substrate.

Scheme 2.10 First-generation Diels–Alder reaction.



[118] (a) Kraus, G. A.; Fulton, B. S. *J. Org. Chem.* **1985**, *50*, 1782–1784. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820. (c) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T. von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D. Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594. (c) Imagawa, H. Saijo, H.; Yamaguchi, H.; Maekawa, K.; Kurisaki, T.; Yamamoto, H.; Nishizawa, M.; Oda, M.; Kabura, M.; Nagahama, M.; Sakurai, J.; Kubo, M.; Nakai, M.; Makino, K.; Ogata, M.; Takahashi, H.; Fukuyama, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22,* 2089–2093.

We reasoned that the electron withdrawing C14 ester substituent of **2.82** increased the acidity of the C12–H bond and thereby facilitated β-elimination of the benzyloxy substituent upon exposure to a Lewis acid. Furthermore, in the process of screening Lewis acids for the Diels–Alder reaction we observed significant diene polymerization, which we attributed to the 1-acetoxy substitution. A variety of alternative 1-substituted dienes were also investigated for this reaction, all of which showed a similar trend toward Lewis acid-mediated decomposition via polymerization. Consequently, a second-generation *ent*-AB/HG-enone (**2.69**) synthesis plan was developed that continued to rely on a Lewis acid-catalyzed contrasteric Diels–Alder reaction, but utilized substrates pair that lacked the aforementioned substituents.

Our second-generation retrosynthesis of *ent*-AB/HG-enone (**2.69**) is outlined in Figure 2.8. We anticipated that the enone functionality in **2.69** could be installed through the oxidation of the corresponding allylic silane **2.87**. Additionally, stereocontrolled introduction of the *n*-propyl substituent at C13 could be accomplished through an organometallic addition to α-hydroxy ketone **2.87** from the convex face of the rigid *cis*-decalin carbon framework. Next, **2.87** could be accessed via a regio- and diastereoselective silyl zincate 1,6-addition to dienone **2.88**, followed by in situ oxidation of the resultant extended zinc enolate. A key Lewis acid-catalyzed contrasteric Diels–Alder reaction between cyclohexenone **2.89** and 1,3-butadiene could then be employed to assemble decalin **2.88** with the requisite relative stereochemistry at the challenging C9 stereocenter. Finally, suitably protected cyclohexenone **2.89** could be prepared through ring-closing metathesis (RCM) of a linear precursor derived from readily available methyl α-D-glucopyranoside (**2.73**).

An analogous sequence of stereospecific transformations on cyclohexenone enantiomer **2.90** could potentially furnish AB/HG-enone (**2.68**). We imagined cyclohexenone **2.90** could be prepared by taking advantage of the latent C_2-symmetry exhibited by methyl α-D-glucopyranoside (**2.73**). Rather than a RCM-type annulation, a type-II Ferrier rearrangement could be employed to construct **2.90**. The ability to produce gram quantities of both AB/HG-enone (**2.68**) and *ent*-AB/HG-enone (**2.69**) was deemed essential for a successful total synthesis of hibarimicin B (**2.1**). Recognition of the common

stereochemical elements shared by **2.68**, **2.69**, and methyl α-D-glucopyranoside (**2.73**) will help enable the realization of this goal.

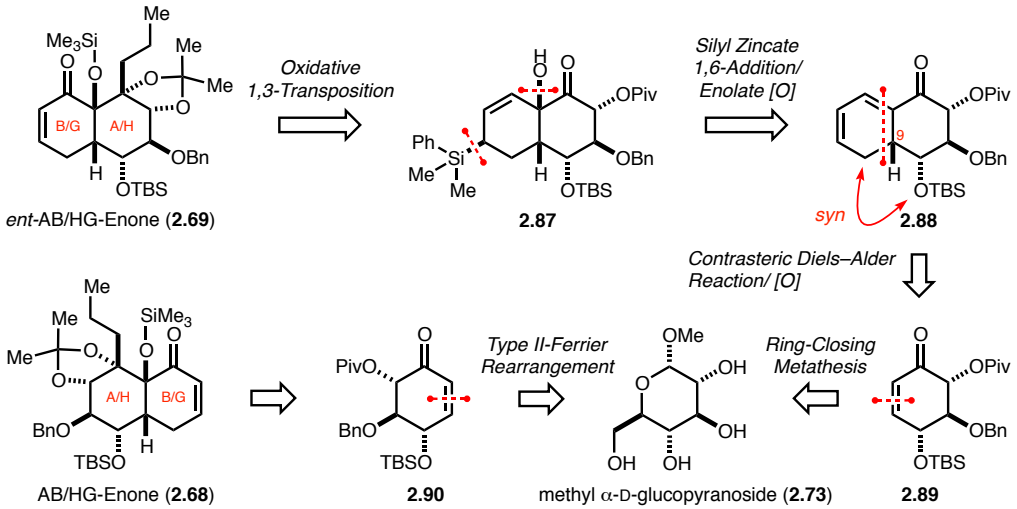


Figure 2.8 Second-generation retrosynthesis of *ent*-AB/HG-enone **2.69** and AB/HG-enone **2.68**.

The synthesis of *ent*-AB/HG-enone (**2.69**) began with iodide (+)-**2.79** prepared according to the previously described procedure (Scheme 2.11).[119] Sonication of (+)-**2.79** with activated zinc powder promoted reductive fragmentation to generate an aldehyde intermediate (**2.80**), which upon treatment with an organocerium reagent derived from vinylmagnesium bromide furnished allylic alcohol **2.91** as an inconsequential diastereomeric mixture in 75% yield over two steps.[120] Exposure of **2.91** to first-generation Grubbs olefin metathesis catalyst[121] in dilute CH_2Cl_2 followed by Parikh–Doering oxidation[122] of the resultant diastereomeric cyclohexenols afforded cyclohexenone (–)-**2.89** in 82% yield over two steps. Over thirty grams of (–)-**2.89** was synthesized through this protocol.

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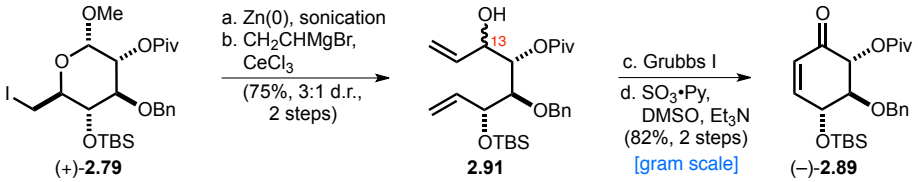
[119] Milgram, B. C.; Liau, B. B.; Shair, M. D. *Org. Lett.* **2011**, *13*, 6436–6439.

[120] Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444–8452.

[121] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.

[122] Parikh, J. P.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

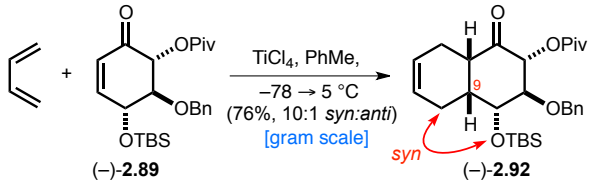
Scheme 2.11 Synthesis of Diels–Alder substrate (–)-**2.89**.



Reagents and conditions: (a) Zn(0), THF-H_2O (4:1), sonication, 40 °C; (b) $CH_2CHMgBr$, $CeCl_3$, THF, –78 °C, 75%, 3:1 d.r. at C13 (two steps); (c) Grubbs I (5 mol %), CH_2Cl_2, 85%; (d) SO_3•Py, $^iPr_2NEt$, DMSO, CH_2Cl_2, 0 °C, 97%.

Following our synthesis of (–)-**2.89**, we attempted a Lewis acid-catalyzed contrasteric Diels–Alder reaction depicted in Scheme 2.12. The variety of Lewis acids we screened for this reaction include: $AlCl_3$, $AlMeCl_2$, $AlMe_2Cl$, BCl_3, TBSOTf, and $TiCl_4$. Eventually we discovered that addition of a freshly prepared solution of $TiCl_4$ in PhMe to (–)-**2.89** at –78 °C followed by dropwise addition of liquid 1,3-butadiene and warming the reaction mixture to 5 °C for 3.5 h afforded a 10:1 mixture of cycloaddition adducts, favoring the desired *syn* diastereomer (–)-**2.92**. The use of PhMe as a solvent was critical to suppress the formation of a benzyl deprotected side product. This reaction was performed on multi-gram scale with similarly high levels of diastereoselectivity and is to our knowledge the most complex example of a contrasteric Diels–Alder yet reported.

Scheme 2.12 Second-generation Lewis acid-promoted contrasteric Diels–Alder reaction.



The stereoselectivity of this reaction is likely governed by subtle steric and stereoelectronic effects. Approach of 1,3-butadiene to (–)-**2.89** *syn* to the γ-OTBS substituent is sterically occluded by both the γ-OTBS and α-OPiv groups and is thus counterintuitive (transition state **2.93**, Figure 2.9). However, stereoelectronic considerations suggest that pseudo-axial approach of 1,3-butadiene to C9 of

the chair-like ground state conformation of **2.94** is kinetically favored.[123] Additionally, the Cieplak model has been invoked to rationalize the stereochemical outcome for the aforementioned Diels–Alder reaction.[124] In accordance with this line of reasoning, formation of the β-C–C bond *syn* with the electron-withdrawing γ-OTBS group stabilizes the forming σ*-C–C orbital through hyperconjugation with the electron-donating σ-C–H bond (transition state **2.94**, Figure 2.9). It is plausible that a synergism of individually small stereoelectronic effects bias the reaction pathways towards the observed major product diastereomer (–)-**2.92**.[125,126]

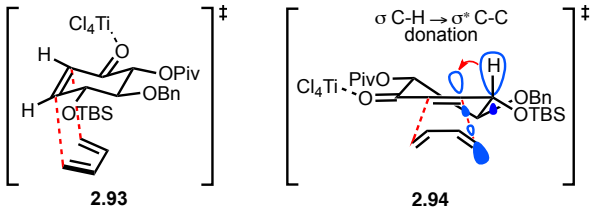


Figure 2.9 Possible explaination for contrasteric outcome of Lewis Acid-promoted Diels–Alder reaction.

The next challenge in the synthesis of **2.69** was the installation of the C14–OH and C15 carbonyl groups. Exposure of (–)-**2.92** to TMSI, generated in situ from TMSCl and NaI, promoted thermodynamic enolization of the ketone to afford enol silane **2.95** as a single regioisomer (Scheme 2.13).[127] This regioselection is particularly noteworthy since C12–H is presumably more acidic than C14–H.[128]

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[123] Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem*. **1986**, *51*, 2642–2649.
[124] (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103,* 4540–4552. (b) Ohkata, K.; Tamura, Y.; Shetuni, B. B.; Takagi, R.; Miyanaga, W. Kojima, S.; Paquette, L. A. *J. Am. Chem. Soc*. **2004**, *126*, 16783–16792. (c) Carreño, M. C.; González, M. P.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128–9137.

[125] A similar sense of facial selectivity was observed for copper(I) mediated 1,4-addition of organometallic reagents to a benzyl protected inositol derivative in the presence of BF_3•OEt_2: Bian, J.; Schneider, S. R.; Maguire, R. J. *Tetrahedron Lett.* **2011**, *52*, 5417–5420.

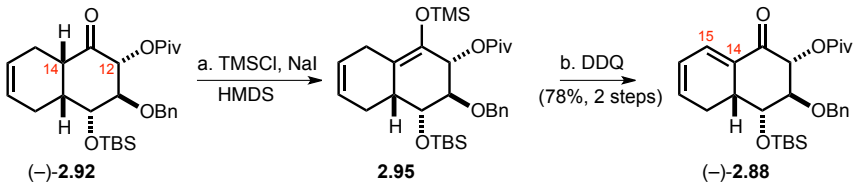
[126] A similar sense of facial selectivity was observed for $LiClO_4$ catalyzed conjugate addition of an *O*-silylated ketene acetal on a benzyl protected inositol derivative: Lastdrager, B.; Timmer, M. S. M.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *J. Carbohydr. Chem.* **2007**, *26*, 41–59.

[127] (a) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, *9*, 730–732. (b) Moher, E. D.; Collins J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764–2765. (c) Krafft, P. A.; Holton, R. A. *Tetrahedron Lett*. **1983**, *24*, 1345–1348.

[128] Interestingly, deprotonation of (–)-**2.92** with KHMDS at –78 °C followed by quenching the resultant enolate with D_2O or DOAc resulted in equivalent deuterium incorporation at C9 and C12.

Oxidation of **2.95** was accomplished through exposure to DDQ to furnish dienone (–)-**2.88** in 78% overall yield, again as a single regioisomer.[129]

Scheme 2.13 Synthesis of dieneone (–)-2.88.

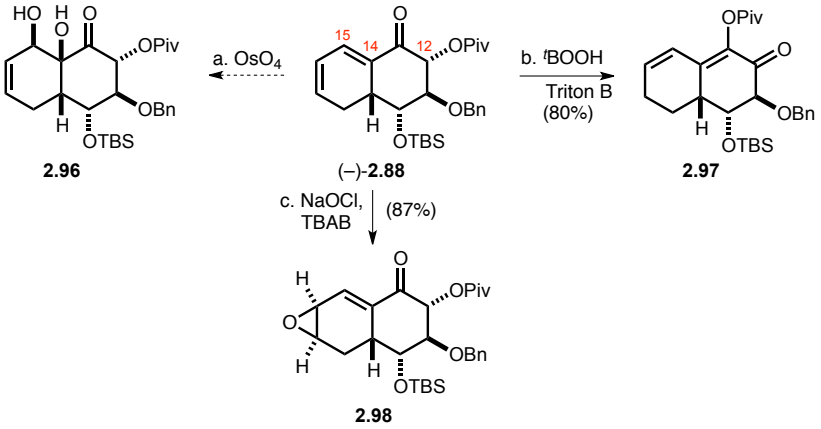


Reagents and conditions: (a) TMSCl, NaI, HMDS, MeCN, 82 °C; (b) DDQ, CH_2Cl_2, 78% (two steps).

Several conceptually similar stratigies were considered for introduction of oxygen at C14 and C15 (Scheme 2.14). Chemoselective dihydroxylation of the C14–C15 olefin of (–)-**2.88** was attempted using catalytic OsO_4, but led to only substrate decomposition. Alternatively, treatment of (–)-**2.88** with ^{t}BOOH and Triton B was expected to promote nucleophilic epoxidation of the C14–C15 olefin; instead, an unexpected dieneone **2.97** was formed in 80% yield. The formation of **2.97** presumably occured via: (1) C12–H deprotonation, (2) pivaloyl migration, and (3) reprotonation of the resultant extended enolate at the terminal position. This finding prompted us to attempt electrophilic epoxidation of (–)-**2.88**. Exposure of (–)-**2.88** to NaOCl, under phase transfer conditions, furnished epoxide **2.98** in 87% yield. While **2.98** was not regarded as a potential intermediate for the synthesis of **2.68**, the apparent selectivity demonstrated for distal epoxidation in this reaction inspired us to imagine an alternative reaction sequence that could utilize this discovery.

[129] (a) Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, *19*, 3455–3458. (b) Corey, E. J.; Guzman–Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611–3612.

Scheme 2.14 Attempted oxidation of dienone (–)-**2.88**.



Reagents and conditions: (a) OsO_4 (10 mol%), NMO, Me_2CO-H_2O (3:1); (b) ^{t}BOOH, Triton B, PhH, 80%; (c) NaOCl, TBAB, PhMe-H_2O (2:1), 87%.

Based on the previous observation, we anticipated addition of a silyl nulcleophile to (–)-**2.88** would occur in a diastero- and regioselective fasion from the convex face of the molecule at C7 to generate an extended enolate intermediate, which could in turn be diastero- and regioselectively oxidized to introduce the C14–OH. Several important discoveries were made in the process of developing this concept into an efficient process (Scheme 2.15). First, we found the use of a silyl zincate nucleophile rather than a silyl cuprate was critical to prevent base mediated pivaloyl migration. Second, the steric bulk of the silyl nucleophile was essential for controlling the facial selectivity of conjugate addition. Exposure of (–)-**2.88** to a trimethylsilyl zincate derived from trimethylsilyl lithium and diethyl zinc furnished conjugate addition adduct **2.100** upon trapping the resultant enolate with TMSCl in only 2:1 d.r. at C7. In contrast, dimethylphenylsilyl zincate added exclusively from the convex face of (–)-**2.88** to yield a single stereoisomer at C7.[130,131]

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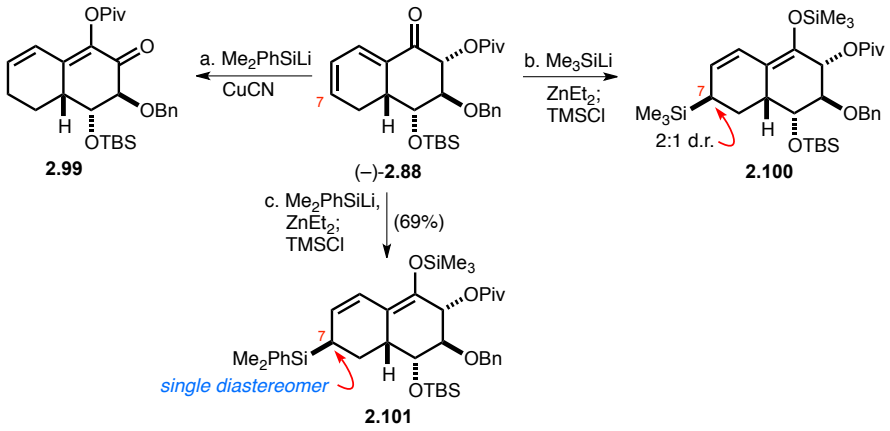
[130] It was usefull to isolate the intermediate enolate as its cooresponding enol silane to assess the diastereo- and regioselectivity of the process.

[131] (a) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661. (b) Vaughan, A.; Singer, R. D. *Tetrahedron Lett.* **1995**, *36*, 5683–5686. (c) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021–4022. (d) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701–706. (e) Tckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581–1593.

Scheme 2.15 Development of an efficient silyl 1,6-addition.



Reagents and conditions: (a) $Me_2PhSiLi$, CuCN, THF, –78→ 0 °C; then (–)-**2.88**; (b) Si_2Me_6, ^{n}BuLi, HMPA, THF –78→ 0 °C; then $ZnEt_2$, PhMe, –78 °C; then (–)-**2.88**, –78→ 0 °C; then TMSCl, 31%, 2:1 d.r.; (b) $Me_2PhSiLi$, $ZnEt_2$, THF-PhMe, –78 °C; then (–)-**2.88**, –78 → 0 °C; then TMSCl, 69%.

Next, the oxidation of the extended zinc enolate intermediate (**2.102**) was studied with a variety of known oxidants including: ^{m}CPBA, Oxone, DMDO (**2.105**), Davis oxaziridine ((±)-**2.106**), and MoOPH (**2.107**). The product formed in this transformation depended on the oxidant that was employed (Scheme 2.16). The use of ^{m}CPBA or Oxone in this reaction afforded C16 peroxide **2.203** as the sole product. Interestingly, addition of aqueous ammonium chloride solution to the intermediate extended zinc enolate **2.102** also resulted in exclusive formation of **2.203**.[132] Utilization of Davis oxaziridine ((±)-**2.106**) as an oxidant[133] supplied the desired α-hydroxy ketone (+)-**2.87**; unfortunately it was difficult to separate (+)-**2.87** from the Davis oxiziridine by-products through silica gel chromatography or acid extraction.[134] Oxidation of (–)-**2.88** using an anhydrous solution of DMDO in acetone cleanly afforded (+)-**2.87** on

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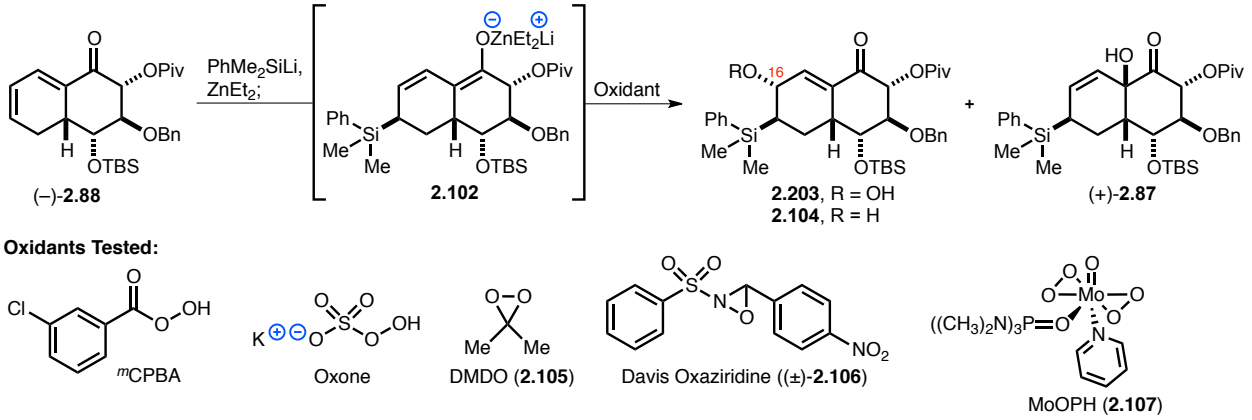
[132] The presence of a peroxide functional group in **2.103** was confirmed by O–O bond reduction through treatment with PPh_3 to afford the cooresponding C16 alcohol **1.104**.

[133] (a) Davis, F. A.; Abdul-Malik, N. F.; Awad S. B.; Harakal, M. E. *Tetrahedron Lett.* **1981**, *22*, 917–923. (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241–3243. (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934. (d) Kummer, D. A.; Li, D.; Dion, A.; Myers, A. G. *Chem. Sci.* **2011**, *2*, 1710–1718.

134 Work-up of the reaction with acid was attempted in order to remove the oxidation by-products formed by Davis oxaziridine, however this procedure caused immediate decomposition of the α-hydroxy ketone product (+)-**2.87**.

milligram scale; however, on gram-scale, C16 alcohol **2.104** became the major product of the reaction. Eventually we discovered MoO_5•pyr•HMPA (MoOPH) (**2.107**)[135] was an ideal oxidant for the preparation of α-hydroxy ketone (+)-**2.87** on gram-scale.

Scheme 2.16 Development of an efficient in situ enolate oxidantion proceedure.



The synthesis of C14-hydroxy *ent*-AB/HG-enone ((–)-**2.110**) is depicted in Scheme 2.17. Regio- and diastereoselective addition of dimethylphenylsilyl zincate to the δ-position of dienone (–)-**2.88** generated an extended zinc enolate intermediate, which upon treatment with (MoOPH, **2.107**), underwent in situ α-oxidation to deliver *cis*-decalin (+)-**2.87** as a single regio- and diastereoisomer in 82% yield on gram-scale. Overall, this reaction sequence installed the sterically congested C14 tertiary carbinol and introduced an allylic silane functional group, which was planned to serve as a latent enone surrogate. Next, exposure of (+)-**2.87** to an organocerium reagent derived from *n*-propylmagnesium chloride led to carbonyl addition exclusively from the convex face of the molecule and promoted cleavage of the pivaloyl ester upon warming the reaction mixture to 0 °C.[136] The use of a organocerium reagent was required to avoid ketone enolization and reduction.[137] The resultant 1,2-diol was protected as an acetonide

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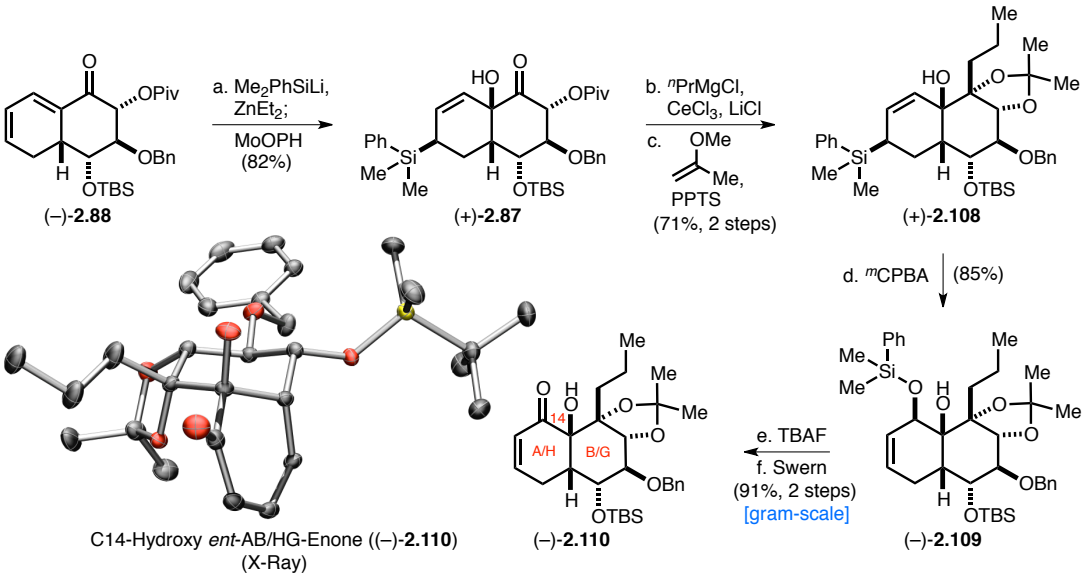
[135] (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944–5946. (b) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127–132 and references therein.

[136] (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906. (b) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424–16434. (c) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787–6790.

[137] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

to afford (+)-**2.108** in 71% yield over two steps. Addition of ^{m}CPBA to a cold mixture of (+)-**2.108** and $NaHCO_3$ in CH_2Cl_2 induced epoxidation of the allylic silane. The intermediate epoxide underwent subsequent 1,5-silyl migration with concomitant epoxide opening to provide silyl ether (–)-**2.109** in 85% yield.[138] Chemoselective removal of the dimethylphenylsilyl group with TBAF at –78 °C followed by Swern oxidation[139] of the resultant allylic alcohol delivered (–)-**2.110** in 91% yield over two steps on gram-scale. An X-ray structure of (–)-**2.110** confirmed the relative stereochemistry of the *cis*-decalin carbon skeleton.

Scheme 2.17 Completion of C14-hydroxy *ent*-AB/HG-enone (–)-**2.110**.



Reagents and conditions: (a) $Me_2PhSiLi$, $ZnEt_2$, THF-PhMe, –78 °C; then (–)-**2.88**, –78 → 0 °C; then MoOPH, –78 → –20 °C, 20 min, 82%; (b) $CeCl_3$, LiCl, THF; then ^{n}PrMgCl, –78 ºC; then (+)-**2.105**, –78 → 0 °C, 85%; (c) 2-methoxypropene, PPTS (10 mol %), PhH, 84%; (d) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2, –78 → –5 °C, 85%; (e) TBAF, THF, –78 ºC, 99%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then diol, –78 °C; then Et_3N, –78 → 0 °C, 92%.

The synthesis of the AB/HG-enone enantiomer ((+)-**2.68**), which corresponds to the absolute stereochemistry of **2.2**, is illustrated in Scheme 2.18. The route began with benzylidine acetal **2.77**, which was also a key intermediate in our synthesis of *ent*-AB/HG-enone **2.69**. The benzylidine acetal was

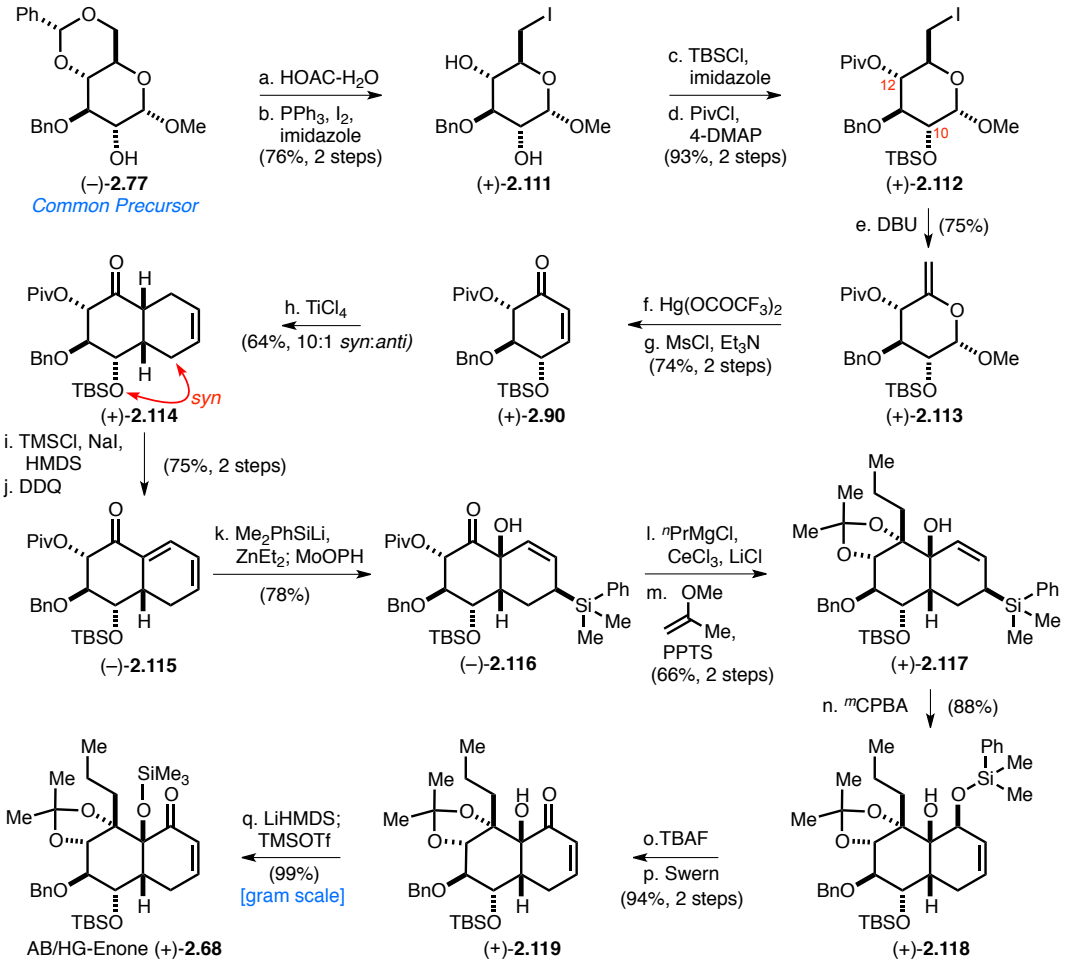
[138] Lee, K.-S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900.

[139] Omura, K.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651–1660.

hydrolyzed by exposure of **2.77** to warm aqueous HOAc and the resultant primary alcohol was iodinated to afford diol (+)-**2.111** in 76% yield over two steps. Next, chemoselective monosilylation of (+)-**2.111** with TBSCl was accomplished by exploiting a subtle steric difference between its two secondary hydroxyl groups. The remaining secondary hydroxyl group was then pivoylated under forcing conditions to furnish differentially protected pyranose (+)-**2.112**. Addition of DBU to a warm solution of (+)-**2.112** in MeCN promoted elimination of the primary iodide. The resultant exocyclic enol ether (+)-**2.113** underwent type-II Ferrier rearrangement upon treatment with catalytic $Hg(OCOCF_3)_2$[140] to yield a β-hydroxy-cyclohexanone intermediate which was dehydrated with methanesulfonyl chloride and pyridine to provide (+)-**2.90** on multi-gram scale. Following the previously described procedure, cyclohexenone (+)-**2.90** was converted to (+)-**2.119**. Finally, deprotonation of (+)-**2.119** with LiHMDS followed by exposure of the resultant alkoxide to TMSOTf delivered AB/HG-enone (+)-**2.68** for the key two-directional annulation reaction.

[140] Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458.

Scheme 2.18 Synthesis of AB/HG-Enone (+)-**2.68**.



Reagents and conditions: (a) AcOH/H_2O, 80 °C; (b) PPh_3, I_2, imidazole, PhMe-CH_2Cl_2, RT → 45 °C, 76% (two steps); (c) TBSCl, imidazole, CH_2Cl_2, 0 °C → RT, 99%; (d) PivCl, 4-DMAP, $ClCH_2CH_2Cl$, 50 °C, 94%; (e) DBU, MeCN, 80 °C, 75%; (f) $Hg(OCOCF_3)_2$ (30 mol%), Me_2CO-H_2O; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C → RT, 74% (two steps); (h) $TiCl_4$, 1,3-butadiene, PhMe, –78 → 5 °C, 64%, 10:1 *syn*:*anti*; (i) TMSCl, NaI, HMDS, MeCN, 82 °C; (j) DDQ, CH_2Cl_2, 75% (two steps); (k) $Me_2PhSiLi$, $ZnEt_2$, THF-PhMe, –78 °C; then (–)-**2.115**, –78 → 0 °C; then MoOPH, –78 → –20 °C, 20 min, 78%; (l) $CeCl_3$, LiCl, THF; then ^{n}PrMgCl, –78 ºC; then (–)-**2.116**, –78 → 0 °C, 80%; (m) 2-methoxypropene, PPTS (10 mol %), PhH, 82%; (n) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2, –78 → –5 °C, 88%; (o) TBAF, THF, –78 ºC, quantitative; (p) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; then diol, –78 °C; then Et_3N, –78 → 0 °C, 94%. (q) LiHMDS, THF, 0 °C; then TMSOTf, 0 °C → RT, 99%.

2.7 Total Synthesis of Hibarimicin Aglycons

As previously mentioned, the size and complexity of hibarimicin B (**2.1**) necessitated that Brian B. Liau and I work as a team toward the completion of its total synthesis. While I developed and scaled the the synthesis of both the AB/HG- and *ent*-AB/HG-enone annulation acceptors, Brian developed an efficient synthesis of the DE-biaryl annulation donor, explored model napthol and hydroquinone annulation reactions, and applied the methods he established toward the synthesis of what we later learned to be *ent*-hibarimicinone. While working on the synthesis of the AM-AT dissacharide and DG-monosaccharide glycosyl donors, I helped Brian complete enantioselective total syntheses of hibarimicinone (**2.2**) and atrop-hibarimicinone (**2.135**, Scheme 2.20), and the first total syntheses of the biosynthetically related natural product aglycons HMP-Y1 (**2.9**), atrop-HMP-Y1, and HMP-P1 (**2.12**).[141] Specifically, my contributions were (1) to provide Brian with enough AB/HG-enone to accomplish the total synthesis of **2.2** and **2.135** and (2) to complete the total syntheses of HMP-Y1 (**2.9**) and atrop-HMP-Y1 and investigate their respective barriers to atropismerism. The chemical transformations described in this section of the text were developed by Brian B. Liau.

Brian's synthesis of the DE-biaryl annulation donor (±)-**2.67** is depicted in Scheme 2.19. For a detailed description of this work see Reference 141. Key steps in the synthesis of (±)-**2.67** included a regioselective *ortho*-lithiation of **2.121** at C2' followed by an $FeCl_3$-mediated oxidative dimerization of the intermediate aryllithium species to form the sterically hindered *ortho*, *ortho'*-tetrasubstituted biaryl C2–C2' bond as a mixture of atropisomers. The ability to form this bond early in the synthesis allowed us to avoid issues associated with a napthol cross-coupling strategy encountered by Roush.[104a,c] Additionally, Brian was able to desymmetrize bis-*ortho*-toluate intermediate (±)-**2.123** through treatment with 1.25 equiv of LiTMP followed by a short exposure to $(BrCF_2)_2$ to furnish benzyl bromide (±)-**2.125** in 82% yield. (±)-**2.125** was then elaborated to the DE-biaryl annulation donor **2.67** through an effiecient series of chemical trasformations.

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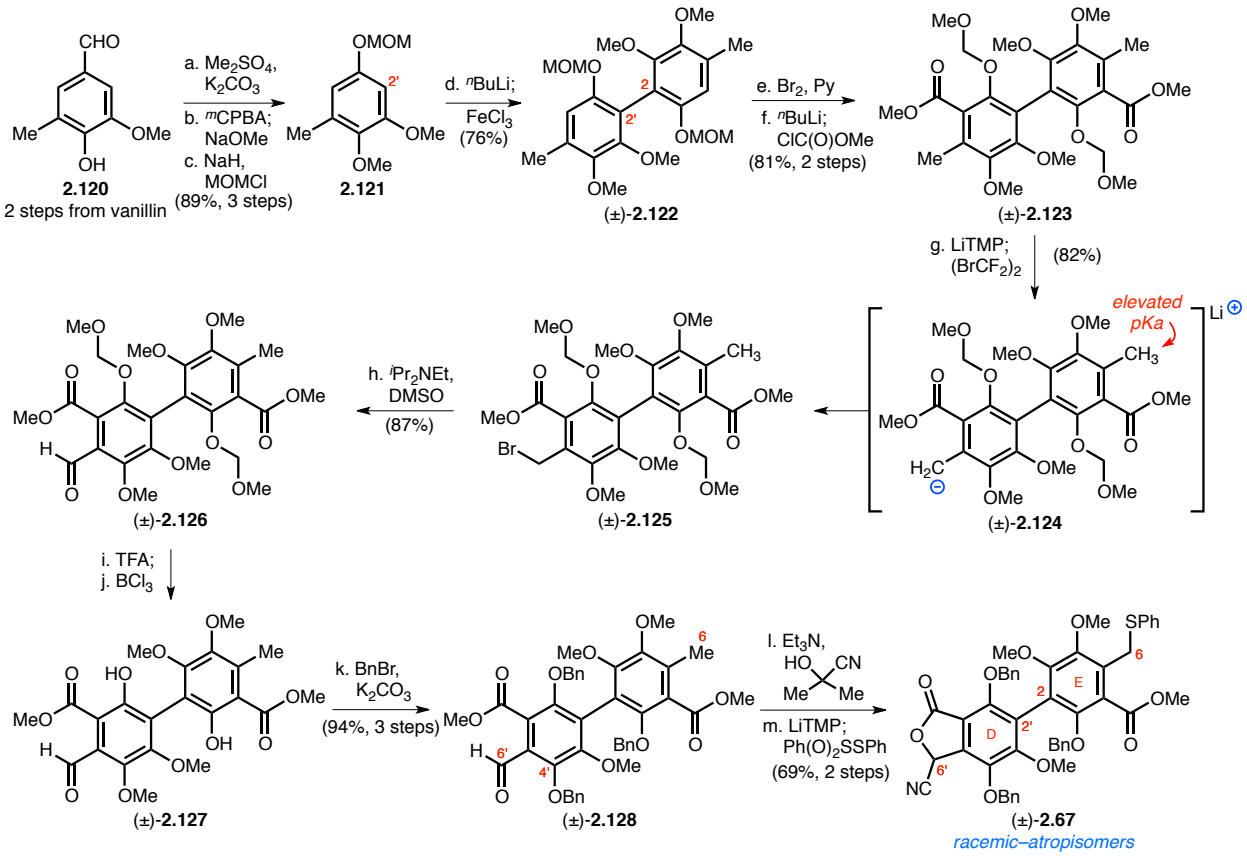
[141] Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772.

Scheme 2.19 Synthesis of unsymmetrical DE-biaryl annulation donor.



Reagents and conditions: (a) Me_2SO_4, K_2CO_3, Me_2CO, 98%; (b) ^{m}CPBA, $NaHCO_3$, CH_2Cl_2; then Na_2CO_3, MeOH; (c) NaH, MOMCl, DMF, 0 °C → RT, 91% (two steps); (d) ^{n}BuLi, TMEDA, THF, –78 → 0 °C; then $FeCl_3$, 0 °C → RT, 76%; (e) Br_2, Py, CH_2Cl_2, 0 °C, 91%; (f) ^{n}BuLi, THF, –78 °C; then ClC(O)OMe, –78 °C → RT, 89%; (g) LiTMP, THF, –78 °C; then $(BrCF_2)_2$, 82%; (h) ^{i}Pr$_2$NEt, DMSO, 70 °C, 87%; (i) TFA, CH_2Cl_2, 0 °C → RT; (j) BCl_3, CH_2Cl_2, –78 → 0 °C; (k) BnBr, K_2CO_3, DMF, 0 → 60 °C, 94% (three steps); (l) $Me_2C(OH)CN$, Et_3N, $CHCl_3$, 97%; (m) LiTMP, THF, –78 °C; then $Ph(O)_2SSPh$, 71%.

The total synthesis of hibarimicinone (**2.2**) and atrop-hibarimicinone (**2.135**) is depicted in Scheme 2.20. The synthesis began with a two-directional annulation reaction between DE-biaryl annulation donor (±)-**2.67** and two equivalents of the AB/HG-enone annulation acceptor (+)-**2.68**. Specifically, contruction of the C-ring hydroquinone was anticipated to involve a Kraus annulation of the lithiated cyanothalide of (±)-**2.67** with one equivalent of (+)-**2.68** and the F-ring was expected to be assembled through a Michael–Claisen annulation of the lithiated benzyl phenyl sulfide of (±)-**2.67** with a

second equivalent of (+)-**2.68**. Treatment of a deoxygenated solution of (±)-**2.67** and (+)-**2.68** in THF at –78 °C with LiHMDS promoted double-deprotonation of (±)-**2.67**. Warming the intermediate bis-anion to 0 °C for 16 h facilitated the desired Kraus annulation[142] and the Michael step of the proposed F-ring annulation sequence. The final Claisen condentation step of the F-ring annulation was accomplished by addition of KHMDS to the reaction mixture, which was warmed to ambient temperature for 12 h. Overall, this protocol reliably provided octacycle (–)-**2.128** and (+)-**2.129** as a ~1.3:1 mixture of atropisomers in 34% and 25% yield, respectively. At this stage, the atropisomers were separated via silica gel chromatography and carried through the subsequent steps of the total synthesis independently. Aromatization of the F-ring, via elimination of the C6 thiophenyl substituent, was accomplished by exposure of the annulation products to dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) to afford binaphthalenes (–)-**2.130** and (+)-**2.131** in good yield. The C-ring was then oxidized with DDQ and the resultant quinone was treated with anhydrous HCl to furnish nonacycle (–)-**2.133** and (+)-**2.134** via biomimetic formation of the C8'–C13' ether bridge. This transformation presumably occured via intramolecular attack of the proximal acetonide oxygen atom on the *ortho*-quinone methide of intermediate **2.132** with concomitant acetonide cleavage. Finally, Brian was able to complete the total synthesis of **2.2** and **2.135** through a three step sequence involving: (1) deprotection of the acid-labile protecting groups with HF, (2) hydrogenolysis of the benzyl groups, and (3) exposure to air to promote oxidation of the D-ring hydroquione. It was discovered that addition of acidic methanol to the reaction mixture prior to aerobic oxidation was critical to suppress isomerization between **2.2** and **2.135** and formation of HMP-P1 (**2.12**). In this way, we revealed that rotation of the molecule about the C2'–C2 bond is pH dependent.[143]

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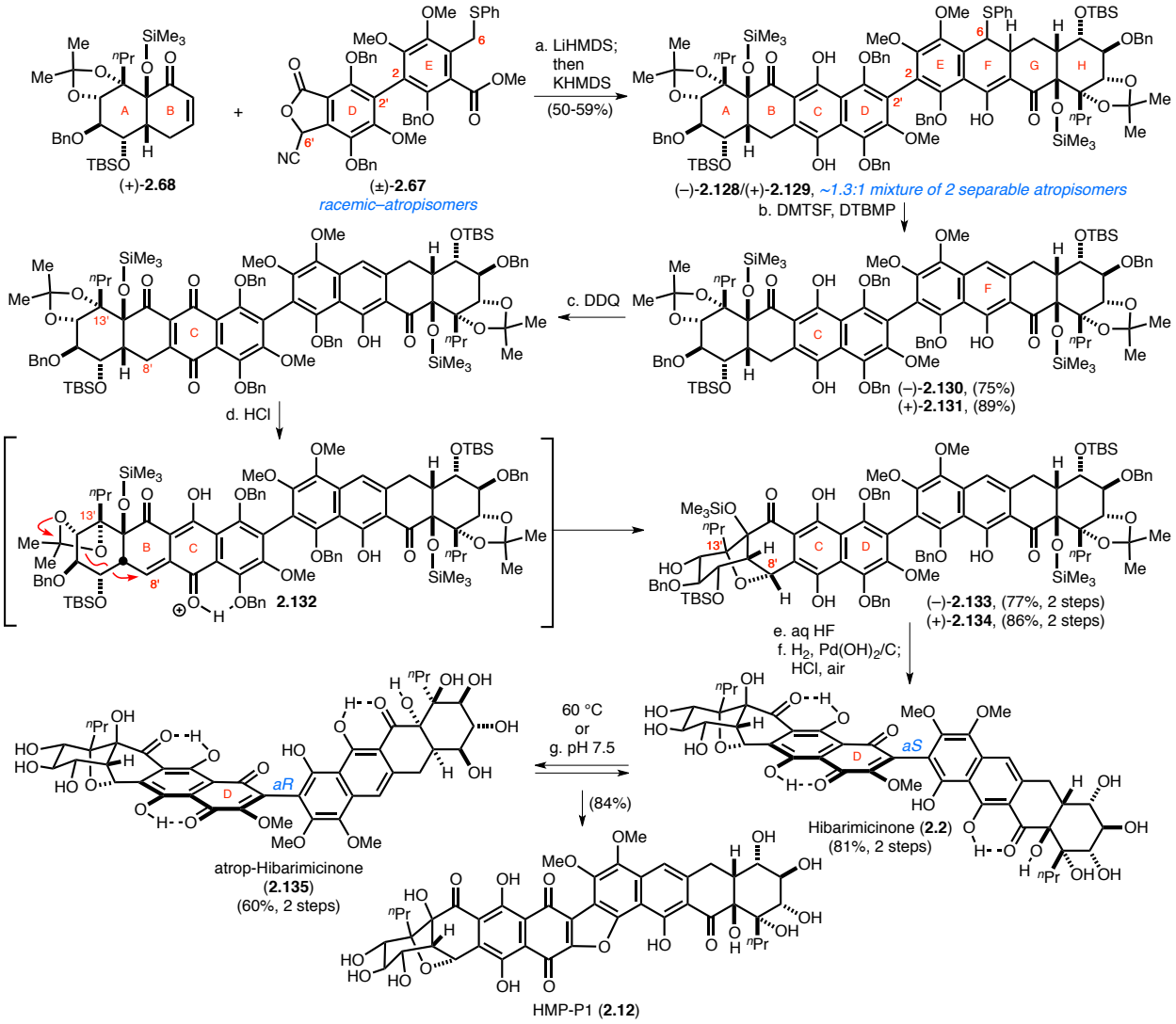
[142] Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *19*, 2263–2266.

[143] For additional information regaurding the pH dependence of atrop-isomerization, see: Ref. 141 and experimental section.

Scheme 2.20 Total synthesis of hibarimicinone and atrop-hibarmicinone.



Reagents and conditions: (a) LiHMDS, THF, –78 → 0 °C; then KHMDS, 0 °C → RT; for (–)-**1.128**, 34%; for (+)-**2.129**, 25%; (b) DMTSF, DTBMP, MeCN, 0 °C → RT; for (–)-**2.130**, 75%; for (+)-**2.131**, 89%; (c) for (–)-**2.130**: DDQ, PhMe, 0 °C; for (+)-**2.131**: DDQ, PhMe, 0 °C → RT; (d) HCl, $ClCH_2CH_2Cl$, 5 °C; for (–)-**2.133**, 77% (two steps); for (+)-**2.134**, 86% (two steps); (e) aq. HF, MeCN-THF; (f) H_2, $Pd(OH)_2$/C, EtOAc; then HCl, MeOH, air; for **2.2**, 81% (two steps); for **2.135**, 60% (two steps); (g) aq. pH 7.5 NaH_2PO_4-NaOH buffer, MeOH, RT; from **2.2**, 84%; from **2.135**, 84%.

Many aspects of the synthesis of **2.2** are anticipated to be important for completion of the total synthesis of **2.1**. Specifically, we expect **2.2** and **2.1** to share a common absolute stereochemistry for their

C2'–C2 axis. Therefore, chiral resolution of the DE-biaryl annulation donor (±)-**2.67** might allow us to improve the efficiency of the annulation step of the synthesis. Additionally, we anticipate that **2.1** will also exhibit pH-dependent atrop-isomerization. However, the use of acidic methanol in the synthesis of **2.1** to suppress atrop-isomerization will be incompatible with the 2-deoxyglycosidic linkages and will require the development of alternative reaction conditions.

2.8 2-Deoxyglycosides in Natural Product Total Synthesis

Many classes of biologically active molecules are conjugated to carbohydrates including: proteins, lipids, and secondary metabolites.[144] Within the secondary metabolite natural product class, glycol-conjugated subclasses include: glycopeptides, enediynes, anthracyclines, polyenes, macrolides, vitamins, alkaloids, steroids, terpenes, and polyphenols. A broad array of structural diversity within the carbohydrate subunit is also observed; prokaryotic organisms produce glycosylated natural products which exhibit over one hundred different sugars.[103,145] These sugars vary in terms of their oxidation level and functionalization. Secondary metabolite glycosides display a diversity of biological activities including: antibiotic,[146] antitumor[147], and ionotropic activity.[148] However, the role the glycosyl unit plays with respect to the molecule's activity widely differs. Certain biological targets are known to bind the overall molecular structure of the glycoside.[149] In other cases, the glycosyl unit simply improves the

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[144] (a) Kennedy, J. F.; White, C. A. In *Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*; Horwood, E., Ed.: Chichester, 1983. (b) Kirschning. A.; Bechthold, A. F. W.: Rohr, *J. Top. Curr. Chem.* **1997**, *188*, 1–84. (c) Ernst, B.; Hart, G. W.; Sinaý, P. *Carbohydrates in Chemistry and Biology*; Wiley-VCH: Weinheim, 2000. Thorson, J. S.; Hosted, T. J.; Jiang, J.; Biggins, J. B.; Ahlert, J. *Curr. Org. Chem.* **2001**, *5*, 139–167.

[145] Rale, M.; Schneider, S.; Sprenger, G. A.; Samland, A. K. Fessner, W.-D. *Chem. Eur. J.* **2011**, *17*, 2623–2632.

[146] Levine, D. P. *Clin Infect Dis.* **2006**, *42*, S5–S12.

[147] La Ferla, B.; Airoldi, C. Zona, C.; Orsato, A.; Cardona, F.; Merlo, S. Sironi, E. D'Orazio, G.; Nicotra, F. *Nat. Prod. Rep.* **2011**, *28*, 630–648.

[148] (a) Weymouth-Wilson A. C. *Nat Prod Rep.* **1997***, 14,* 99–110. V. Kren, L. Martinkova, *Curr. Med. Chem*. **2001**, *8*, 1303–1328.

[149] (a) Silva, D. J.; Kahne, D. E. *J. Am. Chem. Soc*. **1993**, *115*, 7962–7970. (b) Silva, D. J.: Goodnow, R.; Kahne, D. *Biochemistry* **1993**, *32*, 463–471. (c) Waller, G.R., Yamasaki, K. *Adv. Exp. Med. Biol.,* **1996**, *40,* 1–11.

pharmacokinetics of the molecule.[150] Additionally, it is interesting to note that glycoconjugation of several non-glycosylated therapeutics such as mitomycin,[151] colchicine,[152]and taxol[153] has improved their biological activity through enhanced target delivery.

2-Deoxyglycosides are of particular pharmacological importance. Figure 2.10 depicts the structures of several representative 2-deoxyglycosides. Vancomycin (**2.136**) is a glycopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria. **2.136** binds the D-alanyl-D-alanine terminus of mucopeptide precursors of bacterical cell walls, thus preventing their polymerization and cross-linking.[154] The dissacharide is believed to enhance the activity of **2.136** by anchoring to the cell membrane.[155] Calichaemicin γ_1 (**2.137**) is a highly toxic enedyine antibiotic known to bind to the minor groove of DNA with a high level of sequence specificity and cause double strand cleavage through H-atom abstraction.[156] The sequence specificity exhibited by **2.137** has been attributed to the oligosaccharide subunit.[157] Digtoxin (**2.138**) is a steroidal glycoside that has historically been used for the treatment of cardiac failure. **2.138** elicits a positive ionotropic effect on heart muscle cells through inhibition of the α-subunit of the Na^+/K^+-ATPase pump.[158] Interestingly, the trisaccharide portion of **2.138**

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[150] Thorson, J. S.; Vogt, T. In *Carbohydrate-Based Drug Discovery;* Wong, C. H., Ed.; Wiley-VCH: Weinheim, 2003.

[151] Ghiorghis, A.; Talebian, A.; Clarke, R. *Cancer Chemother. Pharmacol.* **1992**, *29*, 290–296.

[152] Ahmed, A.; Peters, N. R.; Fitzgerald, M. K.; Watson, J. A.; Hoffmann, F. M.; Thorson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 14224–14225.

[153] Liu, D.; Sinchaikeul, S.; Reddy, P. V. G.; Chang, M.; Chen, S. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 617–620.

[154] Hammes, W. P.; Neuhaus, F. C. *Antimicrob Agents Chemother.* **1974**, *6*, 722–728.

[155] Nicas, T. I.; Mullen, D. L.; Flokowitsch, J. E.; Preston, D. A.; Snyder, N. J.; Zweifel, M. J.; Wilkie, S. C.; Rodriquez, M. J.; Thompson, R. C.; Cooper, R. D. G. *Antimicrob. Agents Chemother.* **1996**, *40*, 2194–2199.

[156] Walker, S. L.; Andreotti, A. H.; Kahne, D.E. *Tetrahedron*, **1994**, *50*, 1351–1360.

[157] Drak, J.; Iwasawa, N.; Danishefsky, S.; Crothers, D.M. *Proc. Natl. Acad. Sci. USA*, **1991**, *88*, 7464–7468.

[158] (a) Fullerton, D. S.; Kihara, M.; Deffo, T.; Kitatsuji, E.; Ahmed, K.; Simat, B.; From, A. H. L.; Rohrer, D. C. *J. Med. Chem*., **1984**, *27*, 256–261. (b) Schmidt, T. A.; Kjeldsen, K. *Prog. Exp. Cardiol*. **2003**, *5*, 501–510. (c) Wasserstrom, J. A.; Aistrup, G. L. *Am. J. Physiol.* **2005**, *289*, H1781–H1793.

is believed to be important for uptake and distribution by impoving the molecule's aqueous solubility.[159] Erythromycin A (**2.139**) is a macrolide antibiotic generally administered for the treatment of various infections in patients with penicillin allergies. **2.139** and other macrolide antibiotics inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome, thereby blocking the exit of the growing peptide chain.[160] The overall molecular structure of the glycoside is important for protein target recognition.[161] Finally, landomycin (**2.140**) is a potent antitumor angucycline antibiotic. While the precise mechanism of action of **2.140** remains to be determined, it appears to be directly linked to the oligosaccharide component of the molecule.[162] The 2-deoxyglycoside natural products presented constitute only a small portion of known molecules with potential biological activity. For this reason, the synthesis of 2-deoxyglycoside natural products and their structural analogues is essential for the discovery of new biological targets with therapeutic activity.

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[159] (a) Wallick, E. T.; Pitts, B. J. R.; Lane, L. K.; Schwartz, A.; *Arch. Biochem. Biophys.,* **1980**, *202*, 442–449. (b) Williams, J. D.; A. M. Sefton. *J. Antimicrob. Chemother.* **1993**. *31*, 11–26. (c) Kanoh, S.; Rubin, B. K. *Clin. Microbiol. Rev.* **2010**, *23*, 590–615 and references therein.

[160] (a) Menninger, J. R.; Otto, D. P. *Antimicrob Agents Chemother*. **1982**, *21*, 811–818. (b) Abu-Gharbieh, E.; Vasina, V.; Poluzzi, E.; De Ponti, F. *Pharmacol. Res.* **2004**, *50*, 211–222.

[161] Tu, D.; Blaha, G.; Moore, P. B.; Steitz, T. A. *Cell*, **2005**, *121*, 257–270 and references therein.

[162] (a) Crow, R. T.; Rosenbaum, B.; Smith, R., III; Guo, Y.; Ramos, K. S.; Sulikowski, G. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1663–1666. (b) Korynevska, A.; Heffeter, P.; Matselyukh, B.; Elbling, L.; Micksche, M.; Stoika, R.; Berger, W. *Biochem. Pharmacol.* **2007**, *74*, 1713–1726.

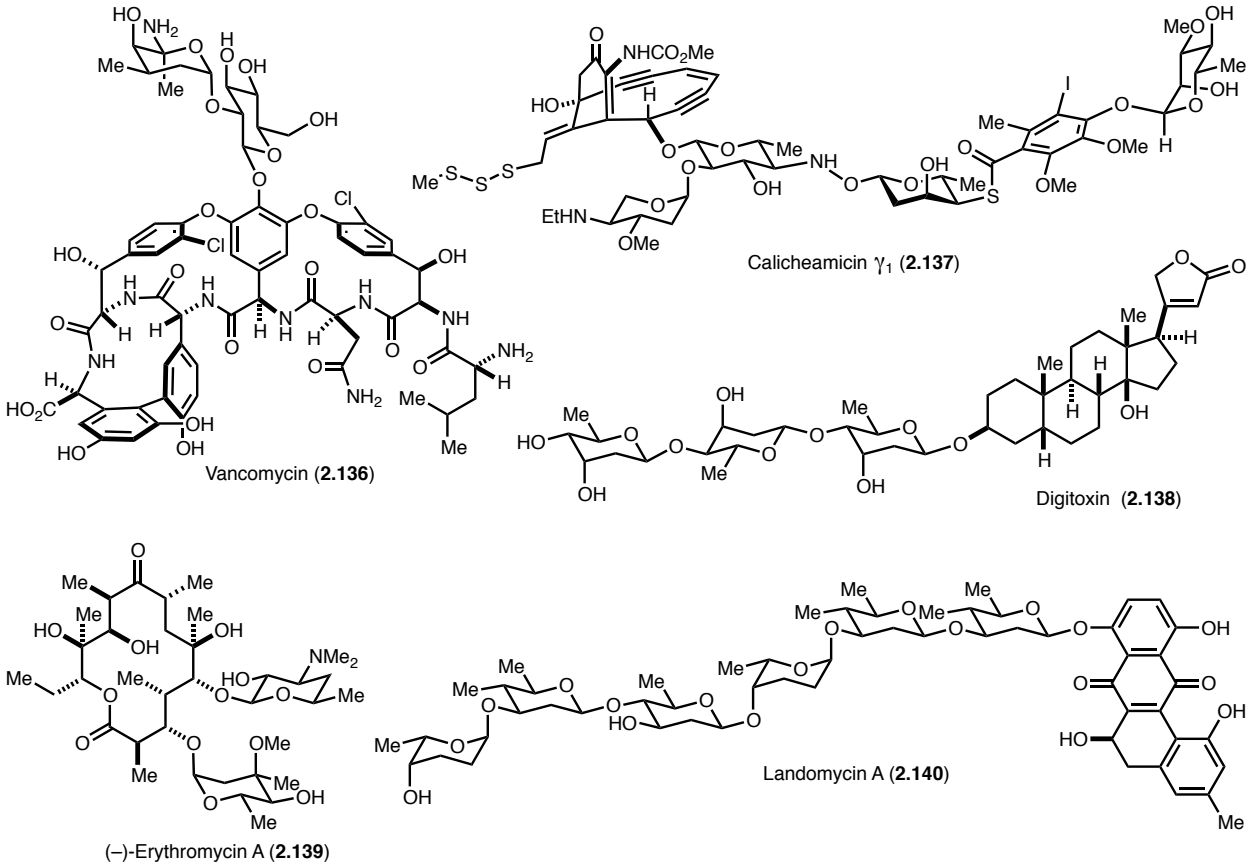

Figure 2.10 Representative biologically important 2-deoxyglycoside natural products.

The efficient, stereocontrolled formation of 2-deoxyglycosides presents two fundamental synthesis challenges. First, in the absences of a C2 oxygen substituent, which provides stereocontrol through anchimeric assistance, glycosylation often leads to an anomeric mixture. Second, 2-deoxyglycosidic bonds are easily hydrolyzed under acidic conditions as a result of the absence of a C2 electron-withdrawing oxygen substituent.[163] Numerous methods have been developed to overcome these obstacles and have been thoroughly reviewed on multiple occasions.[164] The six conceptually distinct,

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[163] Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429–3440.

[164] (a) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285–333. (b) Schmidt, R. R. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Winterfeld, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6; pp 33–64. (c) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9,* 103–137. (d) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93,* 1503–1531. (e) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50,* 21–123. (f) Danishefsky, S. J. in *Modern Methods in Carbohydrate Synthesis*; Khan, H.; O'Neill, R.A. Eds.; Harwood Academic Publishers: Amsterdam, 1996; pp 171–193. (g) Kirschning, A.; Rohr, J.; Bechthold, A. *Top. Curr. Chem.* **1997**, *188*, 1–84. (h) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385–8417. (i) Pellissier, H. *Tetrahedron* **2005**, *61,* 2947–2993. (j)

primary strategies for the synthesis of 2-deoxy-β-glycosidic bonds are depicted in Figure 2.11 and include: (1) direct substitution of a C1 leaving group (Lg) activated by an electrophilic reagent, (2) use of a removable C2 directing group capable of participating in anchimeric assistance, (3) activation of a glycal precursor with an electrophilic reagent (generally this occurs through the in situ incorporation of a removable C2 directing group), (4) use of an axial C3 directing group capable of participating in anchimeric assistance, (5) application of structural constraints, and (6) the de-novo synthesis of the 2-deoxyglycoside following formation of the β-glycosidic bond.

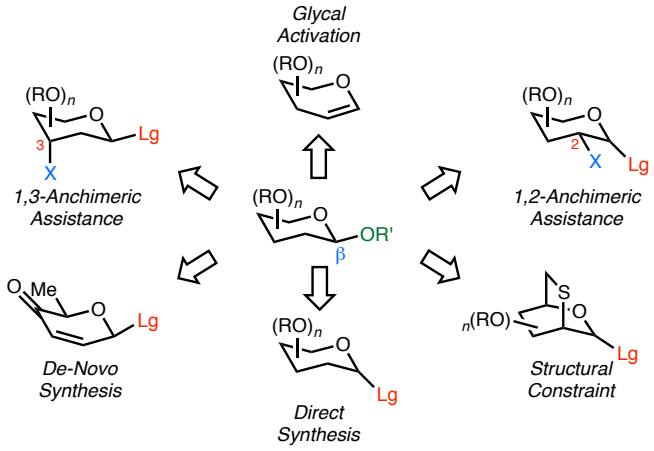

Figure 2.11 General strategies for the synthesis of 2-deoxy-β-glycosides.

The five common stratagies for the stereocontrolled construction of 2-deoxy-α-glycosides delineated in Figure 2.12 are similar to those utilized for the synthesis of 2-deoxy-β-glycosides. While the formation of 2-deoxy-α-glycosidic bonds through the direct substitution of a leaving group is generally considered to be favorable, the reasons for this stereochemical outcome are disputed.[165] Application of most of these strategies for the stereoselective formation of α- and β-linked 2-deoxyglycosides in the context of natural product total synthesis have been reported. A brief description of a selection of these examples will help the reader choose an approach that best suits his or her needs.

Toshima, K. *Carbohydr. Res.* **2006**, *341*, 1282–1297. (k) Gin, D. Y.; Galonić, D. P. *Nature* **2007**, *446*, 1000–1007. (l) Zhu, X.; Schmidt, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934. (m) Hou, D.; Lowary T. L. *Carbohydr. Res.* **2009**, *344*, 1911–1940.

[165] (a) Cumpstey, I. *Org. Biomol. Chem.,* **2012**, *10*, 2503–2508 and references therein. (b) Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107–1118.

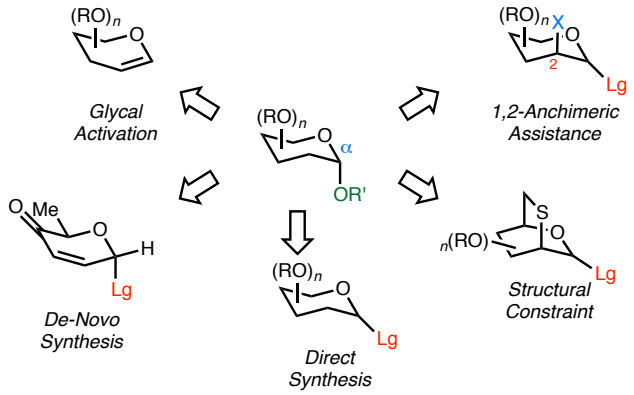

Figure 2.12 General strategies for the synthesis of 2-deoxy-α-glycosides.

2.8.A Direct Synthesis of 2-Deoxyglycosides

An acetal exchange process for the direct synthesis of 2-deoxyglycosides is outlined in Figure 2.13a. In this strategy, a suitably protected carbohydrate glycosyl donor **2.141** possessing a C1 leaving group is activated by an electrophilic reagent (El^+) to undergo C–O bond formation with a nucleophilic coupling partner (glycosyl acceptor, R'OH) though an S_N1 or S_N2 pathway. This procedure allows for the potential formation of both α- and β-glycosides, **2.142** and **2.143**, respectively, depending on the mechanism through which the reaction proceeds. Many factors influence this mechanistic selection, including: (1) the type of leaving group used, (2) the type of electrophilc reagent used, (3) the conditions under which the reaction is conducted (e.g. solvent, temperature, etc.), (4) the substitution pattern of the glycosyl donor, (5) the protecting groups on the glycosyl donor, and (6) the nucleophilicity of the glycosyl acceptor. For this reason, the reliability and predictability of stereoselection for this strategy is highly variable. Figure 2.13b illustrates a variety of leaving groups and electrophilic promotors that have been used for this transformation. The application of this strategy in natural product total synthesis has been reported on numerous occasions.

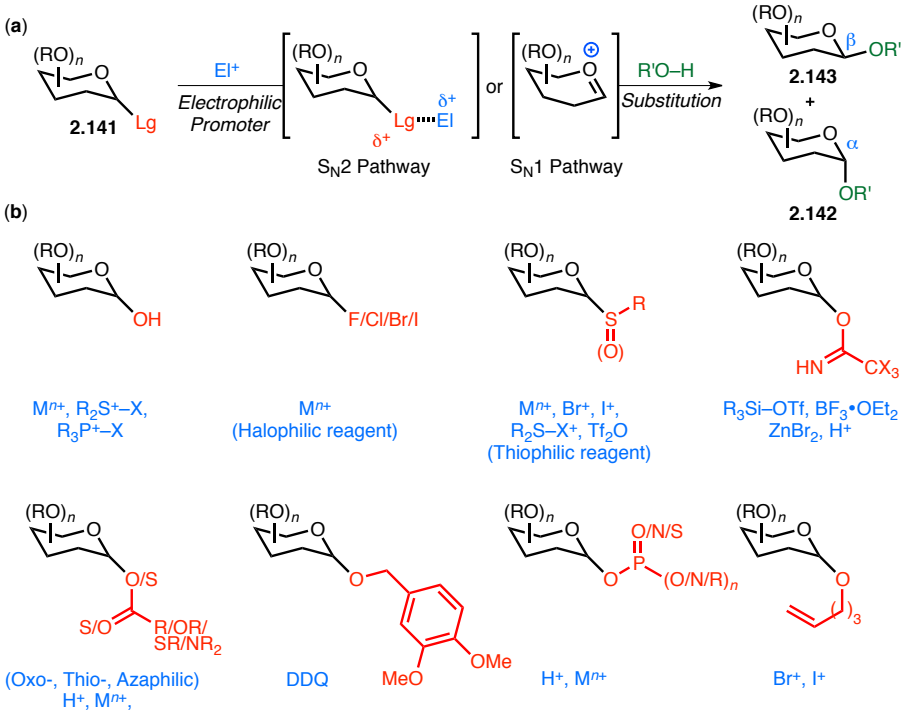

Figure 2.13 (a) Direct glycoslyation of 2-deoxyglycosyl donors. (b) Leaving groups (Lg, red) and electrophilic promotors (El^+, blue) for direct glycosylation.[166]

During the course of synthesizing analogs of the anticancer agent mithramycin,[167] Binkley observed that treatment of α-bromo glycosyl donor **2.144** and glycosyl acceptor **2.145** with silver silicate (standard Koenigs and Knorr conditions) [168] afforded 2-deoxy-β-glycoside **2.147** with high anomeric selectivity (Scheme 2.21). Presumably, insoluble silver in this reaction activated the bromide for direct substitution by **2.145** with inversion of configuration at C1 through an S_N2 pathway (**2.146**). Interestingly, it was previously reported by Van Boeckel and Beetz that the type of protecting group used under these conditions greatly influenced the anomeric selecitivity of the transformation.[169]

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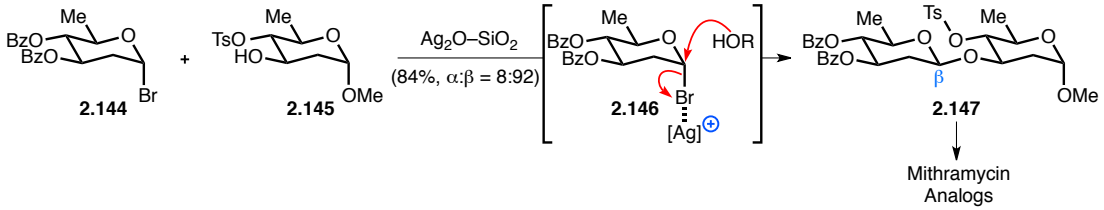
[166] Figure 2.13 is a modified version of a figure found in Ref. 164k.

[167] Binkley, R. W.; Koholic, D. J. *J. Org. Chem*. **1989**, *54*, 3577–3581.

[168] Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957–981.

[169] Van Boeckel, C. A.; Beetz, T.; van Aelst, S. F. *Tetrahedron* **1984**, *40*, 4097–4107.

Scheme 2.21 Koenigs and Knorr synthesis of 2-deoxy-β-glycosides.



Reagents and conditions: Ag_2O-SiO_2, PhMe, 84%, α:β = 8:92.

Evans and coworkers reported an intriguing example of an acid catalyzed β-selective formation of a 2-deoxyglycosidic bond during their synthesis of the macrolide antibiotic cytovaricin (**2.152**, Scheme 2.22). They discovered that addition of catalytic trityl perchlorate to a solution of hydroxy amide **2.148** and glycosyl acetate **2.149** in PhMe at –20 °C resulted in the formation of a 1:3 distribution of glycosides favoring the α-anomer **2.151**. However, warming the reaction mixture to –3 °C resulted in equilibration of the glycosidic linkage to favor the β-anomer **2.150**. The α-anomer was recycled through repetition of this process to provide a 70% yield of **2.150**. Evans and coworkers later confirmed that the reaction was catalyzed by perchloric acid. This example illustrates the highly acid-labile nature of the 2-deoxyglycosidic linkage and is an interesting case of β-anomeric selectivity under thermodynamic control; generally, the α-anomer is favored by the anomeric effect under thermodynamic control.[170,171]

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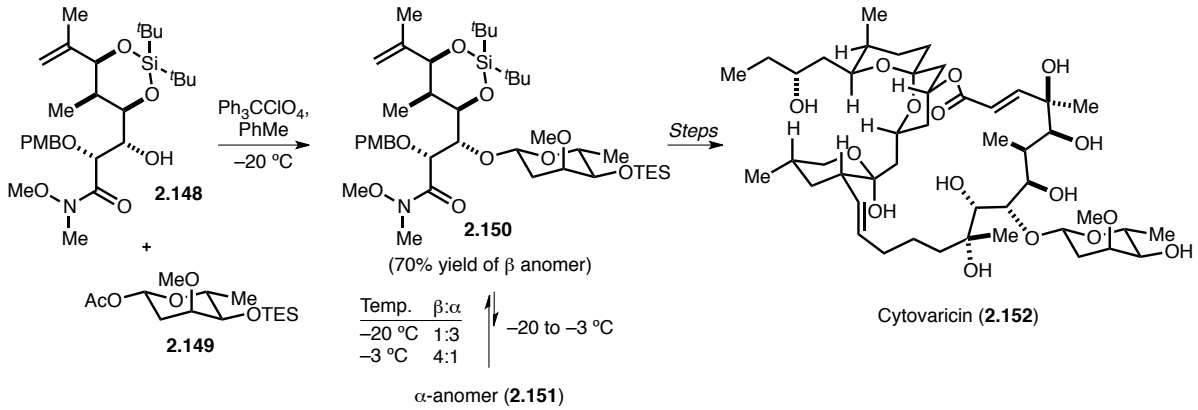
[170] Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983.

[171] The β-anomer in this particular example is likely favored due to a 1,3-diaxial interaction with the C3–OMe substituent in the α-anomer.

Scheme 2.22 Reversible formation of 2-deoxy-β-glycosides.

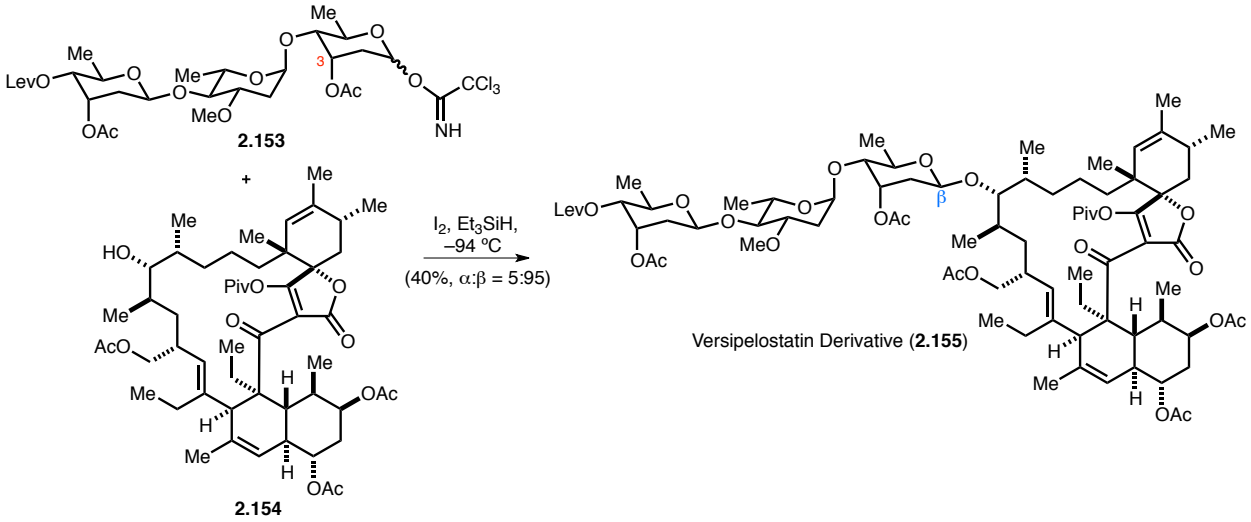


More recently, Takahashi and coworkers have developed a highly β-selective method for the direct synthesis of 2-deoxyglycosides.[172] During their synthesis and structural reassignment of versipelostatin, a cold solution of aglycon **2.154** and trichloroacetimidate glycosyl donor **2.153** in PhMe was treated with iodine and triethylsilane to afford 2-deoxy-β-glycoside **2.155** in 40% yield (Scheme 2.23). The reaction conditions used in this transformation appear to be generally useful for 2-deoxy-β-glycoside synthesis irrespective of the substitution pattern of the glycosyl donor.[173] However, the mechanism and rational for high β-selectivity has not been determined.

[172] Tanaka, H.; Yoshizawa, A.; Chijiwa, S.; Ueda, J.-y.; Takagi, M.; Shin-ya, K.; Takahashi, T. *Chem. Asian J.* **2009**, *4*, 1114–1125.

[173] Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem., Int. Ed*. **2007**, *46*, 2505 –2507.

Scheme 2.23 Takahashi's method for direct stereoselective synthesis of 2-deoxy-β-glycosides.



Reagents and conditions: I_2, Et_3SiH, 4 Å MS, PhMe, –94 °C, 40%, α:β = 5:95.

Kahne and Raghavan reported an impressive one-step synthesis of the ciclamycin trisaccharide (**2.160**, Scheme 2.24) that takes advantage of the differential reactivity of aryl sulfoxide glycosyl donors.[174] Previous studies had shown that *p*-methoxyphenyl sulfoxide donors underwent glycosylation faster than their unsubstituted phenyl sulfoxide counterparts. Addition of TfOH to a solution of phenyl sulfoxide **2.156**, *p*-methoxyphenyl sulfoxide **2.157**, and phenyl sulfide **2.158** promoted initial α-selective glycosidic bond formation between **2.157** and **2.158** with concominant trimethylsilyl cleavage to yield dissacharide glycosyl acceptor **2.159**. A slower second α-selective glycosylation then took place with **2.156** to deliver thiophenyl trisaccharide **2.160** in 25% overall yield.[175] Notably, no other products containing a β-glycosidic linkage were detected. This example demonstrates the inherent propensity of 2-deoxyglycosyl donors of the L-olivose substitution pattern to undergo α-selective glycosylation ostensibly through pseudo-axial attack on the half-chair oxocarbenium intermediate **2.162**.

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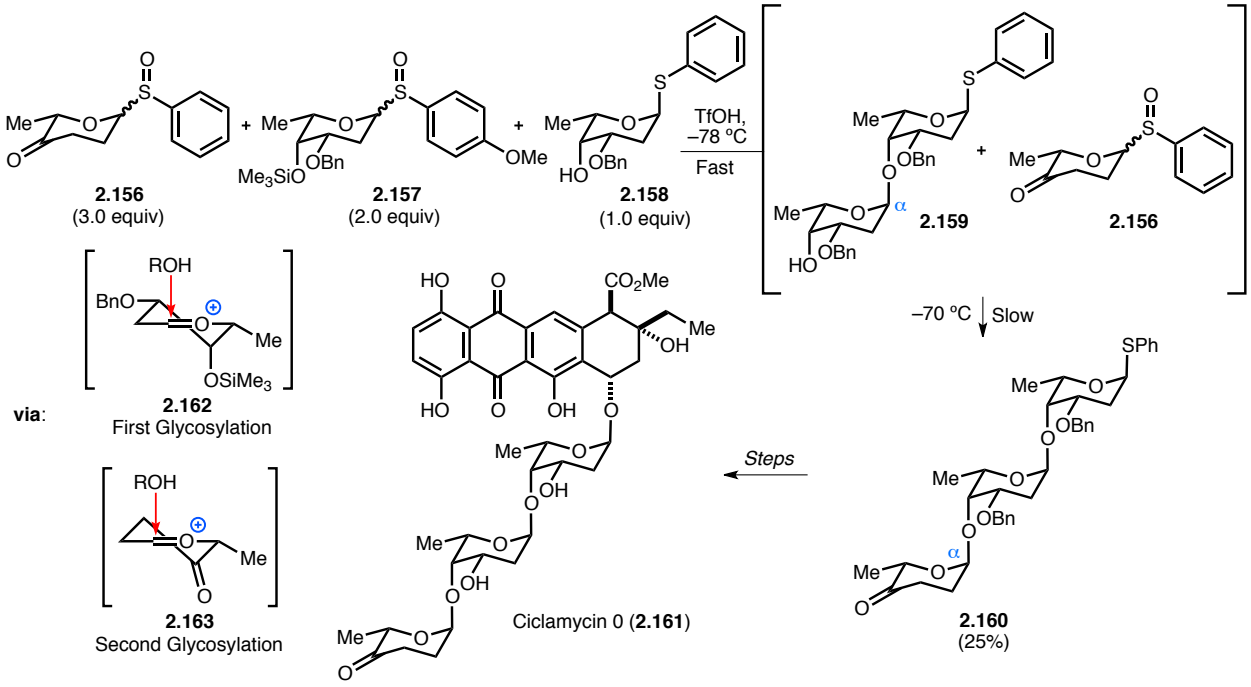
[174] (a) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580–1581. (b) Gildersleeve, J.; Smith, A.; Sakurai, K., Raghavan, S.; Kahne, D. *J. Am. Chem. Soc*. **1999**, *121*, 6176–6182.

[175] Optimization of this process was reported in a subsequent publication: Ref. 165b.

Scheme 2.24 Iterative α-selective 2-deoxyglycoside formation using anomeric phenyl sulphoxide glycosyl donors.

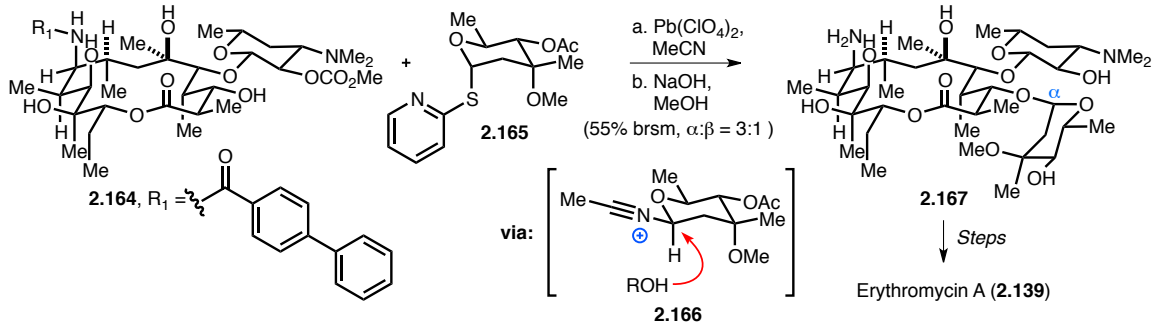


Reagents and conditions: Et_2O-CH_2Cl_2 (1:1), methyl propiolate, TfOH, –78 → –70 °C, 25%.

Woodward and coworkers reported the first total synthesis of erythromycin A (**2.139**) in 1981.[176] Their synthesis utilized a late-stage solvent dependent α-selective glycosylation reaction to install the L-cladinosyl monosaccharide (Scheme 2.25). They discovered that treatment of a solution of L-cladinoside thiopyridine glycosyl donor **2.165** and protected aglycon **2.164** in acetonitrile with $Pb(ClO_4)_2$ facilitated α-selective formation of 2-deoxyglycoside **2.167** in 55% yield (based on consumed **2.164**) after NaOMe mediated protecting group removal. The anomeric selectivity of this process was attributed to participation of the solvent (i.e. MeCN), which promoted a double inversion process via intermediate **2.166**.

[176] Woodward, R. B.; *et. al. J. Am. Chem. Soc.* **1981**, *103*, 3215–3217.

Scheme 2.25 Solvent controlled α-selective formation of 2-deoxyglycosides via an acetal exchange strategy in the synthesis of erythromycin A.



Myers and coworkers utilized two interesting α-selective glycosylation reactions in their total synthesis and structural revision of the kedarcidin chromophore (Scheme 2.26).[177] A variety of different glycosyl donors (e.g. trichloroacetimidate, thiophenyl, acetate, and fluoride) were investigated for the synthesis 2-deoxy-α-glycoside intermediate **2.170** (Scheme 2.26a). Eventually, fluoro glycoside **2.168** was found to be the most effective donor. Treatment of alcohol **2.169** and fluoride **2.168** with Cp_2HfCl_2-$AgClO_4$, according to Suzuki's protocol,[178] afforded 2-deoxy-α-glycoside **2.170** in 74% yield with 4:1 α/β selectivity. The stereochemical origin for α-anomeric selectivity in this transformation is likely due to substrate control via pseudo-axial attack by **2.169** on a half-chair oxocarbenium intermediate **2.171** or attack on ammonium intermediate **2.172**. Next, completion of kedarcidin was accomplished though a second α-selective glycosylation using Hirama's method (Scheme 2.26b).[179] Accordingly, $AgPF_6$ was added to a solution of thioglycosyl donor **2.174**, aglycon **2.173**, and 2,6-di-tert-butyl-4-methylpyridine (DTBMP) at 0 °C to give 2-deoxy-α-glycoside **2.175** in 50% yield. Hirama's protocol seems to be highly α-selective over a broad range of 2-deoxyglycosyl donors and acceptors and relies on the use of a PF_6 counterion for silver to obtain high α-selectivity.

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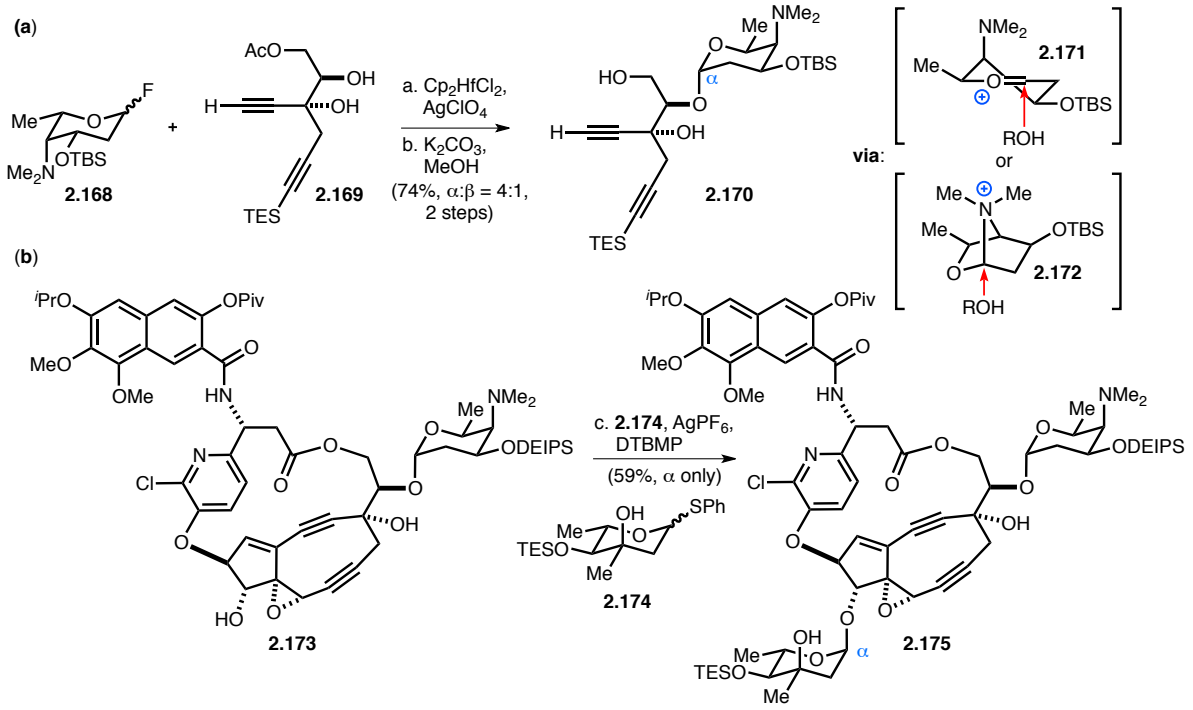
[177] (a) Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *Org. Lett*. **2007**, *9*, 1923–1925. (b) Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381. (c) Ren, F. Ph.D. Thesis, Harvard University, 2007 and references therein.

[178] (a) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29,* 3567–3570. (b) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29,* 3571–3574.

[179] Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed*. **2001**, *40*, 946–946.

Scheme 2.26 α-Selective formation of 2-deoxyglycosides using an acetal exchange strategy in the synthesis of the kedarcidin chromophore.



Reagents and conditions: (a) Cp_2HfCl_2, $AgClO_4$, CH_2Cl_2, 0 °C; (b) K_2CO_3, MeOH, 74%, α:β = 4:1 (two steps); (c) **2.174**, $AgPF_6$, DTBMP, CH_2Cl_2, 0 °C; Py, 59%.

2.8.B Synthesis of 2-Deoxyglycosides Through Electrophilic Glycal Activation

Glycals have served as competent glycosyl donors for the stereoselective synthesis of 2-deoxyglycosides since Lemieux first report glycal iodoglycosylation in 1964.[180] The general mechanism for this process is outlined in Figure 2.14. The first step involves activation of the glycal **2.176** by an electrophilic promotor to generate two potential reactive intermediates **2.177** and **2.178**. Next, nucleophilic attack on **2.177** and **2.178** by a glycosyl acceptor provides C2 substituted β- or α-glycoside **2.179** or **2.180**, respectively. When X ≠ H, the C2 substituent can be subsequently removed through C–X bond reduction. Overall, the anomeric selectivity induced by this strategy is governed by the facial selectivity of the initial electrophilic glycal activation step and is thus highly substrate specific.

[180] Lemieux, R. U.; Levine, S. *Can. J. Chem*. **1964**, *42*, 1473–1480.

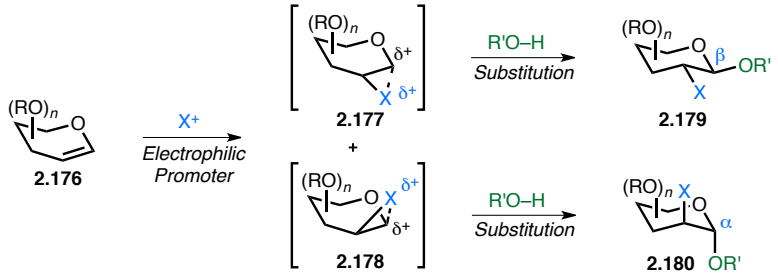


Figure 2.14 Synthesis of 2-deoxyglycosides through electrophilic glycal activation.

Figure 2.15 depicts a selection of known reagents for electrophilic glycal activation and the products they can form. Specifically, haloglycosylation of a glycal (**2.176**) with a reagent such as NIS or NBS generally provides 2-deoxy-α-glycosides after C2–X bond reduction. In contrast, glycosylation using sulphur- or selenium-based reagents typically yields 2-deoxy-β-glycosides after C2–X bond reduction. Alternatively, glycals can be directly activated by an acid or metal catalyst in the presence of a glycosyl acceptor to yield either 2-deoxy-α-glycosides or 2-deoxy-β-glycosides. An interesting variation on electrophilic glycal activation is the allylic substitution of a glycal by glycosyl acceptor promoted by a Lewis acid or a metal catalyst, also known as a Ferrier reaction.[181] The anomeric selectivity in this process is generally controlled by the stereochemistry of the C3 leaving group and has been primarily used to prepare 2-deoxy-α-glycosides after olefin hydrogenation. Overall, the facial selectivity for electrophilic glycal activation is based on a combination of reagent and substrate control.

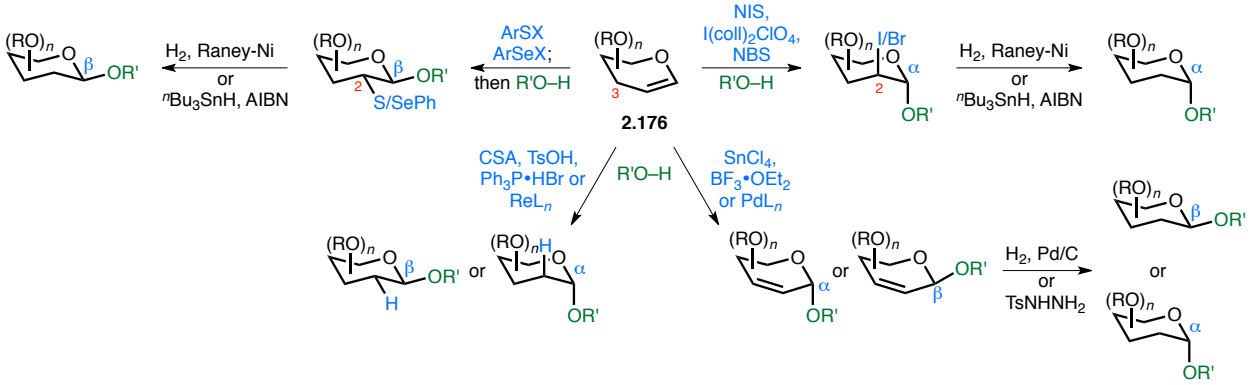


Figure 2.15 Methods for electrophilic glycal activation.

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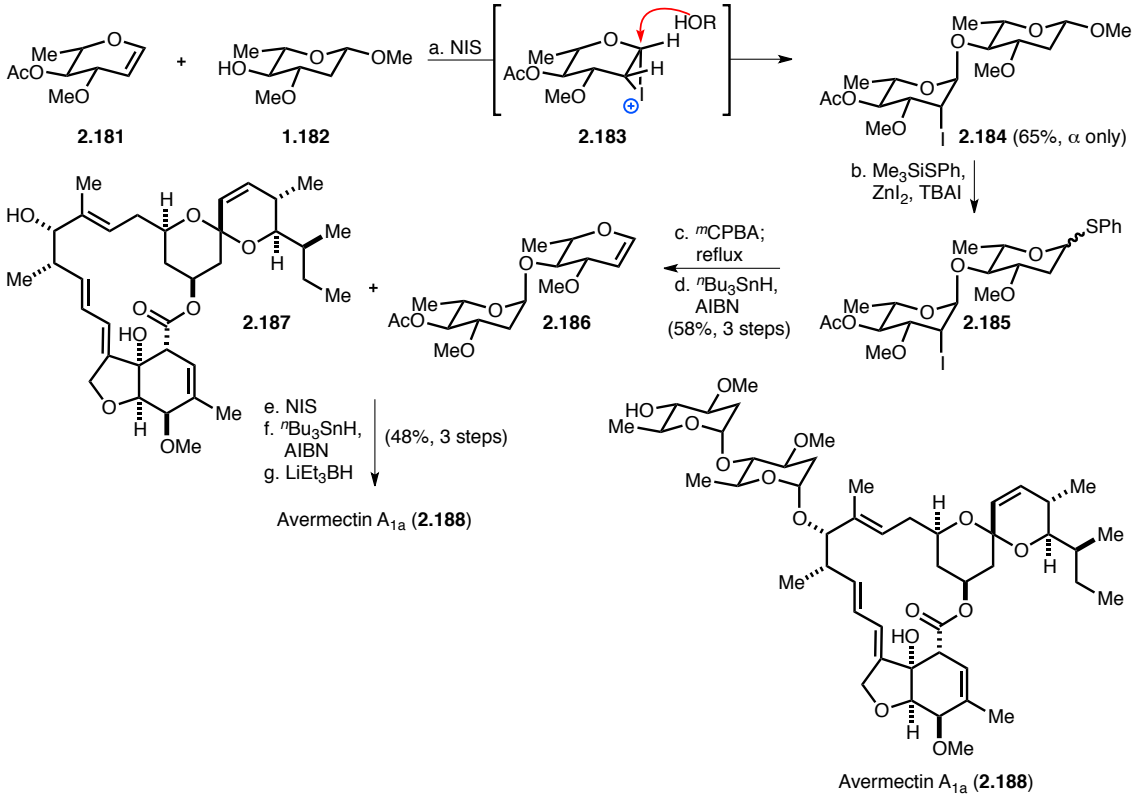
[181] (a) Ferrier, R. J. *J. Chem. Soc. Perkin Trans 1,* **1979**, 1455–1458. (b) Ferrier, R. J.; Zubkov, O. A. *Org. React.* **2003**, *62*, 569–736.

Danishefsky and coworkers have utilized glycal iodoglycosylation extensively for the synthesis of 2-deoxy-α-glycoside natural products as part of broader research program aimed at the assembly of oligosaccharides and glycoconjugates.[182] An example of this strategy can be found in their synthesis of avermectin A_{1a} (**2.188**, Scheme 2.27), which utilized an iterative glycal iodoglycosylation sequence.[183] Exposure of glycal **2.181** and methyl glycoside **2.182** to NIS promoted iodoglycosylation ostensibly through *trans*-diaxial attack of **2.182** on iodonium interemediate **2.183** to afford 2-iodo-α-glycoside **2.184** in 65% yield as a single stereoisomer. Exposure of methyl glycoside **2.184** to Me_3SiSPh, ZnI_2 and TBAI provided thioglycoside **2.185**. Notably, the C2–I substituent is believed to prevent cleavage of the α-glycosidic linkage under these conditions. Next, glycal **2.186** was obtained through thiophenyl oxidation, sulfoxide elimination, and C–I bond reduction with $^{n}Bu_3SnH$. Finally, a second NIS mediated iodoglycoylation reaction between avermectin A_{1a} aglycon **2.187** and **2.186** followed by C–I bond reduction and deprotection yielded avermectin A_{1a} (**2.188**) as a single anomeric stereoisomer.

[182] Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed*. **1996**, *35*, 1380–1419.

[183] (a) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc*. **1987**, *109*, 8119–8120. (b) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G. *J. Am. Chem. Soc.* **1989**, *111*, 2961–2980.

Scheme 2.27 An iterative glycal iodoglycosylation strategy for the synthesis of 2-deoxy-α-glycosides.



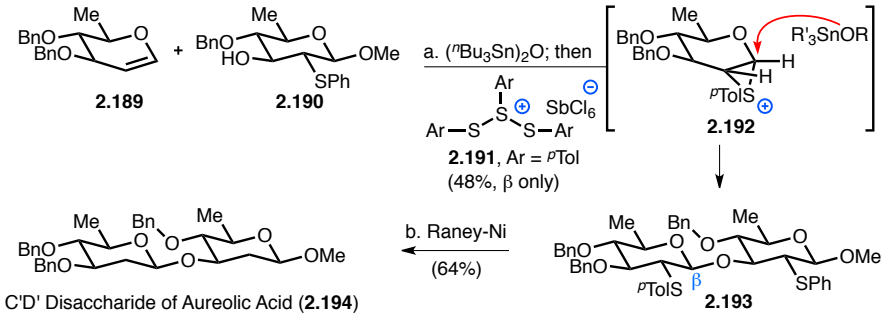
Reagents and conditions: (a) NIS, MeCN, 0 °C, 65%; (b) Me_3SiSPh, ZnI_2, TBAI, CH_2Cl_2, reflux; (c) ^{m}CPBA, CH_2Cl_2, 0 °C, 72% (two steps); (d) $^{n}Bu_3SnH$, AIBN, PhH, reflux, 81%; (e) NIS, MeCN, 64%; (f) $^{n}Bu_3SnH$, AIBN, PhMe, reflux, 78%; (g) $LiEt_3BH$, THF, –78 °C, 97%.

In pursuit of a total synthesis of aureolic acid, Franck and coworkers reported a method for β-selective 2-deoxyglycoside synthesis through electrophilic glycal activation with an arylbis(arylthio)sulfonium salt (**2.191**, Scheme 2.28).[184] This method required an increase in the nucleophilicity of the glycosyl acceptor through conversion to the corresponding tin alkoxide. Accordingly, the tin alkoxide of methyl glycoside **2.190** was prepared by refluxing with $(^{n}Bu_3Sn)_2O$ in PhH for 12 h. A solution of the resultant tin alkoxide and glycal **2.189** in CH_2Cl_2 was cooled to –60 °C before arylbis(arylthio)sulfonium reagent **2.191** was added to the reaction mixture leading to the formation of 2-thioaryl-β-glycoside **2.193** in 48% yield. The β-anomer was presumably favored by attack

[184] Franck, R. W.; Kaila, N.; *Carbohydrate Research*, **1993**, *239*, 71–83.

on episulphonium ion intermediate **2.192**. Finally, the C2–SAr substituent was reductively excised with Raney-Ni to furnish 2-deoxy-β-glycoside **2.194**. Not suprisingly, the stereoselectively of this method was found to be highly variable depending on the substitution pattern of the glycal.[185]

Scheme 2.28 Synthesis of 2-deoxy-β-glycosides via electrophilic glycal activation.



Reagents and conditions: (a) **2.190**, $(^{n}Bu_3Sn)_2O$, PhH, 4 Å MS, reflux; **2.189**, CH_2Cl_2, –60 °C; **2.291**, 48%. (b) Raney-Ni, THF, 64%.

In the course of a formal synthesis of C_2-symmetric macrolide elaiophylin (**2.199**),[186] Wakamatsu and coworkers utilized an acid catalyzed glycal activation strategy for the synthesis of an intermediate 2-deoxy-α-glycoside **2.198** (Scheme 2.29). Treatment of silyl protected glycal **2.195** and glycosyl acceptor **2.196** with CSA afforded 2-deoxy-α-glycoside **2.198** as a single stereoisomer in 57% yield. The α-selective nature of this transformation was likely a result of kinetically favored pseudo-axial attack by **2.196** on oxocarbenium ion intermediate **2.197**. However, it was not reported whether glycosidic bond formation in this reaction was reversible; therefore, the anomeric product distribution might simply have been a result of a thermodynamic preference for the α-anomer based on the anomeric effect.

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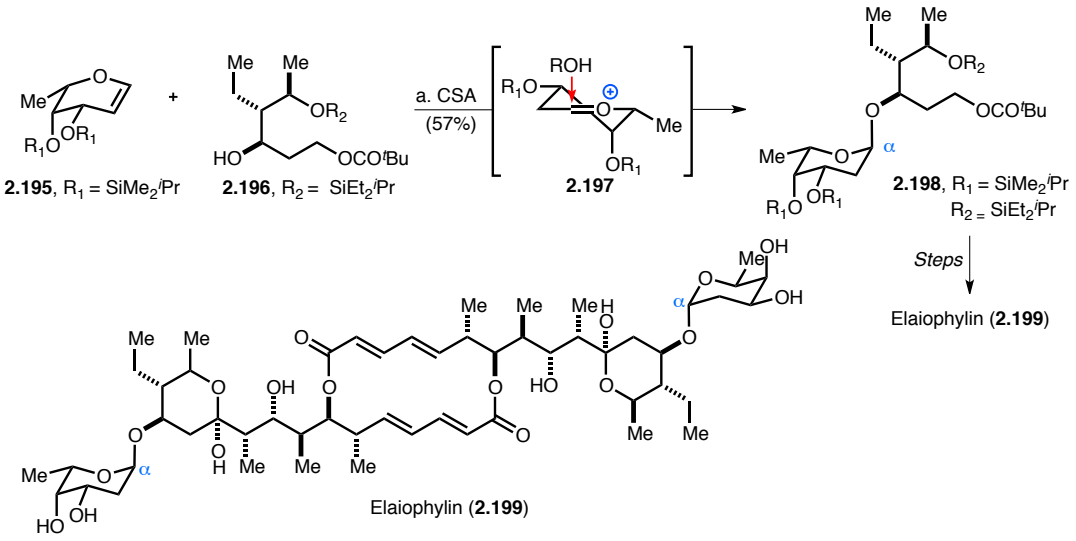
[185] (a) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem*. **1990**, *55*, 5–7. (b) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem*. **1992**, *57*, 2084–2092.

[186] (a) Wakamatsu, T.; Nakamura, H.; Naka, E. *Tetrahedron Lett.* **1986**, *27*, 3895–3898. (b) Nakamura, H.; Arata, K.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2435–2441.

Scheme 2.29 Direct synthesis of 2-deoxy-α-glycosides via acid-catalyzed glycal activation.



Reagents and conditions: (a) CSA, CH_2Cl_2, 57%.

2-deoxy-α-glycosides have also been directly accessed through an acid catalyzed electrophilic glycal activation strategy. As part of a research program directed toward the total synthesis of saccharomicin A (**2.204**) and B (**2.205**) (Scheme 2.30), the McDonald group developed an iterative tungsten-catalyzed cycloisomerization/acid-catalyzed glycosylation methodology for the synthesis of 2-deoxyoligosaccharides.[187] Exposure of glycal **2.200** and rhamanose glycosyl acceptor **2.201** to CSA in the presence of molecular sieves afforded the fucose-saccharosamine-rhamnose unit of saccharomicin B (**2.203**) in 90% yield as a single stereoisomer. The stereochemical outcome of this reaction is believed to be a result of neighboring group participation by the axial C3 carbamate group via bridged intermediate **2.202**. The α-face of intermediate **2.202** is shielded from nucleophilic attack, which concequently favors the formation of the 2-deoxy-β-glycoside **2.203**. Axial C3 ester substituents have also been known to induce β-selective 2-deoxyglycosyl bond formation through 1,3-anchimeric assistance (*vide infra*).[188]

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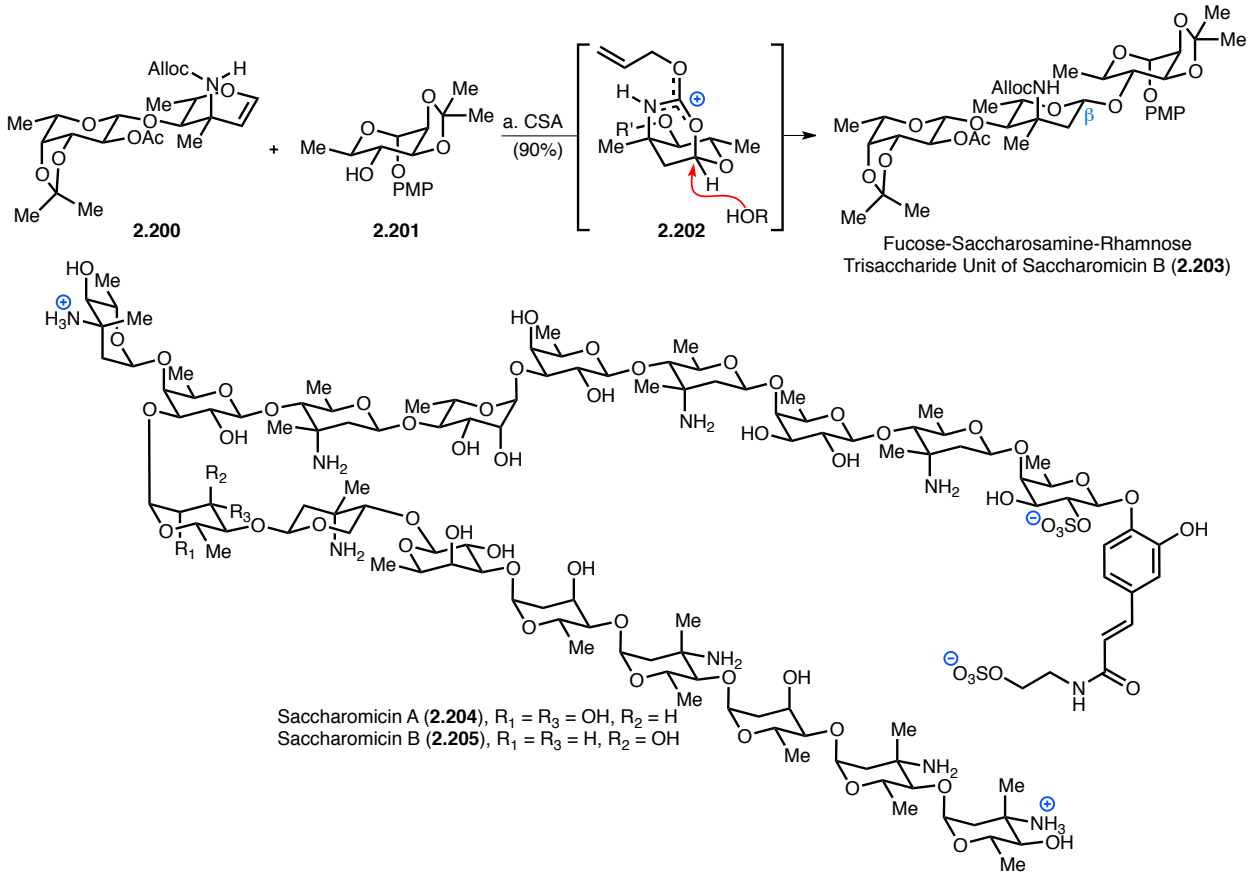
[187] (a) Balthaser, B. R.; McDonald, F. E. *Org. Lett.*, **2009**, *11*, 4850–4853. (b) Kong, F.; Zhao, N.; Siegel, M. M.; Janota, K.; Ashcroft, J. S.; Koehn, F. E.; Borders, D. B.; Carter, G. T. *J. Am. Chem. Soc.* **1998**, *120*, 13301–13311.

[188] (a) Tsai, T. Y. R.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403–1405. (b) Wiesner, K.; Tsai, T. Y. R. Jin, H. *Helv. Chim. Acta* **1985**, *68,* 300–314. (c) Binkley, R.W.; Koholic, D. J. *J. Carbohydr. Chem.* **1988**, *21*, 487–499. (d) Thiem, J.; Kopper, S. *Tetrahedron* **1990**, *46*, 113–138. (e) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem.*

Scheme 2.30 Direct synthesis of 2-deoxy-β-glycosides via acid-catalyzed glycal activation.



Reagents and conditions: (a) CSA, 3 Å MS, PhMe, 90%.

Koert and coworkers utilized a Ferrier reaction of a glycal to synthesize the challenging 2,3-dideoxy-β-glycosidic linkage of their revised structure of the antibacterial agent fulicineroside (**2.212**) (Scheme 2.31)[189] Exposure of glycal **2.206** and glycosyl acceptor **2.207** to $Pd(OAc)_2$, $ZnEt_2$, and DTBBP provided β-glycoside **2.209** in 86% yield as a single anomer through allylic displacement of the C3–OAc. Presumably, the stereochemical outcome of this reaction can be attributed to nucleophilic attack by the

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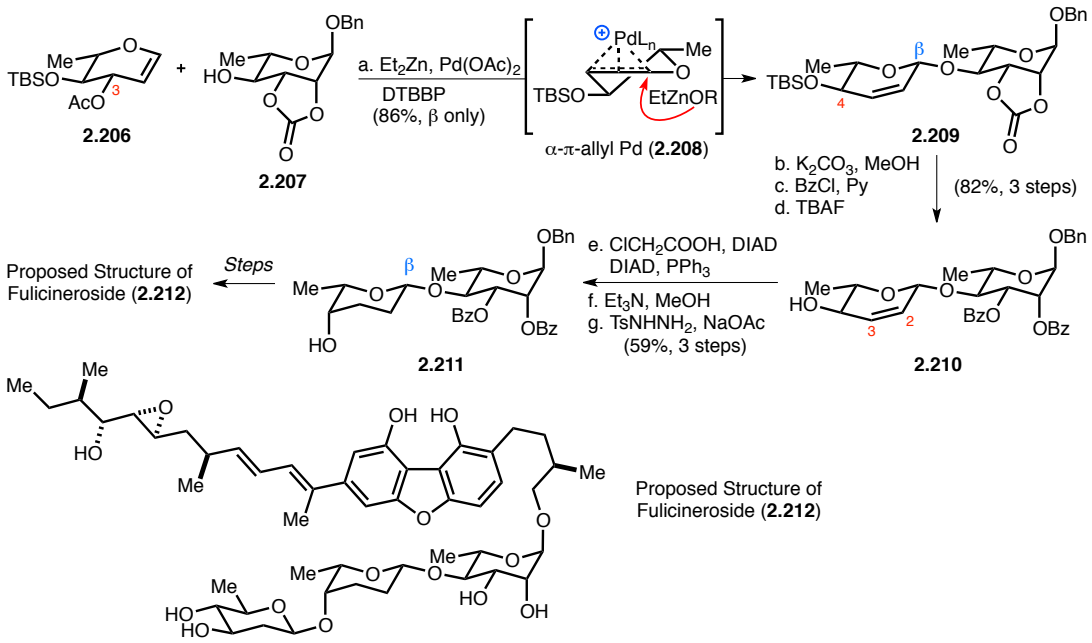
Soc. **2006**, *128,* 6931–6937. (f) Baek, J. Y.; Lee, B.-Y.; Jo, M. G.; Kim, K. S. *J. Am. Chem. Soc*. **2009**, *131,* 17705–17713.

[189] Bartholomäus, R.; Dommershausen, F.; Thiele, M.; Karanjule, N. S.; Harms, K.; Koert, U. *Chem. Eur. J.* **2013**, *19*, 7423–7436.

glycosyl acceptor on π-allyl palladium interemediate **2.208**.[190] The Zn^{2+} ion in this transformation is believed to serve both to activate the acetate group for allylic substitution and activate the glycosyl acceptor through the in situ formation of the corresponding zinc alkoxide.[191] Unfortunately, the Ferrier reaction required equatorial orientation of the C4 silyloxy substituent in **2.206**; therefore, a Mitsunobu inversion process was necessary. After C4 inversion, 2,3-dideoxy-β-glycoside **2.211** was accessed via diimide reduction of the C2–C3 olefin.

Scheme 2.31 Synthesis of 2-deoxy-β-glycosides via transition-metal catalyzed Ferrier reaction.



Reagents and conditions: (a) $Pd(OAc)_2$, DTBBP, $ZnEt_2$, 3 Å MS, THF, 86%; (b) K_2CO_3, MeOH, 92%. (c) BzCl, Py, CH_2Cl_2, 96%; (d) TBAF, THF, 93%; (e) $ClCH_2COOH$, PPh_3, DIAD, THF, 0 °C → RT; (f) Et_3N, MeOH, 65% (two steps); (g) $TsNHNH_2$, NaOAc, DME, 90%.

2.8.C Synthesis of 2-Deoxyglycosides Using a Preinstalled C2 Directing Group

The utilization of a preinstalled C2 directing group as a stereocontrolling element for the synthesis of 2-deoxyglycosides has proven to be an extremely versatile and reliable strategy (Figure 2.16).

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[190] The use of a bulky DTBBP ligand generally results in a double inversion net retention mechanism for transition metal-catalyzed allylic alkylation reactions: Trost, B. M.; Van Vranken, F. L. *Chem. Rev*. **1996**, *96*, 395–422.

[191] Steinhuebel, D. P.; Fleming, J. J.: Du Bois, J. *Org. Lett*. **2002**, *4*, 293–295.

This method generally allows for the stereoselective formation of either α- or β-anomer depending on the orientation of the preinstalled C2 heteroatom directing group (equatorial gives β and axial gives α). Treatment of the appropriate glycosyl donor **2.213** or **2.218** with an electrophilic reagent promotes formation of oxocabenium ion intermediate **2.214** or **2.219**, respectively. The C2 heteroatom substituent is capable of stabilizing this high energy intermediate through neighboring group participation to generate intermediates **2.215** and **2.220**. In doing so, it controls the facial sense of nucleophilic substitution to give either β- or α-glycoside (**2.217** or **2.222**) after C2–X bond reduction.

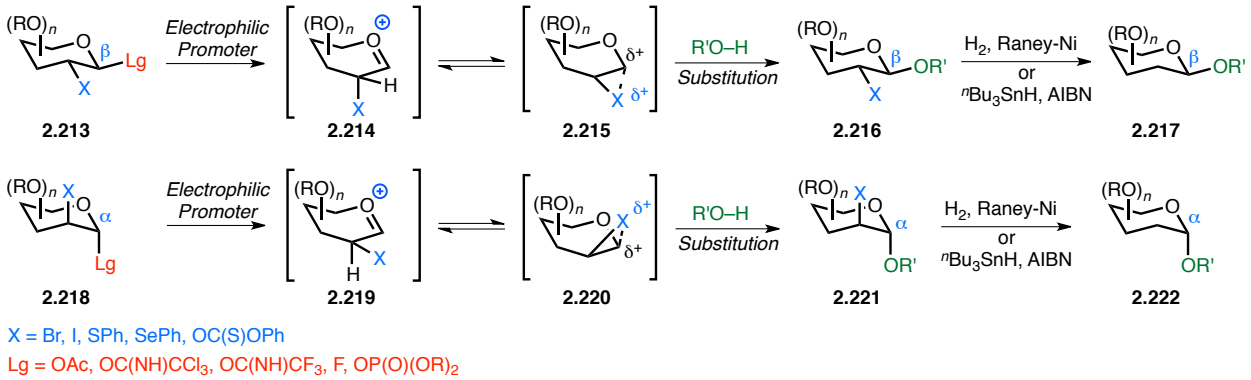

Figure 2.16 Synthesis of 2-deoxyglycosides using a preinstalled C2 directing group.

The use of a preinstalled C2 directing group to control the anomeric selectivity of 2-deoxyglycoside formation is often preferable to the previously described approaches. First, it circumvents the selectivity issues observed for the direct substitution glycosylation approach. Second, it affords direct access to the either intermediate **2.215** or **2.220** (Figure 2.16), which generally controls the stereochemical course of the glycosylation event. In contrast, electrophilic glycal activation often generates a mixture of both **2.215** and **2.220**, depending on the substitution patern of the glycosyl donor, which leads to the formation of a mixture of both 2-deoxy-β- and α-glycosides **2.216** and **2.221**, respectively. In effect, this method serves to decouple glycal activation from glycosylation. Third, this method can utilize mild electrophilic promotors, such as TMSOTf or $SnCl_2$, which makes it particularly valuable for the late-stage glycosylation of highly sensitive natural product aglycons.

The Roush group has explored many of the intricacies of the C2 directing group strategy for stereocontrolled synthesis of 2-deoxyglycosides.[192,193] They have applied this approach to the total synthesis of a variety of natural products. In particular, their total synthesis of olivomycin A (**2.239**)[194] illustrates the versatility of this technique for the construction of both 2-deoxy-α- and β-glycosides (Schemes 2.32 and 2.33). Their synthesis of the AB-dissacharide glycosyl donor **2.230** is depicted below in Scheme 2.32. Treatment of glycal **2.223** with NIS and HOAc resulted in the formation of two major isomeric products: 2-iodo-β-glycosyl acetate **2.224** and 2-iodo-α-glycosyl acetate **2.225** in 13% and 77% yield, respectively after HPLC separation. Next, addition of TMSOTf to a cold solution of **2.225** and glycal **2.226** afforded 2-iodo-α-glycoside **2.228** in 74% yield as a single stereoisomer. The anomeric selectivity observed in this transformation can be explained by α-selective nucleophilic attack by **2.226** on iodonium intermediate **2.227**. Importantly, the mild nature of the reaction conditions prevented decomposition of the sensitive glycal functional unit. Glycal **2.228** was then converted to trichloacetimidate glycosyl donor **2.230** through a three step sequence involving: (1) thiochlorination, (2) glycosyl chloride hydrolysis, and (3) trichloroacetimidate formation. Notably, installation of the equatorial C2 thiophenyl substituent was critical for a future β-selective glycosylation reaction (*vide infra*).

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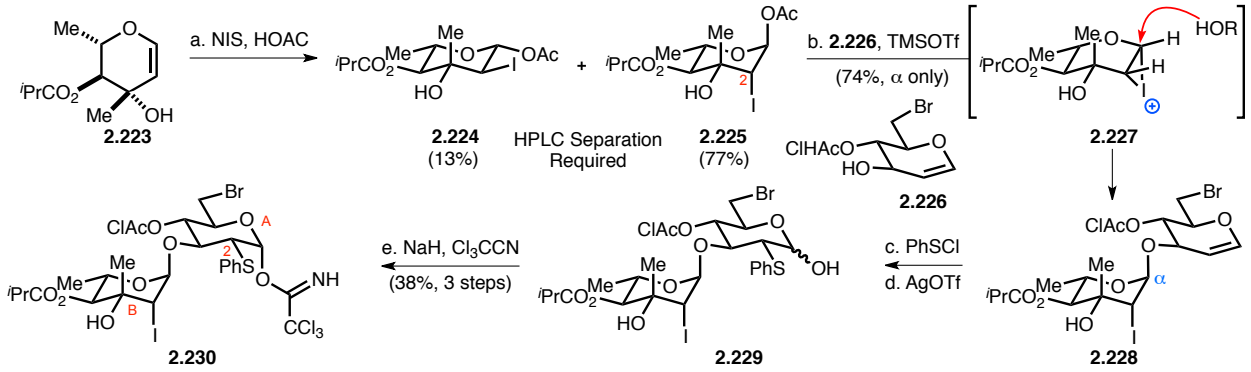
[192] For synthesis of 2-deoxy-β-glycosides see: (a) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, 53, 8825–8836. (b) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, 53, 8837–8852. (c) Roush, W. R.; Gung, B. W.; Bennett, C. E. *Org. Lett.* **1999**, *1,* 891–893. (d) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121,* 3541–3542. (e) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122,* 6124–6125. (f) Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, 4523–4526. (g) Blanchard, N.; Roush, W. R. *Org. Lett.* **2003**, *5,* 81–84. (h) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5,* 1871–1874. (i) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5,* 1875–1878.

[193] For synthesis of 2-deoxy-α-glycosides see: (a) Roush, W. R.; Briner, K.; Sebesta, D. P. *Synlet*t **1993**, 264–266. (b) Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett*. **1999**, *1*, 895–897 (c) Roush, W. R.; Narayan, S. *Org. Lett.* **1999**, *1*, 899–902. (d) Handa, M.; Smith III, W. J.; Roush, W. R.; *J. Org. Chem.* **2008**, *73,* 1036–1039.

[194] Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121,* 1990–1991.

Scheme 2.32 Stereoselective synthesis of a 2-deoxy-2-iodo-α-glycoside using a 2-deoxy-2-iodo-glycosyl acetate donor.



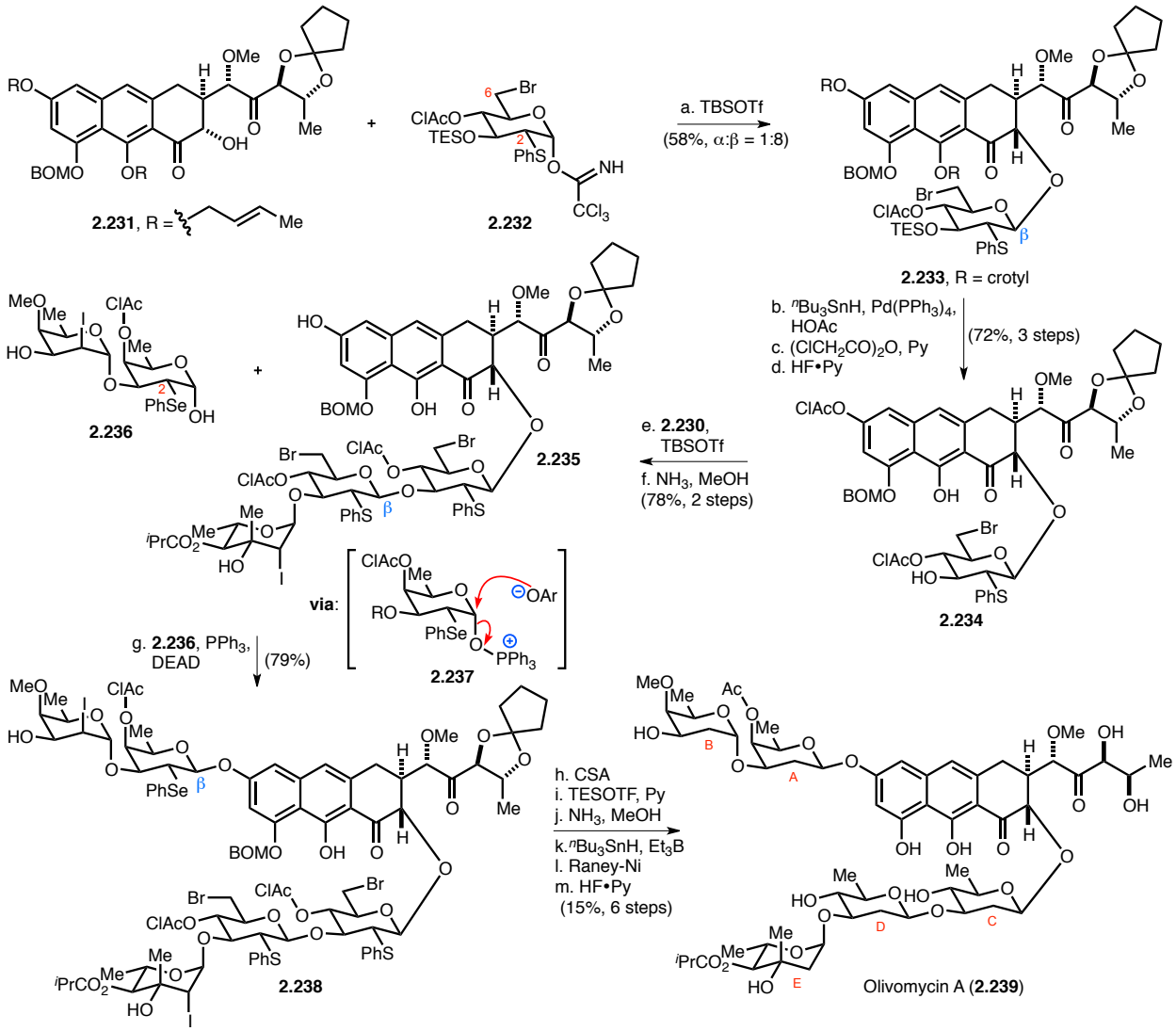
Reagents and conditions: (a) NIS, HOAc, EtCN, –78 °C, 77% for **2.225** and 13% for **2.224**; (b) **2.226**, TMSOTf, CH_2Cl_2, –78 °C, 4 Å MS, 74%; (c) PhSCl, CH_2Cl_2, 0 °C → RT; (d) AgOTf, TMU, THF-H_2O; (e) NaH, Cl_3CCN, –40 → –20 °C, 38% (3 steps).

The CDE-trisaccharide unit of olivomycin A was then attached to aglycon **2.231** through two sequential β-selective glycosylation reactions using a C2-thiophenyl directing group (Scheme 2.33). β-selective glycosylation based on this strategy depended on two primary factors: (1) the nature of the substituent at C6 (C6–Br being the most selective donor) and (2) the steric requirements of the glycosyl acceptor (optimal α-selectivity was observed for sterically unhindered alcohols).[192a,b] Addition of catalytic TBSOTf to a cold solution of trichloroacetimidate glycosyl donor **2.232** (prepared in a similar fashion to **2.230**) and aglycon **2.231** provided 2-thiophenyl-2-deoxy-β-glycoside **2.233** in good yield and anomeric selectivity. Protecting group manipulation and a second β-selective glycosylation gave CDE-glycoside **2.235**. Next, the challenging aryl 2-deoxy-β-glycosidic linkage of olivomycin A was constructed utilizing a Mitsunobu glycosylation protocol.[195] Coupling of **2.235** and AB-disaccharide **2.236** was accomplished by exposure to PPh_3 and DEAD to afford pentasaccharide **2.238** in 73–79% yield. Interestingly, the β-glycosidic linkage appears to have been formed though an S_N2-like substitution process of the activated α-hydroxy hemiacetal intermediate **2.237**. In this way, the equatorial 2-selenophenyl substituent imparted β-selectivity by increasing the α/β anomeric ratio of the pyranose starting material (**2.236**). Finally, the

[195] Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236–2250.

total synthesis of olivomycin A (**2.239**) was completed through: (1) protecting group manipulations, (2) reduction of the 6-bromo, 2-iodo, and 2-selenophenyl substituents with $^{n}Bu_3SnH$ and catalytic Et_3B, (3) reduction of the 2-thiophenyl substituents with Raney-Ni, and (4) silyl ether deprotection using HF•Py.

Scheme 2.33 Stereoselective synthesis of a 2-deoxy-β-glycosides using a 2-deoxy-2-thiophenyl glycosyl trichloroacetimidate donor and a Mitsunobu glycosylation process.

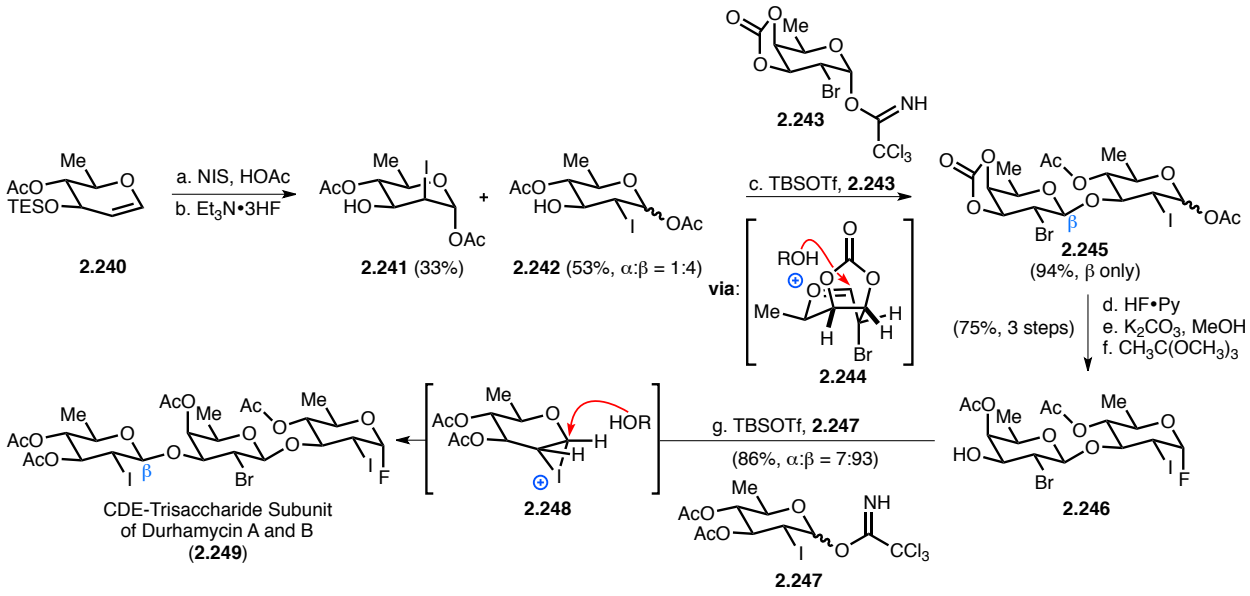


Reagents and conditions: (a) TBSOTf, CH_2Cl_2-hexanes (1:2), 4 Å MS, –60 °C, 58%, α:β = 1:8; (b) $Pd(PPh_3)_4$, $^{n}Bu_3SnH$, HOAc, 90%; (c) $(ClAc)_2O$, CH_2Cl_2, Py, –30 °C, 84%; (d) HF•Py, THF, 0 °C, 95%; (e) **2.230**, TBSOTf, CH_2Cl_2-hexanes (1:1), 4 Å MS, –35 °C; (f) NH_3, MeOH, 78% (two steps); (g) **2.236**, PPh_3, DEAD, CH_2Cl_2, 4 Å MS, 0 °C, 79%; (h) CSA, MeOH-THF, 0 °C, 54% and 14% **2.238**; (i) TESOTf, Py, CH_2Cl_2, –60 °C, 95%; (j) NH_3,

Reagents and conditions for Scheme 2.33 continued: MeOH-CH_2Cl_2, 0 °C, 78%; (k) $^{n}Bu_3SnH$, Et_3B, 45 °C, 84%; (l) Raney-Ni, THF-EtOH, sonication, 57%; (m) HF•Py, THF, Py, 0 °C, 76%.

The Roush group has also demonstrated the utility of an equatorial 2-iodo substituent as a stereocontrolling element for the formation of 2-deoxy-β-glycosides in their synthesis of the CDE-trissacharide subunit of Durahamycin A and B (**2.249**) (Scheme 2.34).[192i] Their synthesis began with addition of NIS and HOAc to a solution of 6-deoxyglycal **2.240** to provide a mixture of α- and β-glycosyl acetates, **2.241** and **2.242** after TES deprotection. While this method for the installation of a 2-iodo directing group was relatively inefficient, it provided sufficient quantities of the equatorial iodide diastereomer **2.242** to carry out the remainder of their synthesis. Next, **2.242** was coupled with 2-bromo-galactopyranosyl trichloroacetimidate donor **2.243** to afford β-glycoside **2.245** in 94% through exposure to TBSOTf. Interestingly, the glycosyl trichloroacetimidate leaving group was selectively activated by TBSOTf in the presence of the glycosyl acetate leaving group at low temperatures. Additionally, the rigidifying 3,4-carbonate protecting group for 2,6-dideoxy-2-bromo-galactosyl donor **2.243** was critical to obtain high β-selectivity in the glycosylation reaction, presumably through the nucleophilic substitution of unusual oxocarbenium ion intermediate **2.244**. Next, glycosyl acetate **2.245** was converted to the corresponding glycosyl fluoride **2.246** and a second β-selective glycosylation with glycosyl donor **2.247** furnished the CDE-trisaccharide **2.249** in good yield and anomeric selectivity.

Scheme 2.34 Stereoselective synthesis of a 2-deoxy-β-glycosides using a 2-deoxy-2-iodo-glycosyl trichloroacetimidate.

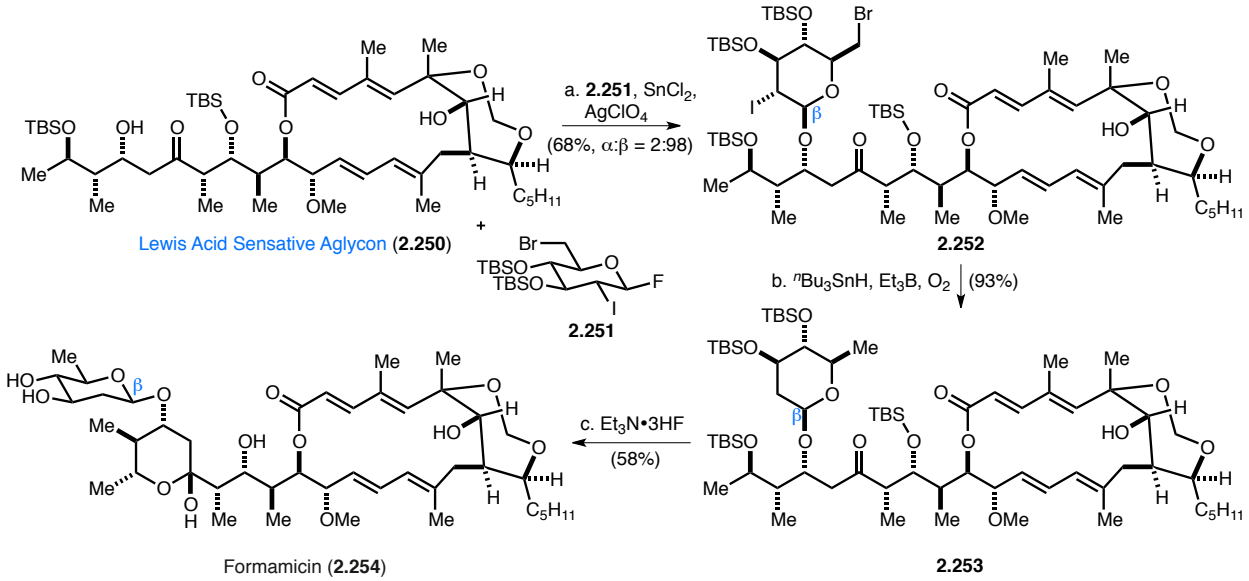


Reagents and conditions: (a) NIS, HOAc, PhMe, reflux; (b) $Et_3N•3HF$, MeCN, 0 °C, 86%, 37% for **2.241**, 63% for **2.242**; (c) **2.243**, TBSOTf, CH_2Cl_2, –78 °C, 94%; (d) HF•Py, CH_2Cl_2, 0 °C, 79%–89%; (e) K_2CO_3, MeOH, 0 °C, 93%; (f) $CH_3C(OCH_3)_3$, CH_2Cl_2, 0 °C, 91%; (g) **2.247**, TBSOTf, CH_2Cl_2, –78 °C, 86%, α:β = 7:93.

Roush has utilized a 2-iodo-glycosyl fluoride donor to stereoselectivly introduce the 2-deoxyglycosyl subunit of the macrolide natural product formamicin (**2.254**) (Scheme 2.35). The use of a fluoride glycosyl donor (**2.251**) was necessitated by the highly acid sensitive nature of the aglycon (**2.250**), which decomposed in the presence of various Lewis acids such as TMSOTf and $BF_3•OEt_2$. Exposure of **2.250** and **2.251** to $SnCl_2$ and $AgClO_4$ (Mukaiyama's conditions)[196] furnished the desired 2-iodo-β-glycoside (**2.252**) in 68% yield with excellent anomeric selectivity. The synthesis of formamicin (**2.254**) was completed through reductive removal of the 2-iodo substituent with $^nBu_3SnH$, Et_3B, and O_2 followed by global deprotection with $Et_3N•HF$.

[196] Mukaiyama, T.; Murai, Y.; Shoda, S.-i. *Chem. Lett.* **1981**, 431–440.

Scheme 2.35 Stereoselective synthesis of a 2-deoxy-β-glycosides using a 2-deoxy-2-iodo-glycosyl fluoride donor.

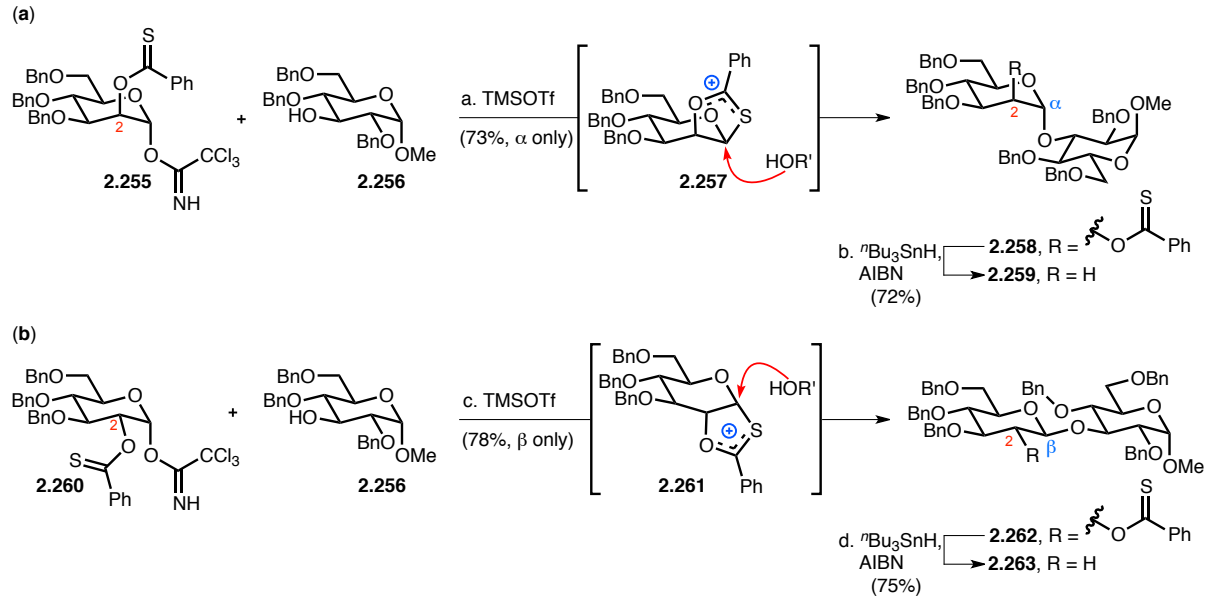


Reagents and conditions: (a) **2.251**, $SnCl_2$, $AgClO_4$, Et_2O, 4 Å MS, –20 → –15 °C, 68%, α:β = 2:98; (b) $^nBu_3SnH$, Et_3B, O_2, 93%; (c) Et_3N•3HF, Et_3N, MeCN-THF (1:1), 3 days; Et_3N•3HF, Et_3N, MeCN, 11 days, 58%.

Schmidt and coworkers have employed a 2-*O*-thiocarbonyl directing group to prepare 2-deoxy-α- and β-glycosides after C2–O bond reduction (Scheme 2.36).[197] Treatment of axial 2-*O*-thiocarbonyl-glycosyl trichloroacetate donor **2.255** and glycosyl acceptor **2.256** with TMSOTf resulted in the formation of the corresponding α-glycoside **2.258** in good yield (Scheme 2.36a). Presumably, the stereochemical outcome of this reaction was dictated by nucleophilic attack on intermediate **2.257**. Reductive removal of the 2-*O*-thiocarbonyl substituent was accomplished using $^nBu_3SnH$ and catalytic AIBN to afford 2-deoxy-α-glycoside **2.259**. The corresponding 2-deoxy-β-glycoside **2.263** was prepared in an analogous fashion starting from equatorial 2-*O*-thiocarbonyl-glycosyl donor **2.260** (Scheme 2.36b). While this method has not been utilized in the context of natural product total synthesis, it helped inspire our stereocontrolled glycosylation strategy for the installation of the hibarimicin B AT-AM and AT'-AM' dissacharides (*vide infra*).

[197] Castro-Palomino, J. C.; Schmidt, R. R. *Synlett* **1998**, 501–502.

Scheme 2.36 Stereoselective synthesis of 2-deoxy-α-glycosides and 2-deoxy-β-glycosides using a 2-*O*-thiocarbonyl directing group.



Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 0 °C, 73%; (b) ^{n}Bu$_3$SnH, AIBN, PhMe, 110 °C, 72%; (c) TMSOTf, CH_2Cl_2, 0 °C, 78%; (d) ^{n}Bu$_3$SnH, AIBN, PhMe, 110 °C, 75%.

2.8.D Synthesis of 2-Deoxy-β-glycosides Using a C3 Directing Group

As previously mentioned, C3 directing groups have been utilized in several instances for the stereoselective synthesis of 2-deoxy-β-glycosides.[188] Conceptually, this strategy mirrors that of a preinstalled C2 directing group; however, in certain cases, the synthesis of the corresponding glycosyl donor is often more direct and efficient. Weisner and coworkers have exploited an axial C3 *para*-methoxybenzoyl ester as a directing group in their synthesis of the cardiac glycoside digitoxin (**2.138**) (Scheme 2.37). Treatment of thioethyl glycoside **2.264** and glycosyl acceptor **2.265** with $HgCl_2$, $CdCO_3$, and a catalytic amount of DMF supplied 2-deoxy-β-glycoside **2.267** in 60% yield with excellent β-anomeric selectivity. This procedure was reiterated to achieve a total synthesis of digitoxin (**2.138**). It is important to note that not all axial 3-*O*-esters are capable of neighboring group assistance and in certain cases this strategy is unreliable.[188c,198]

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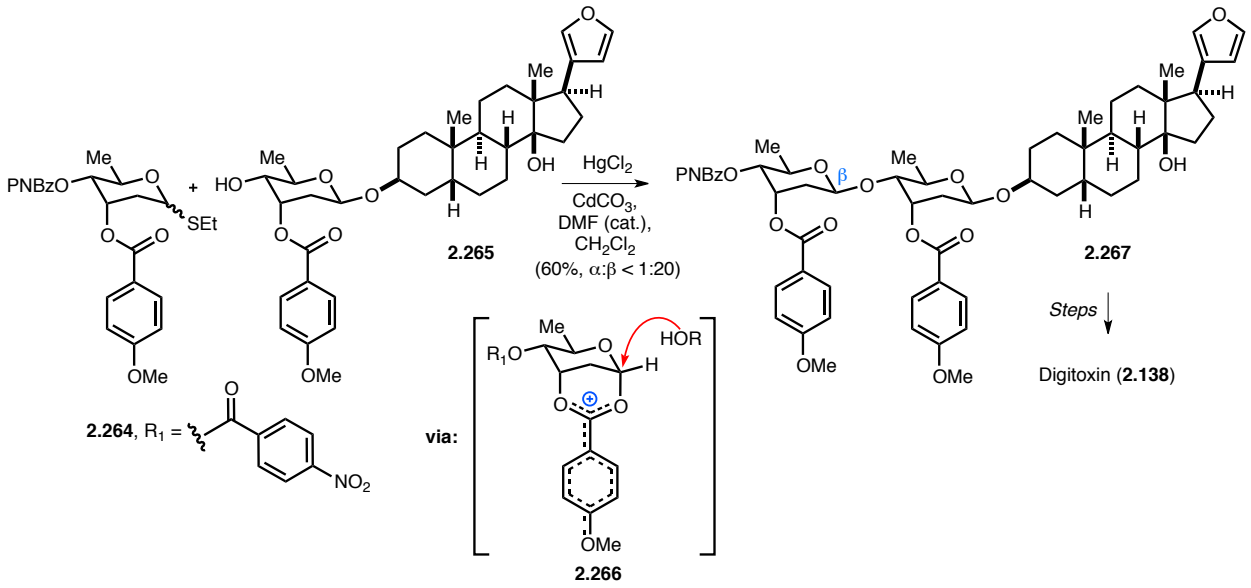
[198] (a) Hashimoto, S.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271–1273. (b) Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120,* 1392–1397. (c) Pongdee, R.; Wu, B.; Sulikowski, G. A.

Scheme 2.37 Synthesis of 2-deoxy-β-glycosides using an axial 3-*O*-*para*-methoxybenzoyl ester directing group.



2.8.E Synthesis of 2-Deoxy-α-glycosides and 2-Deoxy-β-glycosides Using Conformation Control

Tatsuda and Toshima[199] have developed a strategy for the synthesis of both of 2-deoxy-α-glycosides and 2-deoxy-β-glycosides based on conformational control of the glycosyl donor. By introducing a thioether bridge between C2 and C6, they have prepared a variety of bicyclic glycosyl donors such as **2.268**, **2.269**, and **2.270** (Scheme 2.38). They discovered that 2,6-anhydro-2-thio-α-glycoside **2.272** could be stereoselectively prepared via two independent glycosylation methods using a common glycosyl acceptor **2.271**, including: (1) treatment of thiophenyl glycosyl donor **2.268** with NBS or (2) exposure of an analogous fluoro glycosyl donor **2.269** to $SnCl_2$ and $AgClO_4$. In contrast, addition of TMSOTf to a solution of glycosyl acetate **2.270** and glycosyl acceptor **2.271** provided 2,6-anhydro-2-thio-β-glycoside **2.274**. Tatsuda and coworkers rationalized the stereochemical outcome of these reactions

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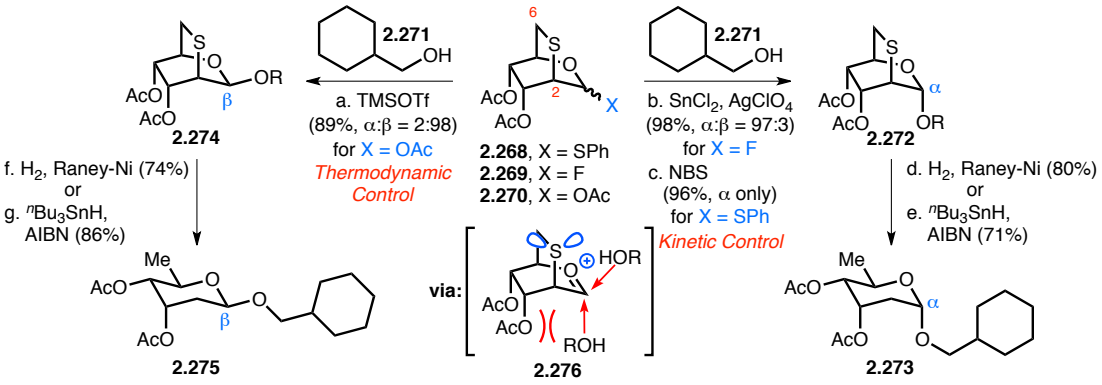
Org. Lett. **2001**, *3,* 3523–3525.

[199] (a) Toshima, K.; Mukaiyama, S.; Ishiyama, T.; Tatsuta, K. *Tetrahedron Lett.* **1990**, *31*, 3339–3342. (b) Toehima, K.; Mukaiyama, S.; Ishiyama, T.; Tatauta, K. *Tetrahedron Lett.* **1990**, *31*, 6361–6362. (c) Toshima, K.; Mukaiyama, S.; Yoehida, T.; Tamai, T.; Tatauta, K. *Tetrahedron Lett.* **1991**, *32*, 6155–6158. (d) Toehima, K.; Nozaki, Y.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1992**, *33*, 1491–1494. (e)Toshima, K.; Nozaki, Y.; Inokuchi, H.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1993**, *34*, 1611–1614. (f) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K. *J. Am. Chem. Soc.* **1994**, *116*, 9042–9051. (g) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K. Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717–3727.

through two primary interactions of the approaching alcohol with oxocarbenium ion intermediate **2.276**. They proposed that formation of the α-glycosidic linkage is kinetically favored by repulsive electronic interaction with sulfur atom. Alternatively, formation of **2.274** was shown to be reversible in the presence of TMSOTf and CH_2Cl_2 as a solvent. Therefore, the β-selectivity observed under these conditions is likely a result of minimization of a potential 1,3-diaxial interaction in the corresponding α-anomer (**2.272**). Finally, 2-deoxy-α-glycoside **2.273** and 2-deoxy-β-glycoside **2.275** were accessed via C–S bond reduction with Raney-Ni or through radical desulfurization using ^{n}Bu$_3$SnH and AIBN.

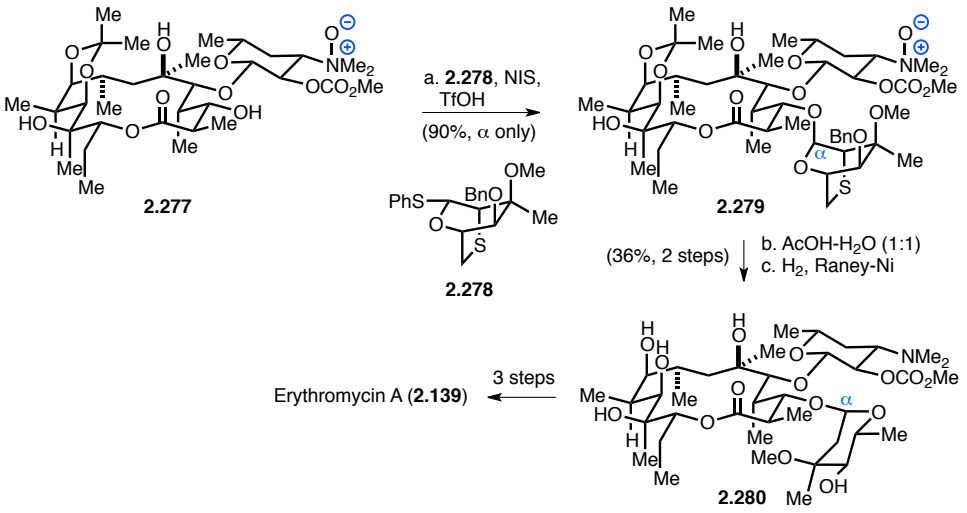
Scheme 2.38 Synthesis of 2-deoxy-α-glycosides and 2-deoxy-β-glycosides using conformation control.



Reagents and conditions: (a) **2.270**, TMSOTf, CH_2Cl_2, –10 °C, 89%, α:β = 2:98; (b) **2.269**, $SnCl_2$, $AgClO_4$, Et_2O, –10 °C, 98%, α:β = 97:3; (c) **2.268**, NBS, 4 Å MS, Et_2O, –25 °C, 96%; (d) H_2, Raney-Ni, EtOH, 80 %; (e) ^{n}Bu$_3$SnH, AIBN, PhMe, 71%; (f) H_2, Raney-Ni, EtOH, 74 %; (g) ^{n}Bu$_3$SnH, AIBN, PhMe, 86%.

Tatsuda was able to apply this method to the synthesis of erythromycin A (**2.139**) (Scheme 2.39). Exposure of aglycon **2.277** and 2,6-anhydro-2-thio-β-glycosyl donor **2.278** to NIS and TfOH promoted formation of the kinetically favored α-glycoside **2.279** in 90% yield. Next, the acetal protecting group was hydrolyzed and the 2-deoxy-α-glycoside **2.280** was obtained via desulfurization with Raney-Ni. Three additional steps delivered erythromycin A (**2.139**).[199g]

Scheme 2.39 Application of conformation control for the synthesis of 2-deoxy-α-glycosides to the total synthesis of erythromycin A.



Reagents and conditions: (a) **2.278**, NIS, TfOH, CH_2Cl_2, 4 Å MS, –35 °C, 90%; (b) HOAc-H_2O (1:1), 40 °C, 66%; (c) H_2, Raney-Ni, EtOH, 40 °C, 54%.

2.8.F De Novo Synthesis of 2-Deoxy-α-glycosides and 2-Deoxy-β-glycosides

De novo synthesis has become an extremely powerful strategy for the construction of 2-deoxyglycosides.[200] In particular, the O'Doherty group has demonstrated the utility of this approach in the context of natural product and oligosaccharide total synthesis.[201] Their synthesis of the trisaccharide subunit of landomycin A (**2.290**) (Scheme 2.40) exemplifies this tactic for the formation of both 2-deoxy-α- and β-glycosidic linkages. The first step of their synthesis featured a palladium-catalyzed β-selective glycosylation reaction between β-Boc-pyranone **2.282** and β-D-olivose glycosyl acceptor **2.281**. Treatment of **2.282** and **2.281** with catalytic $Pd_2(dba)_3$•$CHCl_3$ and PPh_3 furnished β-glycoside **2.283** in 85% yield as a single diastereomer. The stereochemical outcome of this reaction is believed to be a result of a double inversion net retention process, wherein attack by the Pd(0) catalyst on **2.282** provides α-π-allyl Pd intermediate **2.291** followed by a second nucleophilic substitution reaction by **2.281** to afford β-

[200] For a review on the de novo synthesis of 2-deoxyglycosides see: (a) Kirschning, A.; Jesberger, M.; Schöning K.-U. *Synthesis* **2001**, 507–540 and references therein. (b) Harris, J. M. Li, M. Scott, J. G.; O'Doherty, G. A. *Strategy and Tactics in Organic Synthesis,* **2004**, *5*, 221–253.

[201] Babu, R. S.; Chen, Q.; Kang, S.–W.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2012**, *134*, 11952−11955 and references therein.

glycoside **2.283**. Next, disaccharide **2.285** was prepared through a multi step sequence involving: (1) Luche reduction[202] of the enone, (2) Myers' reductive 1,3-allylic transposition,[203] (3) protecting group exchange, and (4) dihydroxylation. Mitsunobu[204] inversion of the **2.285** C3–OH and protecting group manipulations provided glycosyl acceptor **2.286** for the second glycosylation reacton. In this case, exposure of **2.286** and α-Boc-pyranone **2.287** to catalytic $Pd_2(dba)_3$•$CHCl_3$ and PPh_3 afforded α-glycoside **2.288** in excellent yield via β-π-allyl Pd intermediate **2.292**. Finally, the landomycin A trisaccharide **2.290** was completed through: (1) Luche reduction, (2) C3–OH Mitsunobu inversion/deprotection, (3) Myers' reductive 1,3-allylic transposition, (4) diimide reduction with NBSH, and (5) global deprotection using TBAF.

While de novo synthesis has been demonstrated to be a reliable strategy for the construction of 2-deoxy-α-glycosidic and 2-deoxy-β-glycosidic bonds, it is not without liabilities. The requirement for sequential introduction of the C3 and C4 hydroxyl substituents after glycosylation makes this strategy problematic for the synthesis of natural products exhibiting complex and highly sensitive aglycons. Therefore, this approach appears to be best suited for building the 2-deoxyoligosaccharide glycosyl donor, which can then be incorporated at a late-stage of a total synthesis by employing one of the previously described strategies for stereoselective glycosylation (e.g. direct substitution of an anomeric leaving group or C2/C3 neighboring group assistance).

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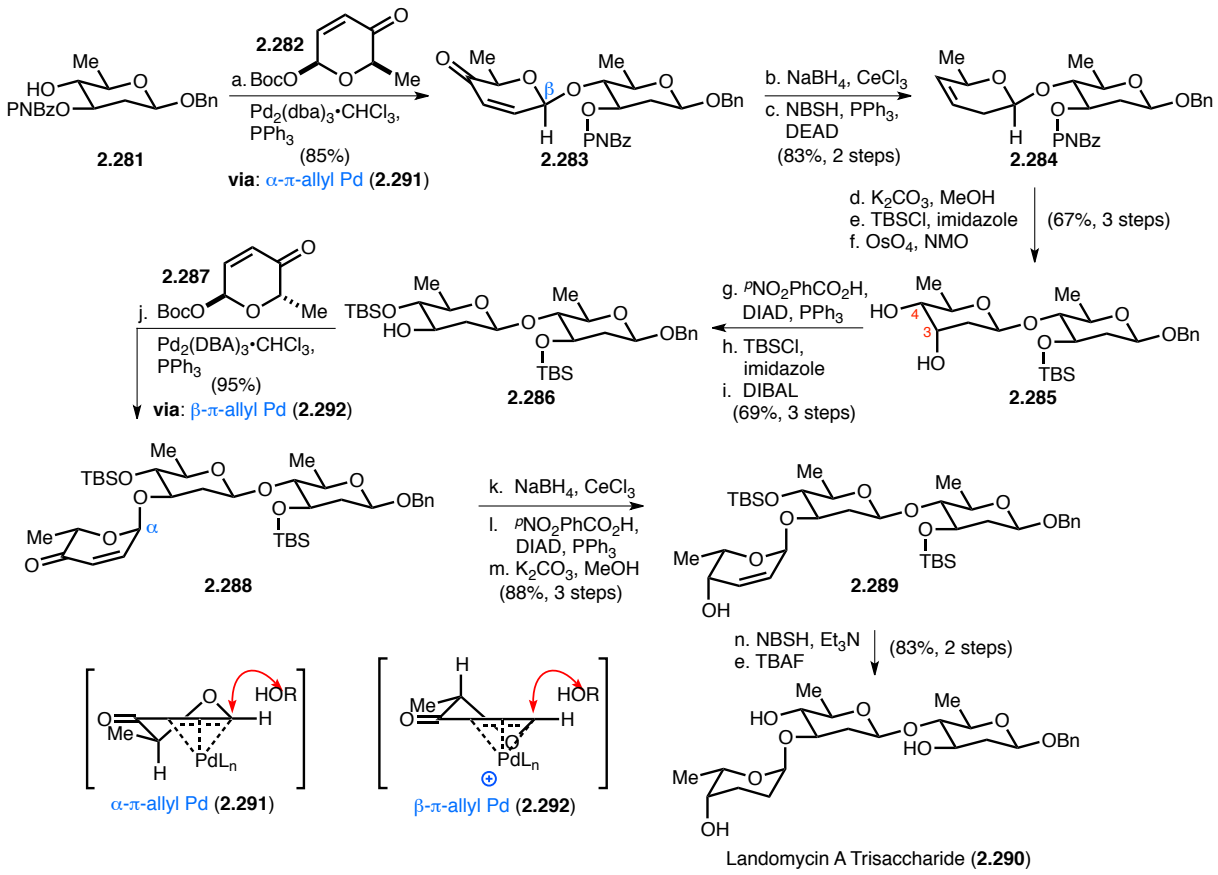
[202] Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

[203] Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493.

[204] For reviews on the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. Prep*. **1996**, *28*, 127–164.

Scheme 2.40 De novo synthesis of 2-deoxy-α-and β-glycosides.



Reagents and conditions: (a) **2.282**, $Pd_2(dba)_3$•$CHCl_3$, PPh_3, CH_2Cl_2, 0 °C, 85%; (b) $NaBH_4$, $CeCl_3$, MeOH, –78 °C, 95%; (c) PPh_3, DIAD, NMM; NBSH, –30 °C → RT, 85%; (d) K_2CO_3, MeOH, 98%; (e) TBSCl, imidazole, DMF-$ClCH_2CH_2Cl$ (1:1), 72%; (f) OsO_4, NMO, CH_2Cl_2-H_2O (10:1), 0 °C, 95%; (g) PPh_3, DIAD, *para*-nitrobenzoic acid, 0 °C → RT, 85%; (h) TBSCl, imidazole, DMF-$ClCH_2CH_2Cl$ (1:1), 82%; (i) DIBAL, CH_2Cl_2, –78 °C, 99%; (j) **2.287**, $Pd_2(dba)_3$•$CHCl_3$, PPh_3, CH_2Cl_2, 0 °C, 95%; (k) $NaBH_4$, $CeCl_3$, MeOH, –78 °C, 93%; (l) PPh_3, DIAD, *para*-nitrobenzoic acid, 0 °C → RT, 97%; (m) K_2CO_3, MeOH, 98%; (n) NBSH, Et_3N, CH_2Cl_2, 86%; (e) TBAF, THF, 97%.

2.9 Retrosynthesis of AM-AT/AM'-AT' and DG/DG' Glycosyl Donors for the Total Synthesis of Hibarimicin B

We were inspired by the work of Hirama and Roush in considering two potential glycosylation strategies for bidirectional installation of the C10–DG1/C10'–DG1' 2-deoxy-α-glycosidic linkages found in hibarimicin B (**2.1**, Figure 2.17). We anticipated that treatment of suitably protected thiophenyl

glycosyl donor **2.293** and an orthogonally protected aglycon (R'OH, green) with $AgPF_6$ and DTBMP at low temperature, according to Hirama's procedure,[179] would preferentially afford the 2-deoxy-α-glycoside **2.294** (Figure 2.17a). Alternatively, if oxidative glycosyl activation conditions were found to be incompatible with the aglycon we could potentially employ a C2 directing group strategy illustrated in Figure 2.17b; this approach involves: (1) concurrent installation of an axial C2 directing group and a C1 leaving group (Lg) via electrophilc activation of glycal **2.295**, (2) Lewis acid-promoted α-selective glycosylation via C2 anchimeric assistance, and (3) C–X bond reduction using $^{n}Bu_3SnH$ and AIBN. Decoupling the electrophilic glycal activation from glycosylation was expected to allow for the use of relatively mild reaction conditions to install the C10–DG1/C10'–DG1' 2-deoxy-α-glycosidic bonds.[205]

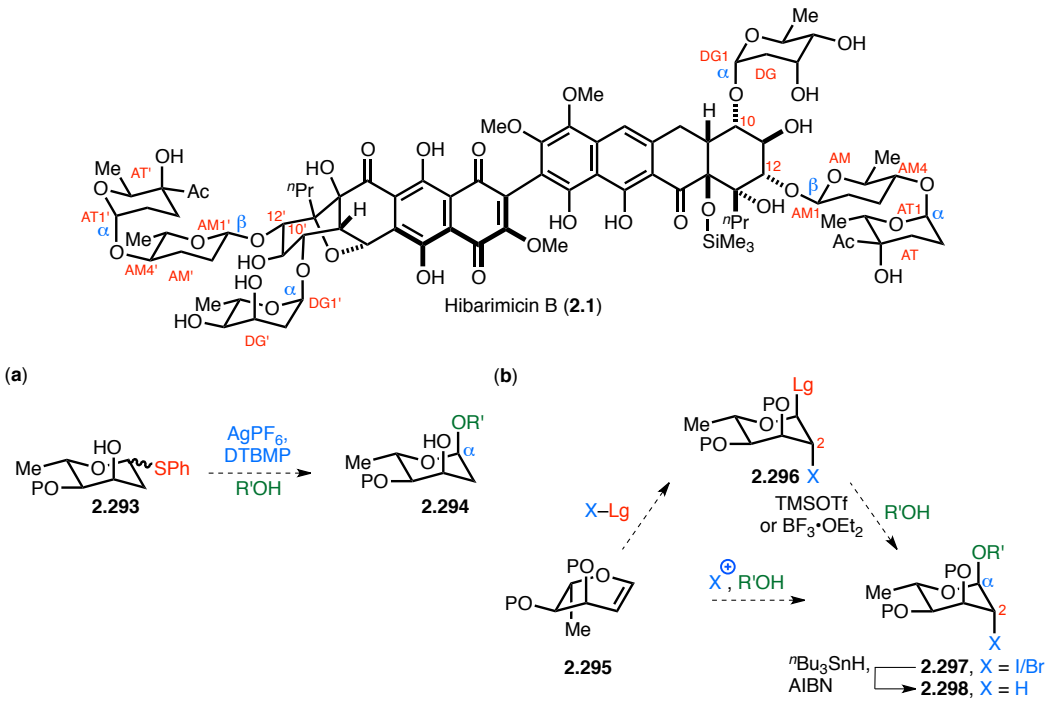


Figure 2.17 Proposed synthesis of the hibarimicin B C10–DG1/C10'–DG1' 2-deoxy-α-glycosidic linkages via: (a) application of Hirama's method or (b) use of a preinstalled C2 directing group.

Next, the work of Weisner[188a,b] and Schmidt[197] inspired the development of a novel C3 directing group strategy for the synthesis of the C12–AM1/C12'–AM1' 2,3-dideoxy-β-glycosidic linkages of **2.1**

[205] Theim and coworkers utilized a NIS mediated glycal activation strategy for the synthesis of the kijanimicin oligosaccharides: Thiem, J.; Köpper, S. *Tetrahedron* **1990**, *46*, 113–138. However, we anticipated that NIS, like $AgPF_6$, might promote decomposition of the sensitive aglycone.

(Figure 2.18). Specifically, we hypothesized that a C3 phenyl thionocarbonate substituent could encourage β-selective glycosylation via 1,3-neighboring group participation illustrated in intermediate **2.300**. Additional, the phenyl thionocarbonate group could potentially be removed directly after the glycosylation reaction with $^{n}Bu_3SnH$ and AIBN to access the corresponding 2,3-dideoxy-β-glycoside **2.302**.

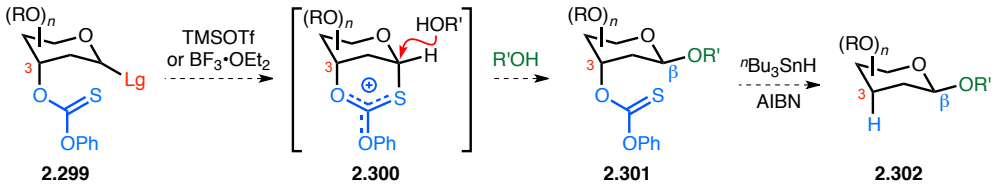


Figure 2.18 Development of a C3 phenyl thionocarbonate directing group for the synthesis of the hibarimicin B C12–AM1/C12'–AM1' 2,3-dideoxy-β-glycosidic linkages.

Application of the aforementioned strategies provided AM-AT/AM'-AT' disaccharide glycosyl donor **2.62** and DG/DG' monosaccharide glycosyl donors **2.63** and **2.64** (Figure 2.19). A trichloroacetimidate leaving group was chosen for **2.62** and **2.64** due to its high reactivity toward Lewis acids, reliability, and ease of formation. We elected to employ benzyl protecting groups for the DG/DG' monosaccharide glycosyl donors **2.63** and **2.64** to allow for late-stage global benzyl deprotection via hydrogenolysis under conditions similar to those used for hibarimicinone (**2.2**). Additionally, the axial DG3/DG3' hydroxyl group in **2.63** was left unprotected due to literature precedent, which suggested that protection might hinder formation of the desired α-anomeric linkage.[179] Comparison of the AM/AM' and DG/DG' ring precursors, **2.304** and **2.305**, revealed their shared relative stereochemistry (digitoxose). This prompted us to consider application of O'Doherty's de novo strategy for their synthesis.[206] Additionally, we anticipated that the AM4–AT/AM4'–AT' α-glycosidic linkages could be formed via Pd-catalyzed glycosylation between α-Boc-pyranone **2.303** and a protected version of **2.304**. Next, we envisioned that stereoselective installation of the AT4/AT4' *C*-acyl substituent could be accomplished through an isopropenyl organometallic carbonyl addition/oxidative cleavage sequence. Finally, we

[206] (a) Zhou, M. O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339–4342. (b) Zhou, M. O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485–2493.

expected α-Boc-pyranone **2.303** and the enantiomeric β-Boc-pyranone precursors to benzyl digitoxosides **2.304** and **2.305** ((+)-**2.282** and (–)-**2.309** respectively, Scheme 2.41) could be obtained through a three steps sequence from 2-furyl methyl ketone (**2.306**). [207]

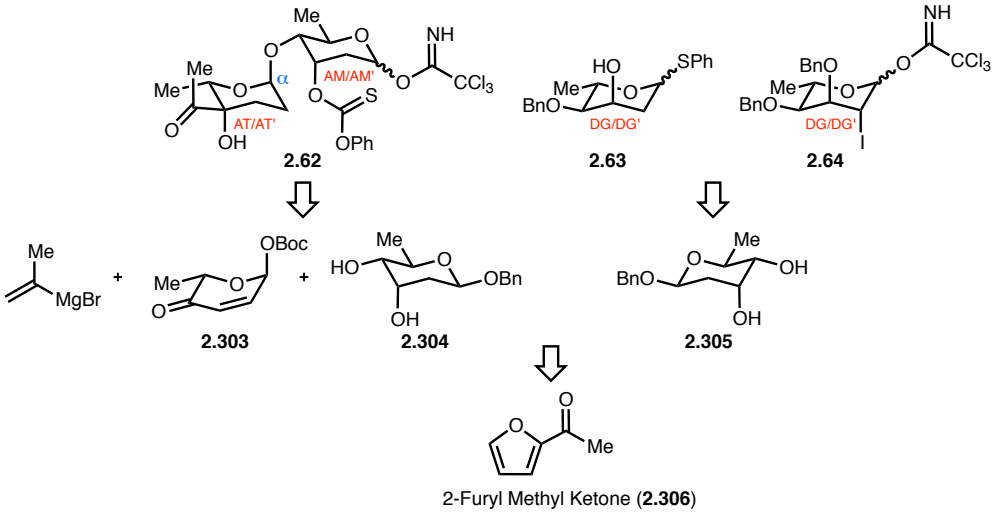


Figure 2.19 Retrosynthesis or AM-AT/AM'-AT' dissacharide glycosyl donor **2.62** and DG/DG' monosaccharide glycosyl donors **2.63** and **2.64**.

2.10 Synthesis of AM-AT/AM'-AT' and DG/DG' Glycosyl Donors

Our synthesis of the AM-AT/AM'-AT' and DG/DG' glycosyl donors began with asymmetric hydrogenation of 2-furyl methyl ketone (**2.306**) under Noyori's conditions on multi-gram scale (Scheme 2.41). [208] A solution of **2.306**, Ru-catalyst (*R*,*R*)-**2.307**, and ^{t}BuOK in ^{i}PrOH-^{t}BuOH were stirred under a H_2 atmosphere at 900 psi to afford alcohol (*S*)-alcohol **2.308** as a single enationmer in 63% yield after distillation. Next α- and β-Boc-pyranones ((+)-**2.287** and (–)-**2.309**) were then prepared in two steps including: (1) NBS promoted Achmatowicz rearrangement[209] and (2) Boc protection of the resultant hemiacetal. The enantiomeric α- and β-Boc-pyranones (–)-**2.311** and (+)-**2.282** were obtained through an analogous reation sequence beginning with asymmetric hydrogenation of **2.306** using Ru-catalyst (*S*,*S*)-

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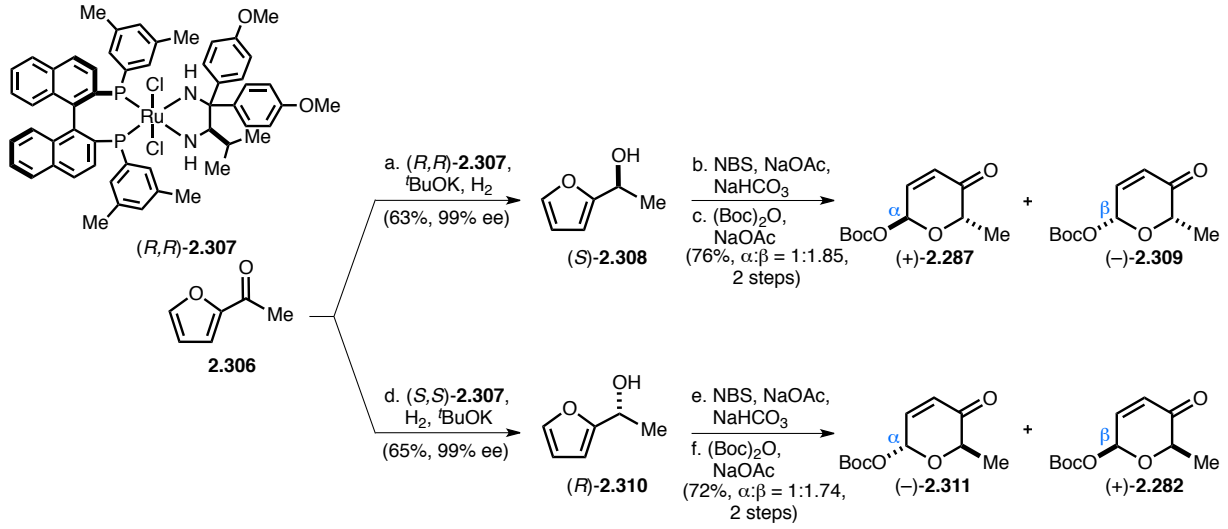
[207] (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118,* 2521–2522. (b) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45,* 1005–1009. (c) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45,* 6407–6411.

[208] Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749–1751.

[209] Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55,* 165–176.

2.307. Three of the four Boc-pyranone products ((+)-**2.287**, (–)-**2.309**, and (+)-**2.282**) were carried forward to prepare the AM-AT/AM'-AT' and DG/DG' glycosyl donors.

Scheme 2.41 Synthesis of α- and β-Boc-pyranone building blocks.

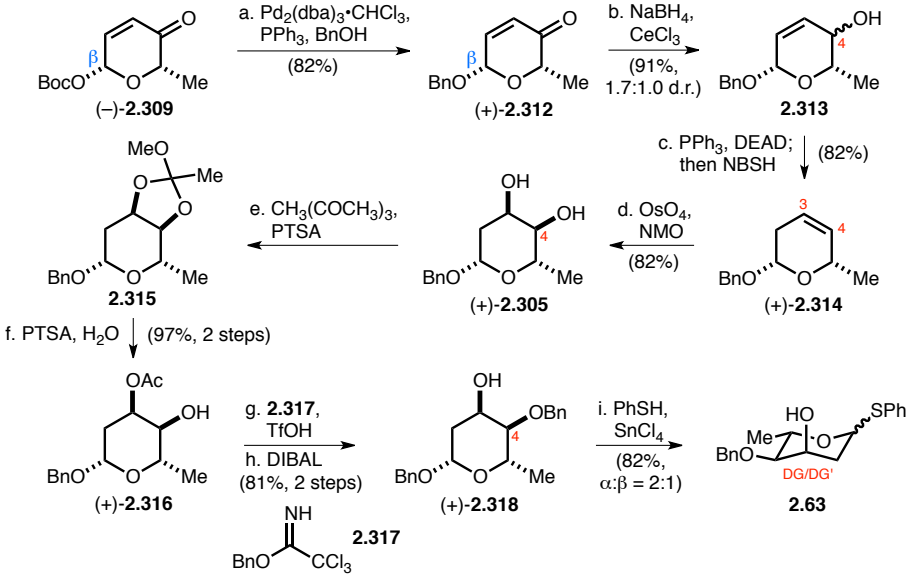


Reagents and conditions: (a) (*R,R*)-**2.307**, H_2 (900 psi), ^{t}BuOK, ^{i}PrOH-^{t}BuOH, 63%, 99% ee; (b) NBS, NaOAc, $NaHCO_3$, THF-H_2O (3:1), 0 °C; (c) $(Boc)_2O$, NaOAc, $NaHCO_3$, PhH, 80 °C, 27% for (+)-**2.287** and 49% for (–)-**2.309**; (d) (*S,S*)-**2.307**, H_2 (900 psi), ^{t}BuOK, ^{i}PrOH-^{t}BuOH, 65%, 99% ee; (e) NBS, NaOAc, $NaHCO_3$, THF-H_2O (3:1), 0 °C; (f) $(Boc)_2O$, NaOAc, $NaHCO_3$, PhH, 80 °C, 26% for (–)-**2.311** and 46% for (+)-**2.282**.

Synthesis of DG/DG' 2-deoxy-thiophenyl glycosyl donor **2.63** is depicted in Scheme 2.42. The first step in the sequence involved a Pd-catalyzed glycosylation between β-Boc-pyranone (–)-**2.309** and benzyl alcohol to afford β-benzyl pyranone (+)-**2.312** as a single diastereomer in 82% yield. Next, Luche reduction of (+)-**2.312** afforded allylic alcohol **2.313** as an inconsequential mixture of C4 diastereomers. Reductive allylic 1,3-transposition was accomplished by exposure of **2.313** to PPh_3, DEAD, and NBSH to provide dihydropyran (+)-**2.314** in 82% yield on multi-gram scale. Treatment of (+)-**2.314** with OsO_4 and NMO furnished diol (+)-**2.305** as a single diastereomer. Regioselective protection of the C4–OH as its corresponding benzyl ether was accomplished through a four step sequence involving: (1) formation of cyclic othoester **2.315**, (2) regioselective orthoester hydrolysis, (3) benzyl protection of the resultant C4–OH, and (4) reductive deprotection of the C3–OAc group with DIBAL. Finally, treatment of benzyl glycoside (+)-**2.318** with thiophenol and $SnCl_4$ at –78 °C delivered **2.63** in 84% yield as an anomeric

mixture of thiophenylglycosides.

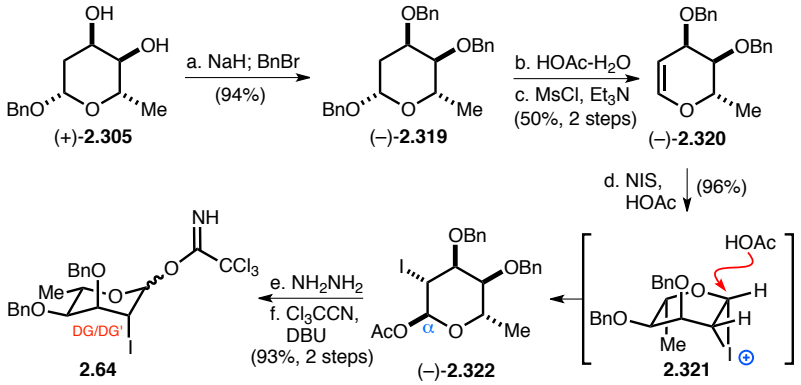
Scheme 2.42 Synthesis of 2-deoxy-thiophenyl-glycosyl donor **2.63**



Reagents and conditions: (a) $Pd_2(dba)_3$•$CHCl_3$, PPh_3, BnOH, CH_2Cl_2, 0 °C, 82%; (b) $NaBH_4$, $CeCl_3$•$7H_2O$, CH_2Cl_2-H_2O (1:1), –78 °C, 91%, 1.7:1.0 d.r.; (c) PPh_3, DEAD, THF, –15 °C; then **2.313**; then NBSH, –15 °C → RT; (d) OsO_4, NMO, CH_2Cl_2-H_2O (4:1), 82%; (e) $CH_3(COCH_3)_3$, PTSA, PhH; (f) PTSA, THF-H_2O (1:1), 97% (two steps); (g) $BnOC(=NH)CCl_3$ (**2.317**), TfOH, CH_2Cl_2-cyclohexane (2:1), 4 Å MS, –20 → –10 °C, 82%; (h) DIBAL, CH_2Cl_2, –78 °C, 81% (two steps); (g) PhSH, $SnCl_4$, CH_2Cl_2, –78 °C, 84%, α:β = 2:1.

The synthesis of DG/DG' 2-deoxy-2-iodo-glycosyl trichloroacetimidate donor **2.64** is depicted in Scheme 2.43. Diol (+)-**2.305** was benzyl protected with sodium hyride and benzyl bromide to afford bis-benzyl ether (–)-**2.319** in 94% yield. Exposure of (–)-**2.319** to warm aqueous HOAc promoted hydrolysis of the benzyl glycoside. The resultant hemiacetal was dehydrated with MsCl and Et_3N to furnish glycal (–)-**2.320**. Iodoacetoxylation of (–)-**2.320** with NIS and HOAc provided 2-deoxy-2-iodo-glycosyl acetate (–)-**2.322** in 96% yield as a single diastereomer. Stereoselective introduction of the requisite axial C2 iodide was likely a result of nucleophilic attack by acetic acid on iodonium intermediate **2.321**. The synthesis of **2.64** was completed by cleavage of the anomeric acetate with hydrazine and exposure of the resultant hemiacetal to trichloroacetonitrile and DBU.

Scheme 2.43 Synthesis of 2-deoxy-2-iodo-glycosyl trichloroacetimidate donor **2.64**.



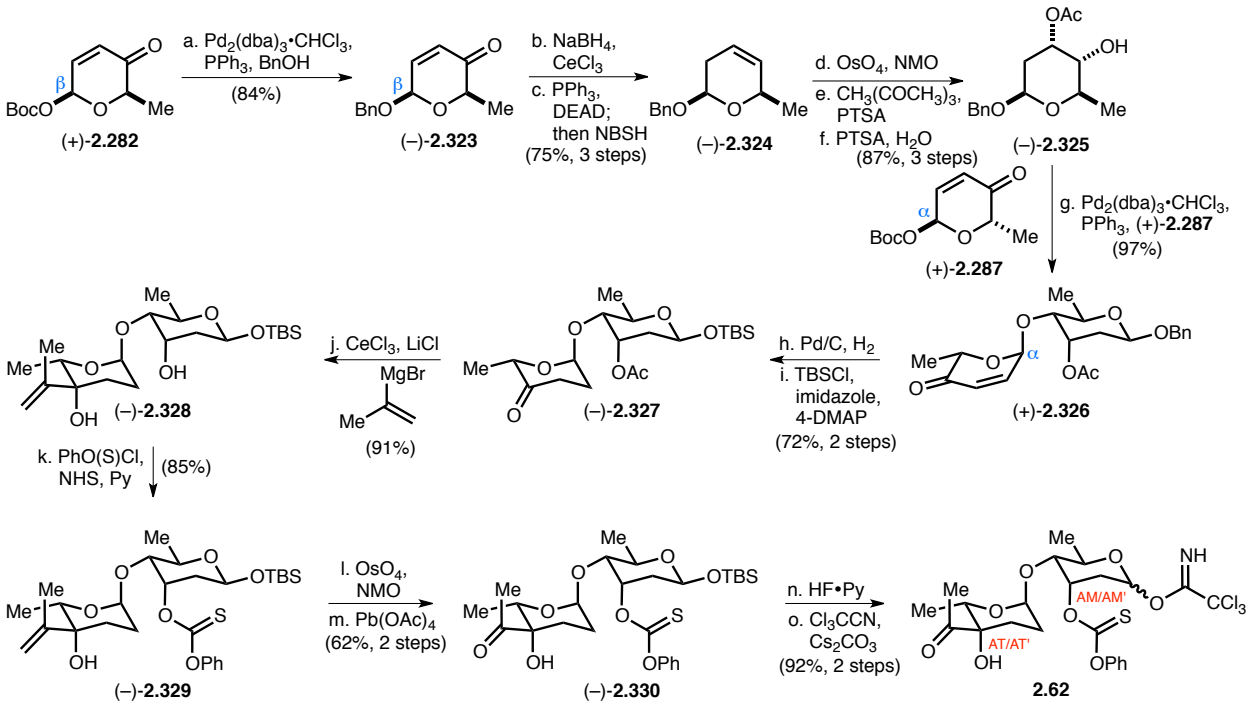
Reagents and conditions: (a) BnBr, NaH, THF, 0 °C → RT, 94%; (b) HOAc-H_2O (3:1), 80 °C, 99%; (c) MsCl, Et_3N, THF, 0 °C → RT, 51% (two steps); (d) NIS, HOAc, –78 → 0 °C, 96%; (e) NH_2NH_2•H_2O, MeOH; (f) Cl_3CCN, DBU, CH_2Cl_2, –10 → 0 °C, 93% (two steps).

Our synthesis of the AM-AT/AM'-AT' disaccharide glycosyl trichloroacetimidate **2.62** is illustrated in Scheme 2.44. Tetrahydropyran (–)-**2.324** was synthesized in six steps from β-Boc-pyranone (+)-**2.282** through our previously established route. Exposure of (–)-**2.324** and α-Boc-pyranone (+)-**2.287** to catalytic $Pd_2(dba)_3$•$CHCl_3$ and PPh_3 afford α-glycoside (+)-**2.326** in 97% yield as a single anomer. Next, olefin reduction and benzyl deprotection was accomplished via hydrogentation with Pd/C and the resultant hemiactetal was subsequently TBS protected to afford β-silyl glycoside (–)-**2.327** as a single anomer in 72% yield. Addition of (–)-**2.327** to a solution of an organocerium reagent derived from isopropenylmagnesium bromide and $CeCl_3$ furnished allylic alcohol (–)-**2.328** as a single diastereomer. As we had anticipated, the sterically bulky organocerium reagent had undergone equatorial nucleophilic attack on the C4 carbonyl group, opposite the C5 methyl substituent.[210] Additionally, the use of excess organocerium reagent in this transformation conviently cleaved the acetate protecting group. Next, the C3 phenyl thionocarbonate directing group was introduced using *O*-phenyl chlorothionoformate, pyridine and NHS to provide disaccharide (–)-**2.329**. OsO_4 catalyzed dihydroxylation of the isopropenyl substituent and $Pb(OAc)_4$ promoted oxidative cleavage of the resultant diol, delivering α-hydroxyketone

[210] The relative stereochemistry of organometallic addition was assigned based on a X-ray crystal structure of a benzyl glycoside analog (compound (–)-**S2.22**). See experimental section for further detail.

(–)-**2.330** in 62% yield over two steps. The synthesis of AM-AT/AM'-AT' disaccharide glycosyl donor **2.62** was completed through removal of the anomeric silyl protecting group with HF•Py followed by formation of the corresponding glycosyl trichloroacetimidate using trichloroacetonitrile and Cs_2CO_3. Glycosyl trichloroacetimidate **2.62** was unstable to silica gel chromatography and to aqueous workup, but could be used directly in the subsequent glycosylation reaction after filteration through neutral Celite with excess CH_2Cl_2.

Scheme 2.44 Synthesis of AM-AT/AM'-AT' disaccharide glycosyl trichloroacetimidate **2.62**.



Reagents and conditions: (a) $Pd_2(dba)_3$•$CHCl_3$, PPh_3, BnOH, CH_2Cl_2, 0 °C, 84%; (b) $NaBH_4$, $CeCl_3$•$7H_2O$, CH_2Cl_2-H_2O (1:1), –78 °C, 91%, 1.7:1.0 d.r.; (c) PPh_3, DEAD, THF, –15 °C; then allylic alcohol; then NBSH, –15 °C → RT, 82%; (d) OsO_4, NMO, CH_2Cl_2-H_2O (4:1), 89%; (e) $CH_3(COCH_3)_3$, PTSA, PhH; (f) PTSA, THF-H_2O (1:1), 98% (two steps); (g) (+)-**2.287**, $Pd_2(dba)_3$•$CHCl_3$, PPh_3, BnOH, CH_2Cl_2, 0 °C, 97%; (h) Pd/C, H_2, MeOH; (i) TBSCl, imidazole, 4-DMAP, CH_2Cl_2, 72% (two steps); (j) $CeCl_3$, LiCl, –78 → 0 °C, 91%; (k) PhO(S)Cl, *N*-hydroxysuccinimide, Py, PhH, 85%; (l) OsO_4, NMO, CH_2Cl_2-H_2O (16:1); (m) $Pb(OAc)_4$, MeOH-PhH (1:1), 0 °C, 62% (two steps); (n) HF•Py, Py, 0 °C; (o) Cl_3CCN, Cs_2CO_3, CH_2Cl_2, 92% (two steps).

2.11 Synthesis of Hibarimicin B Models and the Development of 2-Deoxy-α- and β-selective Glycosylation Methods

With AM-AT/AM'-AT' glycosyl donor **2.62** and DG/DG' glycosyl donors **2.63** and **2.64** in hand, we were in a position to study their respective glycosylation chemistries. A detailed retrosynthesis plan for hibarimicin B (**2.1**) is outlined in Figure 2.20. We envisioned tetraglycosylated precursor **2.331** could be converted to **2.1** in three steps including: (1) simultaneous reductive cleavage of the iodide and thionocarbonate directing groups or the thionocarbonate group alone, (2) global benzyl deprotection, and (3) D-ring oxidation under mildly acidic conditions. In turn, **2.331** could potentially be obtained via α-selective two-directional double glycosylation of bis-glycosylated precursor **2.332** with DG/DG' glycosyl donors **2.63** or **2.64**. Lastly, a β-selective two-directional double glycosylation of orthogonally protected aglycon **2.333** with AM-AT/AM'-AT' glycosyl donor **2.62** could provide **2.332**.

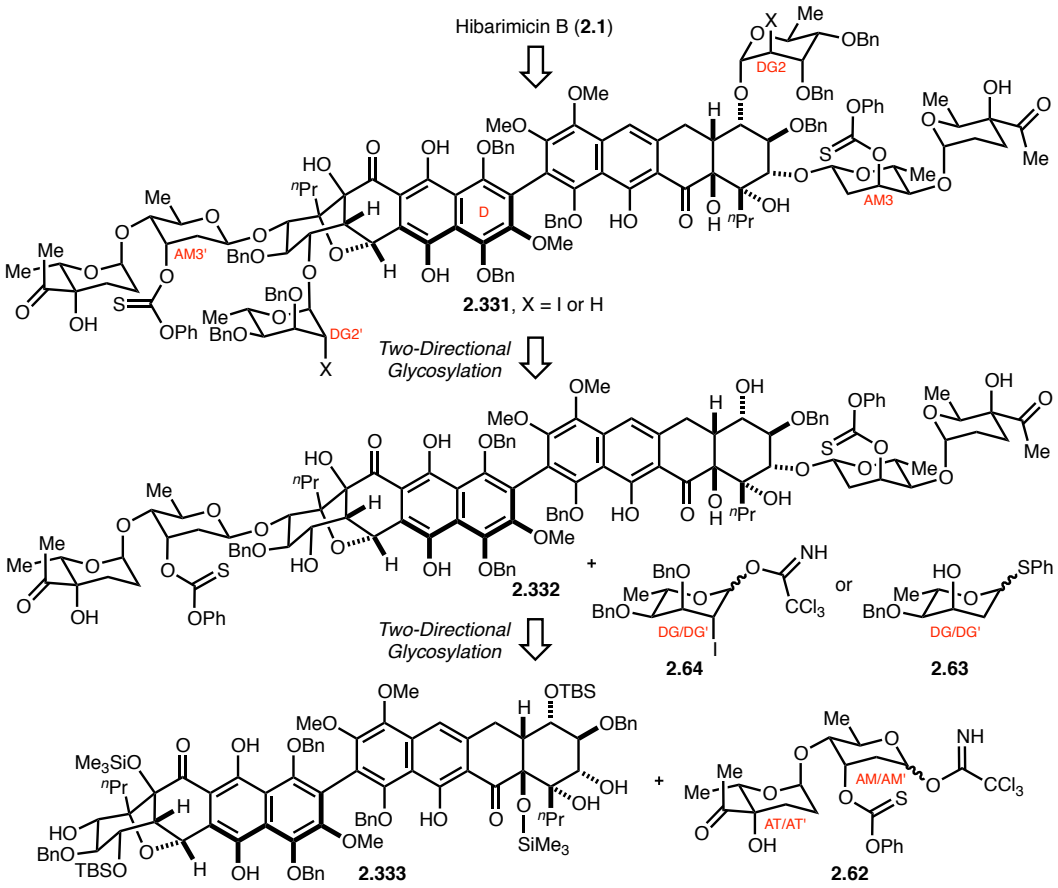


Figure 2.20 Detailed retrosynthesis of hibarimicin B.

We anticipated that the development of conditions for our key two-directional glycosylation reactions would be extremely challenging due to the pseudo-C_2-symmetric nature of hibarimicin B (**2.1**). Therefore, we elected to first investigate the synthesis of hibarimicin B models A (**2.334**) and B (**2.335**) from which the C2–C2' bond of **2.1** had been exsized (Figure 2.21). We imagined targeting **2.334** and **2.335** would simplify our analysis of the stereoselectivity in the proposed glycosylation reactions. Additionaly, the biological activity of **2.334** and **2.335** could be compared to hibarimicin B (**2.1**) in order to help ascertain the pharmacophore of the natural product.

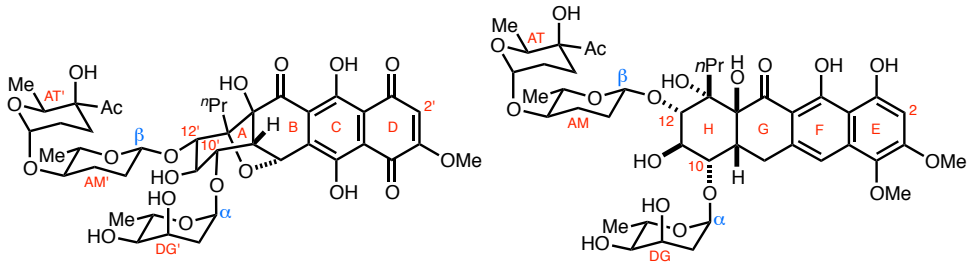


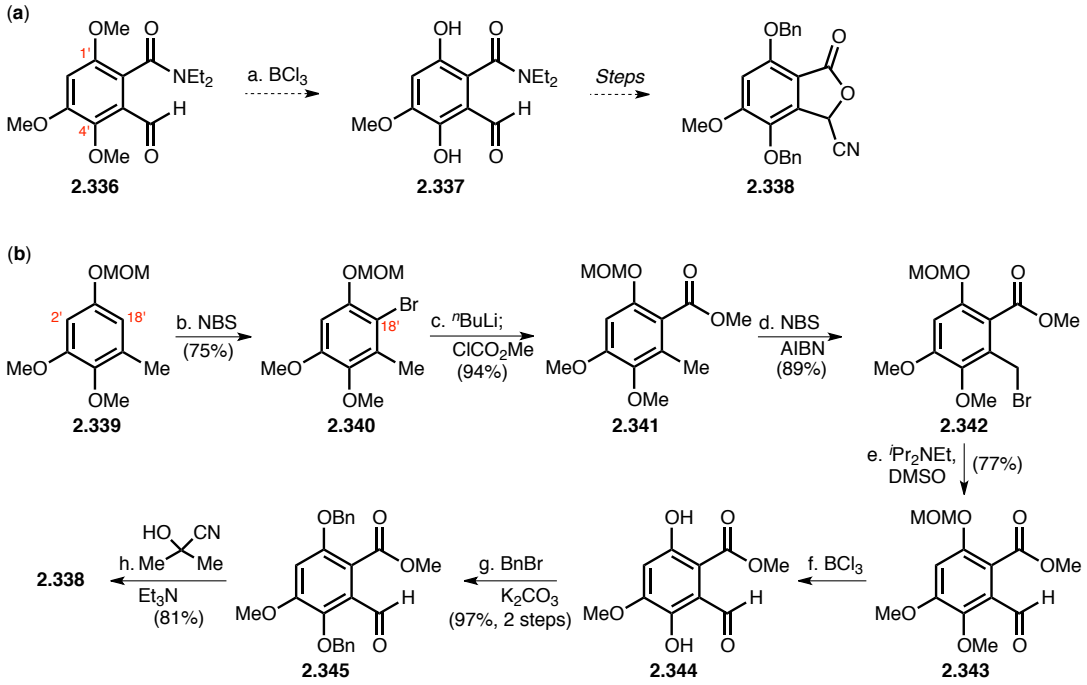
Figure 2.21 Hibarimicin B Models A and B.

Our first approach to the synthesis of hibarimicin B model A (**2.334**) began with known aldehyde **2.336**, which was accessed in three steps on multi-gram scale from 2,4,5-trimethoxybenzoic acid (Scheme 2.45a).[211] Exposure of **2.336** to BCl_3 was expected to promote chemoselective deprotection of the C1' and C4' methyl ethers based on the potential *ortho* directing effect of the aldehyde and amide substituents. We then planned to elaborate the prospective hydroquinone product **2.337** to cyanothalide annulation donor **2.338** in the usual manner. Unfortunately, treatment of **2.336** with BCl_3 at low temperature facilitated only mono-deprotection of the C4' methyl ether. Warming the reaction mixture to ambient temperature, in order to facilitate the second deprotection, led to decomposition of the intermediate bis-methyl ether. Therefore an alternative strategy for the synthesis of **2.338** was developed (Scheme 2.45b). Our revised synthesis of **2.338** began with trialkoxytoluene **2.339**, which was accessed in five steps from vanillin on

[211] Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519–5527.

multi-gram scale.[212] Chemoselective bromination of **2.339** with NBS occurred at C18' rather than C2' to give aryl bromide **2.340**.[213] Next, the C18' carbomethoxy group was installed through lithium–halogen exchange followed by acylation to afford *ortho*-toluate **2.341**. The methyl substituent was mono-brominated under free-radical halogenation conditions and the resultant benzylic bromide **2.342** was converted to the corresponding aldehyde **2.343** through Kornblum oxidation.[214] Chemoselective deprotection of **2.343** with BCl_3 provided hydroquinone **2.344**, which was reprotected with BnBr to afford bis-benzyl ether **2.345** in 97% over two steps. Finally, treatment of **2.345** with a controlled source of hydrogen cyanide afforded hibarimicin B model A cyanophthalide annulation donor **2.338**.

Scheme 2.45 Synthesis of hibarimicin B model A cyanophthalide annulation donor.



Reagents and conditions: (a) BCl_3, CH_2Cl_2, –78 °C → RT; (b) NBS, DMF, 75%; (c) ^{n}BuLi, THF, –78 ºC; then $ClCO_2Me$, –78 ºC → RT, 94%; (d) NBS, AIBN, CCl_4, reflux, 89%; (e) $^i Pr_2NEt$, DMSO, 70 °C, 77%; (f) BCl_3,

---

[212] Trialkoxytoluene **2.339** was prepared according to the protocol detailed in Ref. 141.

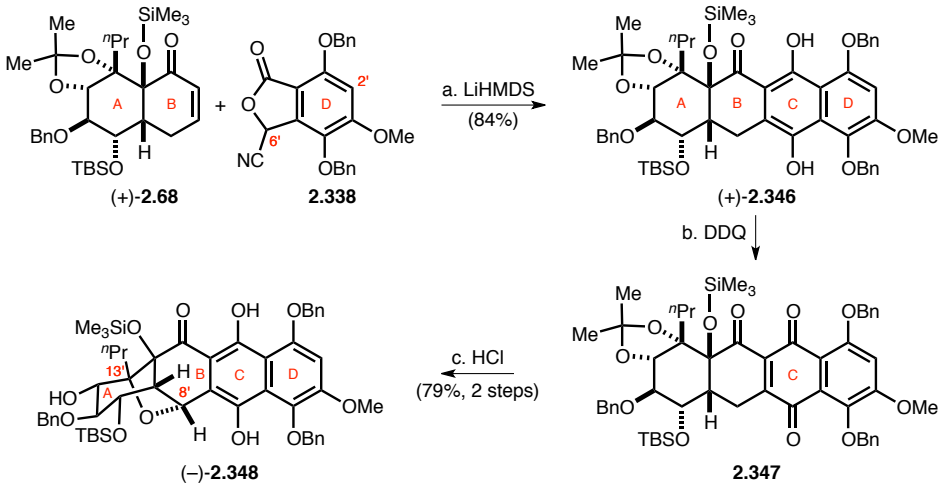
[213] The same selectivity trend was observed for similar 1,3,4-trialkoxybenzene substrates and was attributed to increased steric hinderence of the C2' position relative to the C18' position, see Ref. 104c.

[214] Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114.

Reagents and conditions for Scheme 2.45 continued: CH_2Cl_2, –78 → 0 °C; (g) BnBr, K_2CO_3, DMF, 0 → 60 °C, 97% (two steps); (h) $Me_2C(OH)CN$, Et_3N, $CHCl_3$, 81%.

Synthesis of the hibarimicin B model A aglycon (–)-**2.348**, comprising the ABCD-rings of **2.1**, was accomplished via a protocol used for the synthesis of hibarimicinone (**2.2**) (Scheme 2.46). Kraus annulation of cyanophthalide **2.338** with AB-/HG-enone (+)-**2.68** under rigorously oxygen-free conditions afforded ABCD-tetracycle (+)-**2.346** in 84% yield. The C-ring hydroquinone of (+)-**2.346** was then oxidized with DDQ to the corresponding C-ring quinone (**2.347**), which upon exposure to anhydrous HCl underwent biomimetic etherification to furnish pentacycle (–)-**2.348** in 79% yield over two steps.

Scheme 2.46 Synthesis of hibarimicin B model A aglycon.

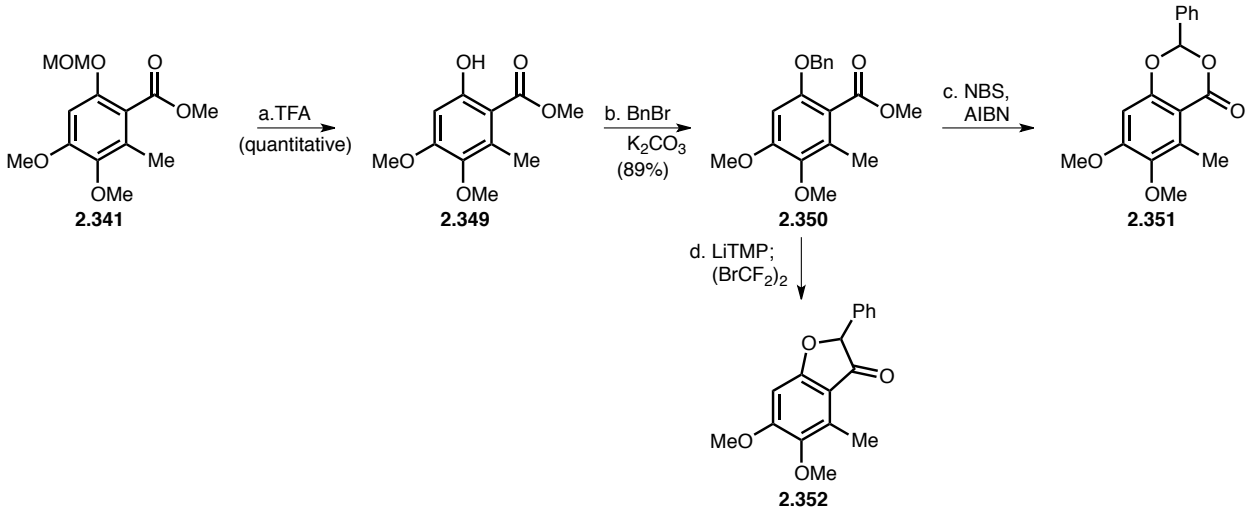


Reagents and conditions: (a) LiHMDS, THF, –78 → 0 °C, 84%; (b) DDQ, CH_2Cl_2, –10 °C; (c) HCl, $ClCH_2CH_2Cl$, 0 °C, 79% (two steps).

Our first approach to the synthesis of hibarimicin B model B (**2.335**) began with conversion of the previously prepared MOM protected *ortho*-toluate **2.341** to the corresponding benzyl protected *ortho*-toluate **2.350** via: (1) acid-promoted hydrolysis of the MOM group with TFA and (2) reprotection with BnBr (Scheme 2.47). Bromination of the C5–Me group was attempted under standard conditons; treatment of **2.350** with NBS and AIBN at an elevated temperature led to selective bromination of the C1 benzyl ether rather than the C5–Me, followed by cyclization of the pendant methyl ester onto the resultant benzylic bromide with concomitant loss of a methyl substituent to give acetal **2.351**. Alternatitvely, a

lithiation/bromination sequence was attempted by exposure of **2.350** to LiTMP at –78 °C followed by addition of $(BrCF_2)_2$. Under these conditions, the C1 benzyl ether was selectively lithiated and the resultant benzylic anion cyclized onto the methyl ester to give ketone **2.352** after loss of lithium methoxide.

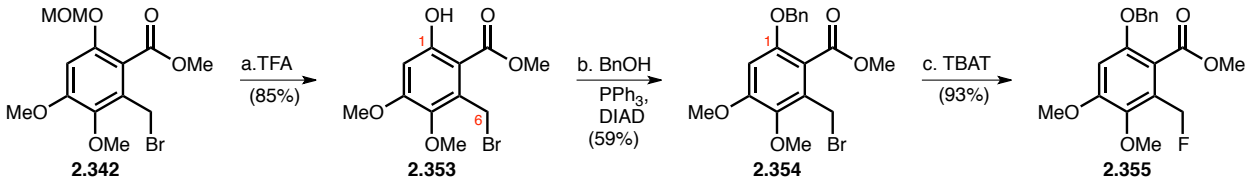
Scheme 2.47 Attempted synthesis of hibarimicin B model B annulation donor.



Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C → RT, quantitative. (b) BnBr, K_2CO_3, DMF, 0 → 60 °C, 89%. (c) NBS, AIBN, CCl_4, reflux, 3 h (d) LiTMP, THF, –78 °C; then $(BrCF_2)_2$, –78 °C.

Our second approach to the synthesis of **2.335** began with previously prepared MOM protected benzyl bromide **2.342** (Scheme 2.48). The MOM group was hydrolyzed with TFA to afford phenol **2.353** in 85% yield. The electrophilic nature of the C6 benzyl bromide substituent prevented the use of base for the installation of the corresponding C1 benzyl ether (**2.354**). Instead, benzyl protection of **2.353** was accomplished under Mitsunobu conditions with BnOH, PPh_3, and DIAD. Finally **2.354** was converted to benzyl fluoride annulation donor **2.355** using TBAT in 93% yield.

Scheme 2.48 Synthesis of hibarimicin B model B benzyl fluoride annulation donor.



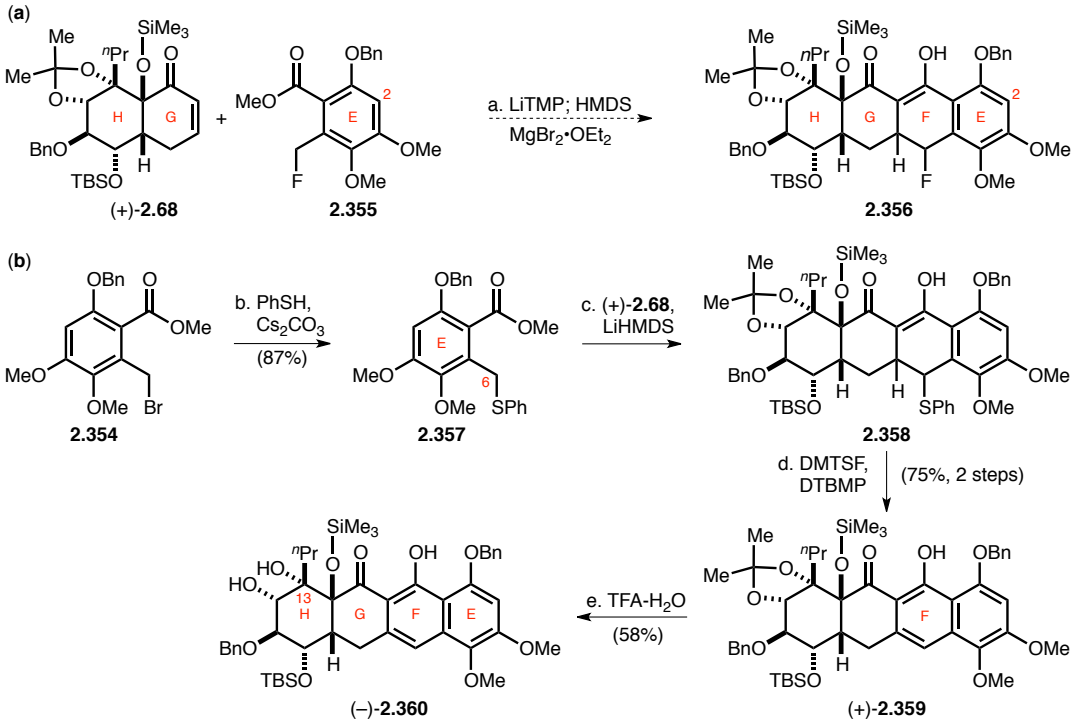
Reagents and conditions: (a) TFA, CH_2Cl_2, –78 → 0 °C, 85%. (b) BnOH, PPh_3, DIAD, 0 °C → RT, 59%. (c) TBAT,

Reagents and conditions for Scheme 2.48 continued: MeCN, 82 °C, 93%.

Synthesis of the hibarimicin B model B aglycon **2.335**, which comprises the EFGH-rings of **2.1**, was attempted using a benzyl fluoride Michael–Claisen reaction sequence developed for the synthesis of HMP-Y1 (**2.9**) (Scheme 2.49a).[141] In accordance with this protocol, a cold solution of (+)-**2.68** and **2.355** in THF was treated with LiTMP to facilitate the Michael addition step of the proposed tandem reaction sequence. Next, HMDS and $MgBr_2$•OEt_2 were sequentially introduced and the reaction mixture was warmed to facilitate a Claisen condensation and thereby generate tetracycle **2.356**. Unfortunately, this procedure afforded multiple products, none of which corresponded to **2.356**. Therefore, C6 thiophenyl substituted *ortho*-toluate annulation donor **2.357** (Scheme 2.49b) was prepared through substitution of benzyl bromide **2.354** with thiophenol. Exposure of **2.357** and (+)-**2.68** to LiHMDS at –78 °C followed by warming the reaction mixture to 0 °C over three hours promoted an alternative Michael–Claisen reaction sequence to supply tetracycle **2.358**. Aromatization of the F-ring was accomplished using precisely one equivalent of DMTSF and excess DTBMP to give naphthalene **2.359** in 75% yield over two steps. The use of greater than one equivalent DMTSF in this reaction promoted thiomethylation of the C6 position of (+)-**2.359**. In contrast, the analogous octacyclic intermediates for the synthesis of hibarimicinone (**2.2**) ((–)-**2.130** and (+)-**2.131**) could be exposed to excess DMTSF without the formation of any thioalkylated by-products. This observation was the first of many that demonstrated the differential reactivity of the hibarimicin B model B intermediates relative to the octacyclic intermediates for the synthesis of **2.2**. Next, hydrolysis of the acetonide protecting group was found to be extremely challenging due to three complicating factors: (1) hydrolylis of the acetonide and the trimethylsilyl ether were competitive, (2) the desired triol product (–)-**2.360** was extremely sensitive to oxidative decomposition, and (3) (–)-**2.360** was also sensitive to acid promoted decomposition via ionization of the C13 tertiary carbinol. A variety of Brønsted acids were screened for this transformation including: HCl, Cl_3CCO_2H, Cl_2HCCO_2H, ClH_2CCO_2H, PPTS, PTSA and TFA. After extensive experimentation, it was found that (–)-**2.360** could be reliably obtained by treatment of a rigorously deoxygenated solution of (+)-**2.359** in 1,2-dichloroethane with a deoxygenated aqueous solution of TFA for 2-3 h at ambient

temperature. Purification of the resultant yellow residue via semi-preparatory HPLC afforded pure (–)-**2.360** in 58% yield.

Scheme 2.49 Synthesis of hibarimicin B model B aglycon.

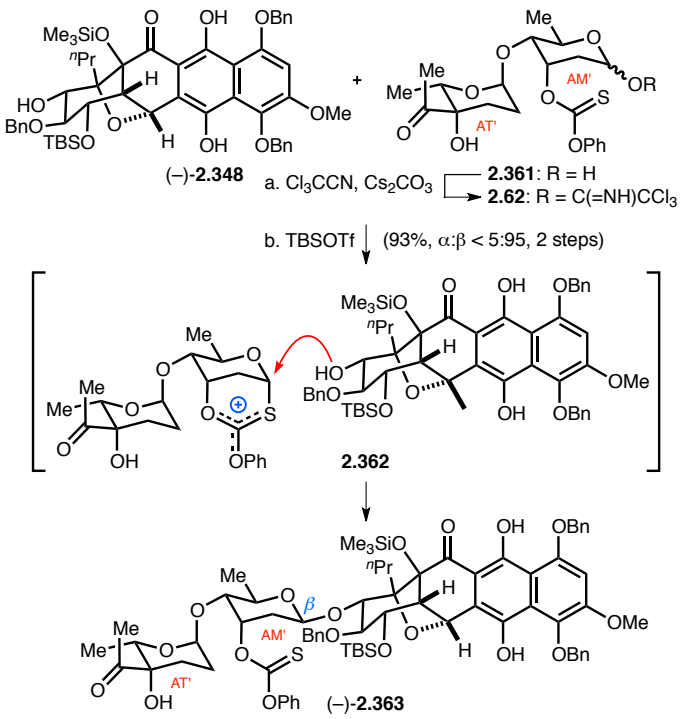


Reagents and conditions: (a) LiTMP, THF, –78 °C; then HMDS, –78 → –35 °C; then $MgBr_2$•OEt_2, –35 → 0 °C; (b) PhSH, Cs_2CO_3, DMF, 87%; (c) LiHMDS, THF, –78 → 0 °C; (d) DMTSF, DTBMP, MeCN, 0 °C → RT, 75% (two steps); (e) TFA-H_2O-$ClCH_2CH_2Cl$ (4:1:1), 3 h, 58%.

With a route to hibarimicin B model A and B aglycons established, we attempted β-selective installation of the AM'-AT' disaccharide (Scheme 2.50). We imagined that the AM3' axial thionocarbonate group would induce a β-selective glycosylation reaction between trichloroacetimidate glycosyl donor **2.62** and aglycon (–)-**2.348** through neighboring group assistance. Specifically, we anticipated that exposure of **2.62** to a suitable Lewis acid would generate stabilized oxocarbenium ion **2.362** in which the α-face of the intermediate would be blocked by the bridging thionocarbonate group, thereby favoring β-selective glycosylation. AM'-AT' glycosyl donor **2.62** was freshly prepared from hemiacetal **2.361** using Cl_3CCN and Cs_2CO_3. A solution of **2.62** and algycon (–)-**2.348**, in a 2.5:1.0 molar ratio, was treated with a stoichiometric quantity of TBSOTf at –78 °C to afford 2-deoxyglycoside (–)-

2.363 in 93% yield over two steps with a < 5:95 α:β anomeric ratio.

Scheme 2.50 Formation of model AM'-AT' glycoside.



Reagents and conditions: (a) Cl_3CCN, Cs_2CO_3, CH_2Cl_2, 12 h; (b) TBSOTf, CH_2Cl_2, –78 °C, 5 h, 93%, α:β < 5:95 (two steps).

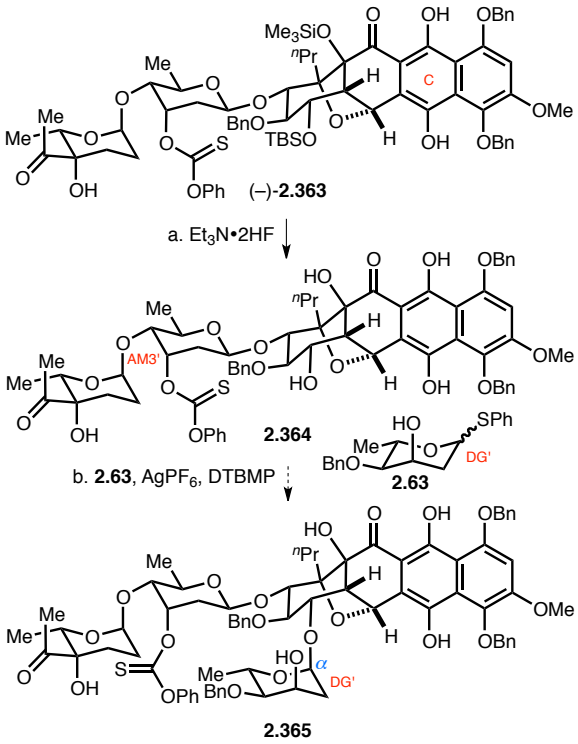
Next, silyl ether deprotection and installation of the remaining DG' α-glycosidic linkage were investigated. The C-ring hydroquinone subunit of (–)-**2.636** rendered it sensitive to base promoted decomposition by reagents such as TBAF, TASF, or TBAT. Alternatively, we discovered that exposure of (–)-**2.636** to a deoxygentated solution of Et_3N•2HF[215] in MeCN cleanly removed the TMS and TBS ethers after 36 h at ambient temperature (Scheme 2.51).[216] A solution of the resultant pentaol **2.364**, DG' thiophenyl glycosyl donor **2.63**, DTBMP, and 4 Å MS was prepared in CH_2Cl_2 and cooled to –78 °C before $AgPF_6$ was added to the reaction mixture according to Hirama's procedure in order to generate DG' α-glycoside **2.365**.[179] Unfortunately, under these conditions the C-ring hydroquinone was readily

[215] Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527–6530.

[216] The TMS ether was completely removed within the first 90 min of the reaction as ascertained by 1H NMR of the unpurified product mixture.

oxidized and the resultant quinone underwent decomposition. Use of the analogous C-ring quinone starting material in this reaction similarly led to the formation of an indiscernable product mixture. Additionally, we hypothesized that the presence of the AM3' thionocarbonate group during the Ag(I) promoted glycosylation might contribute to substrate decomposition. Therefore we decided to reductively remove the AM3' thionocarbonate group and to benzyl protect the C-ring hydroquinone, in order to suppress oxidative decomposition pathways during DG' glycoside formation.

Scheme 2.51 Attempted DG' glycoside formation.

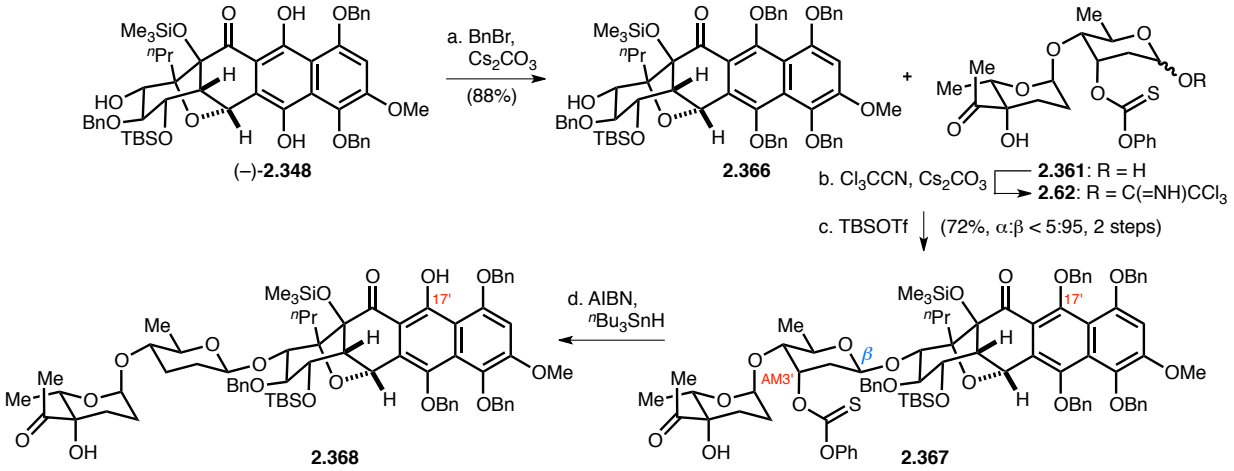


Reagents and conditions: (a) Et_3N•3HF, Et_3N, MeCN, 36 h; (b) **2.63**, $AgPF_6$, DTBMP, 4 Å MS, CH_2Cl_2, –78 °C, 1 h.

Penta-benzyl protected aglycon **2.366** (Scheme 2.52) was prepared according to the following procedure: a deoxygentated solution of (–)-**2.348** and BnBr in DMF was frozen in the liquid nitrogen cooled well of a glovebox and charged with Cs_2CO_3; the reaction vessel was sealed and immediately removed from the glovebox and placed in a ice-water bath; the resultant heterogeneous reaction mixture was vigorously stirred for 3 h to provide **2.366**, after aqueous work-up, in 88% yield. Next, the AM'–AT' dissacharide subunit was installed in a β-selective fashion according to the previously described

procedure to afford 2-deoxy-β-glycoside **2.367** in 72% yield. Unexpectedly, exposure of **2.367** to AIBN and $^{n}Bu_3SnH$ at 80 °C for 1 h promoted simultaneous reductive removal of the AM3' thionocarbonate group and undesired cleavage of the C17'–OBn ether to provide C17' phenol **2.368**.

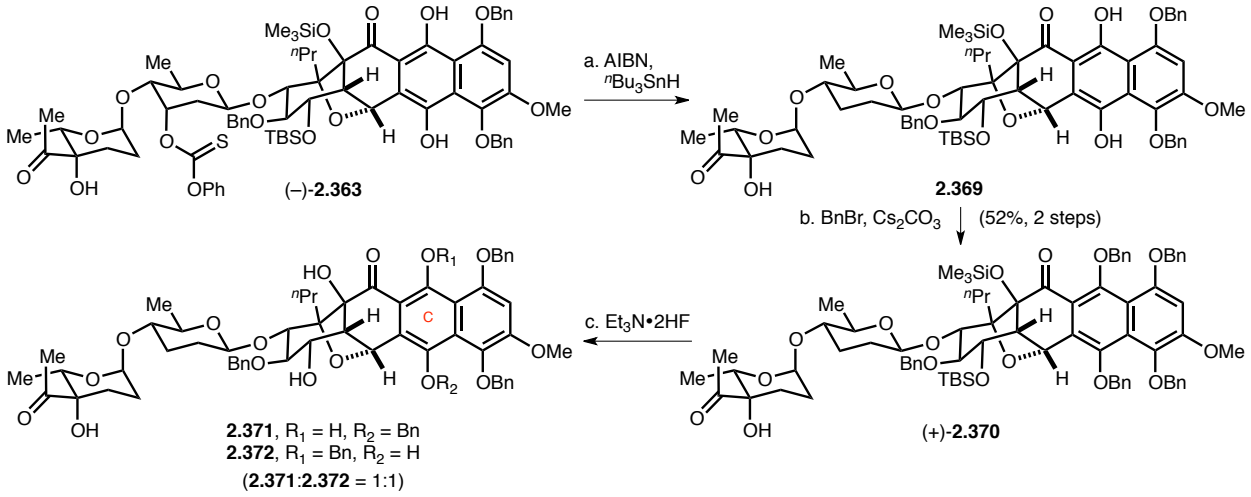
Scheme 2.52 Attempted preparation of penta-benzyl protected model aglycon .



Reagents and conditions: (a) BnBr, Cs_2CO_3, DMF, 0 °C, 88%; (b) Cl_3CCN, Cs_2CO_3, CH_2Cl_2; (b) TBSOTf, CH_2Cl_2, –78 °C, 72%, α:β < 5:95 (two steps); (d) AIBN, $^{n}Bu_3SnH$-PhH (1:1), 80 °C.

Given this result, we elected to protect the C-ring hydroquine after reductive removal of the AM3' thionocarbonate group. A dry/deoxygenated mixture of AM'-AT' β-glycoside (–)-**2.363**, AIBN, $^{n}Bu_3SnH$, and PhH was heated to 80 °C for 1 h to afford 2,3-dideoxy-β-glycoside **2.369** (Scheme 2.53). Next, treatment of **2.396** with BnBr and Cs_2CO_3 furnished penta-benzyl protected disaccharide (+)-**2.370** in 52% yield over two steps. Unfortunately, exposure of (+)-**2.370** to Et_3N•2HF, under previously optimized conditions for silyl ether deprotection, resulted in the formation of two regioisomeric products, **2.371** and **2.372**, in which one of the two C-ring benzyl ethers had been removed. This observation prompted us to reexamine the use of TBAF for silyl ether deprotection.

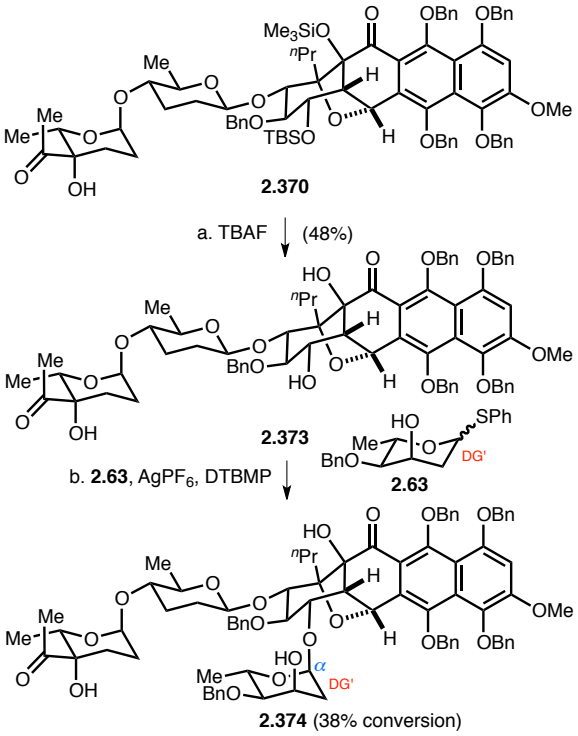
Scheme 2.53 Protection of C-ring hydroquinone and attempted silyl deprotection.



Reagents and conditions: (a) AIBN, $^{n}Bu_3SnH$-PhH (1:1), 80 °C, 1 h; (b) BnBr, Cs_2CO_3, DMF, 0 °C, 3 h, 52% (two steps); (c) $Et_3N•3HF$, Et_3N, MeCN, 36 h.

Accordingly, (+)-**2.370** was treated with TBAF at ambient temperature for 26 h to provide sufficient quanitities of triol **2.373** to test DG' glycoside formation (Scheme 2.54). Exposure of **2.373** and **2.63** to Hirama's conditions afforded 2-deoxy-α-glycoside **2.374** as an inseperable mixture with glycosyl acceptor **2.373** (**2.374**:**2.373** = 1.0:1.6). Attempts to improve the conversion in this reaction included: (1) lengthening the reaction time, (2) increasing the stoichiometry of glycosyl donor **2.63**, (3) increasing the stoichiometry of $AgPF_6$ and DTBMP, (4) increasing the reaction temperature to 0 °C, and (5) slowly adding the glycosyl donor **2.63** to a solution of **2.373**, $AgPF_6$, and DTBMP over several hours via syringe pump. Unfortunately, none of these operational modifications improved the efficiency of the glycosylation. Based on these observations we hypothesized that steric hinderence around C10'–OH was impeding glycosylation and causing self-condensation of the glycosyl donor **2.63**. We anticipated that benzyl protection of the free DG3'–OH would prevent unproductive substrate degradation.

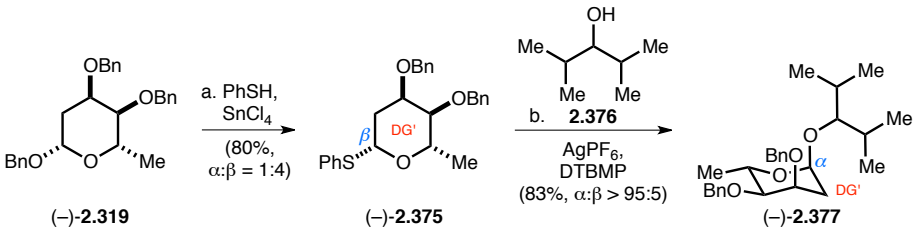
Scheme 2.54 Successful silyl deprotection and attempted glycosylation of penta-benzyl protected aglycon **2.373**.



Reagents and conditions: (a) TBAF, THF, 0 °C → RT, 48%. (b) **2.63**, $AgPF_6$, DTBMP, 4 Å MS, CH_2Cl_2, –78 °C → 0 °C, (38% conversion based on **2.373**).

Benzyl glycoside (–)-**2.319** was treated with PhSH and $SnCl_4$ to furnish bis-benzyl protected thiophenyl glycosyl donor (–)-**2.375** in 80% yield with a 1:4 α/β anomeric ratio (Scheme 2.55). The potential anomeric selectivity of the desired DG' glycoside formation was assessed using 2,4-dimethyl-3-pentanol (**2.376**) as a model glycosyl acceptor. Exposure of β-thiophenyl glycoside (–)-**2.375** and **2.376** to Hirama's conditions cleanly afforded 2-deoxy-α-glycoside (–)-**2.377** in 83% yield with a >95:5 α:β anomeric ratio.

Scheme 2.55 Preparation of bis-benzyl protected thiophenyl glycosyl donor (–)-**2.375** and α-selective model glycosylation reaction.

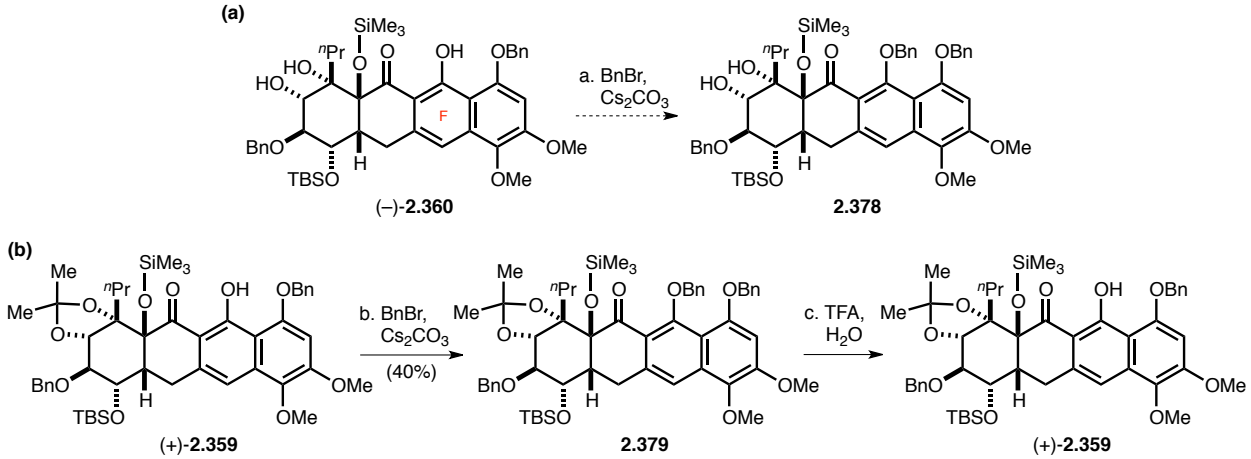


Reagents and conditions: (a) PhSH, $SnCl_4$, CH_2Cl_2, –78 °C, 80%, α:β = 1:4. (b) 2,4-dimethyl-3-pentanol (**2.376**),

Reagents and conditions for Scheme 2.55 continued: $AgPF_6$, DTBMP, 4 Å MS, CH_2Cl_2, 0 °C, 83%, α:β > 95:5.

While the DG' model glycosylation result was promising, concurrent investigations concerning benzyl protection of hibarimicin B model B discouraged us from pursuing this approach (Scheme 2.56). Exposure of the napthol triol (–)-**2.360** to BnBr and Cs_2CO_3 under oxygen-free conditions at 0 °C resulted in a complex mixture of products (Scheme 2.56a). Alternatively, acetonide (+)-**2.359** could be protected to afford benzyl ether **2.379** in 40% yield under the same conditions. However, exposure of **2.379** to TFA-H_2O, under previously optimized conditions for acetonide hydrolysis, provided benzyl-deprotected napthol (+)-**2.359** as the major product (Scheme 2.56b). These results indicated that benzyl protection of an analogous hibarimicin B (**2.1**) precursor would be problematic. Therefore, an alternative strategy for α-selective DG/DG' monosaccharide installation was investigated.

Scheme 2.56 Unsuccessful hibarimicin B model B benzyl protection.

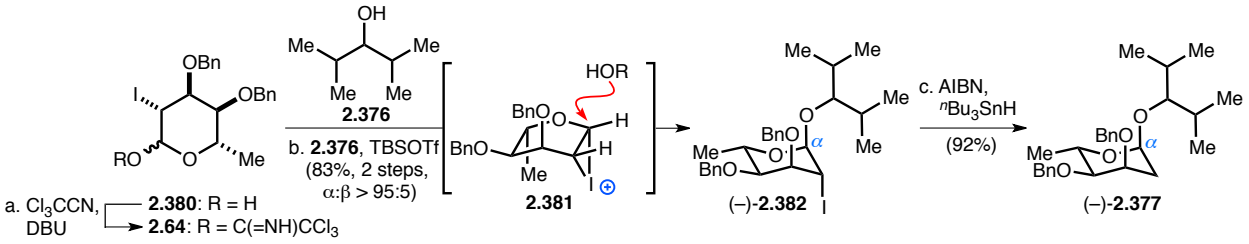


Reagents and conditions: (a) BnBr, Cs_2CO_3, DMF, 0 °C. (b) BnBr, Cs_2CO_3, DMF, 0 °C, 40%. (c) $ClCH_2CH_2Cl$-TFA-H_2O (4:1:1).

Our revised aproach for formation of the remaining 2-deoxy-α-glycosidic linkage relied on the use of an axial 2-iodo directing group to control anomeric selectivity (Scheme 2.57). 2-Iodo-glycosyl trichloroacetimidate **2.64** was prepared from hemiacetal **2.380** under standard conditions. Exposure of a solution of **2.64** and 2,4-dimethyl-3-pentanol (**2.376**) in CH_2Cl_2 to TBSOTf at –78 °C provided 2-deoxy-2-iodo-α-glycoside (–)-**2.382** in 83% yield with >95:5 α:β anomeric ratio. Presumably the high level of α-selectivity in this transformation was due to nucleophilic attack of **2.376** on iodonium intermediate **2.381**.

Finally, the 2-iodo substituent was reductively cleaved with AIBN and $^{n}Bu_3SnH$ at 80 °C to give 2-deoxy-α-glycoside (–)-**2.377** in 92% yield.

Scheme 2.57 Preparation of model DG/DG' α-glycoside.

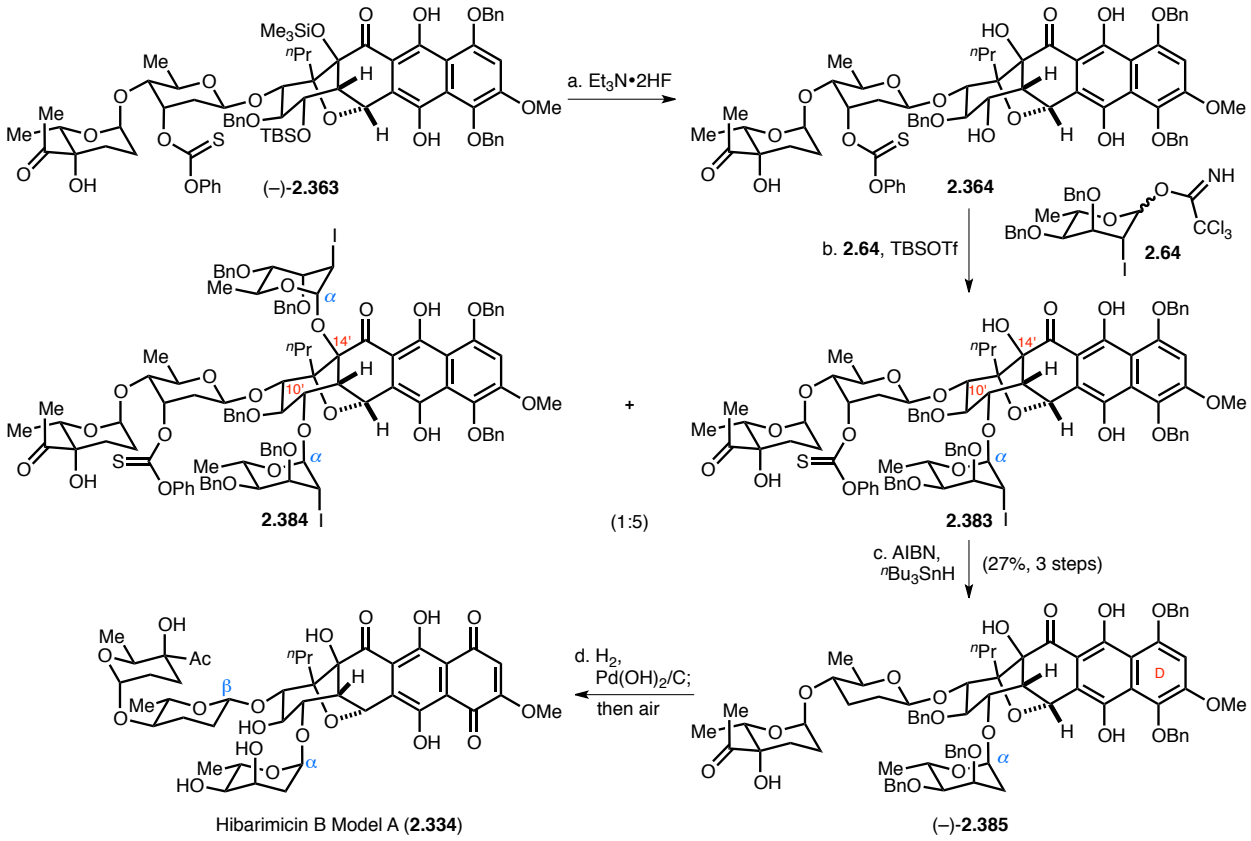


Reagents and conditions: (a) Cl_3CCN, DBU, CH_2Cl_2, –10 → 0 °C; (b) TBSOTf, 4 Å MS, CH_2Cl_2, –78 °C, 83%, α:β > 95: 5 (two steps); (c) AIBN, $^{n}Bu_3SnH$-PhH (1:1), 80 °C, 92%.

Given this promising result, the same conditions were applied toward glycosylation of the hibiramicin B model A algycon **2.364**, which was prepared through silyl deprotection of (–)-**2.363**, under previously optimized conditions (Scheme 2.58). A solution of **2.364** and trichloroacetimidate glycosyl donor **2.63** in CH_2Cl_2 was exposed to a variety of Lewis acids including: BF_3•OEt_2, $ZnCl_2$•OEt_2, TIPSOTf, and TBSOTf, resulting in the α-selective formation of mono- and bis-glycosylated products **2.383** and **2.384**, respectively. Complete consumption of **2.364** was achieved using all of the aformentioned Lewis acids. However, it was surprising to observe that the C14' tertiary carbinol of the mono-glycosylated product (**2.383**) underwent a second glycosylation reaction at a rate commensurate with the first glycosylation of **2.364**. Under optimized conditions, a solution of **2.64** (3.7 equiv) in CH_2Cl_2 was added via syringe pump to a solution of **2.364** (1.0 equiv) and TBSOTf (1.0 equiv) in CH_2Cl_2 at –78 °C over 90 min to afford mono- and bis-α-glycosides **2.383** and **2.384** in a 5:1 ratio. Next, the DG2' iodo and AM3' thionocarbonate directing groups were simultaneously removed from **2.383** using AIBN and $^{n}Bu_3SnH$ at 80 °C to give compound (–)-**2.385** in 27% yield over three steps. The poor overall yield for these transformations stems from the unstable nature of the intermediates toward purification and handling, combined with the marginal selectivity for mono- over bis-glycosylation. Finally, global benzyl deprotection/D-ring oxidation of (–)-**2.385** was attempted via hydrogenolysis in EtOAc with Pearlman's

catalyst[217] followed by filtering and exposure to air to yield a product which we have tentatively assigned as hibarimicin B model A (**2.334**) based on the ^{1}H NMR and the mass spectrum of the unpurified product mixture.

Scheme 2.58 Synthesis of hibarimicin B model A.



Reagents and conditions: (a) Et_3N•3HF, Et_3N, MeCN. (b) **2.64**, TBSOTf, 4 Å MS, CH_2Cl_2, –78 °C, **2.383**:**2.384** (5:1 ratio)[218] (c) AIBN, $^nBu_3SnH$-PhH (1:1), 80 °C, 27% (three steps). (d) H_2, $Pd(OH)_2$/C, EtOAc; then air.

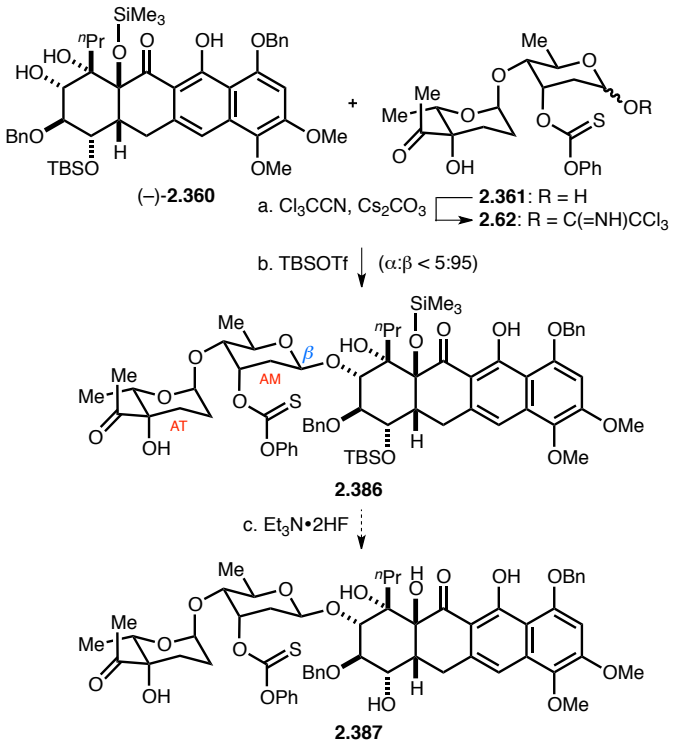
With a tentative route to the hibarimicin B model A (**2.334**) established, we sought to apply the same reaction conditions toward the synthesis of hibarimicin B model B (**2.335**) (Scheme 2.59). Glycosylation of aglycon (–)-**2.360** and trichloroacetimidate **2.62** was accomplished with TBSOTf to yield β-glycoside **2.386**. However, **2.386** was extremely unstable to purification on silica gel, which prevented accurate determination of the product yield. Treatment of **2.386** with a deoxygenated solution

[217] Pearlman, W. M. *Tetrahedron Lett.* **1967**, *8*, 1663–1664.

[218] Relative product distribution based on the intergration of ^{1}H NMR spectrum of unpurified product mixture.

of Et_3N•2HF at ambient temperature resulted in the formation of a variety of undesired products, including several in which the disaccharide had been cleaved from the aglycon based on mass spectroscopy. While this result was discouraging, we anticipated the corresponding pseudodimeric substrate would be much more stable to silyl deprotection conditions based on our previous experience with intermediates toward the synthesis of hibarimicinone (**2.2**).

Scheme 2.59 Hibarimicin B model B glycosylation and attempted silyl deprotection.



Reagents and conditions: (a) Cl_3CCN, Cs_2CO_3, CH_2Cl_2; (b) TBSOTf, CH_2Cl_2, –78 °C, α:β < 5:95 (two steps); (c) Et_3N•3HF, Et_3N, MeCN.

2.12 Progress Toward a Total Synthesis of Hibarimicin B

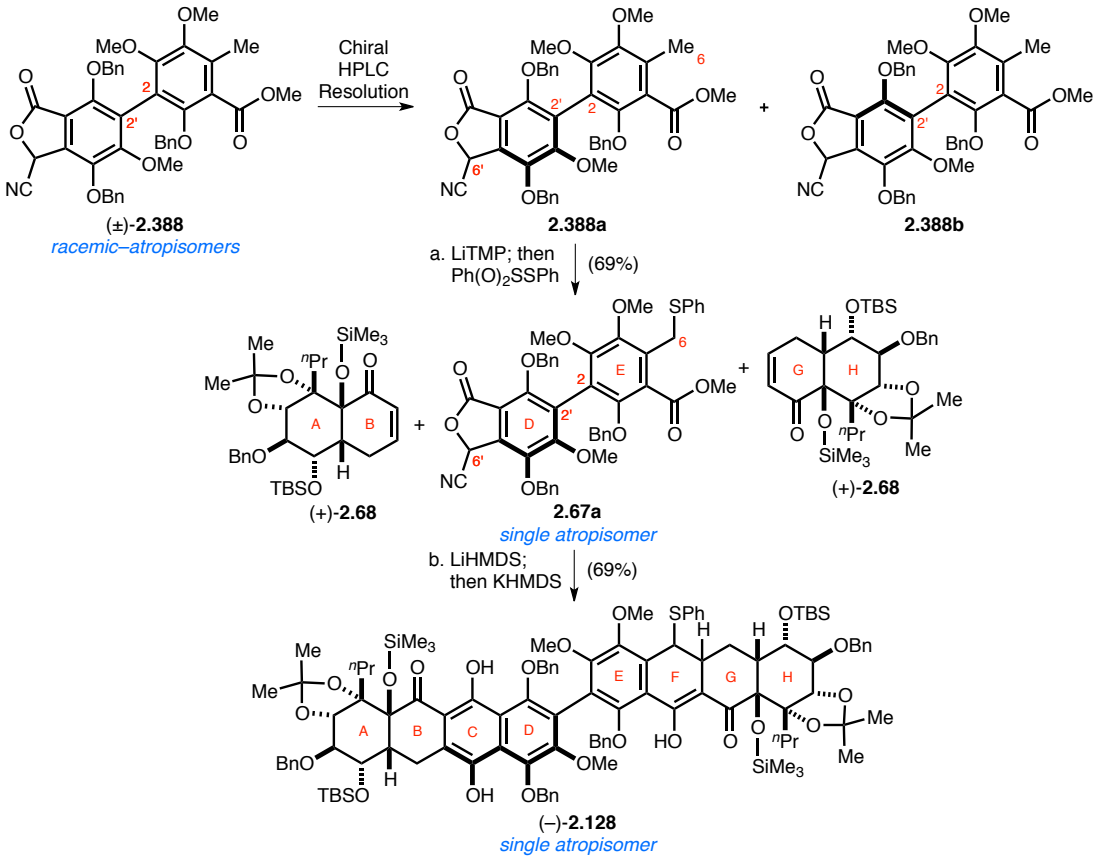
Satisfied with our model studies, we turned our attention to the synthesis of hibarimicin B (**2.1**). While the absolute stereochemistry of the C2–C2' biaryl linkage of **2.1** had not yet been confirmed, we assumed that it corresponded to the stereochemistry of hibarimicinone (**2.2**). Therefore, the atropisomers

of unsymmetrical biaryl annulation donor precursor **2.388a** and **2.388b**[219] were separated through chiral semi-preparatory HPLC (Scheme 2.60).[220] Unsymmetrical biaryl annulation donor **2.67a** was then prepared via double deprotonation of enantiopure **2.388a** with LiTMP followed by a short exposure to *S*-phenyl benzenethiosulfonate to chemoselectively install the phenyl sulfide moiety at C6. Treatment of **2.67a** and AB-/HG-enone (+)-**2.68** with LiHMDS under rigorously oxygen-free conditions followed by addition of KHMDS after 20 h at 0 °C and warming the rection mixture to ambient temperature for an additional 12 h yielded octacycle (–)-**2.128** as a single atropisomer in 69% yield.

[219] The absolute stereochemistry of biaryl precursor **2.388a** was assigned based on its corresponding annulation product ((–)-**2.128**).

[220] Direct chiral resolution of the racemic unsymmetrical biaryl annulation donor (±)-**2.67** was inefficient due to solubility issues.

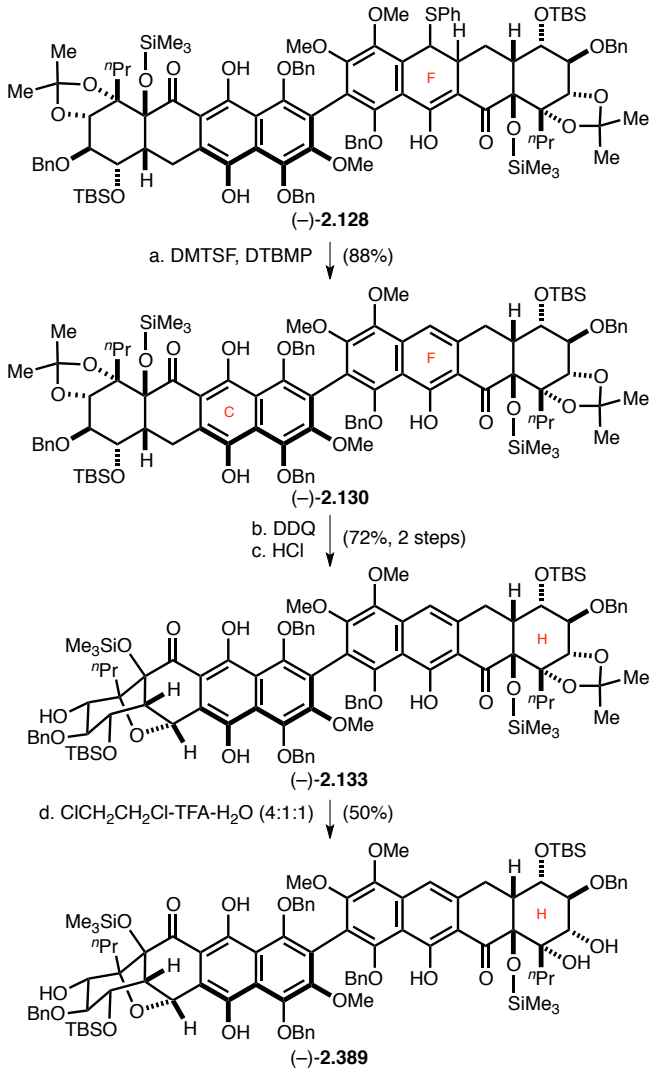
Scheme 2.60 Chiral HPLC resolution of unsymmetrical biaryl annulation donor precursor (±)-**2.388** and two-directional double annulation reaction.



Reagents and conditions: (a) LiTMP, THF, –78 °C; then $Ph(O)_2SSPh$, 69%. (b) LiHMDS, THF, –78 → 0 °C; then KHMDS, 0 °C → RT, 69%.

Next, octacycle (–)-**2.128** was converted to nonacycle (–)-**2.133** in three steps including: (1) F-ring aromatization via elimination of the C6-benzylic phenyl sulfide with DMTSF, (2) DDQ oxidation of the C-ring hydroquinone to quinone, and (3) biomimetic etherification promoted by anhydrous HCl (Scheme 2.61). Next, the H-ring acetonide diol protecting group was hydrolyzed by exposure of (–)-**2.133** to a deoxygenated solution of 1,2-dichloroethane-TFA-H_2O (4:1:1) at ambient temperature for 2 h to furnish hibarimicin B aglycon (–)-**2.389** in 50% yield.

Scheme 2.61 Synthesis of hibarimicin B algycon (–)-**2.389**.



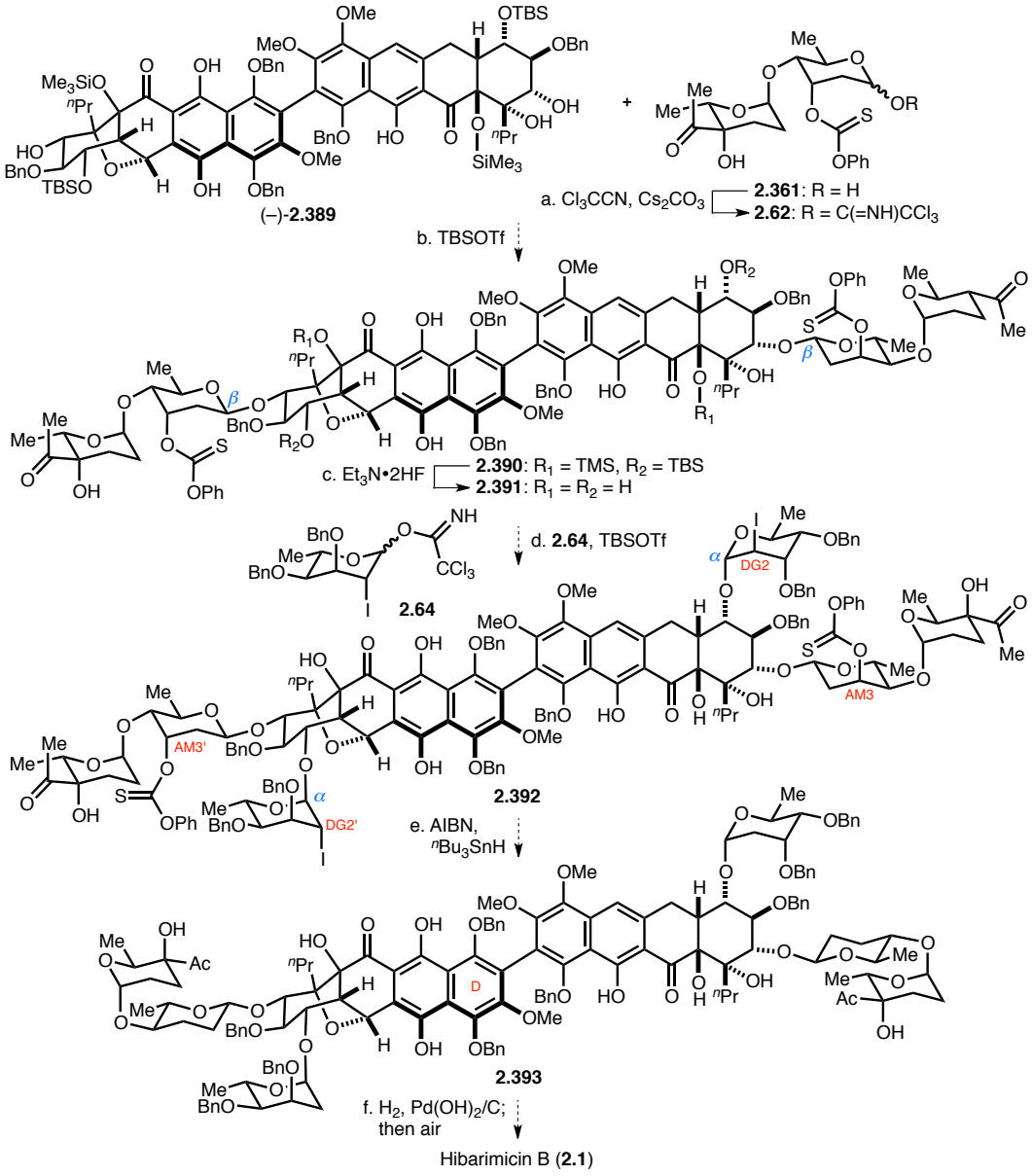
Reagents and conditions: (a) DMTSF, DTBMP, MeCN, 0 °C → RT, 88%; (b) DDQ, PhMe, 0 °C; (c) HCl, $ClCH_2CH_2Cl$, 4 °C, 72% (two steps); (c) $ClCH_2CH_2Cl$-TFA-H_2O (4:1:1), 50%.

2.13 Proposed Completion of the Total Synthesis of Hibarimicin B

Our proposed completion of hibarimicin B (**2.1**) follows the steps developed for the synthesis of hibarimicin B model A (**2.334**) and is outlined in Scheme 2.62. We anticipate that a two-directional double glycosylation between algycon (–)-**2.389** and trichloroacetimidate **2.62** promoted by TBSOTf will provide bis-glycoside **2.390** with high levels of β-selectivity. Preliminary studies on this transformation indicated that full conversion to a bis-glycosylated product was possible using five equivalents of **2.62**.

Additionally, one major diasteromeric product was formed in this reaction, which we assumed corresponded to the structure of **2.390**. Once this procedure has been optimized and the product fully assigned, we plan to remove the silyl ether protecting groups with Et_3N•2HF to provide aglycon **2.391** for the second key two-directional double glycosylation reaction. α-Selective glycosylation between **2.391** and 2-iodo-glycosyl trichloroacetimidate **2.64** will then be attempted to potentially access tetra-glycoside **2.392**. One problem we anticipate in this transformation is the undesired glycosylation of the C14 and C14' tertiary carbinols. However, we expect these byproducts will be easily separated from **2.392**. Next, the AM3/AM3' and DG2/DG2' directing groups will be removed using AIBN and $^{n}Bu_3SnH$ to give hibarimicin B precursor **2.393**. Finally, global benzyl ether deprotection of **2.393** via hydrogenation followed by mild acidification of the reaction mixture to prevent atropisomerism and exposure of the resultant D-ring hydroquinone to air is expected to afford hibarimicin B (**2.1**) as a single atropisomer. Further progress towards the completion of this goal will be reported in due course.

Scheme 2.62 Proposed completion of hibarimicin B.



2.14 Conclusion

In conclusion, Brian B. Liau and I have made significant progress toward the completion of the total synthesis of hibarimicin B (**2.1**). We have prepared C14-hydroxy *ent*-AB/HG-enone (–)-**2.110** and AB-/HG-enone annulation acceptor (+)-**2.68** on multi-gram scale starting from methyl-α-D-glucopyranoside. The synthesis of (–)-**2.110** and (+)-**2.68** featured a key Lewis acid-promoted contrasteric Diels–Alder reaction to set the relative stereochemistry of the *cis*-decalin carbon framework and a tandem

silyl-zincate 1,6-addition/enolate oxidation sequence to functionalize the carbon skeleton. Additionally, we have completed enantioselective syntheses of hibarimicinone (**2.2**), atrop-hibarimicionone (**2.135**), HMP-Y1 (**2.9**), atrop-HMP-Y1, and HMP-P1 (**2.12**) via a two-directional double annulation strategy. The use of a racemic biaryl annulation donor for the synthesis of **2.2** and **2.135** enabled assessment of their barriers to atropisomerism, which was anticipated to be critical for the total synthesis of **2.1**. Chiral resolution of a biaryl annulation donor precursor has enabled the synthesis of the orthogonally protected aglycon of hibarimicin B ((–)-**2.389**) as a single atropisomer.

In order to develop conditions for two-directional installation of the sugar subunits of **2.1**, the synthesis of hibarimicin B models A (**2.334**) and B (**2.335**) were been investigated. Towards this end, AM-AT/AM'-AT' and DG/DG' glycosyl donors were prepared. A 3-thionocarbonate directing group was demonstrated to be a useful stereocontrolling element for the formation of 2-deoxy-β-glycosidic bonds. Furthermore, reductive removal of the 3-directing group provided access to 2,3-didexoy-β-glycosides, typified by the AM-AT/AM'-AT' glycosidic linkage, in high overall efficieny. The highly oxidizable nature of the hibarimicin B model A aglycon necessitated the development of an axially oriented 2-iodo directing group for the α-selective installation of the DG/DG' sugar subunits of **2.1** under Lewis acidic conditions. This well-known strategy has been applied for the first time to the stereoselective installation of a digitoxose sugar after reductive removal of the 2-iodo directing group. We are currently pursuing the completion of **2.1** using the methods developed for the synthesis of hibarimicin B model A (**2.334**).

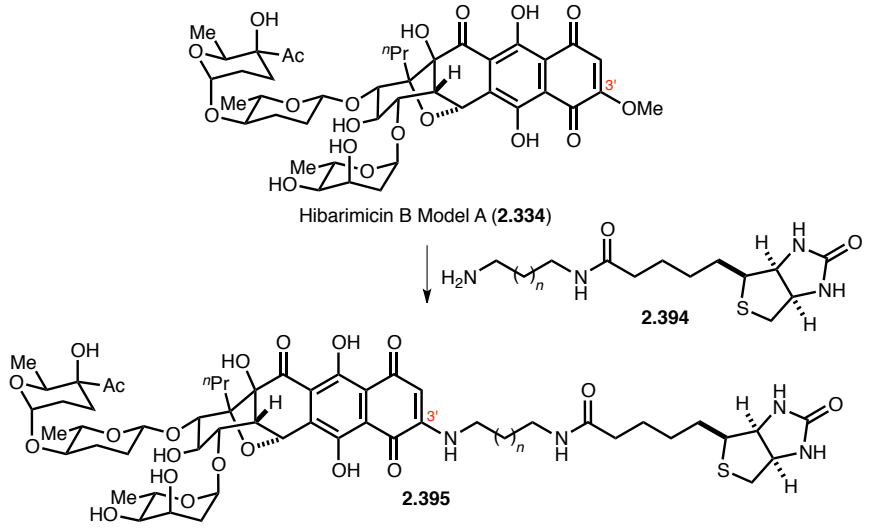
2.15 Future Goals

Ultimately, our goal is to determine the cellular target of **2.1** in order to understand the mechanism by which it elicits growth-inhibitory and proliferation-inducing activity on various cancer cell lines. One approach to achieve this goal is to compare the biological activity of hibarimicin B (**2.1**) with its model **2.334**. If **2.334** exhibits commensurate activity and selectivity with **2.1**, we plan to perform affinity chromatography on a matrix bond analog of **2.334** in order to identify its molecular target.[221] To do so, a

[221] Ong, S.-E.; Schenone, M.; Margolin, A. A.; Li, X.; Do, K.; Doud, M. K.; Mani, D. R.; Kuai, L.; Wang, X.; Wood,

linker attachment site on **2.334**, which does not perturb target-binding of the small-molecule, will be identified. Since the AM-AT/AM'-AT' and DG/DG' sugar subunits of **2.1** appear to be associated with its anti-cancer activity,[99g] it seems logical to locate the linker attachment site at the distal end of **2.334**. One could imagine modifying the C3' position of **2.334** with a variety of affinity labels through a Michael addition/methoxide elimination sequence (Scheme 2.63).[222] For instance, treatment of **2.334** with biotin conjugated amine **2.394** of variable chain length is expected to deliver biotin labeled hibarimicin B model A (**2.395**).

Scheme 2.63 Preparation of biotin labeled hibarimicin B model A (**2.395**).

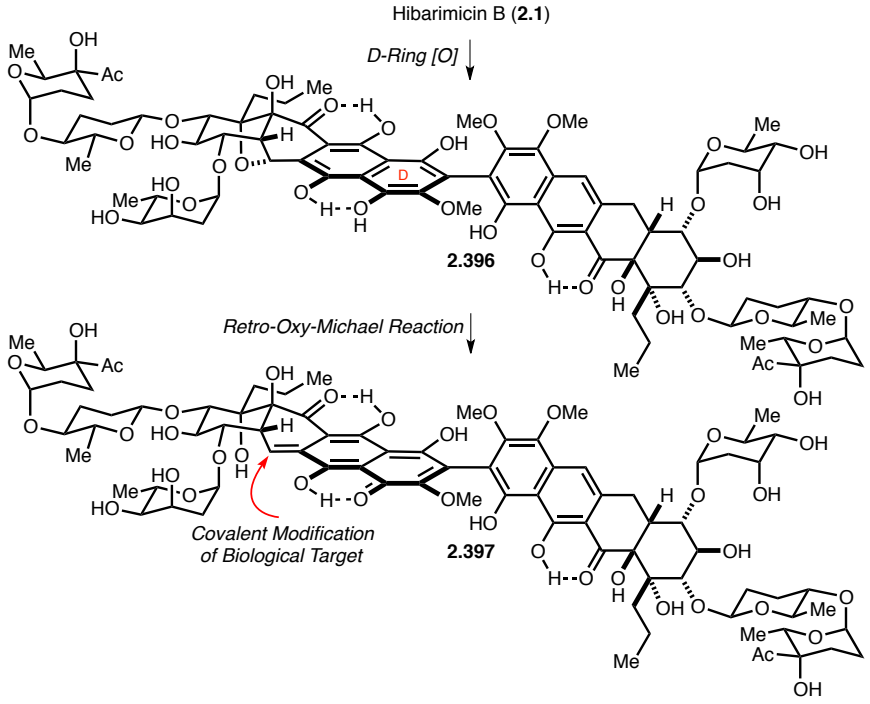


While the mechanism by which **2.1** interacts with its biological target is not known, we hypothesize that it could be through covalent modification (Scheme 2.64). Specifically, we imagined the D-ring quinone in **2.1** could be reduced to generate naphthol intermediate **2.396**. Expulsion of the ether bridge in **2.396** would then provide a highly reactive, electrophilic *ortho*-quinone methide intermediate **2.397**, which could engage in covalent modification of a biological target. A crystal structure of **2.1** bound to its target might prove or disprove this hypothesis.

J. L.; Tolliday, N. J.; Koehler, A. N.; Marcaurelle, L. A.; Golub, T. R.; Gould, R. J.; Schreiber, S. L.; Carr, S. A. *Proc. Natl. Acad. Sci. USA*, **2009**, *106*, 4617–4622 and references therein.

[222] Abel, U.; Simon, W.; Eckard, P.; Hansske, F. G. *Bio. Med. Chem Lett.* **2006**, *16,* 3292–3297.

Scheme 2.64 Hypothetetical interaction of hibarimicin B with its unknown biological target.



Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried glassware equipped with a Teflon® PTFE coated stirring bar under a positive pressure of argon unless otherwise noted. Where necessary (so noted), reactions were performed in Schlenk tubes fitted with a PTFE stopcock or pressure tubes fitted with a PTFE bushing. Flash column chromatography was performed as described by Still et al. employing silica gel 60 (40-63 μm, Whatman).[223] Preparatory thin-layer chromatography (PTLC) was performed using 0.50 mm silica gel 60 F_{254} plates purchased from EMD Chemicals. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F_{254} plates or 0.25 mm silica gel RP-18 F_{254s} plates (so noted) purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to an aqueous solution of ceric ammonium molybdate (CAM) followed by heating on a hot plate. Purification and isomerization studies were performed on an Agilent 1200 series 6120 quadrupole HPLC.

Materials. Commercial reagents and solvents were used as received with the following exceptions: tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), hexamethyldisilazane (HMDS), toluene (PhMe), benzene (PhH), and *N,N*-dimethylformamide (DMF) were degassed with argon and passed through a solvent purification system (designed by J.C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al.[224] Triethylamine, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, pyridine, and chlorotrimethylsilane were distilled over calcium hydride before use. *N,N,N′,N′*-Tetramethylethylenediamine was distilled over potassium hydroxide immediately before use. Trimethylsilyl trifluoromethanesulfonate was distilled before use. The Celite used was Celite® 545, purchased from J.T. Baker. The molarities of *n*-butyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of three determinations). The molarity of *n*-propylmagnesium chloride solution was determined by titration with iodine according to the

[223] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[224] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

protocol of Knochel and Krasovsky (average of three determinations).[225] Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH) was prepared according to the procedure of Vedejs and Larsen.[226] Anhydrous cerium(III) chloride was obtained by drying cerium(III) chloride heptahydrate under reduced pressure according to the procedure of Dimitrov and coworkers.[227] A 1.0 M solution of dimethylphenylsilyllithium in THF was prepared according to the procedure of Fleming and coworkers.[228] Where necessary (so noted), solutions were deoxygenated by alternating freeze (liquid nitrogen)/evacuation/thaw cycles (FPT, five iterations).

Instrumentation. ^{1}H NMR spectra were recorded with a Varian INOVA-600, Varian INOVA-500, or Varian Mercury 400 spectrometer, are reported in parts per million (δ), and are calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 7.26 ($CHCl_3$), CD_2Cl_2: δ 5.32 ($CDHCl_2$), CD_3OD: δ 3.31 (CD_2HOD), C_6D_6: δ 7.15 (C_6D_5H). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. ^{13}C NMR spectra were recorded with a Varian INOVA-600, Varian INOVA-500, or Varian Mercury 400 spectrometer, are reported in parts per million (δ) and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.00, CD_2Cl_2: δ 54.00, CD_3OD: δ 49.15, C_6D_6: δ 128.06, DMSO-d_6: 39.51). Infrared (IR) data were recorded on a Varian 1000 Scimitar FT-IR spectrophotometer, were referenced to a polystyrene standard, and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectroscopy experiments on an Agilent 6210 TOF LC/MS. Optical rotations were measured on a Jasco P-2000 digital polarimeter with a sodium

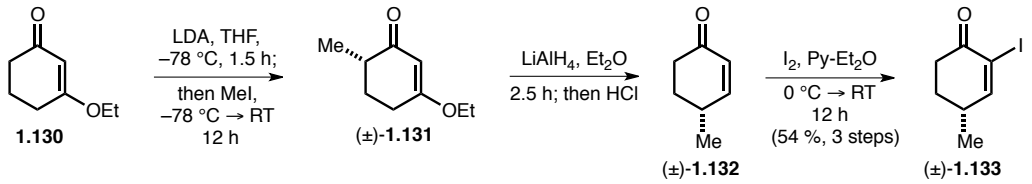
[225] Krasovsky, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

[226] Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127–132.

[227] Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett*. **1996**, *37*, 6787–6790.

[228] Fleming I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. I* **1981**, 2527–2532. An adaptation of this procedure was also consulted: Lettan II, R. B.; Milgram, B. C.; Scheidt, K. A. *Org. Synth.* **2007**, *84*, 22–31.

lamp (average of at least four measurements for each sample). Circular dichroism (CD) spectra were collected on a Jasco J-710 spectropolarimeter equipped with a temperature controller (at 23 ± 0.1 °C) using the following standard measurement parameters: 0.5 nm step resolution, 50 nm/sec speed, 4 accumulations, 1 sec response, 1 nm bandwidth, 1.0 cm path length. All spectra were converted to a uniform scale of molar ellipticity after background subtraction. Curves shown are smoothed with standard parameters. Microwave irradiation was accomplished using a CEM Discover microwave reactor.



2-Iodo-4-methylcyclohex-2-enone ((±)-**1.133**):

A 2-L, 3-necked, round-bottomed flask equipped with a 500-mL equal pressure graduated addition funnel, and two rubber septa was charged with a solution of diisopropylamine (72.4 mL, 512 mmol, 1.15 equiv) and THF (245 mL) and cooled to 0 °C. A solution of ^{n}BuLi in hexanes (2.60 M, 189 mL, 490 mmol, 1.10 equiv) was added dropwise to the stirred reaction mixture over 30 min via addition funnel and then cooled to –78 °C. A separate 1-L round-bottomed flask was charged with 3-ethoxy-2-cyclohexen-1-one (**1.130**)(62.4 g, 445 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (450 mL) was introduced and the resultant solution was added dropwise to the cooled reaction mixture via cannula over 1 h. The transfer was completed with two additional portions of THF (50 mL). After 30 min, iodomethane (33.2 mL, 75.7 g, 534 mmol, 1.20 equiv) was added quickly to the cold, bright yellow mixture via syringe. After 15 min, the mixture was allowed to warm to ambient temperature over 12 h. A saturated aqueous ammonium chloride solution (500 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with water (2 × 500 mL) and brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and *carefully* concentrated under reduced pressure to furnish alkoxy cyclohexenone (±)-**1.131** as a volatile, yellow oil that was used without further purification.

A 3-L, 2-necked, round-bottomed flask was charged with a slurry of lithium aluminum hydride (13.0 g, 343 mmol, 0.77 equiv) and Et_2O (1.00 L). A separate 1-L round-bottomed flask was charged with a solution of alkoxy cyclohexenone (±)-**1.131** and Et_2O (440 mL), which was added dropwise to the cooled reaction mixture via cannula over 2 h at ambient temperature. The transfer was completed with two additional portions of Et_2O (100 mL). After 30 min, sodium sulfate decahydrate (300 g, 96.7 mmol,

2.17 equiv) was added portion wise over 1 h. The resultant mixture was *carefully* acidified to pH 2-3 with an aqueous solution of HCl (2.0 N). The layers were separated and the organic layer was washed with a saturated aqueous sodium bicarbonate solution (1.0 L), and brine (1.0 L), dried over anhydrous magnesium sulfate, filtered, and *carefully* concentrated under reduced pressure to furnish 4-methyl-2-cyclohexene-1-one (±)-**1.132** a volatile, pale-yellow oil that was used without further purification.

A 1-L round-bottomed flask was charged with a solution of iodine (243 g, 957 mmol, 2.15 equiv), pyridine (340 mL) and Et_2O (340 mL) and cooled to 0 °C. A separate 1-L round-bottomed flask was charged with a solution of (±)-**1.132**, pyridine (340 mL) and Et_2O (340 mL), which was added dropwise to the stirred, cooled reaction mixture via cannula over 1 h. The transfer was completed with two additional portions of Et_2O (50 mL). The resultant mixture was allowed to warm to ambient temperature over 12 h before water (1.0 L) was added. The layers were separated and the organic layer was washed with an aqueous solution of HCl (1.0 M, 2 × 1.0 L), water (1.0 L), an aqueous solution of sodium thiosulfate (10% w/v, 1.0 L mL), and brine (1.0 L), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 10 % EtOAc in hexanes) to afford 2-iodo-4-methylcyclohex-2-enone (±)-**1.133** (60.0 g, 57% over three steps) as a yellow oil.

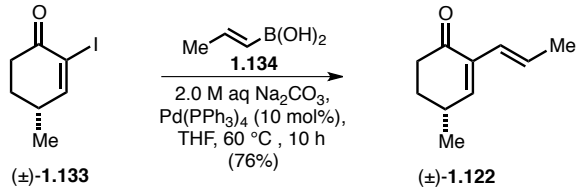
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 3.1, 1.2 Hz, 1 H), 2.75 (td, *J* = 4.8, 16.4 Hz, 2 H), 2.71–2.63 (m, 1 H), 2.54 (ddd, *J* = 4.8, 12.6, 16.4 Hz, 1 H), 2.20–2.11 (m, 1 H), 1.79–1.69 (m, 1 H), 1.18 (d, *J* = 7.1 Hz, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.0, 164.7, 103.0, 35.7, 35.6, 30.7, 19.7.

FTIR (thin film) cm^{-1}: 2957, 2929, 2870, 1685, 1584, 1452, 1317, 1153, 944, 805.

HRMS (ESI) (*m/z*) calc'd for C_7H_9INaO $[M+Na]^+$: 258.9596, found 258.9614.

TLC (15% EtOAc in hexanes), R_f: 0.35 (UV, CAM).



(*E*)-4-Methyl-2-(prop-1-en-1-yl)cyclohex-2-enone ((±)-**1.122**):

A 100-mL round-bottomed flask was charged with (±)-**1.133** (1.60 g, 7.00 mmol, 1.00 equiv), (*E*)-prop-1-en-1-ylboronic acid (**1.134**), an aqueous sodium carbonate solution (2.0 M, 11.6 mL), and THF (23.3 mL) before it was equipped with a reflux condenser. The reaction mixture warmed to 60 °C for 10 h. The resultant mixture was allowed to cool to ambient temperature before it was diluted with EtOAc (50 mL) and washed with brine (50 mL). The layers were separated and the organic layer dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 5 → 10 % EtOAc in hexanes) to afford (*E*)-4-methyl-2-(prop-1-en-1-yl)cyclohex-2-enone (±)-**1.122** (0.80 g, 76%) as a colorless oil.

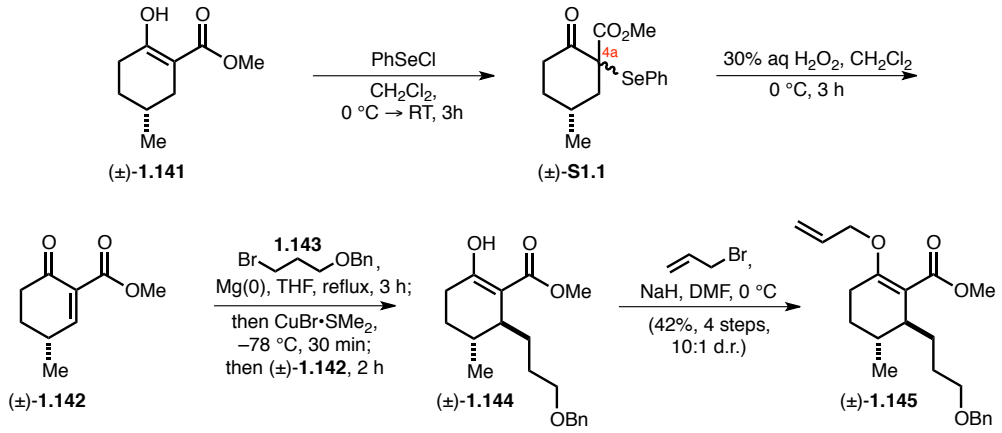
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 1 H), 6.11 (d, *J* = 11.5 Hz, 1 H), 5.82–5.69 (m, 1 H), 2.69–2.58 (m, 1 H), 2.52 (td, *J* = 4.5, 16.5 Hz, 1 H), 2.37 (ddd, *J* = 4.7, 12.7, 17.1 Hz, 1 H), 2.09 (dd, *J* = 4.8, 12.8 Hz, 1 H), 1.70 (s, 3 H), 1.17 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 153.1, 134.2, 128.2, 123.9, 37.2, 31.6, 30.8, 20.7, 14.5.

FTIR (thin film) cm^{-1}: 3023, 2957,3932, 2971, 1676, 1454, 1411, 1345, 1177, 1125, 1110, 937, 723.

HRMS (ESI) (*m/z*) calc'd for $C_{10}H_{14}NaO$ $[M+Na]^+$: 173.0942, found 173.0937.

TLC (15% EtOAc in hexanes), R_f: 0.43 (UV, CAM).



***O*-Allyl β-ketoester (±)-1.145**:

A 2-L round-bottomed flask was charged with a solution of phenylselenyl chloride (67.2 g, 351 mmol, 1.11 equiv) and CH_2Cl_2 (500 mL) and cooled to 0 °C before pyridine (35 mL, 433 mmol, 1.37 equiv) was added via syringe. A separate 500 mL round-bottomed flask was charged with methyl 2-hydroxy-5-methylcyclohex-1-enecarboxylate ((±)-**1.141**) (53.8 g, 316 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (132 mL) was introduced and the resultant solution was added dropwise to the reaction mixture via cannula over 2 h. The transfer was completed with two additional portions of CH_2Cl_2 (25 mL). After 1 h, the reaction mixture was allowed to warm to ambient temperature and poured into an aqueous solution of HCl (10% w/v, 500 mL). The layers were separated and the organic layer was washed with an aqueous solution of HCl (10% w/v, 2 × 500 mL), a saturated aqueous sodium bicarbonate solution (1.0 L), and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish α-phenylseleno β-ketoester (±)-**S1.1** as a bright red syrup that was used without further purification.

A 3-L, 2-necked, round-bottomed flask equipped with a 250-mL equal pressure graduated addition funnel and a rubber septa was charged with a solution of α-phenylseleno β-ketoester (±)-**S1.1** and CH_2Cl_2 (632 mL) and cooled to 0 °C before an aqueous solution of hydrogen peroxide (30% wt., 64.5 mL, 2.00 equiv) was added dropwise via equal pressure graduated addition funnel over 2 h. Stirring continued for an addition 1 h before sodium sulfite (40.0 g, 1.00 equiv) was *carefully* added to decompose any excess hydrogen peroxide. After stirring for 30 min, a saturated aqueous sodium bicarbonate solution

(500 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (500 mL) and brine (1.0 L), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield enone (±)-**1.142** as a yellow oil that was used without further purification.

A 2-L, 2-necked, round-bottomed flask equipped with a 500-mL equal pressure graduated addition funnel, a reflux condenser and a rubber septa was charged with magnesium turnings (36.9 g, 1.52 mol, 4.80 equiv). A separate 500 mL round-bottomed flask was charged with alkyl bromide **1.143** (86.9 g, 379 mmol, 1.20 equiv) and azeotropically dried with three portions of benzene. THF (380 mL) was introduced and the resultant solution added dropwise to the magnesium turnings via cannula over 1 h at a rate to maintain reflux. After the addition was complete, reflux was maintained for an additional 2 h. The reaction mixture was then cooled to –78 °C before a solution of copper(I) bromide dimethyl sulfide complex (15.7 g, 76.5 mmol, 0.250 equiv) and dimethyl sulfide (150 mL) was added dropwise via addition funnel over 30 min. A separate 500 mL round-bottomed flask was then charged with enone (±)-**1.142** and azeotropically dried with three portions of benzene. THF (380 mL) was introduced and the resultant solution was cooled to –78°C before being transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 30 min. The transfer was completed with two additional portions of THF (25 mL). The resultant slurry stirred for 1.5 h before a saturated aqueous ammonium chloride solution (500 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite, which was rinsed with water (100 mL) and EtOAc (2 × 200 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (1.0 L) and brine (1.0 L), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield β-ketoester (±)-**1.144** as a dark brown oil that was used without further purification.

A 2-L, 2-necked, round-bottomed flask equipped with a 250-mL equal pressure graduated

addition funnel and a rubber septa was charged with a dispersion of sodium hydride (60% wt. in mineral oil, 25.3 g, 632 mmol, 2.00 equiv) and DMF (632 mL) and cooled to 0 °C. A separate 500 mL round-bottomed flask was charged with β-ketoester (±)-**1.144** and azeotropically dried with three portions of benzene. DMF (100 mL) was introduced and the resultant solution transferred dropwise to the stirred, cooled reaction mixture via cannula to the over 30 min. The transfer was completed with two additional portions of DMF (25 mL). The resultant reaction mixture was subsequently allowed to warm to ambient temperature. After 45 min, the reaction mixture was re-cooled to 0 °C. Allyl bromide (164 mL, 1.90 mol, 6.00 equiv) was then added dropwise to the stirred reaction mixture via addition funnel over 30 min. After 30 min, the reaction mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. An ice/water mixture was then slowly added to the stirred reaction mixture, which was then allowed to warm to ambient temperature. The mixture was diluted with Et_2O (500 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (3 × 400 mL). The combined organic layers were then washed with water (3 × 1.0 L) and brine (1.0 L), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford *O*-allyl β-ketoester (±)-**1.145** (47.2 g, 42% over four steps, 10:1 d.r.) as a pale yellow oil.

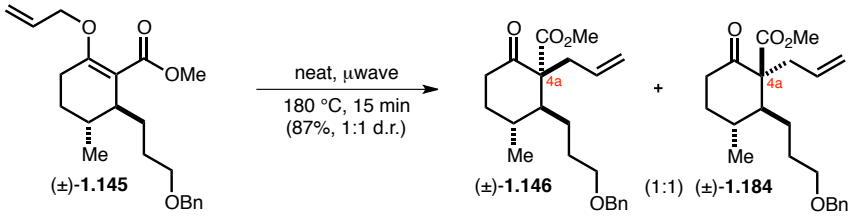
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36–7.30 (m, 4 H), 7.29–7.24 (m, 1 H), 5.93 (tdd, *J* = 5.1, 10.5, 17.1 Hz, 1 H), 5.36 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.19 (dd, *J* = 0.8, 10.5 Hz, 1 H), 4.48 (s, 2 H), 4.41–4.33 (m, 2 H), 3.71 (s, 3 H), 3.49–3.39 (m, 2 H), 2.38–2.32 (m, 1 H), 2.26–2.17 (m, 2 H), 1.84–1.73 (m, 2 H), 1.71–1.62 (m, 1 H), 1.61–1.47 (m, 2 H), 1.47–1.40 (m, 1 H), 1.34 (dddd, *J* = 4.8, 8.4, 10.4, 13.5 Hz, 1 H), 0.93 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 158.5, 138.6, 133.8, 128.2, 127.5, 127.4, 116.8, 112.7, 72.7, 70.5, 68.7, 51.2, 41.4, 31.0, 28.6, 27.3, 24.8, 22.7, 18.5.

FTIR (thin film) cm^{-1}: 2931, 2855, 1712, 1453, 1433, 1369, 1262, 1193, 1168, 1102, 928, 738, 698.

HRMS (ESI) calc'd for $C_{22}H_{30}KO_4$ $[M+K]^+$: 397.1776, found 397.1793.

TLC (15% EtOAc in hexanes), R_f: 0.29 (UV, CAM).



***C*-Allyl β-ketoester (±)-1.146 and (±)-1.184**:

A 7-mL microwave vial was charged with *O*-allyl β-ketoester (±)-**1.145** (3.5 g, 9.76 mmol) then sealed and irradiated in a microwave reactor (200 watt power) to 185 °C and held at that temperature for 15 min. The resulting yellow oil was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 15% EtOAc in hexanes) to afford *C*-allyl β-ketoester (±)-**1.146** (1.49 g, 43%) and (±)-**1.184** (1.55 g, 44%) as a colorless oils.

***C*-Allyl β-ketoester (±)-1.146**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38–7.31 (m, 4 H), 7.30–7.27 (m, 1 H), 5.65 (ddd, *J* = 1.3, 5.1, 12.6 Hz, 1 H), 5.07 (d, *J* = 12.6 Hz, 1 H), 5.05 (d, *J* = 5.1 Hz, 1 H), 4.49 (s, 2 H), 3.66 (s, 3 H), 3.44–3.39 (m, 2 H), 2.96 (tdd, *J* = 1.3, 5.6, 14.3 Hz, 1 H), 2.70 (dt, *J* = 6.4, 14.3 Hz, 1 H), 2.48 (dd, *J* = 8.7, 14.4 Hz, 1 H), 2.42 (ddd, *J* = 3.1, 4.4, 15.0 Hz, 1 H), 2.13–2.05 (m, 1 H), 1.91 (tdd, *J* = 3.2, 6.5, 13.4 Hz, 1 H), 1.73–1.58 (m, 3 H), 1.53–1.45 (m, 1 H), 1.33 (dddd, *J* = 1.2, 5.4, 11.4, 25.2 Hz, 2 H), 1.03 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.5, 171.4, 138.6, 134.3, 128.3, 127.5, 127.5, 118.6, 72.9, 70.4, 64.6, 52.0, 49.2, 40.0, 36.4, 33.9, 33.6, 30.4, 27.2, 20.3.

FTIR (thin film) cm^{-1}: 2931, 2856, 1712, 1453, 1432, 1363, 1262, 1100, 920, 737, 698.

HRMS (ESI) calc'd for $C_{22}H_{30}NaO_4$ $[M+Na]^+$: 381.2042, found 381.2069.

TLC (15% EtOAc in hexanes), R_f: 0.32 (UV, CAM).

***C*-Allyl β-ketoester (±)-1.184**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 4 H), 7.28 (d, *J* = 7.0 Hz, 1 H), 5.84 (dddd, *J* = 5.6, 8.3, 10.0, 17.2 Hz, 1 H), 5.04 (d, *J* = 17.2 Hz, 1 H), 5.00 (d, *J* = 10.0 Hz, 1 H), 4.47 (s, 2 H), 3.71 (s, 3 H), 3.44–3.33 (m, 2 H), 2.45–2.37 (m, 2 H), 2.28 (ddd, *J* = 5.9, 13.4, 15.0 Hz, 1 H), 2.13 (td, *J* = 5.7, 9.1 Hz,

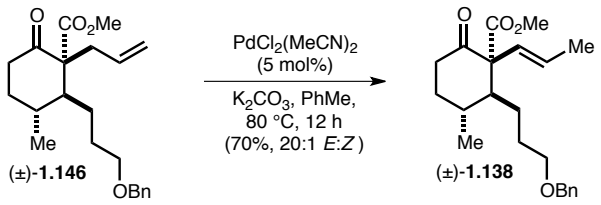
1 H), 1.96–1.88 (m, 1 H), 1.87–1.78 (m, 1 H), 1.71–1.61 (m, 1 H), 1.57–1.43 (m, 2 H), 1.39–1.31 (m, 2 H), 1.07 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.2, 172.9, 138.4, 133.8, 128.2, 127.4, 127.4, 117.5, 72.7, 70.1, 65.3, 51.9, 48.7, 38.8, 34.4, 32.6, 32.4, 28.6, 27.1, 20.3.

FTIR (thin film) cm^{-1}: 2950, 2929, 2857, 1735, 1709, 1453, 1433, 1219, 1101, 919, 738, 699.

HRMS (ESI) calc'd for $C_{22}H_{31}O_4$ $[M+H]^+$: 359.2217, found 359.2250.

TLC (15% EtOAc in hexanes), R_f: 0.22 (UV, CAM).



***C*-Propenyl β-ketoester (±)-1.138**:

A 50-mL round-bottomed flask was charged with *C*-allyl β-ketoester (±)-**1.146** (4.85 g, 13.5 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (135 mL), potassium carbonate (3.75g, 27.1 mmol, 2.00 equiv), and palladium(II) chloride diacetonitrile complex (175 mg, 0.68 mmol, 0.05 equiv) were sequentially introduced and the resultant vigorously stirred heterogeneous mixture was heated to 80 °C. After 12 h, the resultant black reaction mixture was allowed to cool to ambient temperature and filtered through a pad of Celite, which was rinsed with EtOAc (3 × 100 mL) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford *C*-propenyl β-ketoester (±)-**1.138** (3.38 g, 70%, 20:1 *E*:*Z*) as a colorless oil.

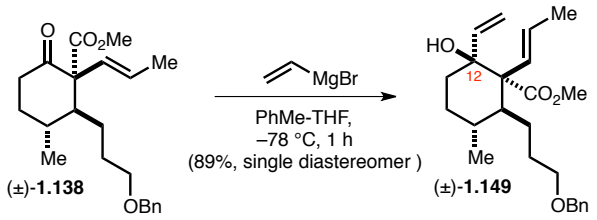
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36–7.30 (m, 4 H), 7.29–7.26 (m, 1 H), 5.64–5.59 (m, J = 16.7 Hz, 1 H), 5.56 (qd, J = 5.4, 16.7 Hz, 1 H), 4.47 (s, 2 H), 3.70 (s, 3 H), 3.45–3.35 (m, 2 H), 2.60 (dt, J = 6.5, 14.5 Hz, 1 H), 2.34 (td, J = 3.6, 15.3 Hz, 1 H), 2.09 (ddd, J = 3.0, 6.7, 9.9 Hz, 1 H), 1.91–1.84 (m, 1 H), 1.83–1.75 (m, 4 H), 1.74 –1.65 (m, 1 H), 1.63–1.41 (m, 3 H), 1.34–1.25 (m, 1 H), 1.06 (d, J = 6.6 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.7, 172.2, 138.5, 132.1, 128.3, 127.5, 127.4, 125.3, 72.7, 70.3, 68.4, 52.3, 49.3, 38.0, 33.4, 33.2, 29.7, 28.6, 20.1, 18.8.

FTIR (thin film) cm^{-1}: 2948, 2856, 1736, 1708, 1453, 1433, 1361, 1236, 1100, 738, 699.

HRMS (ESI) calc'd for $C_{22}H_{31}O_4$ $[M+H]^+$: 359.2217, found 359.2248.

TLC (15% EtOAc in hexanes), R_f: 0.28 (UV, CAM).



Allylic alcohol (±)-1.149:

A 500-mL round-bottomed flask was charged with *C*-propenyl β-ketoester (±)-**1.138** (3.38 g, 9.44 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (95 mL) was introduced and the resultant solution was cooled to –78 °C. A solution of vinylmagnesium bromide in THF (0.93 M, 51 mL, 47.2 mmol, 5.00 equiv) was then added dropwise via syringe over 15 min to the stirred reaction mixture. After an additional 1 h, a saturated aqueous ammonium chloride solution (100 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (300 mL) and brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford allylic alcohol (±)-**1.149** (3.26 g, 89%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.30 (m, 4 H), 7.28 (d, *J* = 2.6 Hz, 1 H), 6.32 (dd, *J* = 10.7, 16.8 Hz, 1 H), 5.66 (dd, *J* = 1.3, 15.7 Hz, 1 H), 5.47 (qd, *J* = 6.4, 15.8 Hz, 1 H), 5.35 (dd, *J* = 1.6, 16.8 Hz, 1 H), 5.08 (dd, *J* = 1.6, 10.7 Hz, 1 H), 4.49 (s, 2 H), 3.60 (s, 3 H), 3.48 (s, 1 H), 3.46–3.36 (m, 2 H), 2.01–1.91 (m, 1 H), 1.91–1.76 (m, 2 H), 1.74 (dd, *J* = 1.2, 6.3 Hz, 3 H), 1.64–1.55 (m, 3 H), 1.52–1.43 (m, 1 H), 1.35–1.15 (m, 2 H), 1.13–1.02 (m, 1 H), 1.00 (d, *J* = 6.2 Hz, 3 H).

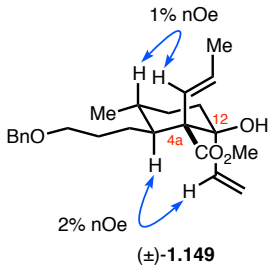
^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.6, 140.3, 138.8, 129.2, 128.2, 128.2, 127.4, 127.3, 126.1, 113.8, 75.2, 72.5, 70.9, 64.1, 51.4, 45.5, 35.3, 34.6, 31.5, 31.1, 20.7, 18.9.

FTIR (thin film) cm^{-1}: 3498, 3027, 2935, 2856, 1736, 1702, 1453, 1361, 1453, 1361, 1226, 1101, 995, 928, 736, 698.

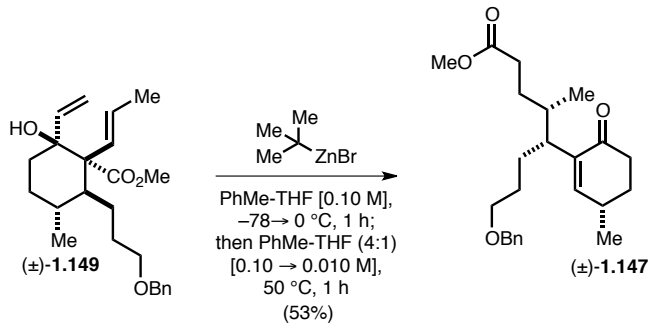
HRMS (ESI) calc'd for $C_{24}H_{35}O_4$ $[M+H]^+$: 387.2530, found 387.2532.

TLC (20% EtOAc in hexanes), R_f: 0.38 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.149**



Cyclohexenone (±)-**1.147**:

A 10-mL round-bottomed flask was charged with allylic alcohol (±)-**1.149** (112 mg, 0.290 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (2.90 mL) was introduced and the resultant solution was cooled to –78 °C. A solution of *tert*-butylzinc bromide in THF (0.50 M, 0.870 mL, 0.435 mmol, 1.5 equiv) was added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 1 h. The reaction mixture was then quickly transferred to a separate 50-mL Schlenk tube containing a stirred solution of PhMe (18.9 mL) and THF (7.25 mL) at ambient temperature via a cannula. The transfer was completed with two additional portions of PhMe (500 μL). The Schlenk tube was sealed and heated to 50 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature. Glacial acetic acid (35 μL, 0.609 mmol, 2.10 equiv) was added via syringe and the reaction mixture stirred for 10 min before being poured into brine (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford cyclohexenone (±)-**1.147** (60.5 mg, 53%) as a colorless oil.

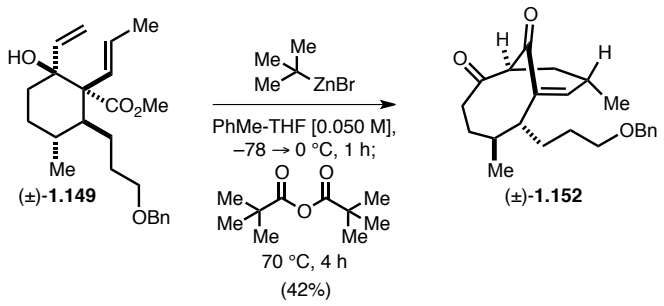
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 4 H), 7.29–7.26 (m, 1 H), 6.43 (s, 1 H), 4.47 (s, 2 H), 3.64 (s, 3 H), 3.40 (dt, *J* = 2.2, 6.4 Hz, 2 H), 2.61–2.52 (m, 2 H), 2.49 (td, *J* = 4.5, 16.6 Hz, 1 H), 2.37–2.30 (m, 2 H), 2.25 (ddd, *J* = 6.6, 9.5, 15.8 Hz, 1 H), 2.05 (ddd, *J* = 4.7, 9.7, 14.1 Hz, 1 H), 1.70–1.63 (m, 2 H), 1.62–1.53 (m, 2 H), 1.53–1.28 (m, 4 H), 1.14 (d, *J* = 7.2 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 174.4, 151.2, 139.3, 138.6, 128.3, 127.6, 127.5, 72.9, 70.4, 51.4, 37.5, 35.7, 31.9, 31.5, 30.8, 29.6, 27.7, 25.5, 20.9, 15.9.

FTIR (thin film) cm^{-1}: 2950, 2930, 2860, 1736, 1670, 1453, 1171, 1101, 738, 698.

HRMS (ESI) calc'd for $C_{24}H_{35}O_4$ $[M+H]^+$: 387.2530, found 387.2572.

TLC (20% EtOAc in hexanes), R_f: 0.33 (UV, CAM).



Bicycle (±)-**1.152**:

A 100-mL Schlenk tube was charged with allylic alcohol (±)-**1.149** (857 mg, 2.22 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (11.1 mL) and PhMe (33.3 mL) were introduced and the resultant solution was cooled to –78 °C. A solution of *tert*-butylzinc bromide in THF (0.50 M, 6.66 mL, 3.33 mmol, 1.5 equiv) was added dropwise via syringe over 2 min to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 1 h. Freshly distilled pivalic anhydride (1.89 mL, 11.1 mmol, 5.00 equiv) was then added dropwise via syringe to the stirred reaction mixture. The Schlenk tube was sealed and heated to 40 °C. After 24 h the reaction mixture was allowed to cool to ambient temperature. Glacial acetic acid (266 μL, 4.66 mmol, 2.10 equiv) was added via syringe and the reaction mixture stirred for 10 min before being poured into brine (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 1% → 5% EtOAc in CH_2Cl_2) to afford bicycle (±)-**1.152** (186 mg, 42%) as a colorless oil.

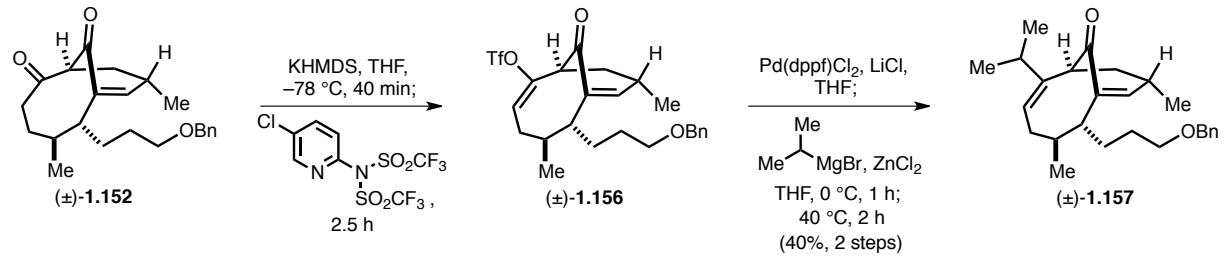
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.31 (m, 4 H), 7.30–7.25 (m, 1 H), 5.98 (s, 1 H), 4.50 (s, 2 H), 3.53–3.44 (m, 2 H), 3.37 (dd, *J* = 4.0, 7.6 Hz, 1 H), 2.68 (ddd, *J* = 1.8, 7.7, 14.9 Hz, 1 H), 2.58–2.43 (m, 2 H), 2.38 (td, *J* = 7.4, 14.4 Hz, 1 H), 1.93 (ddd, *J* = 4.2, 5.9, 14.0 Hz, 1 H), 1.84–1.77 (m, 1 H), 1.72–1.61 (m, 2 H), 1.60–1.48 (m, 2 H), 1.45–1.34 (m, 1 H), 1.29–1.20 (m, 1 H), 1.14 (d, *J* = 7.3 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.8, 202.9, 142.8, 140.1, 138.6, 128.3, 127.5, 127.5, 72.9, 70.1, 61.4, 45.8, 43.6, 41.9, 31.4, 31.3, 27.4, 27.3, 26.4, 21.9, 21.2

FTIR (thin film) cm^{-1}: 2950, 2927, 2868, 1707, 1685, 1454, 1105, 737, 698.

HRMS (ESI) calc'd for $C_{23}H_{30}NaO_3$ $[M+Na]^+$: 377.2087, found 377.2087.

TLC (20% EtOAc in hexanes), R_f: 0.22 (UV, CAM).



(±)-**1.152** (±)-**1.156** (±)-**1.157**

Isopropyl bicycle (±)-**1.157**:

A 50-mL round-bottomed flask was charged with bicycle (±)-**1.152** (254 mg, 0.717 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (18 mL) was introduced and the resultant solution was cooled to –78 °C. A solution of potassium hexamethyldisilazide in THF (0.527 M, 1.22 mL, 0.644 mmol, 0.90 equiv) was then added dropwise via syringe over 2 min to the stirred reaction mixture. After 30 min, additional solution of potassium hexamethyldisilazide in THF (0.527 M, 0.271 mL, 0.143 mmol, 0.20 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 10 min, the reaction mixture was transferred to a separate 50-mL round-bottomed flask containing a stirred –78 °C solution of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (337 mg, 0.858 mmol, 1.20 equiv) and THF (1.8 mL) dropwise via a dry-ice wrapped cannula over 10 min. The transfer was completed with two additional portions of THF (2 mL). After 2.5 h, a saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (300 mL) and brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield bicyclic alkenyl triflate (±)-**1.156** as a tan oil that was used without further purification.

A 25-mL round-bottomed flask was charged with anhydrous lithium chloride (91.1 mg, 2.15 mmol, 3.00 equiv), flame dried under high vacuum and allowed to cool to ambient temperature under vacuum. The process was repeated three times. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (52.5 mg, 0.072 mmol, 0.10 equiv) was

introduced and the flask was evacuated and then backfilled with argon. The process was repeated three times. A separate 5-mL round-bottomed flask was charged with alkenyl triflate (±)-**1.156** and azeotropically dried with three portions of benzene. THF (1 mL) was introduced and the resultant solution was transferred dropwise via cannula to the reaction mixture. The transfer was completed with three additional portions of THF (500 μL). A 10-mL round-bottomed flask was charged with anhydrous zinc chloride (391 mg, 2.87 mmol, 4.00 equiv), flame dried under high vacuum and allowed to cool to ambient temperature under vacuum. The process was repeated three times. The flask was evacuated and then backfilled with argon three times. THF (5.74 mL) was introduced and the resultant solution was cooled to 0 °C. A solution of *iso*propylmagnesium bromide in THF (1.56 M, 1.84 mL, 2.87 mmol, 4.00 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 1 h, the reaction mixture was transferred to the flask containing alkenyl triflate (±)-**1.156** dropwise via a cannula. The transfer was completed with two additional portions of THF (500 μL). The resultant reaction mixture was heated to 40 °C. After 2 h, the reaction mixture was allowed to cool to ambient temperature and a saturated aqueous ammonium chloride solution (5 mL) was added. The mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (25mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford isopropyl bicycle (±)-**1.157** (109 mg, 40% over two steps) as a colorless solid. Crystals suitable for X-ray diffraction were obtained by cooling a saturated solution of (±)-**1.157** in pentane to –20 °C for 48 h.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.31 (m, 4 H), 7.30–7.26 (m, 1 H), 5.53 (br. s., 1 H), 5.38 (t, J = 9.0 Hz, 1 H), 4.50 (s, 2 H), 3.52–3.42 (m, 2 H), 3.05 (br. s., 1 H), 2.60–2.46 (m, 2 H), 2.40 (t, J = 9.6 Hz, 1 H), 2.27–2.17 (m, 1 H), 2.16–2.06 (m, 1 H), 1.86–1.60 (m, 2 H), 1.57–1.36 (m, 2 H), 1.06 (d, J = 7.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H).

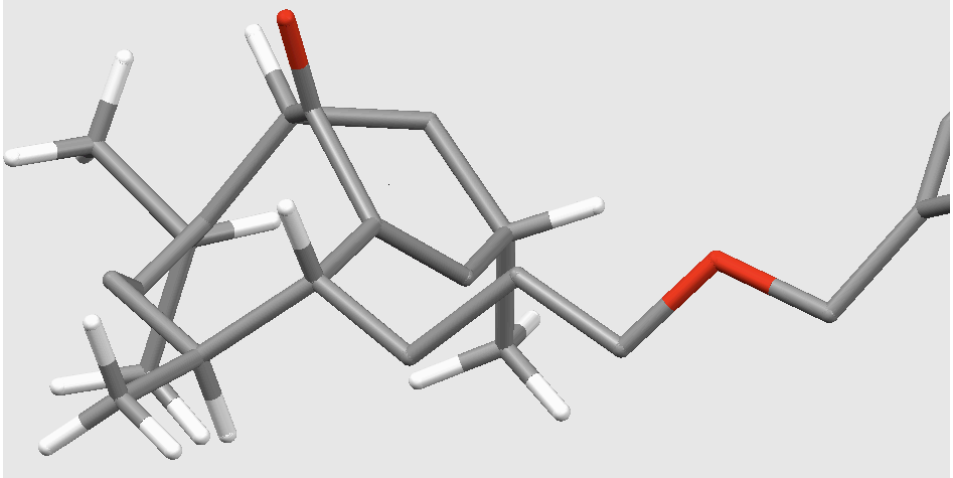
^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.4 (br), 145.5, 141.0, 138.7, 133.8, 128.3, 127.5, 127.4, 122.3, 72.8, 70.3, 48.3, 46.8, 41.3, 35.5, 31.6, 30.1, 28.3, 27.2, 25.2, 23.3, 22.3, 21.3, 20.0.

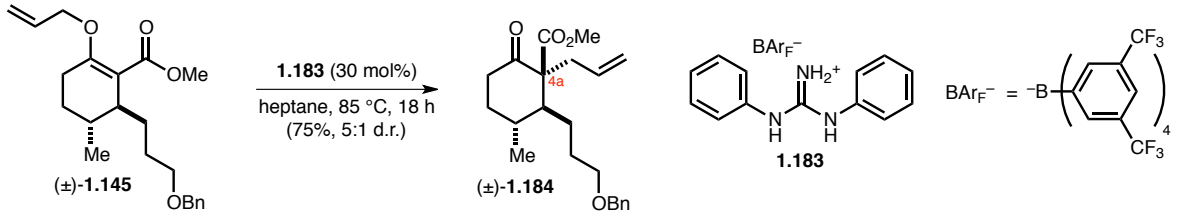
FTIR (thin film) cm^{-1}: 3300 (br), 2957, 2927, 2870, 1795, 1453, 1095, 735, 678.

HRMS (ESI) calc'd for $C_{26}H_{37}O_2$ $[M+Na]^+$: 381.2788, found 381.2807.

TLC (20% EtOAc in hexanes), R_f: 0.51 (UV, CAM).

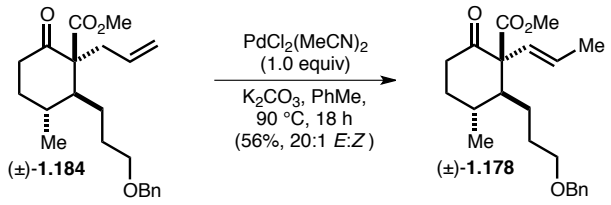
X-Ray Crystal Structure:





***C*-Allyl β-ketoester (±)-1.184**:

A 1-L round-bottomed flask was charged with *O*-allyl β-ketoester (±)-**1.145** (7.42 g, 20.7 mmol, 1 equiv) and azeotropically dried with three portions of benzene. Heptane (400 mL) and *N*,*N*'-diphenylguanidinium catalyst **1.183** (6.70 g, 6.20 mmol, 0.30 equiv) were introduced and the resultant vigorously stirred heterogeneous reaction mixture was heated to 85 °C. After 18 h, the reaction was concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 15% EtOAc in hexanes) to afford *C*-allyl β-ketoester (±)-**1.184** (4.63 g, 62%) and *C*-allyl β-ketoester (±)-**1.146** (925 mg, 13%) as colorless oils.



***C*-Propenyl β-ketoester (±)-1.178**:

A 50-mL round-bottomed flask was charged with *C*-allyl β-ketoester (±)-**1.184** (2.88 g, 8.04 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (100 mL), potassium carbonate (3.33 g, 24.1 mmol, 3.00 equiv), and palladium(II) chloride diacetonitrile complex (1.05 g, 5.02 mmol, 0.50 equiv) were sequentially introduced and the resultant vigorously stirred heterogeneous mixture was heated to 90 °C. After 12 h, the reaction mixture was allowed to cool to ambient temperature and an additional portion of palladium(II) chloride diacetonitrile complex (1.05 g, 5.02 mmol, 0.50 equiv) was added and the reaction mixture was reheated to 90 °C. After 6 h, the reaction mixture was allowed to cool to ambient temperature and filtered through a pad of Celite, which was rinsed with EtOAc (3 × 100 mL) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford *C*-propenyl β-ketoester (±)-**1.178** (1.61 g, 56%, 20:1 *E*:*Z*) as a colorless oil.

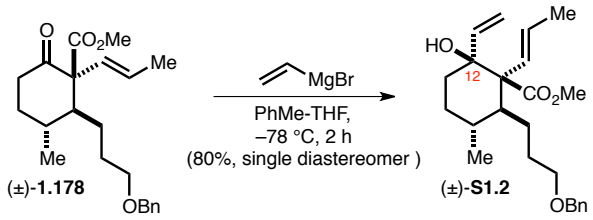
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35–7.30 (m, 4 H), 7.29–7.26 (m, 1 H), 5.56 (dd, *J* = 1.7, 16.1 Hz, 1 H), 5.30 (qd, *J* = 6.4, 16.1 Hz, 1 H), 4.47 (s, 2 H), 3.70 (s, 3 H), 3.42–3.33 (m, 2 H), 2.48 (dt, *J* = 6.0, 13.5 Hz, 1 H), 2.42 (ddd, *J* = 3.2, 4.7, 13.6 Hz, 1 H), 2.04–1.91 (m, 2 H), 1.82–1.75 (m, 1 H), 1.73 (dd, *J* = 1.5, 6.4 Hz, 3 H), 1.71–1.60 (m, 3 H), 1.51–1.42 (m, 1 H), 1.36 (ddt, *J* = 5.0, 11.8, 13.2 Hz, 1 H), 1.12 (ddd, *J* = 2.3, 5.4, 11.0 Hz, 1 H), 1.04 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.5, 170.5, 138.6, 128.4, 128.3, 127.9, 127.5, 127.4, 72.8, 70.4, 68.4, 53.1, 52.0, 39.9, 34.9, 34.3, 31.9, 27.6, 20.0, 18.3.

FTIR (thin film) cm^{-1}: 2923, 2853, 1715, 1453, 1242, 1151, 962, 738, 699.

HRMS (ESI) calc'd for $C_{22}H_{31}O_4$ $[M+H]^+$: 359.2217, found 359.2313.

TLC (15% EtOAc in hexanes), R_f: 0.26 (UV, CAM).



Allylic alcohol (±)-**S1.2**:

A 500-mL round-bottomed flask was charged with *C*-propenyl β-ketoester (±)-**1.178** (303 mg, 0.840 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (8.4 mL) was introduced and the resultant solution was cooled to –78 °C. A solution of vinylmagnesium bromide in THF (1.0 M, 4.2 mL, 4.2 mmol, 5.00 equiv) was then added dropwise via syringe over 5 min to the stirred reaction mixture. After an additional 2 h, a saturated aqueous ammonium chloride solution (25 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (25 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5 → 15% EtOAc in hexanes) to afford allylic alcohol (±)-**S1.2** (259 mg, 80%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06–7.98 (m, 3 H), 7.59–7.51 (m, 1 H), 7.48–7.38 (m, 2 H), 6.20 (dd, *J* = 10.9, 16.9 Hz, 1 H), 5.42 (dd, *J* = 1.9, 17.1 Hz, 1 H), 5.35 (d, *J* = 5.0 Hz, 1 H), 5.34 (d, *J* = 4.0 Hz, 1 H), 5.21 (dd, *J* = 1.9, 10.9 Hz, 1 H), 4.64 (br. s., 1 H), 4.24 (t, *J* = 6.2 Hz, 2 H), 3.73 (s, 3 H), 1.91–1.73 (m, 3 H), 1.71–1.55 (m, 8 H), 1.53–1.41 (m, 1 H), 1.37–1.23 (m, 3 H), 1.02 (d, *J* = 6.3 Hz, 3 H).

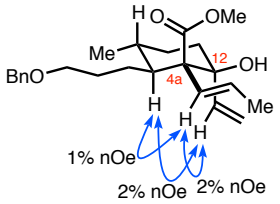
^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.5, 166.6, 138.2, 132.8, 130.4, 130.0, 129.5, 128.3, 127.5, 116.1, 76.0, 65.1, 62.4, 51.7, 47.8, 37.5, 34.7, 32.1, 31.4, 28.6, 20.9, 18.3.

FTIR (thin film) cm^{-1}: 3478 (br), 2949, 2932, 2860, 1716.7, 1451, 1274, 1217, 1115, 714.

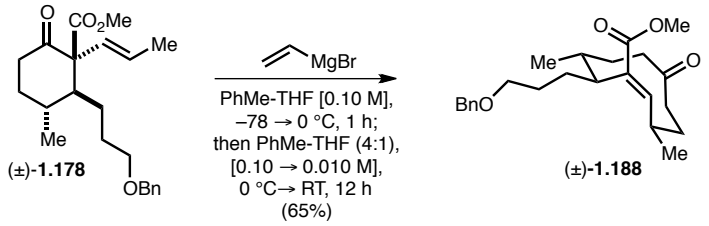
HRMS (ESI) calc'd for $C_{24}H_{34}NaO_4$ $[M+Na]^+$: 409.2349, found 409.2338.

TLC (20% EtOAc in hexanes), R_f: 0.40 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**S1.2**



***cis*-Cyclodecene (±)-1.188**:

A 25-mL Schlenk tube was charged with *C*-propenyl β-ketoester (±)-**1.178** (150 mg, 0.418 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (4.2 mL) was introduced and the resultant solution was cooled to –78 °C. A solution of vinylmagnesium bromide in THF (1.2 M, 523 μL, 0.627 mmol, 1.5 equiv) was added dropwise via syringe over 2 min to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 1 h. The resultant reaction mixture was transferred to a 100-mL Schlenk tube containing a solution of PhMe (29.2 mL) and THF (7.84 mL) at ambient temperature quickly via cannula. The Schlenk tube was sealed and stirred at ambient temperature for 12 h. Glacial acetic acid (50.0 μL, 0.878 mmol, 2.10 equiv) was added via syringe and the reaction mixture stirred for 10 min before being poured into brine (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford bicycle (±)-**1.188** (97.4 mg, 65%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.07–7.96 (m, 2 H), 7.59–7.50 (m, 1 H), 7.48–7.41 (m, 2 H), 6.47 (d, *J* = 11.6 Hz, 1 H), 4.23 (d, *J* = 5.4 Hz, 0 H), 4.22 (d, *J* = 5.4 Hz, 1 H), 3.70 (s, 3 H), 2.82 (ddd, *J* = 3.9, 12.9, 17.0 Hz, 1 H), 2.71 (tq, *J* = 5.9, 11.5 Hz, 1 H), 2.44 (dt, *J* = 2.6, 13.0 Hz, 1 H), 2.31 (qd, *J* = 5.5, 10.9 Hz, 1 H), 2.25 (ddd, *J* = 2.4, 6.8, 12.9 Hz, 1 H), 2.20 (dt, *J* = 4.3, 10.8 Hz, 1 H), 2.13 (tt, *J* = 4.3, 13.2 Hz, 1 H), 2.03–1.95 (m, 2 H), 1.74–1.63 (m, 3 H), 1.62–1.53 (m, 1 H), 1.43 (td, *J* = 6.3, 12.1 Hz, 1 H), 1.28–1.16 (m, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.3 Hz, 3 H).

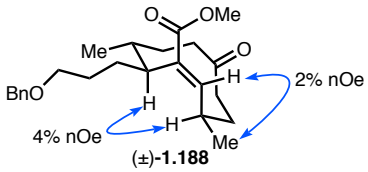
^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.6, 167.5, 166.5, 149.0, 133.3, 132.7, 130.4, 129.5, 128.3, 65.1, 51.4, 42.9, 39.9, 36.4, 33.8, 30.2, 29.8, 29.4, 27.4, 27.3, 20.7, 16.5.

FTIR (thin film) cm^{-1}: 2955, 2926, 2871, 1712, 1451, 1274, 1116, 714.

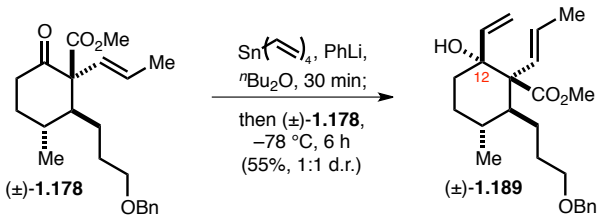
HRMS (ESI) calc'd for $C_{24}H_{34}NaO_4$ $[M+Na]^+$: 409.2349, found 409.2340.

TLC (20% EtOAc in hexanes), R_f: 0.52 (UV, CAM).

1D NOESY data (600 MHz, $CDCl_3$):



(±)-**1.188**



Allylic alcohol (±)-1.189:

A 15-mL, 2-necked, round-bottomed flask equipped with a fritted glass tube connected to a second 25-mL, 2-necked, round-bottomed flask and a septa was charged with a solution of tetravinyltin[229] (158 μL, 0.698 mmol, 1.25 equiv) and dibutyl ether (1.4 ml). A solution of phenyllithium in dibutyl ether (1.85 M, 1.21 mL, 2.23 mmol, 5.00 equiv) was quickly added via syringe to the stirred reaction mixture at ambient temperature. After 30 min, the heterogeneous reaction mixture was filtered into the second 50 mL, 2-necked, round-bottomed flask under positive argon pressure. The transfer was completed with two additional portions of dibutyl ether (1 mL). The resultant clear yellow solution was cooled to –78 °C. A separate 25-mL round-bottomed flask was charged with *C*-propenyl β-ketoester (±)-**1.178** (200 mg, 0.558 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Dibutyl ether (5.60 mL) was introduced and the resultant solution was cooled to –78 °C and transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of vinyl lithium over 30 min. The transfer was completed with three additional portions of dibutyl ether (1 mL). After 6 h, a saturated aqueous ammonium chloride solution (5 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (25 mL) and a saturated aqueous ammonium chloride solution (25 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5 → 7% EtOAc in hexanes) to afford allylic alcohol (±)-**1.189** (62.0 mg, 29%) and allylic

[229] Wade, P. A.; Bereznak, J. F.; Palfey, B. A.; Carroll, P. J.; Dailey, W. P.; Sivasubramanian, S. *J. Org. Chem.* **1990**, *55*, 3045–3051.

alcohol (±)-**S1.2** (55.0 mg, 26%) as colorless oils.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.29 (m, 4 H), 7.29–7.27 (m, 1 H), 5.82 (d, *J* = 8.4 Hz, 1 H), 5.80 (d, *J* = 6.6 Hz, 1 H), 5.78–5.76 (m, 1 H), 5.61 (qd, *J* = 6.3, 16.3 Hz, 1 H), 5.15 (d, *J* = 17.1 Hz, 1 H), 5.03 (d, *J* = 10.7 Hz, 1 H), 4.46 (s, 2 H), 3.68 (s, 3 H), 3.34 (appt, *J* = 6.8 Hz, 2 H), 2.38–2.25 (m, 1 H), 2.04–1.91 (m, 1 H), 1.79 (dd, *J* = 1.2, 6.2 Hz, 3 H), 1.75–1.54 (m, 4 H), 1.53–1.44 (m, 3 H), 1.41–1.30 (m, 1 H), 1.23–1.12 (m, 1 H), 0.97 (d, *J* = 6.6 Hz, 3 H).

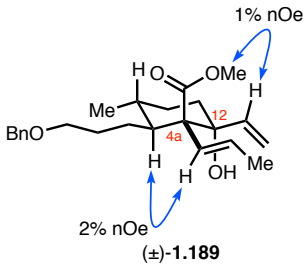
^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.5, 143.2, 138.6, 130.5, 128.2, 127.9, 127.4, 127.4, 113.3, 73.4, 72.6, 70.7, 61.6, 51.5, 42.8, 33.2, 32.8, 30.4, 29.9, 28.2, 21.3, 18.5.

FTIR (thin film) cm^{-1}: 3524 (br), 2947, 2918, 2854, 1721, 1453, 1207, 1098, 986, 926, 735, 698.

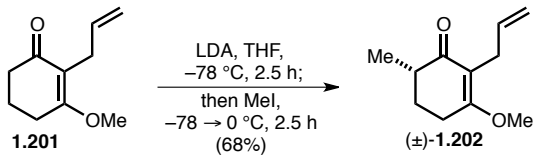
HRMS (ESI) calc'd for $C_{24}H_{34}NaO_4$ $[M+Na]^+$: 409.2349, found 409.2356.

TLC (20% EtOAc in hexanes), R_f: 0.52 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.189**



2-Allyl-3-methoxy-6-methylcyclohex-2-enone ((±)-**1.202**):

A 5-L, 3-necked, round-bottomed flask equipped with 250-mL equal pressure graduated addition funnel, 500-mL equal pressure graduated addition funnel and a rubber septa was charged with a solution of diisopropylamine (110 mL, 785 mmol, 1.10 equiv) and THF (800 mL) and cooled to –78 °C. A solution of ^{n}BuLi in hexanes (2.66 M, 295 mL, 785 mmol, 1.10 equiv) was added dropwise to the stirred reaction mixture over 1 h via 500-mL equal pressure graduated addition funnel. The resultant mixture was warmed to 0 °C for 30 min and then re-cooled to –78 °C. A separate 2-L round-bottomed flask was charged with a solution of 2-allyl-3-methoxycyclohex-2-enone (**1.201**)[86] (118 g, 712 mmol, 1.00 equiv) and THF (720 mL) and was added dropwise to the cooled, stirred reaction mixture via cannula over 2 h. The transfer was completed with two additional portions of THF (50 mL). After 30 min, iodomethane (89.0 mL, 203 g, 1.43 mol, 2.00 eqiuv) was added dropwise to cooled, stirred reaction mixture via 250-mL equal pressure graduated addition funnel over 30 min. After 15 min, the mixture was allowed to warm to 0 °C over 2 h. A saturated aqueous ammonium chloride solution (1.50 L) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (700 mL) and brine (700 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish 2-allyl-3-methoxy-6-methylcyclohex-2-enone (±)-**1.202** as a yellow oil that was purified by distillation (oil bath 120 °C, b.p 90-95 °C, 0.92 mmHg) to afford pure 2-allyl-3-methoxy-6-methylcyclohex-2-enone (±)-**1.202** (87.4 g, 68%) as a clear oil.

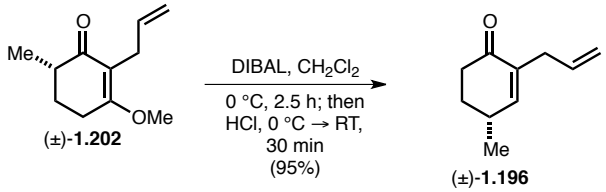
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.75 (tdd, *J* = 6.3, 10.2, 16.9 Hz, 1 H), 4.93 (qd, *J* = 1.7, 17.1 Hz, 1 H), 4.84 (qd, *J* = 1.5, 10.1 Hz, 1 H), 3.77 (s, 3 H), 3.04–2.90 (m, *J* = 6.0, 6.0 Hz, 2 H), 2.63 (td, *J* = 5.3, 18.3 Hz, 1 H), 2.52 (qd, *J* = 5.0, 17.2 Hz, 1 H), 2.30–2.18 (m, 1 H), 2.06 (qd, *J* = 4.8, 13.2 Hz, 1 H), 1.71–1.60 (m, 1 H), 1.11 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.9, 171.1, 136.6, 116.3, 113.7, 55.0, 39.3, 28.6, 26.5, 24.0, 15.4.

FTIR (thin film) cm^{-1}: 3077, 2933, 2862, 1644, 1462, 1424, 1252, 1120, 990, 908.

HRMS (ESI) calc'd for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1223, found 181.1245.

TLC (60% EtOAc in hexanes), R_f: 0.56 (UV, CAM).



2-Allyl-3-methoxycyclohex-2-enone ((±)-**1.196**):

A 3-L, 2-necked, round-bottomed flask equipped with 500-mL equal pressure graduated addition funnel and a septa was charged with a solution of 2-allyl-3-methoxy-6-methylcyclohex-2-enone (±)-**1.202** (40 g, 222 mmol, 1.00 equiv) and CH_2Cl_2 (1.10 L) and cooled to 0 °C. A solution of diisobutylaluminum hydride (50 mL, 39.9 g, 278 mmol, 1.25 equiv) and CH_2Cl_2 (300 mL) was added dropwise to the cooled, stirred reaction mixture over 2 h. After 30 min, an aqueous solution of HCl (10% w/v, 800 mL) was carefully added to the reaction mixture which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (1.0 L) and brine (1.0 L). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to furnish 2-allyl-3-methoxycyclohex-2-enone (±)-**1.196** as a yellow oil that was purified by distillation (oil bath 130 °C, b.p 125 °C, 40.0 mmHg) to afford pure 2-allyl-3-methoxycyclohex-2-enone (±)-**1.196** (31.7 g, 95%) as a clear oil.

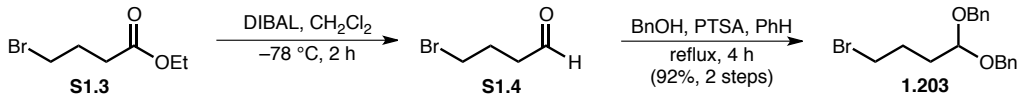
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.52 (dd, J = 1.3, 2.6 Hz, 1 H), 5.86–5.75 (m, 1 H), 5.09–4.97 (m, 2 H), 2.97–2.88 (m, 2 H), 2.60–2.54 (m, 1 H), 2.51 (td, J = 4.8, 16.7 Hz, 1 H), 2.35 (ddd, J = 4.9, 12.7, 17.3 Hz, 1 H), 2.07 (dqd, J = 1.5, 4.8, 13.2 Hz, 1 H), 1.63 (ddt, J = 3.9, 9.4, 13.2 Hz, 1 H), 1.14 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.5, 151.3, 136.5, 135.6, 115.9, 37.0, 33.1, 31.2, 30.9, 20.4.

FTIR (thin film) cm^{-1}: 2960, 2930, 2873, 1670, 1456, 1417, 1372, 1177, 1124, 1016, 910, 731.

HRMS (ESI) calc'd for $C_{10}H_{14}NaO$ $[M+Na]^+$: 173.0937, found 173.0952.

TLC (50% EtOAc in hexanes), R_f: 0.74 (UV, CAM).



Alkyl bromide 1.203:

A 3-L, 3-necked, round-bottomed flask equipped with 500-mL equal pressure graduated addition funnel, an internal temperature probe, and a septa was charged with a solution of ethyl 4-bromobutanoate (**S1.3**) (80.5 mL, 110 g, 563 mmol, 1.00 equiv) and CH_2Cl_2 (1.13 L) and cooled to –78 °C. A solution of diisobutylaluminum hydride (125 mL, 100 g, 703 mmol, 1.25 equiv) and CH_2Cl_2 (370 mL) was added dropwise via 500-mL equal pressure graduated addition funnel to the cooled, stirred reaction mixture over 2 h. It was critical to maintain an internal temperature below –68 °C during the addition process. After addition was complete, the reaction mixture was carefully poured into an aqueous solution of HCl (10% w/v, 1.0 L) at 0 °C. The resultant mixture was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (1.0 L) and brine (1.0 L). The organic layer was dried over anhydrous magnesium sulfate, filtered, and carefully concentrated under reduced pressure to furnish 4-bromobutanal (**S1.4**) as a volatile, clear oil that was used without further purification.

A 2-L, 2-necked, round-bottomed flask equipped with a Dean-Stark apparatus, a reflux condenser, and a rubber septa was charged with a solution of 4-bromobutanal (**S1.4**), PhH (1.40 L), and benzyl alcohol (67.0 mL, 69.9 g, 648 mmol, 2.30 equiv). *para*-Toluenesulfonic acid monohydrate (2.70 g, 14.0 mmol, 0.05 equiv) was introduced to the reaction mixture in one portion. The resultant reaction mixture was heated to reflux for 4 h and allowed to cool to ambient temperature. A saturated aqueous sodium bicarbonate solution (1.0 L) was added and the layers were separated. The organic layer was washed with brine (1.0 L) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 15% EtOAc in hexanes) to afford alkyl bromide **1.203** (181 g, 92 %) as a colorless oil.

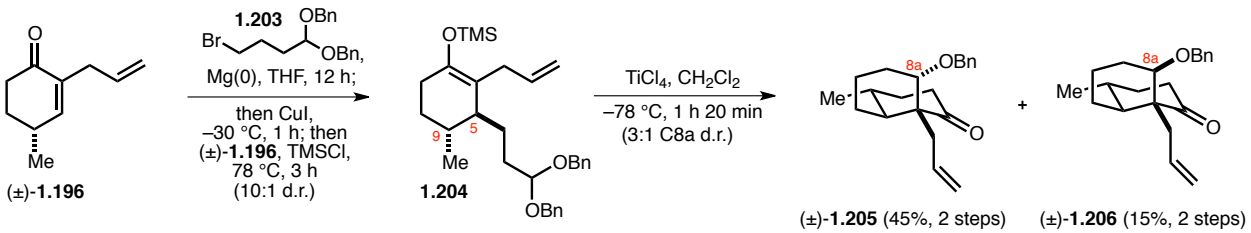
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.28 (m, 10 H), 4.78 (t, *J* = 5.4 Hz, 1 H), 4.69 (d, *J* = 11.8 Hz, 2 H), 4.58 (d, *J* = 11.9 Hz, 2 H), 3.43 (t, *J* = 6.5 Hz, 2 H), 2.04–1.89 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.0, 128.4, 127.8, 127.7, 101.2, 67.4, 33.6, 31.9, 27.9.

FTIR (thin film) cm^{-1}: 3031, 2958, 2874, 1497, 1454, 1346, 1122, 1045, 905, 897.

HRMS (ESI) calc'd for $C_{18}H_{21}BrNaO_2$ $[M+Na]^+$: 371.0617, found 371.0621.

TLC (15% EtOAc in hexanes), R_f: 0.60 (UV, CAM).



***C*-Allyl *cis*-decalin (±)-1.205 and (±)-1.206**:

A 2-L, 2-necked, round-bottomed flask equipped two rubber septa was charged with magnesium turnings (12.2 g, 500 mmol, 3.00 equiv). THF (170 mL) was introduced and 1,2-dibromoethane (100 µL) was added via syringe to the vigorously stirred reaction mixture. A separate 250 mL round-bottomed flask was charged with alkyl bromide **1.203** (87.3 g, 250 mmol, 1.50 equiv) and azeotropically dried with three portions of benzene. THF (100 mL) was introduced and the resultant solution added dropwise to the magnesium turnings via cannula over 2 h. The resultant reaction mixture stirred vigourously at ambient temperature. After 12 h, the reaction mixture was cooled to –30 °C and copper(I) iodide (63.5g, 333 mmol, 2.00 equiv) was added in a single portion to the cold reaction mixture. After 30 min, the resultant slurry was cooled further to –78 °C. A separate 500 mL round-bottomed flask was charged with 2-allyl-3-methoxycyclohex-2-enone ((±)-**1.196**) (25.0 g, 167 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (230 mL) and TMSCl (53.4 mL, 63.5 g, 500 mmol, 3.00 equv) were introduced and the resultant solution was cooled to –78 °C before being transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 30 min. The transfer was completed with two additional portions of THF (50 mL). The resultant slurry stirred for 3 h at –78 °C before triethylamine (81.5 mL, 500 mmol, 3.00 equiv) was added dropwise via syringe and the resultant reaction mixture allowed to warm to ambient temperature. After 12 h a mixture of ammonium hydroxide in saturated aqueous ammonium chloride solution (10% v/v, 500 mL) was *carefully* added to the yellow reaction mixture. The resultant heterogeneous mixture was filtered through a pad of Celite, which was rinsed with Et_2O (2 × 200 mL) and H_2O (2 × 200 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (2 × 500 mL). The combined organic layers were washed with water (1.0 L) and

brine (1.0 L), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield silyl enol ether **1.204** as a tan oil that was used without further purification.

A 2-L round-bottomed flask was charged with silyl enol ether **1.204** and azeotropically dried with three portions of benzene. CH_2Cl_2 (530 mL) was introduced and the resultant solution cooled to –78 °C. A separate 200-mL round-bottomed flask was charged with a solution of titanium (IV) tetrachloride (12.2 mL, 111 mmol, 1.05 equiv) and CH_2Cl_2 (111 mL) and the resultant solution cooled to –78 °C before being transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 20 min. After 1 h, saturated aqueous sodium bicarbonate solution (500 mL) was added and the reaction mixture warmed to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2 (2 × 200 mL) and H_2O (2 × 200 mL). The layers of the filtrate were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (500 mL) and brine (500 mL), filtered, and concentrated under reduced pressure to yield a mixture of *C*-allyl *cis*-decalin (±)-**1.205**, (±)-**1.206** and protodebrominated alkyl bromide **1.203** which was hydrolyzed to facilitate purification.

Accordingly, a 500-mL round-bottomed flask was charged with a solution of the product residue, THF (100 mL) and water (100 mL). *para*-Toluenesulfonic acid monohydrate (1.00 g, 5.30 mmol, 0.05 equiv) was introduced to the stirred reaction mixture in one portion at ambient temperature. After 12 h, the reaction mixture was diluted with EtOAc (200 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% EtOAc in hexanes) to afford *C*-allyl *cis*-decalin (±)-**1.205** (23.5 g, 45%, over two steps) and (±)-**1.206** (7.70 g, 15%, over two steps) as colorless oils.

***C*-Allyl *cis*-decalin (±)-1.205**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.30 (m, 2 H), 7.29–7.22 (m, 3 H), 5.59–5.48 (m, 1 H), 5.06–4.97 (m, 2 H), 4.45 (d, *J* = 11.3 Hz, 1 H), 4.19 (d, *J* = 11.3 Hz, 1 H), 3.45 (br. s., 1 H), 2.74–2.62 (m, 1 H), 2.52–2.32 (m, 3 H), 2.25 (dd, *J* = 9.3, 13.5 Hz, 1 H), 1.90 (d, *J* = 14.3 Hz, 1 H), 1.84–1.66 (m, 3 H), 1.59–

1.43 (m, 3 H), 1.38–1.30 (m, 1 H), 1.25 (ddt, *J* = 5.5, 11.2, 12.9 Hz, 1 H), 0.92 (d, *J* = 6.6 Hz, 3 H).

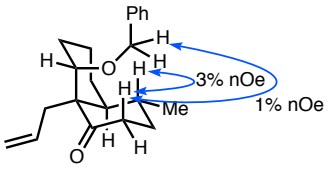
^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.1, 138.5, 134.9, 128.2, 127.5, 127.3, 117.7, 82.8, 71.7, 54.6, 41.9, 41.8, 38.0, 32.2, 28.3, 24.8, 22.3, 20.9, 14.8.

FTIR (thin film) cm^{-1}: 3066, 3031, 2934, 2866, 1697, 1452, 1061, 915, 734, 698.

HRMS (ESI) calc'd for $C_{21}H_{28}NaO_2$ $[M+Na]^+$: 335.1982, found 335.1977.

TLC (15% EtOAc in hexanes), R_f: 0.45 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



***C*-Allyl *cis*-decalin (±)-1.206**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.29 (m, 2 H), 7.29–7.23 (m, 3 H), 5.71 (dtd, *J* = 4.3, 10.0, 17.1 Hz, 1 H), 5.08 (d, *J* = 17.2 Hz, 1 H), 5.02 (d, *J* = 10.1 Hz, 1 H), 4.56 (d, *J* = 12.2 Hz, 1 H), 4.32 (d, *J* = 12.2 Hz, 1 H), 3.98 (dd, *J* = 4.6, 10.5 Hz, 1 H), 3.14–3.06 (m, 1 H), 2.36 - 2.24 (m, 2 H), 2.18 (td, *J* = 3.3, 14.3 Hz, 1 H), 2.11–1.96 (m, 2 H), 1.94–1.85 (m, 1 H), 1.72–1.64 (m, 1 H), 1.62–1.42 (m, 5 H), 1.37–1.25 (m, 1 H), 0.88 (d, *J* = 6.4 Hz, 3 H).

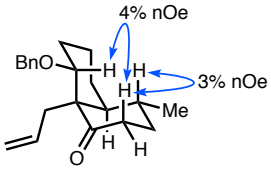
^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.8, 138.4, 135.8, 128.2, 127.6, 127.5, 116.6, 76.3, 70.0, 56.9, 46.0, 38.5, 34.9, 30.7, 28.6, 25.9, 21.4, 19.6, 19.0.

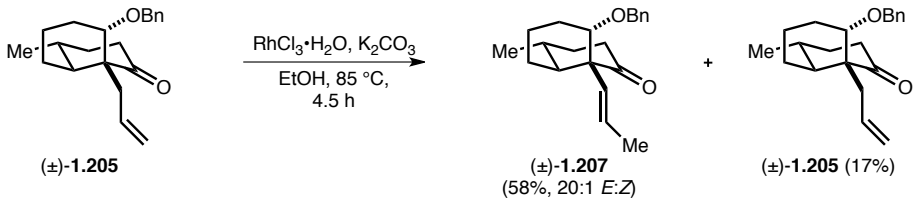
FTIR (thin film) cm^{-1}: 3069, 3030, 2945, 2870, 1708, 1637, 1454, 1097, 908, 739.

HRMS (ESI) calc'd for $C_{21}H_{28}NaO_2$ $[M+Na]^+$: 335.1982, found 335.1940.

TLC (10% EtOAc in hexanes), R_f: 0.23 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):





(±)-**1.205** (±)-**1.207** (58%, 20:1 *E*:*Z*) (±)-**1.205** (17%)

***C*-Propenyl *cis*-decalin (±)-1.207**:

A 350-mL pressure vessel was charged with a solution of *C*-allyl *cis*-decalin (±)-**1.205** (3.70 g, 11.9 mmol, 1.00 equiv) and ethanol (60.0 mL). Potassium carbonate (3.30 g, 2.00 equiv) and rhodium(III) chloride hydrate (248 mg, 0.10 equiv) were introduced. The pressure vessel was sealed and the vigorously stirred reaction mixture was heated to 85 °C. After 4.5 h, the reaction mixture was cooled to ambient temperature, diluted with Et_2O (200 mL), and filtered through a pad of Celite, which was rinsed with Et_2O (3 × 50 mL) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford *C*-propenyl *cis*-decalin (±)-**1.207** (2.14 g, 58%, 20:1 *E*:*Z*) as a colorless oil and recovered starting material *C*-allyl *cis*-decalin (±)-**1.205** (639 mg, 17%).

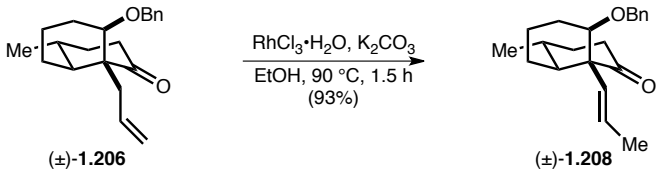
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.31 (m, 2 H), 7.31–7.25 (m, 3 H), 5.60 (qd, *J* = 6.3, 15.8 Hz, 1 H), 5.41 (d, *J* = 15.5 Hz, 1 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.29 (d, *J* = 11.3 Hz, 1 H), 3.79 (br. s., 1 H), 2.54–2.35 (m, 3 H), 1.95–1.82 (m, 2 H), 1.80–1.66 (m, 6 H), 1.61–1.49 (m, 2 H), 1.39 (dtd, *J* = 6.5, 10.1, 13.3 Hz, 1 H), 1.33–1.24 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.8, 138.7, 133.1, 128.2, 127.4, 127.2, 126.3, 82.2, 71.8, 56.7, 45.3, 40.1, 31.7, 28.0, 24.9, 23.5, 21.1, 18.6, 15.3.

FTIR (thin film) cm^{-1}: 3064, 3031, 2940, 2866, 1701, 1454, 1067, 733, 698.

HRMS (ESI) calc'd for $C_{21}H_{28}NaO_2$ $[M+Na]^+$: 335.1982, found 335.1987.

TLC (15% EtOAc in hexanes), R_f: 0.25 (UV, CAM).



***C*-Propenyl *cis*-decalin (±)-1.208**:

A 250-mL pressure vessel was charged with a solution of *C*-allyl *cis*-decalin (±)-**1.206** (2.55 g, 8.17 mmol, 1.00 equiv) and ethanol (41.0 mL). Potassium carbonate (4.50 g, 4.00 equiv) and rhodium(III) chloride hydrate (85.0 mg, 0.05 equiv) were introduced. The pressure vessel was sealed and the vigorously stirred reaction mixture was heated to 90 °C. After 1.5 h, the reaction mixture was cooled to ambient temperature, diluted with Et_2O (150 mL), and filtered through a pad of Celite, which was rinsed with Et_2O (3 × 50 mL) and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford *C*-propenyl *cis*-decalin (±)-**1.208** (2.38 g, 93%, 20:1 *E*:*Z*) as a colorless oil.

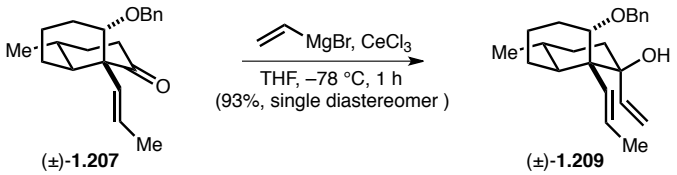
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39– 7.15 (m, 5 H), 5.78 (dd, *J* = 1.5, 16.3 Hz, 1 H), 5.38 (qd, *J* = 6.4, 16.2 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.33 (d, *J* = 12.0 Hz, 1 H), 3.93 (dd, *J* = 3.3, 7.6 Hz, 1 H), 2.35 (td, *J* = 4.4, 15.4 Hz, 1 H), 2.19 (ddd, *J* = 5.4, 12.0, 15.4 Hz, 1 H), 1.97–1.78 (m, 3 H), 1.78–1.70 (m, *J* = 1.6, 6.4 Hz, 4 H), 1.70–1.58 (m, 3 H), 1.56–1.39 (m, 2 H), 1.38–1.30 (m, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.6, 138.7, 132.7, 128.2, 127.7, 127.4, 125.2, 78.7, 76.8, 76.7, 70.5, 59.4, 46.5, 37.6, 31.6, 27.7, 26.3, 21.2, 19.7, 18.5, 14.2.

FTIR (thin film) cm^{-1}: 3389, 3064, 3030, 2931, 2869, 1706, 1454, 1071, 737, 698.

HRMS (ESI) calc'd for $C_{21}H_{28}NaO_2$ $[M+Na]^+$: 335.1982, found 335.1963.

TLC (15% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



Allylic alcohol (±)-1.209:

A 500-mL round-bottomed flask was charged with anhydrous cerium(III) chloride (12.3 g, 50.0 mmol, 4.47 equiv) and heated to 145 °C under reduced pressure (0.05 Torr) for 1 h. The flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (100 mL) was introduced via syringe over 5 min. The resultant heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –78 °C before a solution of vinylmagnesium bromide in THF (1.0 M, 50.0 mL, 50.0 mmol, 4.47 equiv) was added dropwise via syringe over 10 min. The resultant yellow slurry was stirred for 1.5 h at –78 °C. A separate 100 mL round-bottomed flask was charged with *C*-propenyl *cis*-decalin (±)-**1.207** (3.49 g, 11.2 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (50 mL) was introduced and the resultant solution was cooled to –78 °C before being transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 30 min. The transfer was completed with two additional portions of THF (5 mL). After 1 h, a saturated aqueous ammonium chloride solution (300 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (300 mL) and brine (300 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford allylic alcohol (±)-**1.209** (3.54 g, 93%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.32 (m, 4 H), 7.31–7.25 (m, 1 H), 6.31 (dd, J = 10.9, 17.2 Hz, 1 H), 5.37 (qd, J = 6.3, 16.2 Hz, 1 H), 5.13 (dd, J = 1.5, 6.8 Hz, 1 H), 5.10 (dd, J = 1.5, 7.8 Hz, 1 H), 4.92 (dd, J

= 1.6, 10.9 Hz, 1 H), 4.60 (d, *J* = 11.9 Hz, 1 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 4.02 (br. s., 1 H), 2.65 (ddd, *J* = 4.6, 12.0, 14.1 Hz, 1 H), 2.38 (tq, *J* = 5.9, 11.4 Hz, 1 H), 1.83–1.48 (m, 10 H), 1.43 (ddd, *J* = 2.9, 4.0, 11.9 Hz, 1 H), 1.34 (s, 1 H), 1.25 (td, *J* = 2.9, 12.4 Hz, 1 H), 1.16 (ddd, *J* = 4.1, 13.8, 26.2 Hz, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H).

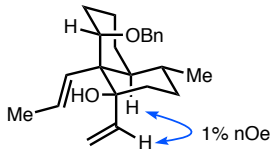
^{13}C NMR (125 MHz, $CDCl_3$) δ: 144.4, 139.3, 137.9, 128.2, 127.4, 127.1, 124.0, 109.9, 78.5, 77.5, 71.1, 49.1, 45.5, 38.1, 32.5, 28.7, 25.6, 23.6, 21.2, 18.6, 15.5.

FTIR (thin film) cm^{-1}: 3584, 3479 (br), 3028, 2929, 2865, 1453, 1093, 1066, 980, 914, 733, 697.

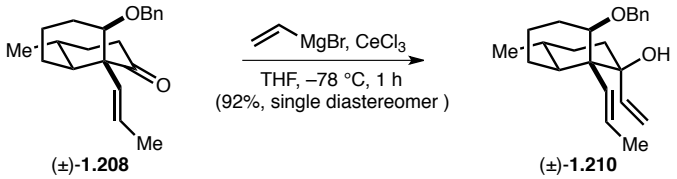
HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2296.

TLC (15% EtOAc in hexanes), R_f: 0.26 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.209**



Allylic alcohol (±)-**1.210**:

A 500-mL round-bottomed flask was charged with anhydrous cerium(III) chloride (21.6 g, 87.4 mmol, 5.00 equiv) and heated to 145 °C under reduced pressure (0.05 Torr) for 1 h. The flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (175 mL) was introduced via syringe over 5 min. The resultant heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 12 h, the reaction vessel was equipped with a 250-mL equal pressure graduated addition funnel and the reaction mixture was cooled to –78 °C. A solution of vinylmagnesium bromide in THF (1.0 M, 88.0 mL, 88.0 mmol, 5.00 equiv) was added dropwise via 250-mL equal pressure graduated addition funnel over 30 min. The resultant yellow slurry was stirred for 1.5 h at –78 °C. A separate 250 mL round-bottomed flask was charged with *C*-propenyl *cis*-decalin (±)-**1.208** (5.46 g, 17.5 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (88 mL) was introduced and the resultant solution was cooled to –78 °C before being transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 1 h. The transfer was completed with two additional portions of THF (10 mL). After 2 h, a saturated aqueous ammonium chloride solution (300 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (300 mL) and brine (300 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford allylic alcohol (±)-**1.210** (5.49 g, 92%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 5 H), 6.28 (ddd, *J* = 0.9, 11.0, 17.0 Hz, 1 H), 5.80 (d, *J* =

1.0 Hz, 1 H), 5.60 (qd, *J* = 6.2, 16.4 Hz, 1 H), 5.47 (dd, *J* = 1.3, 16.5 Hz, 1 H), 5.28 (dd, *J* = 2.3, 16.9 Hz, 1 H), 5.05 (dd, *J* = 2.3, 10.9 Hz, 1 H), 4.70 (d, *J* = 11.1 Hz, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.40 (dd, *J* = 4.1, 11.6 Hz, 1 H), 2.11–2.02 (m, 1 H), 1.92 (dt, *J* = 4.6, 13.8 Hz, 1 H), 1.82 (tt, *J* = 5.7, 11.8 Hz, 1 H), 1.76–1.59 (m, 6 H), 1.58–1.39 (m, 3 H), 1.31 (ddd, *J* = 4.7, 14.4, 27.1 Hz, 1 H), 0.87 (d, *J* = 6.3 Hz, 3 H).

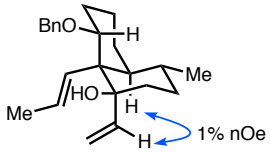
^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.9, 137.2, 130.5, 128.5, 128.1, 127.9, 127.4, 113.5, 79.4, 78.0, 70.4, 50.3, 44.7, 37.5, 32.4, 27.9, 27.0, 22.1, 20.5, 19.5, 18.8.

FTIR (thin film) cm^{-1}: 3442 (br), 3091, 3065, 3031, 2953, 2867, 1498, 1449, 1424, 1301, 1063, 979, 698.

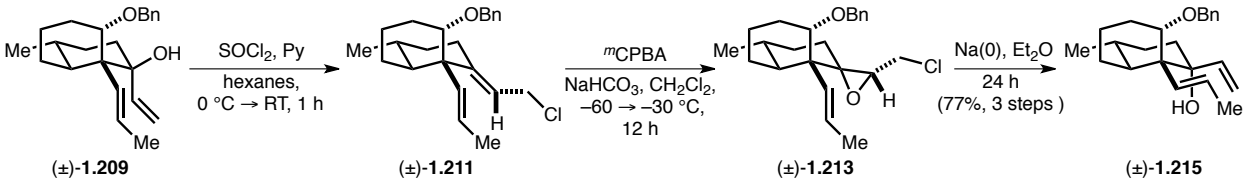
HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2296.

TLC (10% EtOAc in hexanes), R_f: 0.20 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.210**



Allyl alcohol (±)-**1.215**:

A 1-L round-bottomed flask was charged with allyl alcohol (±)-**1.209** (14.8 g, 43.5 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Hexanes (435 mL) was introduced and the resultant solution was cooled to 0 °C. Thionyl chloride (9.53 ml, 131 mmol, 3.00 equiv) and pyridine (17.6 ml, 218 mmol, 5.00 equiv) were sequentially added dropwise via syringe to the cooled, stirred reaction mixture over 10 min. The resultant reaction mixture warmed to ambient temperature over 1h. A saturated aqueous ammonium chloride solution (200 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (2 × 250 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to furnish allylic chloride (±)-**1.211** as a tan oil that was used without further purification.

A 1-L round-bottomed flask was charged with allylic chloride (±)-**1.211** and azeotropically dried with three portions of benzene before CH_2Cl_2 (400 mL) was introduced. Sodium bicarbonate (14.6 g, 174 mmol, 4.00 equiv) was added to the stirred solution at ambient temperature, and the resultant heterogeneous mixture was cooled to –78 °C. A separate 1-L round-bottomed flask was charged with ^{m}CPBA (77 wt. %, 22.4 g, 100 mmol, 2.30 equiv) and diluted with CH_2Cl_2 (400 mL). The resultant solution was then transferred dropwise via cannula to the stirred, cooled reaction mixture over 1.5 h. The resultant heterogeneous reaction mixture was warmed to –30 °C. After 12 h, the reaction mixture was cautiously poured into a 2-L Erlenmeyer flask containing a stirred 1:1 mixture of saturated aqueous sodium bicarbonate solution (200 mL) and 10% (w/v) aqueous sodium sulfite solution (200 mL), which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous magnesium

sulfate, filtered, and concentrated under reduced pressure. The residue was filtered through a silica gel plug, which was eluted with 10% EtOAc in hexanes (3 × 500 mL) to furnish epoxy chloride (±)-**1.213** as an impure clear oil that was used without further purification.

A 500-mL round-bottomed flask was charged with expoxy chloride (±)-**1.213** and azeotropically dried with three portions of benzene. Et_2O (87 mL) was introduced and sodium metal (3.00 g, 131 mmol, 3.00 equiv) was cut from a sodium lump under blanket of argon into the stirred reaction mixture at ambient temperature. After 24 h, the grey reaction mixture was cooled to 0 °C and methanol (40 mL) was added dropwise via syringe. After 1 h, saturated aqueous ammonium chloride solution (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (250 mL) brine (250 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford allylic alcohol (±)-**1.215** (11.4 g, 77% over three steps) as a clear oil.

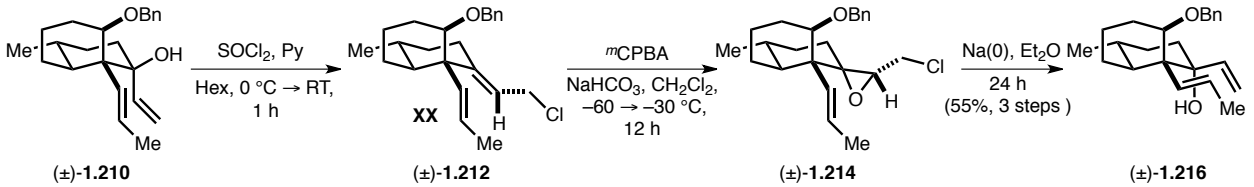
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.35 (m, 4 H), 7.35–7.29 (m, 1 H), 6.02 (dd, *J* = 10.8, 17.3 Hz, 1 H), 5.62 (qd, *J* = 6.4, 16.1 Hz, 1 H), 5.16 (dd, *J* = 1.5, 12.8 Hz, 1 H), 5.13 (dd, *J* = 1.6, 11.9 Hz, 1 H), 5.08 (dd, *J* = 1.6, 10.8 Hz, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 3.58 (br. s., 1 H), 2.55 (q, *J* = 10.8 Hz, 1 H), 2.44 - 2.31 (m, 1 H), 2.04 (s, 1 H), 1.95 (d, *J* = 14.2 Hz, 1 H), 1.81 (d, *J* = 6.3 Hz, 3 H), 1.79–1.72 (m, 1 H), 1.72–1.66 (m, 2 H), 1.60 (tt, *J* = 3.4, 13.0 Hz, 1 H), 1.53–1.42 (m, 4 H), 1.29–1.20 (m, 1 H), 0.94 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.3, 138.7, 134.5, 128.2, 128.1, 127.2, 127.1, 112.6, 80.8, 74.2, 70.7, 51.0, 40.2, 34.5, 30.3, 28.5, 25.0, 22.8, 21.5, 18.5, 15.3.

FTIR (thin film) cm^{-1}: 3538, 3028, 2946, 2922, 2865, 1453, 1363, 1317, 1068, 925, 733, 697.

HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2295.

TLC (15% EtOAc in hexanes), R_f: 0.37 (UV, CAM).



Allylic alcohol (±)-**1.216**:

A 500-mL round-bottomed flask was charged with allyl alcohol (±)-**1.210** (5.40 g, 15.9 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Hexanes (160 mL) was introduced and the resultant solution was cooled to 0 °C. Thionyl chloride (3.47 ml, 47.7 mmol, 3.00 equiv) and pyridine (6.43 ml, 80.0 mmol, 5.00 equiv) were sequentially added dropwise via syringe to the cooled, stirred reaction mixture over 10 min. The resultant reaction mixture warmed to ambient temperature over 1 h. A saturated aqueous ammonium chloride solution (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to furnish allylic chloride (±)-**1.212** as a tan oil that was used without further purification.

A 500-L round-bottomed flask was charged with allylic chloride (±)-**1.212** and azeotropically dried with three portions of benzene before CH_2Cl_2 (160 mL) was introduced. Sodium bicarbonate (4.00 g, 47.7 mmol, 4.00 equiv) was added to the stirred solution at ambient temperature, and the resultant heterogeneous mixture was cooled to –78 °C. A separate 500-mL round-bottomed flask was charged with *m*CPBA (77 wt. %, 8.20 g, 36.6 mmol, 2.30 equiv) and diluted with CH_2Cl_2 (160 mL). The resultant solution was then transferred dropwise via cannula to the stirred, cooled reaction mixture over 45 min. The resultant heterogeneous reaction mixture was warmed to –30 °C. After 12 h, the reaction mixture was cautiously poured into a 1-L Erlenmeyer flask containing a stirred 1:1 mixture of saturated aqueous sodium bicarbonate solution (200 mL) and 10% (w/v) aqueous sodium sulfite solution (200 mL), which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous

magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was filtered through a silica gel plug, which was eluted with 10% EtOAc in hexanes (3 × 500 mL) to furnish epoxy chloride (±)-**1.214** as a colorless oil that was used without further purification.

A 200-mL round-bottomed flask was charged with expoxy chloride (±)-**1.214** and azeotropically dried with three portions of benzene. Et_2O (32 mL) was introduced and sodium metal (1.10 g, 47.7 mmol, 3.00 equiv) was cut from a sodium lump under blanket of argon into the stirred reaction mixture at ambient temperature. After 24 h, the grey reaction mixture was cooled to 0 °C and methanol (20 mL) was added dropwise via syringe. After 1 h, saturated aqueous ammonium chloride solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (150 mL) brine (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford allylic alcohol (±)-**1.216** (2.97 g, 55% over three steps) as a colorless oil.

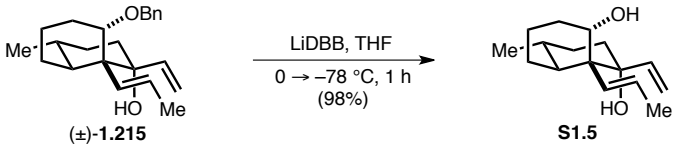
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.34 (m, 4 H), 7.33–7.27 (m, 1 H), 6.31 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.84 (dd, *J* = 1.0, 16.5 Hz, 1 H), 5.67 (qd, *J* = 6.2, 16.5 Hz, 1 H), 4.97 (dd, *J* = 1.4, 17.3 Hz, 1 H), 4.81 (dd, *J* = 1.4, 10.8 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 3.93 (dd, *J* = 4.2, 10.5 Hz, 1 H), 2.14 (br. s., 1 H), 2.09–2.00 (m, 2 H), 1.85 (d, *J* = 6.3 Hz, 4 H), 1.75–1.53 (m, 4 H), 1.53–1.35 (m, 3 H), 0.94 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.1, 138.7, 131.4, 128.0, 127.4, 127.1, 127.0, 108.4, 77.1, 73.6, 70.1, 53.4, 40.7, 32.1, 29.9, 29.2, 27.9, 22.3, 20.5, 19.5, 18.5.

FTIR (thin film) cm^{-1}: 3544, 3087, 3065, 3030, 2933, 2866, 1451, 1359, 1210, 1073, 992, 738.

HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2293.

TLC (15% EtOAc in hexanes), R_f: 0.19 (UV, CAM).



Diol S1.5:

A 500-mL round-bottomed flask was charged with a solution of 4,4-di-*tert*-butylbiphenyl (4.20 g, 16.0 mmol, 12.0 equiv) in THF (80 mL). Lithium (91.0 mg) was introduced at ambient temperature and the resultant suspension stirred until a green color persisted at which time the reaction mixture was cooled to 0 °C. After 4 h, the reaction mixture was cooled to –78 °C. A separate 25-mL round-bottomed flask was charged with allylic alcohol (±)-**1.215** (448 mg, 1.32 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (10 ml) was introduced and the resultant solution was transferred dropwise via syringe to the stirred, cooled reaction mixture. The transfer was completed with two additional portions of THF (2.5 mL). After 30 min, the resultant reaction mixture warmed to 0 °C over 30 min. A saturated aqueous ammonium chloride solution (50 mL) was added and was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (50 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 50 mL) and the combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 10% EtOAc in CH_2Cl_2) diol **S1.5** (323 mg, 98%) as a white solid.

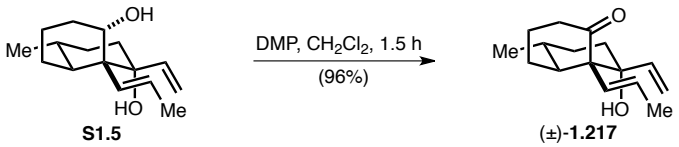
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.18 (dd, *J* = 10.8, 17.3 Hz, 1 H), 5.55 (qd, *J* = 6.3, 16.2 Hz, 1 H), 5.13 (dd, *J* = 1.3, 17.3 Hz, 1 H), 5.08–5.01 (m, 2 H), 3.85 (br. s., 1 H), 2.51–2.40 (m, 1 H), 2.17 (tt, *J* = 5.7, 11.1 Hz, 1 H), 2.01 (d, *J* = 2.4 Hz, 1 H), 1.75 (dd, *J* = 1.1, 6.4 Hz, 3 H), 1.72–1.66 (m, 2 H), 1.66–1.59 (m, 2 H), 1.57–1.39 (m, 6 H), 1.30–1.18 (m, 1 H), 0.88 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.6, 134.4, 128.3, 112.4, 74.3, 73.0, 50.3, 39.9, 34.5, 32.3, 30.1, 29.1, 22.8, 21.6, 18.6, 14.9.

FTIR (thin film) cm^{-1}: 3448 (br), 2920, 2867, 1447, 1375, 1318, 986, 923.

HRMS (ESI) calc'd for $C_{16}H_{26}NaO_2$ $[M+Na]^+$: 273.1825, found 273.1824.

TLC (15% EtOAc in hexanes), R_f: 0.34 (UV, CAM).



S1.5 (±)-**1.217**

Ketone (±)-**1.217**:

A 25-mL round-bottomed flask was charged with a solution of diol **S1.5** (292 mg, 1.17 mmol, 1.00 equiv) and CH_2Cl_2 (12 mL). Dess-Martin periodinane (4.00 g, 4.67, 8.00 equiv) was added to the stirred reaction mixture at ambient temperature in one portion. After 18 h, saturated aqueous sodium bicarbonate solution (10 ml) was added and the resultant heterogeneous mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2 (2 × 25 mL) and H_2O (2 × 25 mL). The layers of the filtrate were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford ketone (±)-**1.217** (278 mg, 96%) as a colorless oil.

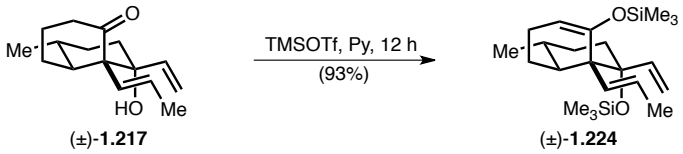
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.51 (dd, *J* = 10.9, 17.5 Hz, 1 H), 5.35 (dd, *J* = 1.3, 16.1 Hz, 1 H), 5.24 (qd, *J* = 6.2, 16.1 Hz, 1 H), 5.00 (dd, *J* = 1.5, 17.5 Hz, 1 H), 4.95 (dd, *J* = 1.5, 10.9 Hz, 1 H), 2.70 (dt, *J* = 8.1, 13.1 Hz, 1 H), 2.20–2.03 (m, 3 H), 1.99–1.89 (m, 1 H), 1.85–1.72 (m, 3 H), 1.71 (dd, *J* = 1.3, 6.2 Hz, 3 H), 1.56–1.34 (m, 5 H), 0.86 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.1, 144.8, 132.0, 130.3, 112.0, 75.4, 63.3, 46.3, 40.1, 34.1, 30.1, 29.5, 22.6, 22.4, 19.4, 18.3.

FTIR (thin film) cm^{-1}: 3021, 2948, 2875, 1695, 1447, 1310, 1227, 1127, 976, 917, 824, 683, 664, 576, 545.

HRMS (ESI) calc'd for $C_{16}H_{24}NaO_2$ $[M+Na]^+$: 271.1669, found 271.1670.

TLC (15% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



(±)-**1.217** (±)-**1.224**

Enol silane (±)-**1.224**:

A 25-mL round-bottomed flask was charged with ketone (±)-**1.217** (273 mg, 1.10 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Pyridine (6 mL) was introduced, and the resultant solution cooled to 0 °C. Freshly distilled trimethylsilyl trifluoromethanesulfonate (1.20 mL, 6.60 mmol, 6.00 equiv) was added dropwise via syringe to a stirred solution, which was subsequently allowed to warm to ambient temperature. After 12 h, saturated aqueous sodium bicarbonate solution (5 mL) and Et_2O (5 mL) were then added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford enol silane (±)-**1.224** (399 mg, 93%) as a colorless oil.

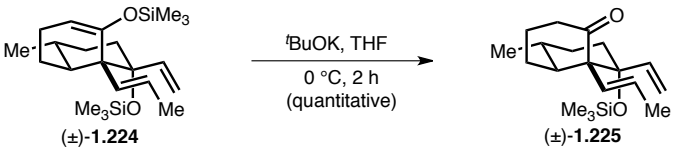
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.16 (dd, *J* = 10.9, 17.9 Hz, 1 H), 5.58 (dd, *J* = 1.5, 15.7 Hz, 1 H), 5.38 (qd, *J* = 6.4, 15.7 Hz, 1 H), 4.95 (dd, *J* = 1.1, 17.8 Hz, 1 H), 4.82 (dd, *J* = 1.3, 10.9 Hz, 1 H), 4.63 (dd, *J* = 2.8, 4.4 Hz, 1 H), 2.06–1.96 (m, 1 H), 1.91 (dd, *J* = 2.9, 10.0 Hz, 1 H), 1.83 (td, *J* = 5.6, 17.4 Hz, 1 H), 1.74 (dd, *J* = 1.5, 6.4 Hz, 3 H), 1.67–1.56 (m, 3 H), 1.55–1.42 (m, 4 H), 0.91 (d, *J* = 5.8 Hz, 3 H), 0.13 (s, 9 H), 0.06 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 151.1, 145.4, 135.9, 125.7, 109.8, 102.9, 77.0, 54.7, 42.0, 30.7, 29.8, 28.1, 20.8, 20.2, 19.8, 18.2, 2.4, 0.5.

FTIR (thin film) cm^{-1}: 2949, 1651, 1247, 1190, 1050, 1015, 911, 839, 753.

HRMS (ESI) calc'd for $C_{22}H_{40}NaO_2Si_2$ $[M+Na]^+$: 415.2459, found 415.2467.

TLC (15% EtOAc in hexanes), R_f: 0.81 (UV, CAM).



Silyl ether (±)-**1.224**:

A 10-mL round-bottomed flask was charged with enol silane (±)-**1.224** (130 mg, 330 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (2 mL) was introduced and the resultant solution transferred dropwise via syringe to a 25-mL round-bottomed flask containing a stirred mixture of potassium *tert*-butoxide (56 mg, 0.580 mmol, 1.50 equiv) and THF (2 ml) at 0 °C. The transfer was completed with two additional portions of THF (1 mL) After 2 h, saturated aqueous ammonium chloride solution (5 mL) and Et_2O (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford silyl ether (±)-**1.225** (106 mg, quantitative) as a colorless oil.

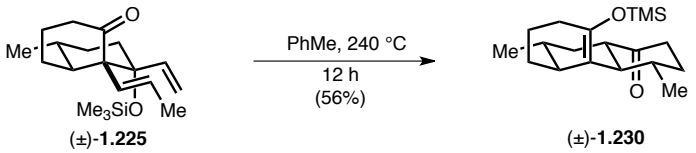
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.10 (dd, *J* = 11.0, 17.7 Hz, 1 H), 5.44 (dd, *J* = 1.6, 16.4 Hz, 1 H), 5.13 (dd, *J* = 1.5, 17.7 Hz, 1 H), 5.08 (dd, *J* = 1.5, 11.0 Hz, 1 H), 5.03 (qd, *J* = 6.4, 16.4 Hz, 1 H), 2.72 (ddd, *J* = 8.0, 12.6, 14.1 Hz, 1 H), 2.10 (td, *J* = 2.7, 11.6 Hz, 1 H), 2.07–1.98 (m, 2 H), 1.96–1.86 (m, 1 H), 1.83–1.67 (m, 7 H), 1.53–1.41 (m, 2 H), 1.41–1.29 (m, *J* = 6.2 Hz, 1 H), 0.86 (d, *J* = 6.4 Hz, 3 H), 0.03 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.1, 142.7, 134.6, 128.4, 113.9, 77.6, 64.6, 47.1, 39.9, 32.1, 30.3, 29.6, 22.8, 21.9, 19.5, 18.3, 2.5.

FTIR (thin film) cm^{-1}: 3089, 3021, 2953, 1705, 1448, 1249, 1083, 919, 754, 656.

HRMS (ESI) calc'd for $C_{22}H_{40}NaO_2Si_2$ $[M+Na]^+$: 415.2459, found 415.2467.

TLC (15% EtOAc in hexanes), R_f: 0.81 (UV, CAM).



(±)-**1.225** (±)-**1.230**

Tricycle (±)-1.230:

A 2-mL vial was charged with a solution of ketone (±)-**1.225** (12.0 mg, 37.5 μmol) and PhMe (400 μL), sealed with a Teflon cap, and heated to 240 °C. After 12 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford tricycle (±)-**1.230** (6.7 mg, 56%) as a colorless oil.

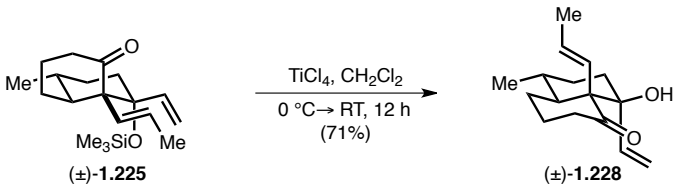
^{1}H NMR (500 MHz, C_6D_6) δ: 3.10 (q, *J* = 10.0 Hz, 1 H), 2.66 (t, *J* = 3.8 Hz, 1 H), 2.60–2.49 (m, 1 H), 2.37–2.25 (m, 1 H), 2.09 (tdd, *J* = 1.8, 4.1, 12.8 Hz, 1 H), 2.06–2.00 (m, 1 H), 1.79 (dt, *J* = 6.8, 13.1 Hz, 1 H), 1.71–1.61 (m, 2 H), 1.61–1.55 (m, 1 H), 1.50–1.23 (m, 7 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 5.9 Hz, 3 H), 0.27 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.3, 142.4, 114.0, 52.8, 48.9, 47.0, 43.8, 34.9, 32.4, 30.6, 30.3, 29.5, 28.0, 23.2, 20.6, 18.9, 0.6.

FTIR (thin film) cm^{-1}: 3075, 2962, 1703, 1441, 1248, 1092, 917, 812, 756.

HRMS (ESI) calc'd for $C_{19}H_{33}O_2Si$ $[M+H]^+$: 321.2244, found 321.2234.

TLC (10% EtOAc in hexanes), R_f: 0.23 (UV, CAM).



(±)-**1.225** (±)-**1.228**

***trans*-Decalin (±)-1.228**:

A 10-mL round-bottomed flask was charged with ketone (±)-**1.225** (12.4 mg, 39.0 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (400 μL) was introduced and the resultant solution was cooled to –78 °C. A solution of boron trifluoride diethyl etherate in CH_2Cl_2 (1.0 M, 39.0 μL, 39.0 μmol, 1.00 equiv) was added to the stirred, cooled reaction mixture, which was subsequently warmed to ambient temperature. After 12 h, saturated aqueous sodium bicarbonate solution (3 mL) and Et_2O (3 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 30% → 40% EtOAc in hexanes) to afford *trans*-decalin (±)-**1.228** (6.9 mg, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.50 (t, *J* = 6.0 Hz, 1 H), 5.36 (dd, *J* = 1.5, 16.3 Hz, 1 H), 5.13 (qd, *J* = 6.3, 16.3 Hz, 1 H), 4.29–4.15 (m, 2 H), 2.76–2.64 (m, 1 H), 2.60 (td, *J* = 3.3, 14.0 Hz, 1 H), 2.33–2.22 (m, 1 H), 2.07–1.73 (m, 9 H), 1.59 (br. s., 2 H), 1.12–0.96 (m, 1 H), 0.89 (d, *J* = 5.6 Hz, 3 H).

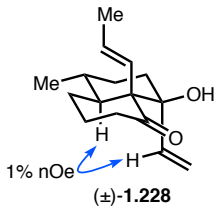
^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4, 143.7, 135.0, 129.2, 125.6, 64.2, 59.2, 53.0, 38.8, 36.0, 31.2, 27.1, 23.2, 21.0, 19.5, 18.4.

FTIR (thin film) cm^{-1}: 3408, 2938, 2875, 1704, 1448, 1384, 1254.

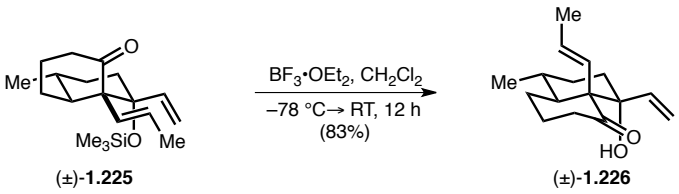
HRMS (ESI) calc'd for $C_{16}H_{24}NaO_2$ $[M+Na]^+$: 271.1669, found 271.1685.

TLC (40% EtOAc in hexanes), R_f: 0.18 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.228**



***cis*-Decalin (±)-1.226**:

A 10-mL round-bottomed flask was charged with ketone (±)-**1.225** (13.0 mg, 41.0 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (400 μL) was introduced and the resultant solution was cooled to 0 °C. A solution of titanium(IV) chloride in CH_2Cl_2 (1.0 M, 41.0 μL, 41.0 μmol, 1.00 equiv) was added to the stirred, cooled reaction mixture, which was subsequently warmed to ambient temperature. After 12 h, saturated aqueous sodium bicarbonate solution (3 mL) and Et_2O (3 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 30% → 40% EtOAc in hexanes) to afford *cis*-decalin (±)-**1.226** (8.5 mg, 83%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.56 (t, *J* = 7.8 Hz, 1 H), 5.37 (dd, *J* = 1.3, 16.4 Hz, 1 H), 5.14 (qd, *J* = 6.4, 16.3 Hz, 1 H), 4.24 (t, *J* = 10.4 Hz, 1 H), 4.03 (dd, *J* = 6.6, 11.4 Hz, 1 H), 2.76–2.62 (m, 2 H), 2.28 (dd, *J* = 4.3, 15.0 Hz, 1 H), 2.07–1.74 (m, 9 H), 1.67–1.57 (m, 2 H), 1.17–1.03 (m, 1 H), 0.90 (d, *J* = 5.7 Hz, 3 H).

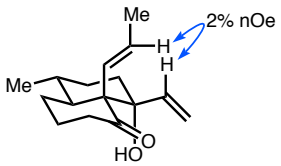
^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9, 147.3, 134.7, 129.6, 122.0, 64.3, 53.0, 40.5, 38.8, 35.8, 31.2, 26.9, 23.1, 20.9, 19.4, 18.3.

FTIR (thin film) cm^{-1}: 3408 (br), 2938, 2875, 1704, 1448, 1384, 1254.

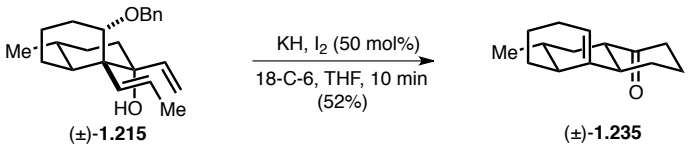
HRMS (ESI) calc'd for $C_{16}H_{24}NaO_2$ $[M+Na]^+$: 271.1669, found 271.1648.

TLC (15% EtOAc in hexanes), R_f: 0.27 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.226**



(±)-**1.215** (±)-**1.235**

Tricycle (±)-**1.235**:

A 5-mL round-bottomed flask was charged with a suspension of potassium hydride (14.0 mg, 350 μmol, 5.00 equiv) and THF (400 μL). Iodine (9.0 mg, 40.0 μmol, 0.50 equiv) was introduced to the stirred reaction mixture at ambient temperature and stirred for 10 min. A separate 5-mL round-bottomed flask was charged with allylic alcohol (±)-**1.215** (24.0 mg, 71.0 μmol, 1.00 equiv) and 18-crown-6 (93.0 mg, 350 μmol, 5.00 equiv) and azeotropically dried with three portions of benzene. THF (500 μL) was introduced and the resultant solution transferred dropwise via syringe to the 5-mL round-bottomed flask containing the stirred mixture of activated potassium hydride at ambient temperature. The transfer was completed with two additional portions of THF (200 μL). After 10 min, ethanol (100 μL) was added to the stirred reaction mixture. After an additional 20 min, saturated aqueous ammonium chloride solution (1 mL) and Et_2O (1 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (15 mL) and brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford tricycle (±)-**1.235** (8.0 mg, 52%) as a colorless oil.

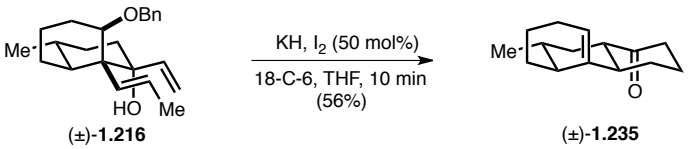
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.46 (t, J = 3.8 Hz, 1 H), 2.45–2.26 (m, 2 H), 2.14–1.91 (m, 5 H), 1.76–1.67 (m, 1 H), 1.66–1.29 (m, 7 H), 1.00 (d, J = 6.1 Hz, 3 H), 0.95 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.4, 141.0, 118.3, 56.4, 54.5, 44.6, 41.3, 37.7, 35.6, 35.0, 30.8, 26.4, 25.6, 19.8, 19.5.

FTIR (thin film) cm^{-1}: 2929, 2870, 1713, 1457, 1375, 1161.

HRMS (ESI) calc'd for $C_{15}H_{22}NaO$ $[M+Na]^+$: 241.1563, found 241.1551.

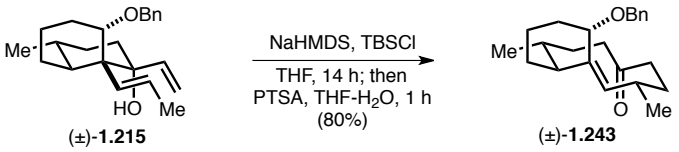
TLC (15% EtOAc in hexanes), R_f: 0.40 (UV, CAM).



(±)-**1.216** (±)-**1.235**

Tricycle (±)-**1.235**:

A 5-mL, 2-necked, round-bottomed flask was charged with a suspension of potassium hydride (34.5 mg, 860 μmol, 5.00 equiv) and THF (900 μL). Iodine (22 mg, 86 μmol, 0.50 equiv) was introduced to the stirred reaction mixture at ambient temperature and stirred for 10 min. A separate 5-mL round-bottomed flask was charged with allylic alcohol (±)-**1.235** (58.5 mg, 172 μmol, 1.00 equiv) and 18-crown-6 (227 mg, 860 μmol, 5.00 equiv) and azeotropically dried with three portions of benzene. THF (500 μL) was introduced and the resultant solution transferred dropwise via syringe to the 5-mL round-bottomed flask containing the stirred mixture of activated potassium hydride at ambient temperature. The transfer was completed with two additional portions of THF (250 μL). After 10 min, ethanol (100 μL) was added to the reaction mixture. After an additional 20 min, saturated aqueous ammonium chloride solution (1 mL) and Et_2O (1 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (15 mL) and brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford tricycle (±)-**1.235** (21.0 mg, 56%) as a colorless oil.



(±)-**1.215** (±)-**1.243**

Bicycle (±)-**1.243**:

A 25-mL round-bottomed flask was charged with allylic alcohol (±)-**1.215** (200 mg, 588 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (2 mL) and *tert*-butyldimethylsilyl chloride (443 mg, 2.94 mmol, 5.00 equiv) were introduced. A solution of sodium bis(trimethylsilyl)amide in THF (0.73 M, 4.0 mL, 2.94 mmol, 5.00 equiv) was added to the stirred reaction mixture at ambient temperature. After 14 h, saturated aqueous ammonium chloride solution (4 mL) and Et_2O (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure.

A 25-mL round-bottomed flask was charged with a solution of the reaction residue, THF (3.00 mL) and water (300 μL). *para*-Toluenesulfonic acid monohydrate (600 mg, 3.15 mmol, 5.36 equiv) was added to the stirred reaction mixture at ambient temperature. After 1 h, saturated aqueous sodium bicarbonate solution (4 mL) and Et_2O (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford bicycle (±)-**1.243** (159 mg, 80%) as a colorless oil.

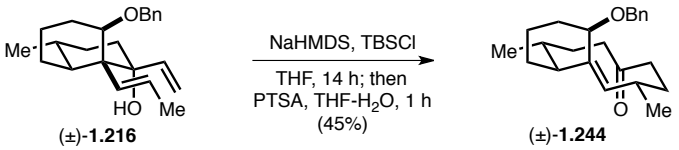
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45–7.35 (m, 5 H), 7.34–7.28 (m, 1 H), 4.73 (dd, *J* = 11.2, 19.5 Hz, 2 H), 4.49 (t, *J* = 2.3 Hz, 1 H), 4.46 (d, *J* = 11.6 Hz, 1 H), 3.43 (ddd, *J* = 1.0, 7.0, 17.0 Hz, 1 H), 2.41 (ddt, *J* = 4.6, 6.4, 11.0 Hz, 1 H), 2.32–2.13 (m, 3 H), 2.07–1.95 (m, 3 H), 1.94–1.64 (m, 5 H), 1.63–1.54 (m, 1 H), 1.36–1.18 (m, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 216.0, 138.9, 135.6, 128.3, 127.7, 127.4, 73.6, 70.4, 52.5, 42.9, 42.0, 36.2, 34.0, 33.1, 32.0, 30.8, 30.6, 21.5, 20.7, 16.1.

FTIR (thin film) cm^{-1}: 2929, 2866, 1703, 1454, 1052, 1028, 735, 699.

HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2292.

TLC (10% EtOAc in hexanes), R_f: 0.29 (UV, CAM).



(±)-**1.216** (±)-**1.244**

Bicycle (±)-**1.244**:

A 10-mL, 2-necked, round-bottomed flask was charged with allylic alcohol (±)-**1.216** (97.1 mg, 290 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (1 mL) and *tert*-butyldimethylsilyl chloride (216 mg, 1.43 mmol, 5.00 equiv) were introduced. A solution of sodium bis(trimethylsilyl)amide in THF (0.73 M, 1.95 mL, 1.43 mmol, 5.00 equiv) was added to the stirred reaction mixture at ambient temperature. The reaction vessel was equipped with a reflux condenser and heated to reflux. After 12 h, the reaction mixture cooled to ambient temperature and saturated aqueous ammonium chloride solution (3 mL) and Et_2O (3 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (15 mL) and brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure.

A 25-mL round-bottomed flask was charged with a solution of the reaction residue, THF (4.00 mL) and water (400 μL). *para*-Toluenesulfonic acid monohydrate (100 mg, 526 μmol, 1.80 equiv) was added to the stirred reaction mixture at ambient temperature. After 1 h, saturated aqueous sodium bicarbonate solution (5 mL) and Et_2O (5 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 5% → 15% EtOAc in hexanes) to afford bicycle (±)-**1.244** (19.8 mg, 45%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.34 (m, 5 H), 7.34–7.28 (m, 1 H), 4.75 (d, J = 11.8 Hz, 1 H), 4.66 (d, J = 10.9 Hz, 1 H), 4.54 (d, J = 11.7 Hz, 1 H), 4.33 (dd, J = 4.2, 10.8 Hz, 1 H), 3.50 (tt, J = 5.5, 11.2 Hz, 1 H), 2.50 (dd, J = 7.8, 16.9 Hz, 1 H), 2.43 (t, J = 12.9 Hz, 1 H), 2.34–2.24 (m, 1 H), 2.19 (dd, J = 11.6,

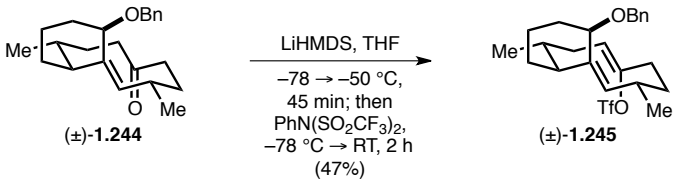
16.7 Hz, 1 H), 2.03–1.96 (m, J = 6.0, 13.5 Hz, 1 H), 1.95–1.69 (m, 6 H), 1.67–1.54 (m, 2 H), 1.46 (tdd, J = 3.5, 13.6, 26.6 Hz, 1 H), 1.40–1.23 (m, 2 H), 0.89 (s, 3 H), 0.84 (d, J = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.0, 139.6, 138.7, 133.8, 128.3, 127.8, 127.5, 79.2, 70.9, 54.7, 42.9, 41.6, 37.0, 33.9, 32.7, 32.5, 31.6, 30.7, 21.2, 20.5, 20.1.

FTIR (thin film) cm^{-1}: 3064, 3031, 2928, 2866, 1703, 1454, 1051, 1028, 957, 734, 699.

HRMS (ESI) calc'd for $C_{23}H_{32}NaO_2$ $[M+Na]^+$: 363.2295, found 363.2322.

TLC (10% EtOAc in hexanes), R_f: 0.67 (UV, CAM).



Alkenyl triflate (±)-1.245:

A 10-mL round-bottomed flask was charged with bicycle (±)-**1.244** (28.0 mg, 82.0 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (200 μL) was introduced and the resultant solution cooled to –78 °C. In a separate 10-mL round-bottomed flask, a solution of *n*-butyllithium in hexanes (2.44 M, 51.0 μL, 123 μmol, 1.5 equiv) was added dropwise via syringe to a stirred solution of hexamethyldisilazane (26.0 μL, 123 μmol, 1.5 equiv) in THF (400 μL) at –20 °C. After 30 min, the reaction mixture was cooled to –78 °C. The cold solution of bicycle (±)-**1.244** in THF was then added dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 5 min and the transfer was completed with an additional portion of THF (200 μL). The resultant solution warmed to –60 °C. After 45 min, reaction mixture was cooled to –78 °C and a freshly prepared solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (88.0 mg, 250 μmol, 3.00 equiv) in THF (400 μL) was added dropwise via syringe over 2 min and the resultant reaction mixture warmed to ambient temperature. After 2h, saturated aqueous ammonium chloride solution (5 mL) was added to the stirred reaction mixture, which was subsequently diluted with Et_2O (10 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (3 × 10 mL) and the combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 3% EtOAc in hexanes) to afford alkenyl triflate (±)-**1.245** (18.0 mg, 47%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.32 (m, 4 H), 7.32–7.26 (m, 1 H), 5.58 (dd, *J* = 4.7, 12.5 Hz, 1 H), 5.24 (dd, *J* = 1.2, 11.0 Hz, 1 H), 4.62 (d, *J* = 12.2 Hz, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 3.79 (dd, *J* = 3.6,

11.5 Hz, 1 H), 2.58–2.41 (m, 3 H), 2.23–2.00 (m, 4 H), 1.91 (td, *J* = 3.6, 13.3 Hz, 1 H), 1.87–1.76 (m, 2 H), 1.66–1.46 (m, 3 H), 1.38–1.19 (m, 4 H), 1.01–0.97 (m, 6 H).

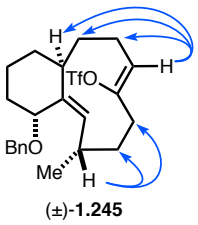
^{13}C NMR (125 MHz, $CDCl_3$) δ: 150.5, 140.4, 138.8, 128.4, 127.6, 127.4, 125.4, 118.6, 76.2, 71.3, 41.6, 35.8, 32.3, 31.1, 30.4, 29.1, 29.0, 27.7, 21.8, 20.0, 16.9.

FTIR (thin film) cm^{-1}: 2930, 2864, 1454, 1413,1209, 1141, 1094, 938, 883, 735.

HRMS (ESI) calc'd for $C_{24}H_{31}F_3NaO_4S$ $[M+Na]^+$: 495.1787, found 495.1804.

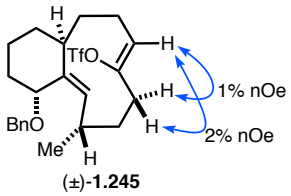
TLC (15% EtOAc in hexanes), R_f: 0.54 (UV, CAM).

1D TOCSY data (500 MHz, $CDCl_3$):

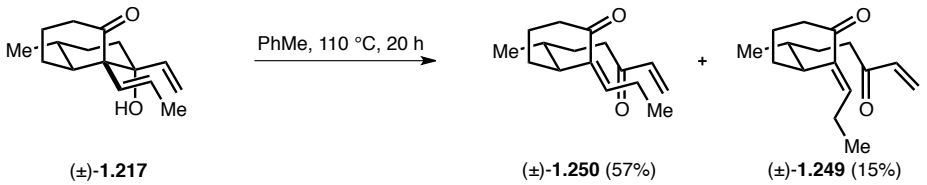


(±)-**1.245**

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.245**



(±)-**1.217** (±)-**1.250** (57%) (±)-**1.249** (15%)

Bis-enone (±)-1.249 and (±)-1.250:

A 10-mL Schlenk tube was charged with a solution of ketone (±)-**1.217** (103 mg, 415 µmol) and PhMe (5 mL), sealed, and heated to 110 °C. After 20 h, the reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford bis-enone (±)-**1.250** (59.0 mg, 57%) and bis-enone (±)-**1.249** (15.2 mg, 15%) as colorless oils.

Bis-enone (±)-1.250:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.33 (dd, *J* = 10.6, 17.3 Hz, 1 H), 6.20 (d, *J* = 17.6 Hz, 1 H), 5.81 (d, *J* = 10.5 Hz, 1 H), 5.50 (t, *J* = 7.4 Hz, 1 H), 2.63–2.47 (m, 2 H), 2.46–2.30 (m, 2 H), 2.29–2.13 (m, 3 H), 1.93–1.66 (m, 5 H), 1.50–1.40 (m, 1 H), 1.38–1.27 (m, 1 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H).

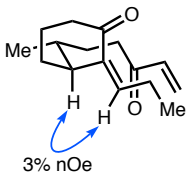
^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.5, 200.9, 140.8, 138.4, 136.4, 128.0, 49.8, 42.7, 37.8, 33.9, 28.5, 26.8, 22.3, 21.0, 16.1, 14.3.

FTIR (thin film) cm^{-1}: 2954, 2927, 2874, 1685, 1385.

HRMS (ESI) calc'd for $C_{16}H_{24}NaO_2$ $[M+Na]^+$: 271.1669, found 271.1661.

TLC (40% EtOAc in hexanes), R_f: 0.65 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.250**

Bis-enone (±)-**1.249**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.33 (dd, *J* = 10.5, 17.6 Hz, 1 H), 6.29 (t, *J* = 7.3 Hz, 1 H), 6.19 (d, *J* = 17.4 Hz, 1 H), 5.80 (dd, *J* = 0.8, 10.6 Hz, 1 H), 2.74 (dd, *J* = 5.7, 13.3 Hz, 1 H), 2.64–2.47 (m, 2 H), 2.45–2.29 (m, 2 H), 2.21–2.00 (m, 2 H), 1.92–1.79 (m, 2 H), 1.78–1.66 (m, 3 H), 1.51–1.40 (m, 1 H), 1.37–1.26 (m, 1 H), 1.04 (t, *J* = 7.4 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H).

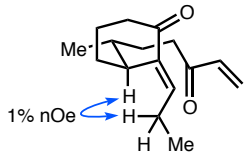
^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.3, 200.6, 141.2, 140.0, 136.4, 127.9, 40.8, 40.1, 38.0, 35.3, 28.3, 25.0, 21.5, 19.4, 15.8, 13.3.

FTIR (thin film) cm^{-1}: 2922, 2850,1709, 1450, 1376, 1177, 1078, 942, 758.

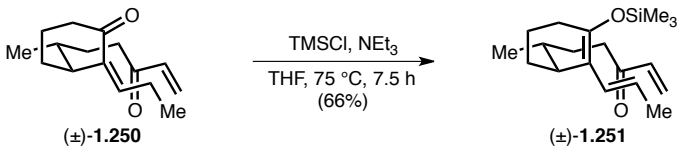
HRMS (ESI) calc'd for $C_{24}H_{31}F_3NaO_4S$ $[M+Na]^+$: 495.1787, found 495.1804.

TLC (15% EtOAc in hexanes), R_f: 0.12 (UV, CAM).

1D NOESY data (500 MHz, $CDCl_3$):



(±)-**1.249**



(±)-**1.250** (±)-**1.251**

Enol silane (±)-**1.251**:

A 5-mL Schlenk tube was charged with bis-enone (±)-**1.250** (53.4 mg, 215 μmol) and azeotropically dried with three portions of benzene. THF (2 mL), triethylamine (300 μL, 2.15 mmol, 10.0 equiv), and chlorotrimethylsilane (273 μL, 2.15 mmol, 10.0 equiv) were sequentially introduced and the resultant reaction mixture was sealed and heated to 75 °C. After 7.5 h, the reaction mixture was cooled to ambient temperature and saturated aqueous ammonium chloride solution (2 mL) was added to the stirred reaction mixture, which was subsequently diluted with Et_2O (5 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (3 × 10 mL) and the combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford enol silane (±)-**1.251** (45.2 mg, 66%) as a colorless oil.

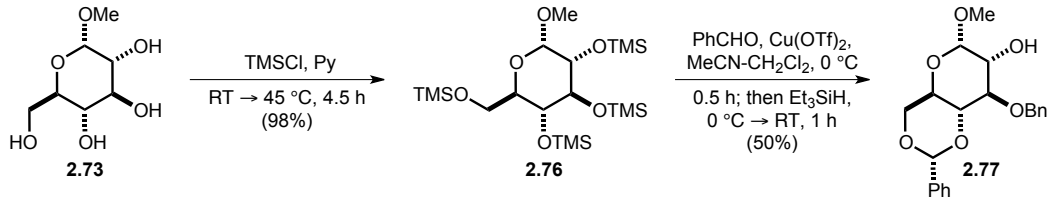
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.41–6.31 (m, 2 H), 6.22 (dd, *J* = 0.7, 17.5 Hz, 1 H), 5.81 (dd, *J* = 0.9, 10.6 Hz, 1 H), 5.40 (qd, *J* = 6.6, 15.8 Hz, 1 H), 2.68–2.52 (m, 3 H), 2.14–1.98 (m, 2 H), 1.98–1.86 (m, 1 H), 1.80–1.63 (m, 5 H), 1.61–1.43 (m, 4 H), 0.73 (d, *J* = 6.9 Hz, 3 H), 0.19 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.2, 147.7, 136.5, 127.8, 126.6, 121.4, 117.5, 77.3, 76.7, 38.4, 37.4, 34.2, 30.8, 29.5, 22.6, 20.9, 18.9, 15.3, 0.7

FTIR (thin film) cm^{-1}: 3032, 2957, 2933, 2874, 1701, 1685, 1617, 1457, 1399, 1361, 1252, 1180, 955, 844, 756.

HRMS (ESI) calc'd for $C_{19}H_{32}NaO_2Si$ $[M+Na]^+$: 343.2064, found 343.2052.

TLC (10% EtOAc in hexanes), R_f: 0.28 (UV, CAM).



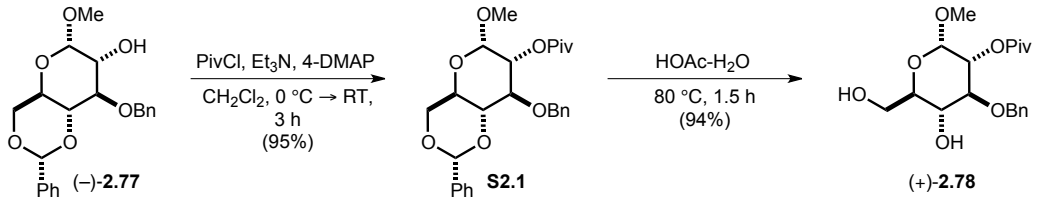
Methyl 3-*O*-benzyl-4,6-*O*-benzylidine-α-D-glucopyranoside (2.77):

A 3-L, two-necked, round-bottomed flask was equipped with an internal thermocouple, a 500-mL graduated addition funnel, and two rubber septa. The reaction flask was charged with methyl α-D-glucopyranoside (**2.73**) (138 g, 709 mmol, 1.00 equiv) and pyridine (709 mL). The mixture was vigorously stirred for 30 min to break-up the white-solid. Chlorotrimethylsilane (450 mL, 3.60 mol, 5.00 equiv) was added dropwise via graduated addition funnel over 3 h while maintaining an internal reaction temperature between 40 to 45 °C. After the addition was completed, the reaction was stirred for 1.5 h at ambient temperature and was then diluted with Et_2O (700 mL) and water (700 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 500 mL). The combined organic layers were washed with water (1 L) and brine (1 L). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford methyl 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-glucopyranoside (**2.76**)[230] (334 g, 98%) as a clear, colorless oil, which was used without further purification.

A 250-mL round-bottomed flask was charged in a glove box with copper(II) trifluoromethanesulfonate (750 mg, 2.07 mmol, 0.010 equiv) and then sealed with a rubber septa. The flask was removed from the glove box and placed under an argon atmosphere before MeCN (90 mL) was added to form a clear, blue solution. A 1-L round-bottomed flask was charged with **2.76** (100 g, 207 mmol, 1.00 equiv), CH_2Cl_2 (360 mL), and benzaldehyde (63.2 mL, 622 mmol, 3.00 equiv). The reaction solution was cooled to 0 °C, and the solution of copper(II) trifluoromethanesulfonate in MeCN was added dropwise over 30 min via cannula. The resultant pink solution was allowed to warm to ambient

[230] For spectroscopic and physical characterization of **2.77** see: Franais, A.; Urban, D.; Beau, J.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8662–8665.

temperature over 30 min, and then cooled to 0 °C. Triethylsilane (36.4 mL, 228 mmol, 1.10 equiv) was added dropwise over 15 min via syringe. The reaction mixture was stirred for an additional 30 min before a saturated aqueous sodium bicarbonate solution (500 mL) was added. After stirring for 15 min, the reaction mixture was diluted with Et_2O (500 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with water (750 mL) and brine (750 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to furnish a tan solid. The solid was purified by recrystallization from ethanol to afford pure methyl 3-*O*-benzyl-4,6-*O*-benzylidine-α-D-glucopyranoside (**2.77**)[230] (39.0 g, 50%) as a white solid.



Methyl 3-*O*-benzyl-2-*O*-pivaloyl-α-D-glucopyranoside ((+)-**2.78**):

A 1-L round-bottomed flask was charged with (–)-**2.77** (28.5 g, 76.6 mmol, 1.00 equiv) and azeotropically distilled with benzene (3 × 100 mL). CH_2Cl_2 (383 mL) was added, and the resultant solution cooled to 0 °C. Triethylamine (21.4 mL, 153 mmol, 2.00 equiv), pivaloyl chloride (14.1 mL, 115 mmol, 1.50 equiv), and 4-(dimethylamino)pyridine (941 mg, 7.70 mmol, 0.100 equiv) were sequentially added to the stirred solution, which was subsequently allowed to warm to ambient temperature over 3 h. A saturated aqueous solution of sodium bicarbonate (400 mL) was added and layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with water (400 mL) and brine (400 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a yellow syrup. The product was purified by flash-column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford methyl 3-*O*-benzyl-4,6-*O*-benylidene-2-*O*-pivaloyl-α-D-glucopyranoside (**S2.1**)[230] (33.2 g, 95%) as a yellow oil.

A 500-mL round-bottomed flask was charged with a solution of **S2.1** (33.2 g, 72.7 mmol, 1.00 equiv), water (39 mL), and acetic acid (155 mL). The reaction vessel was sealed with a plastic cap and heated to 80 °C for 1.5 h. The reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The resultant colorless syrup was directly purified by flash-column chromatography (silica gel, eluent: gradient, 40 → 80% EtOAc in hexanes) to afford methyl 3-*O*-benzyl-2-*O*-pivaloyl-α-D-glucopyranoside ((+)-**2.78**) (25.2 g, 94%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.23 (m, 5 H), 4.91 (d, J = 3.7 Hz, 1 H), 4.84 (d, J = 11.4 Hz, 1 H), 4.73 (dd, J = 3.7, 9.8 Hz, 1 H), 4.68 (d, J = 11.4 Hz, 1 H), 3.90–3.82 (m, 1 H), 3.82–3.74 (m, 2 H), 3.67–3.60 (m, 2 H), 3.35 (s, 3 H), 3.01 (br. s., 1 H), 2.55 (br. s, 1 H), 1.22 (s, 9 H).

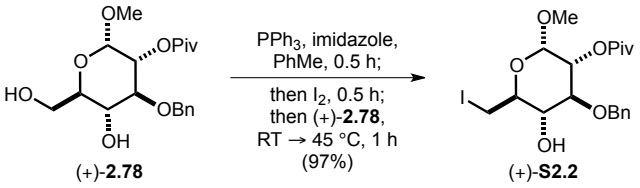
^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.9, 138.3, 128.5, 127.8, 127.6, 97.0, 79.6, 75.0, 73.6, 70.8, 70.2, 62.0, 55.3, 38.7, 27.0.

FTIR (thin film) cm^{-1}: 3436, 2959, 2933, 1731, 1481, 1455, 1363, 1397, 1284, 1162, 1124, 1053, 1039.

HRMS (ESI) (*m/z*) calc'd for $C_{19}H_{28}O_7Na$ $[M+Na]^+$: 391.1727, found 391.1728.

$[\alpha]_D^{23}$: +73.6 (*c* = 0.57, $CHCl_3$).

TLC (20% acetone in PhMe), R_f: 0.22 (UV, CAM).



Methyl 2-*O*-pivaloyl-3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**S2.2**):

A 1-L round-bottomed flask was charged with triphenylphosphine (23.3 g, 89.0 mmol, 1.30 equiv), imidazole (14.0 g, 205 mmol, 3.00 equiv), and PhMe (342 mL). The reaction mixture was vigorously stirred for 30 min to break-up the solids before iodine (22.6 g, 89.0 mmol, 1.30 equiv) was added in one portion. The reaction mixture was stirred for 30 min before a solution of (+)-**2.78** (25.2 g, 68.4 mmol, 1.00 equiv) in PhMe (102 mL) was added via cannula. The resultant inhomogeneous reaction mixture was stirred for 1 h at 45 °C, and was then allowed to cool to ambient temperature. Brine (400 mL) was added, and the resultant mixture was stirred for 15 min or until all of the solid material had fully dissolved. The layers were then separated and the aqueous layer extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The resultant pale-yellow syrup was purified by flash-column chromatography (silica gel, eluent: 30% EtOAc in hexanes) to afford methyl 3-*O*-benzyl-2-*O*-pivaloyl-3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**S2.2**) (31.7 g, 97%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.34 (m, 2 H), 7.33–7.29 (m, 3 H), 4.94 (d, *J* = 3.7 Hz, 1 H), 4.88 (d, *J* = 11.7 Hz, 1 H), 4.77 (dd, *J* = 3.8, 10.0 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 3.86 (t, *J* = 9.3 Hz, 1 H), 3.55 (dd, *J* = 2.2, 10.6 Hz, 1 H), 3.47 (ddd, *J* = 2.3, 7.1, 9.4 Hz, 1 H), 3.42 (s, 3 H), 3.39 (dd, *J* = 2.7, 9.2 Hz, 1 H), 3.29 (dd, *J* = 7.0, 10.6 Hz, 1 H), 2.23 (d, *J* = 2.7 Hz, 1 H), 1.24 (s, 9 H).

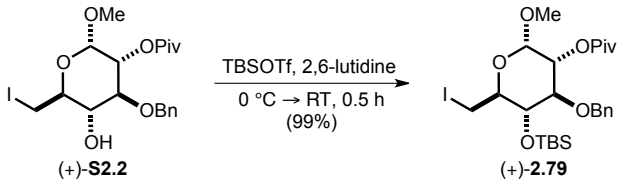
^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.8, 138.1, 128.7, 128.1, 127.7, 97.0, 79.2, 75.1, 73.7, 73.6, 69.9, 55.7, 38.7, 27.1, 6.6.

FTIR (thin film) cm^{-1}: 3444, 2972, 1730, 1644, 1283, 1161, 1126, 1049.

HRMS (ESI) (*m/z*) calc'd for $C_{19}H_{27}IO_6Na$ $[M+Na]^+$: 501.0745, found 501.0747.

$[\alpha]_D^{23}$: +70.0 (*c* = 0.50, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.24 (UV, CAM).



Methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyloxy-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-2.79):

A 500-mL round-bottomed flask was charged with (+)-**S2.2** (59.8 g, 125 mmol, 1.00 equiv) azeotropically dried with three portions of benzene. 2,6-Lutidine (125 mL) was introduced, and the resultant solution was cooled to 0 °C. *t*-Butyldimethylsilyl trifluoromethanesulfonate (57.4 mL, 250 mmol, 2.00 equiv) was added dropwise via syringe to the cooled, stirred reaction mixture over 10 min. After the addition was complete, the reaction was allowed to warm to ambient temperature over 30 min. The reaction mixture was then poured into a saturated aqueous sodium bicarbonate solution (600 mL) and diluted with Et_2O (500 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with water (1 L) and brine (1 L). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resultant pale-yellow syrup was purified by flash-column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford methyl 2-*O*-pivaloyl-3-*O*-benzyl-4-*O*-*t*-butyldimethylsilyloxy-6-deoxy-6-iodo-α-D-glucopyranoside (+)-(**2.79**) (73.0 g, 99%) as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32–7.21 (m, 5 H), 4.90 (d, *J* = 3.7 Hz, 1 H), 4.86 (d, *J* = 11.2 Hz, 1 H), 4.84 (dd, *J* = 3.7, 9.8 Hz, 1 H), 4.69 (d, *J* = 11.4 Hz, 1 H), 3.84 (dd, *J* = 8.1, 9.7 Hz, 1 H), 3.58 (dd, *J* = 2.4, 10.4 Hz, 1 H), 3.51 (ddd, *J* = 2.3, 7.1, 9.4 Hz, 1 H), 3.47 (t, *J* = 8.0 Hz, 1 H), 3.44 (s, 3 H), 3.22 (dd, *J* = 7.0, 10.4 Hz, 1 H), 1.12 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 3 H), –0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.8, 138.4, 128.1, 127.1, 126.6, 96.8, 79.3, 74.7, 74.5, 74.3, 71.0, 55.7, 38.7, 26.9, 25.9, 18.0, 7.4, –3.9, –4.3.

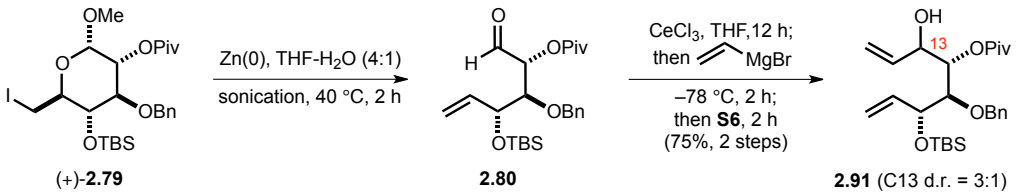
FTIR (thin film) cm^{-1}: 2958, 2931, 2897, 2859, 1742, 1706, 1480, 1383, 1360, 1282, 1253, 1154, 1105 1046, 864, 839, 780.

HRMS (ESI) (*m/z*) calc'd for $C_{25}H_{41}IO_6SiNa$ $[M+Na]^+$: 615.1609, found 615.1590.

$[\alpha]_D^{23}$: +91.8 (*c* = 1.03, $CHCl_3$).

M.**p**.: 102 °C (Et_2O).

TLC (15% EtOAc in hexanes), R_f: 0.55 (UV, CAM).

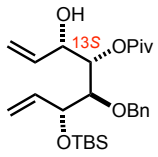


Alcohol 2.91:

A 1-L round-bottomed flask was charged with (+)-**2.79** (25.0 g, 42.2 mmol, 1.00 equiv), activated zinc powder (28.0 g, 422 mmol, 10.0 equiv), THF (338 mL), and water (85 ml). The reaction vessel was sealed with a plastic cap and placed into a sonication bath at 40 °C. The reaction mixture was sonicated for 2 h at a bath temperature of 40 to 45 °C. The flask was then removed from the sonication bath, and its contents were allowed to cool to ambient temperature. The reaction mixture was filtered through a pad of Celite, which was rinsed with water (100 mL) and Et_2O (100 mL). The filtrate was collected and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined and washed with brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to provide aldehyde **2.80** as a pale-yellow syrup, which was used immediately without further purification.

A 2-L, two-necked, round-bottomed flask was charged with anhydrous cerium(III) chloride (12.5 g, 50.7 mmol, 1.20 equiv) and equipped with a greased ground-glass vacuum adapter and rubber septum. The reaction vessel was heated to 145 °C under reduced pressure (0.05 Torr) for 2.5 h. The flask was allowed to cool to ambient temperature and was then flushed with argon. The flask was cooled to 0 °C and THF (507 mL) was added over 10 min. The stirred inhomogeneous, off-white slurry was allowed to warm to ambient temperature over 12 h. The reaction vessel was then cooled to –78 °C, and a solution of vinylmagnesium bromide in THF (0.90 M, 56.3 mL, 50.7 mmol, 1.20 equiv) was added dropwise to the reaction mixture via syringe over 15 min. The resultant tan slurry was stirred for 2 h at –78 °C. A separate 500-mL round-bottomed flask was charged with **2.80** (42.2 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (211 mL) was introduced and the resultant solution was cooled to –78 °C and was transferred dropwise via cannula to the 2-L reaction vessel over 20 min. After 2 h, a

saturated aqueous ammonium chloride solution (500 mL) was added to the stirred, cooled reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant inhomogeneous mixture was filtered through a pad of Celite and was rinsed with water (100 mL) and Et_2O (3 × 150 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3× 300 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resultant yellow oil was purified by flash-column chromatography (silica gel, eluent: gradient, 7 → 15% EtOAc in hexanes) to afford alcohol **2.91** (14.5 g, 75%, 3:1 mixture of (*S*)- and (*R*)-epimers, respectively) as a pale-yellow syrup. In practice the two epimers were not separated prior to use in the subsequent ring-closing metathesis reaction. Analytical samples of the pure epimers were obtained by preparatory high-performance liquid chromatography (HPLC) in three portions using an Agilent Zorbax SB-C18 column [5μm, 250 × 4.6 mm, UV detection at 350 nM, Solvent A: MeCN, Solvent B: water, purified epimeric mixture, concentration 0.05 M (MeCN), injection volume 0.50 mL, gradient elution 90% A for 5 min then 90 → 100 % A over 10 min, flow rate: 10 mL/min]. Fractions eluting at 6.5–7.2 min and 7.6–8.2 min were collected and concentrated, affording (*R*)-alcohol **2.91** and (*S*)-alcohol **2.91**, respectively, as pale-yellow oil. The stereochemistry of (*R*)-alcohol **2.91** and (*S*)-alcohol **2.91** was assigned based on correlation to their respective ring-closing metathesis product, (*R*)-alcohol **S2.3** and (*S*)-alcohol **S2.3**.



(*S*)-**2.91**

(*S*)-Alcohol 2.91:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 5 H), 5.89 (ddd, *J* = 6.0, 10.7, 17.0 Hz, 1 H), 5.80 (ddd, *J* = 5.6, 10.5, 17.1 Hz, 1 H), 5.30 (td, *J* = 1.5, 17.3 Hz, 1 H), 5.23 (td, *J* = 1.4, 17.3 Hz, 1 H), 5.17 (tdd, *J* = 1.4, 2.5, 10.4 Hz, 2 H), 4.94 (dd, *J* = 3.4, 5.6 Hz, 1 H), 4.87 (d, *J* = 11.7 Hz, 1 H), 4.70 (d, *J* = 11.7 Hz, 1

H), 4.31 (t, J = 6.3 Hz, 2 H), 3.69 (dd, J = 3.3, 6.7 Hz, 1 H), 2.88 (d, J = 5.6 Hz, 1 H), 1.20 (s, 9 H), 0.89 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

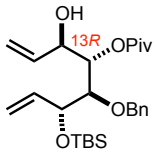
^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 138.3, 137.02, 136.99, 128.4, 127.7, 127.6, 116.9, 116.7, 81.1, 74.2, 74.0, 73.6, 72.8, 38.8, 27.2, 25.9, 18.2, –4.6, –4.8.

FTIR (thin film) cm^{-1}: 3495, 2959, 2930, 2858, 1733, 1281, 1255, 1158, 1029, 929, 837, 777, 737, 697 cm^{-1}.

HRMS (ESI) (*m/z*) calc'd for $C_{26}H_{42}O_5SiNa$ $[M+Na]^+$: 485.2694, found 485.2681.

$[\alpha]_D^{23}$: +4.80 (c = 0.94, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.40 (UV, CAM).



(*R*)-**2.91**

(*R*)-Alcohol 2.91:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 5 H), 6.02 (ddd, J = 4.9, 10.7, 17.3 Hz, 1 H), 5.74 (ddd, J = 4.6, 10.6, 17.2 Hz, 1 H), 5.31 (td, J = 1.7, 7.6 Hz, 1 H), 5.27 (td, J = 1.7, 7.3 Hz, 1 H), 5.23 (td, J = 1.6, 10.6 Hz, 1 H), 5.13 (td, J = 1.7, 10.5 Hz, 2 H), 5.12 (dd, J = 3.1, 6.0 Hz, 1 H), 4.70 (d, J = 11.7 Hz, 1 H), 4.67 (d, J = 11.7 Hz, 1 H), 4.45 (tddd, J = 1.6, 3.1, 4.5, 6.0 Hz, 1 H), 4.36 (tt, J = 1.7, 4.9 Hz, 1 H), 3.71 (dd, J = 4.9, 6.8 Hz, 1 H), 2.81 (d, J = 6.1 Hz, 1 H), 1.18 (s, 9 H), 0.91–0.89 (m, 9 H), 0.021 (s, 3 H), 0.020 (s, 3 H).

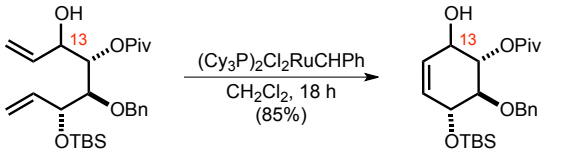
^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.6, 138.2, 136.6, 136.2, 128.4, 127.7, 127.4, 116.4, 115.7, 81.5, 74.02, 73.96, 73.3, 71.3, 38.9, 27.3, 25.9, 18.2, –4.7, –5.1.

FTIR (thin film) cm^{-1}: 3498, 2958, 2930, 2858, 1732, 1462, 1281, 1256, 1147, 1029, 925, 837, 777.

HRMS (ESI) (*m/z*) calc'd for $C_{26}H_{42}O_5SiNa$ $[M+Na]^+$: 485. 2694, found 485.2678.

$[\alpha]_D^{23}$: +40.2 (c = 0.84, CH_2Cl_2).

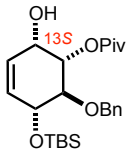
TLC (15% EtOAc in hexanes), R_f: 0.30 (UV, CAM).



2.91 (3:1 dr) **S2.3** (C13 d.r. = 3:1)

Alcohol S2.3:

A 2-L round-bottomed flask was charged with **2.91** (25.6 g, 55.3 mmol, 1.00 equiv), CH_2Cl_2 (1.1 L), and bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (2.28 g, 2.77 mmol, 0.050 equiv). The resultant purple solution was stirred for 18 h at ambient temperature open to the air. The solvent was removed under reduced pressure to furnish a dark-purple solid. The solid was dissolved in a minimal amount of PhMe and purified by flash-column chromatography (silica gel, eluent: 15% EtOAc in hexanes) to afford alcohol **S2.3** (20.4 g, 85%, 3:1 mixture of (*S*)- and (*R*)-epimers, respectively) as a white solid (M.p.: 98-100 °C (Et_2O)). In practice the two epimers were not separated prior to use in the subsequent oxidation reaction. Analytical samples of the pure epimers were obtained by preparatory HPLC in three portions using an Agilent Zorbax SB-C18 column [5μm, 250 × 4.6 mm, UV detection at 350 nM, Solvent A: MeCN, Solvent B: water, purified epimeric mixture, concentration 0.025 M (MeCN), injection volume 0.75 mL, gradient elution 90% A for 5 min then 90 → 100 % A over 12.5 min, flow rate: 10 mL/min]. Fractions eluting at 8.5-9.6 min and 10.0-10.7 min were collected and concentrated, affording (*S*)-alcohol **S2.3** and (*R*)-alcohol **S2.3**, respectively, as white solids.



(*S*)-**S2.3**

(*S*)-Alcohol S2.3:

^{1}H NMR (500 MHz, C_6D_6) δ: 7.36 (d, *J* = 7.6 Hz, 2 H), 7.17 (t, *J* = 7.6 Hz, 2 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 5.52 (dd, *J* = 1.6, 9.8 Hz, 1 H), 5.49 (ddd, *J* = 1.4, 4.3, 10.1 Hz, 1 H), 5.13 (dd, *J* = 4.1, 10.5 Hz, 1 H), 4.80 (d, *J* = 11.8 Hz, 1 H), 4.76 (d, *J* = 11.8 Hz, 1 H), 4.29–4.22 (m, 1 H), 4.20–4.14 (m, 1 H), 3.95 (dd, *J* = 7.1, 10.5 Hz, 1 H), 1.49 (br. s, 1 H), 1.11 (s, 9 H), 0.93 (s, 9 H), 0.01 (s, 3 H), –0.01 (s, 3 H).

^{13}C NMR (125 MHz, C_6D_6) δ: 177.3, 139.4, 133.7, 128.5, 127.5, 127.0, 126.4, 79.3, 74.8, 73.7, 73.4, 66.0, 39.0, 27.3, 26.0, 18.2, –4.5, –4.6.

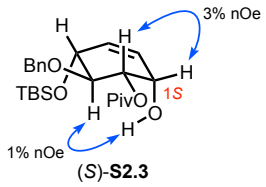
FTIR (thin film) cm^{-1}: 3539, 2957, 2935, 2884, 2856, 1723, 1213, 1175, 1150, 1090, 1036, 991, 840, 783.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{38}O_5SiNa$ $[M+Na]^+$: 457.2381, found 457.2384.

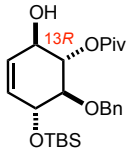
[α]$_D^{23}$: –1.20 (*c* = 1.00, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.13 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(*S*)-**S2.3**



(*R*)-**S2.3**

(*R*)-Alcohol S2.3:

^{1}H NMR (500 MHz, C_6D_6) δ: 7.36 (d, *J* = 7.3 Hz, 2 H), 7.17 (t, *J* = 7.3 Hz, 2 H), 7.06 (t, *J* = 7.3 Hz, 1 H), 5.47 (td, *J* = 1.6, 10.3 Hz, 1 H), 5.38 (td, *J* = 1.6, 10.3 Hz, 1 H), 5.20 (dd, *J* = 7.8, 10.5 Hz, 1 H), 4.80 (d, *J* = 11.7 Hz, 1 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.29–4.24 (m, *J* = 2.3, 5.0 Hz, 1 H), 4.22–4.13 (m, 1 H), 3.46 (dd, *J* = 7.6, 10.5 Hz, 1 H), 2.30 (br. s, 1 H), 1.10 (s, 9 H), 0.93 (s, 9 H), –0.01 (s, 3 H), –0.03 (s, 3 H).

^{13}C NMR (125 MHz, C_6D_6) δ: 179.0, 139.2, 130.6, 128.9, 128.5, 127.5, 126.8, 82.5, 78.0, 75.1, 73.4, 72.2, 39.0, 27.3, 26.0, 18.2, –4.58, –4.62.

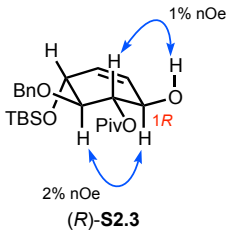
FTIR (thin film) cm^{-1}: 3507, 2955, 2935, 2884, 2855, 1711, 1481, 1386, 1293, 1257, 1148, 974, 863, 840, 777 cm^{-1}.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{38}O_5SiNa$ $[M+Na]^+$: 457.2381, found 457.2384.

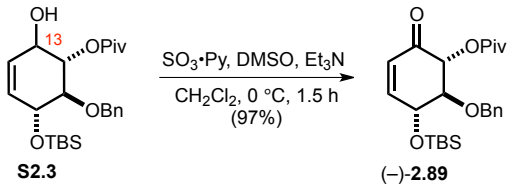
[α]$_D^{23}$: –61.1 (*c* = 0.70, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.13 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(*R*)-**S2.3**



2-Cyclohexenone (–)-2.89:

A 2-L round-bottomed flask was charged with **S2.3** (20.3 g, 46.8, 1.00 equiv) and CH_2Cl_2 (467 mL), and cooled to 0 °C. Dimethyl sulfoxide (33.2 mL, 468 mmol, 10.0 equiv) and *N*,*N*-diisopropylethylamine (40.7 mL, 234 mL, 5.00 equiv) were added to the stirred solution via syringe. Sulfur trioxide pyridine complex (22.3 g, 140 mmol, 3.00 equiv) was then added to the reaction mixture in one portion, which was subsequently stirred at 0 °C for 1.5 h. An aqueous solution of HCl (1.0 M, 250 mL) was added to the reaction mixture and the contents of the flask were allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with an aqueous solution of HCl (1.0 M, 250 mL), water (2 × 250 mL), a saturated aqueous sodium bicarbonate solution (250 mL), and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a pale-yellow syrup. The product was purified by flash-column chromatography (silica gel, eluent: gradient, 5 → 10% EtOAc in hexanes) to afford 2-cyclohexenone (–)-**2.89** (19.6 g, 97%) as a clear, colorless syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.25 (m, 5 H), 6.77 (dd, *J* = 1.8, 10.3 Hz, 1 H), 6.05 (dd, *J* = 2.4, 10.4 Hz, 1 H), 5.43 (d, *J* = 11.2 Hz, 1 H), 4.80 (s, 2 H), 4.65 (td, *J* = 2.1, 8.0 Hz, 1 H), 3.93 (dd, *J* = 8.0, 11.4 Hz, 1 H), 1.24 (s, 9 H), 0.93 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H).

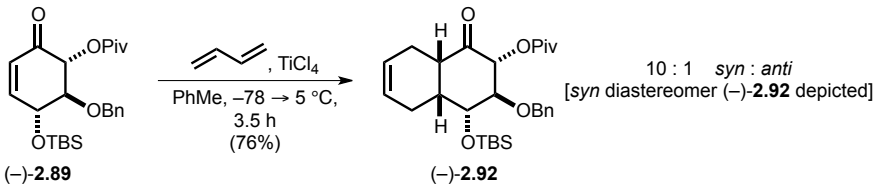
^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.2, 177.5, 151.5, 137.8, 128.2, 127.5, 127.2, 126.9, 83.7, 77.0, 75.2, 72.9, 38.8, 27.2, 25.7, 18.0, –4.7, –4.9.

FTIR (thin film) cm^{-1}: 2957, 2931, 2906, 2858, 1733, 1480, 1362, 1282, 1259, 1153, 1129, 1054, 1002, 838, 779, 737, 697.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{37}O_5Si$ $[M+H]^+$: 433.2405, found 433.2407.

$[\alpha]_D^{23}$: –112.3 (*c* = 1.10, C_6H_6).

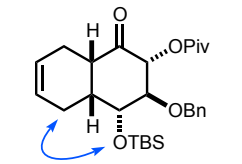
TLC (15% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



***cis*-Decalin (–)-2.92**:

A 500-mL round-bottomed flask was charged (–)-**2.89** (3.78 g, 8.75 mmol, 1.00 equiv) azeotropically dried with three portions of benzene. PhMe (88 mL) was introduced and the resultant solution was cooled to –78 °C. A separate 25-mL round-bottomed flask was charged in a glove box with titanium(IV) chloride (1.66 g, 8.75 mmol, 1.00 equiv) and PhMe (9.0 mL), and then sealed with a rubber septa. The flask was removed from the glove box and placed under an argon atmosphere. The solution of titanium(IV) chloride was then added dropwise to the cooled, stirred solution of (–)-**2.89** via cannula over 10 min. The resultant yellow solution was stirred for 1 h at –78 °C. 1,3-Butadiene (ca. 6.10 mL, 70.0 mmol, 8.00 equiv) was condensed at –78 °C in a 10-mL, two-necked, round-bottomed flask equipped with a dry ice-acetone condenser and a rubber septa, and added to the yellow reaction mixture via cannula. The stirred reaction mixture was allowed to warm to 5 °C over 3.5 h. A saturated aqueous solution of sodium bicarbonate (250 mL) was then added to the reaction mixture which was subsequently allowed to warm to ambient temperature. The resultant inhomogeneous mixture was filtered through a pad of Celite and rinsed with water (100 mL) and Et_2O (2 × 100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3× 100 mL). The combined organic layers were washed with brine (300 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resultant white solid (>10:1 mixture of *syn*:*anti* diastereomers by ^{1}H NMR analysis) was purified by flash-column chromatography on silica gel (elutant: 5% EtOAc in hexanes) to afford pure *cis*-decalin (–)-**2.92** (*syn* diastereomer) (3.23 g, 76%) as a white solid. In practice, *cis*-decalin (–)-**2.92** (*anti* diastereomer) was not isolated. A pure sample of the *cis*-decalin (–)-**2.92** (*anti*

diastereomer) was obtained for spectroscopic analysis and comparison through the use of aluminum(III) chloride rather than titanium(IV) chloride as a Lewis acid-promoter in the Diels–Alder reaction.[231]



(–)-**2.92** (*syn* diastereomer)

***cis*-Decalin (–)-2.92 (*syn* diastereomer)**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.24 (m, 5 H), 5.70–5.60 (m, 2 H), 5.27 (d, J = 9.8 Hz, 1 H), 4.78 (d, J = 11.4 Hz, 1 H), 4.75 (d, J = 11.0 Hz, 1 H), 4.22 (dd, J = 4.7, 8.8 Hz, 1 H), 3.84 (t, J = 9.4 Hz, 1 H), 2.90–2.81 (m, 1 H), 2.61 –2.52 (m, 1 H), 2.41–2.28 (m, 2 H), 2.12–2.04 (m, 1 H), 1.68–1.57 (m, 1 H), 1.23 (s, 9 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.4, 177.6, 138.2, 128.2, 127.5, 127.3, 124.9, 124.4, 82.2, 79.5, 75.4, 74.9, 42.7, 38.7, 38.5, 27.2, 25.9, 23.0, 22.2, 18.1, –4.6, –4.7.

FTIR (thin film) cm^{-1}: 3032, 2931, 2857, 1747, 1733, 1396, 1359, 1286, 1251, 1160, 1127, 1073, 931, 837, 778, 750, 633.

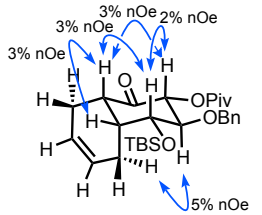
HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{42}O_5SiNa$ $[M+Na]^+$: 509.2694, found 509.2680.

$[\alpha]_D^{23}$: –21.0 (c = 1.00, CH_2Cl_2).

M.p.: 138 °C (Et_2O).

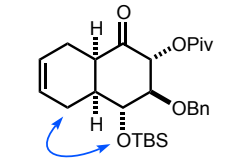
TLC (15% EtOAc in hexanes), R_f: 0.38 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(–)-**2.92** (*syn* diastereomer)

[231] Use of aluminum(III) chloride resulted in a 3.7:1.0 (syn:anti) diastereomeric ratio and an 80% overall yield.



(–)-**2.92** (*anti* diastereomer)

***cis*-Decalin (–)-2.92 (*anti* diastereomer)**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.22 (m, 5 H), 5.73 (d, J = 10.1 Hz, 1 H), 5.70–5.64 (m, 2 H), 4.80 (d, J = 11.2 Hz, 1 H), 4.74 (d, J = 11.2 Hz, 1 H), 4.06 (t, J = 9.2 Hz, 1 H), 3.65 (t, J = 9.2 Hz, 1 H), 2.83 (ddd, J = 4.5, 6.9, 10.8 Hz, 1 H), 2.44 (d, J = 18.3 Hz, 1 H), 2.37–2.19 (m, 2 H), 2.09 (d, J = 18.5 Hz, 1 H), 2.03–1.96 (m, 1 H), 1.20 (s, 9 H), 0.91 (s, 9 H), 0.03 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.3, 177.6, 138.2, 128.2, 127.3, 126.9, 125.2, 123.7, 84.9, 77.6, 74.9, 70.8, 46.0, 38.7, 36.7, 27.1, 26.0, 24.3, 23.7, 18.1, –3.7, –4.4.

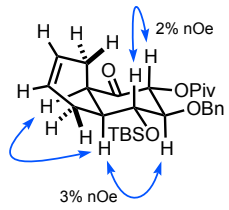
FTIR (thin film) cm^{-1}: 3031, 2957, 2929, 2897, 2857, 1744, 1729, 1473, 1397, 1362, 1284, 1256, 1154, 1132, 1076, 1042, 874, 837, 777, 736, 697.

HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{42}O_5SiNa$ $[M+Na]^+$: 509.2694, found 509.2700.

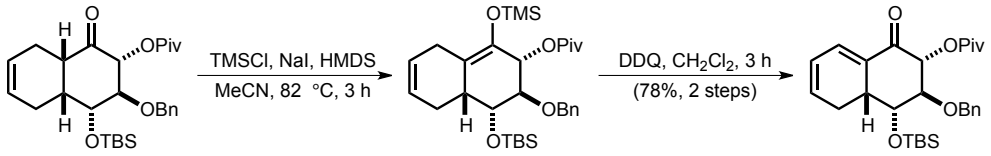
$[\alpha]_D^{23}$: –121.4 (c = 1.40, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.47 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(–)-**2.92** (*anti* diastereomer)



Dienone (–)-**2.88**:

A 350-mL glass round-bottomed pressure vessel was charged sequentially with (–)-**2.92** (4.00 g, 8.23 mmol, 1.00 equiv), MeCN (165 mL), hexamethyldisilazane (34.3 mL, 164 mmol, 20.0 equiv), sodium iodide (18.5 g, 124 mmol, 15.0 equiv), and chlorotrimethylsilane (10.5 mL, 82.3 mmol, 10.0 equiv) under an argon atmosphere. The reaction vessel was sealed with a Teflon bushing and heated to 82 °C for 3 h. The resultant orange reaction mixture was allowed to cool to ambient temperature and then poured into a saturated aqueous sodium bicarbonate solution (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish enol silane **2.95** as a yellow syrup, which was used immediately without further purification.

A 500-mL round-bottomed flask was charged with **2.95** (8.23 mmol, 1.00 equiv) and azeotropically distilled with benzene (3 × 100 mL). The residue was concentrated under reduced pressure (0.05 Torr, 12 h, 23 °C) and flushed with argon. CH_2Cl_2 (165 mL) was added to the reaction vessel and the resultant mixture was stirred for 15 min or until homogeneous. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (5.60 g, 24.7 mmol, 3.00 equiv) was then added to the reaction solution in one portion to produce a dark-green, inhomogeneous mixture. The reaction mixture was stirred for 3 h at ambient temperature and was slowly poured into a 1-L Erlenmeyer flask containing a 1:1 mixture of a saturated aqueous sodium bicarbonate solution (250 mL) and an aqueous solution of sodium bisulfite (0.1 M, 250 mL). The resultant inhomogeneous mixture was filtered through a pad of Celite and was rinsed with water (100 mL) and Et_2O (2 × 200 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL). The organic layer was dried over anhydrous

magnesium sulfate, filtered, and concentrated to furnish an orange oil, which was purified by flash-column chromatography (silica gel, eluent: gradient, 7 → 10% EtOAc in hexanes) to afford dienone (–)-**2.88** (3.10 g, 78%) as a clear, colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38–7.33 (m, 2 H), 7.33–7.28 (m, 3 H), 6.79 (dd, *J* = 3.4, 4.5 Hz, 1 H), 6.15–6.11 (m, 1 H), 6.05 (ddd, *J* = 3.4, 5.3, 9.2 Hz, 1 H), 5.43 (d, *J* = 2.3 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.81–3.79 (m, 1 H), 3.76 (t, *J* = 2.6 Hz, 1 H), 3.41–3.34 (m, 1 H), 2.41 (tdd, *J* = 2.8, 17.1, 19.5 Hz, 1 H), 2.12 (ddd, *J* = 6.3, 8.2, 17.1 Hz, 1 H), 1.28 (s, 9 H), 0.79 (s, 9 H), 0.00 (s, 3 H), –0.06 (s, 3 H).

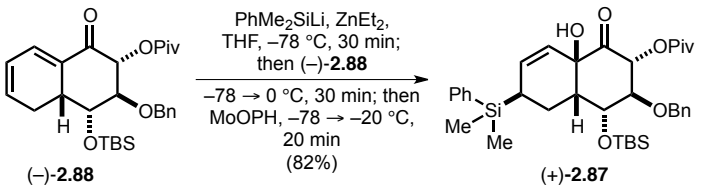
^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.1, 177.2, 137.2, 132.9, 131.3, 129.6, 128.5, 128.0, 127.9, 124.0, 83.6, 77.1, 71.2, 70.2, 38.7, 36.5, 27.2, 25.7, 25.5, 17.9, –4.6, –4.8.

FTIR (thin film) cm^{-1}: 3040, 2958, 2930, 2899, 2858, 1738, 1706, 1637, 1567, 1480, 1397, 1362, 1255, 1155, 1119, 922, 837, 777, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{40}O_5SiNa$ $[M+Na]^+$: 507.2537, found 507.2540.

$[\alpha]_D^{23}$: –42.0 (*c* = 0.96, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.46 (UV, CAM).



α-Hydroxy Ketone (+)-**2.87**:

A 250-mL, two-necked, round-bottomed flask equipped with a Merlic solid addition adapter, containing MoOPH (6.60 g, 17.2 mmol, 2.64 equiv), was flushed with argon and charged with THF (29 mL) and a solution of diethylzinc in PhMe (1.0 M, 8.60 mL, 8.60 mmol, 1.50 equiv) and cooled to –78 °C. A deep-purple solution of dimethylphenylsilyllithium in THF (1.0 M, 8.60 mL, 8.60 mmol, 1.50 equiv) was added dropwise to the reaction mixture via syringe and stirred for 30 min. A separate 100 mL round-bottomed flask was charged with (–)-**2.88** (2.78 g, 5.74 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (29 mL) was introduced, and the resultant solution cooled to –78 °C and was transferred dropwise via dry-ice wrapped cannula to the stirred, cooled reaction mixture over 10 min. The resultant yellow solution was allowed to warm to 0 °C over 30 min before being cooled back to –78 °C. MoOPH was then slowly added over 5 min via the solid addition adapter to the vigorously stirred reaction mixture, which was then warmed to –20 °C over 20 min. A 1:1 mixture of a saturated aqueous ammonium chloride solution (25 mL) and a saturated aqueous solution of sodium sulfite (25 mL) was added to the tan, homogeneous reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a yellow syrup. The product was purified by flash-column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford α-hydroxy ketone (+)-**2.87** (3.00 g, 82%) as a clear, colorless gel.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.44–7.39 (m, 2 H), 7.35 (d, J = 7.6 Hz, 2 H), 7.23–7.15 (m, 5 H), 7.07 (t, J = 7.6 Hz, 1 H), 6.24 (d, J = 10.1 Hz, 1 H), 5.82 (dd, J = 3.9, 10.1 Hz, 1 H), 5.47 (dd, J = 2.3, 10.1 Hz, 1

H), 4.83 (d, J = 11.4 Hz, 1 H), 4.78 (dd, J = 5.2, 9.5 Hz, 1 H), 4.73 (d, J = 11.4 Hz, 1 H), 3.72 (t, J = 9.7 Hz, 1 H), 3.01 (s, 1 H), 2.33–2.24 (m, 2 H), 1.78 (ddd, J = 2.5, 4.1, 6.9 Hz, 1 H), 1.31 (s, 1 H), 1.25 (s, 9 H), 0.90 (s, 9 H), 0.29 (s, 3 H), 0.27 (s, 3 H), 0.021 (s, 3 H), 0.020 (s, 3 H).

^{13}C NMR (125 MHz, C_6D_6) δ: 201.3, 177.7, 139.1, 137.9, 134.2, 132.0, 129.6, 128.6, 128.5, 127.6, 127.1, 126.4, 81.5, 78.3, 77.0, 75.3, 70.9, 44.6, 39.0, 27.4, 27.0, 26.3, 19.4, 18.2, –3.4, –3.5, –4.3.

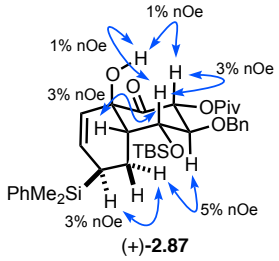
FTIR (thin film) cm^{-1}: 3460, 2957, 2931, 2857, 1744, 1720, 1462, 1397, 1285, 1257, 1159, 1105, 838, 776, 734, 700.

HRMS (ESI) (*m/z*) calc'd for $C_{36}H_{52}O_6Si_2Cl$ $[M+Cl]^-$: 671.2996, found 671.2991.

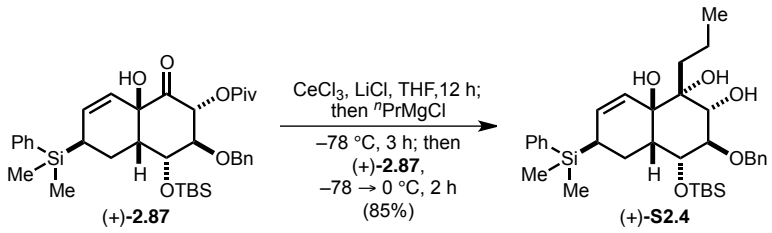
$[\alpha]_D^{23}$: +101.5 (*c* = 1.05, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.28 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(+)-**2.87**



(+)-**Triol S2.4**:

A 1-L round-bottomed flask was charged with anhydrous cerium(III) chloride (11.6 g, 47.2 mmol, 15.0 equiv) and lithium chloride (4.00 g, 94.2 mmol, 30.0 equiv), and heated to 145 °C under reduced pressure (0.05 Torr) for 2.5 h. The flask was allowed to cool to ambient temperature and then was flushed with argon. The flask was cooled to 0 °C and THF (470 mL) was introduced via cannula over 5 min. The resultant inhomogeneous, off-white slurry was allowed to warm to ambient temperature over 12 h. The stirred reaction mixture was cooled to –78 °C and a solution of *n*-propylmagnesium chloride in Et_2O (1.64 M, 23.0 mL, 37.7 mmol, 12.0 equiv) was added dropwise via syringe over 15 min. The resultant yellow slurry was stirred for 3 h at –78 °C. A separate 100 mL round-bottomed flask was charged with (+)-**2.87** (2.00 g, 3.14 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (25 mL) was introduced, and the resultant solution cooled to –78 °C and was transferred dropwise via dry-ice wrapped cannula to the stirred, cooled reaction mixture over 10 min. The resultant mixture was gradually allowed to warm to 0 °C over 2 h and stirred at 0 °C for an additional 1.5 h. A saturated aqueous solution of ammonium chloride (250 mL) was then carefully added to the reaction mixture, and the contents of the flask were allowed to warm to ambient temperature. The resultant inhomogeneous mixture was filtered through a pad of Celite and was rinsed with water (100 mL) and Et_2O (3 × 150 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resultant yellow syrup was purified by flash-column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford triol (+)-**S2.4** (1.59 g, 85%) as a colorless gel.

^{1}H NMR (600 MHz, C_6D_6) δ: 7.49 (d, *J* = 5.9 Hz, 2 H), 7.38 (d, *J* = 7.3 Hz, 2 H), 7.28–7.20 (m, 3 H), 7.18 (t, *J* = 7.3 Hz, 2 H), 7.08 (t, *J* = 7.3 Hz, 1 H), 5.75 (dd, *J* = 3.1, 9.8 Hz, 1 H), 5.36 (d, *J* = 9.1 Hz, 1 H), 4.95 (d, *J* = 11.7 Hz, 1 H), 4.73 (d, *J* = 11.7 Hz, 1 H), 4.34 (dd, *J* = 5.9, 9.7 Hz, 1 H), 3.95 (d, *J* = 8.8 Hz, 1 H), 3.78 (t, *J* = 9.5 Hz, 1 H), 2.58 (dt, *J* = 8.6, 13.8 Hz, 1 H), 2.29 (dd, *J* = 3.8, 13.8 Hz, 1 H), 2.27 (br. s., 1 H), 1.96–1.86 (m, 3 H), 1.83 (dt, *J* = 2.8, 12.5 Hz, 1 H), 1.72 (d, *J* = 7.9 Hz, 1 H), 1.71–1.65 (m, *J* = 2.9, 12.6, 12.6 Hz, 1 H), 1.56–1.45 (m, 2 H), 0.98 (s, 10 H), 0.94 (t, *J* = 6.9 Hz, 3 H), 0.34 (s, 3 H), 0.33 (s, 3 H), 0.14 (s, 3 H), 0.05 (s, 3 H).

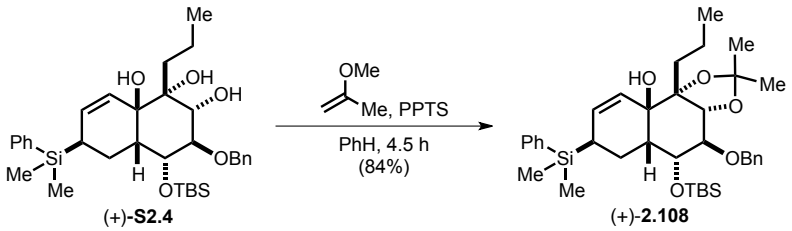
^{13}C NMR (100 MHz, C_6D_6) δ: 139.9, 138.2, 134.3, 133.6, 129.5, 128.69, 128.6, 128.2, 127.7, 127.5, 81.8, 78.4, 75.7, 75.6, 75.0, 72.1, 48.8, 39.3, 26.43, 26.39, 19.8, 18.9, 18.2, 15.6, –3.4, –3.8, –4.2.

FTIR (thin film) cm^{-1}: 3558, 3469, 2957, 2929, 2894, 2857, 1471, 1428, 1250, 1114, 1029, 837, 774, 734, 701.

HRMS (ESI) (*m/z*) calc'd for $C_{34}H_{52}O_5Si_2Na$ $[M+Na]^+$: 619.3246, found 619.3239.

$[\alpha]_D^{23}$: +108.6 (*c* = 0.86, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.25 (UV, CAM).



Acetonide (+)-**2.108**:

A 250 mL round-bottomed flask was sequentially charged with (+)-**S2.4** (3.78 g, 6.33 mmol, 1.00 equiv), PhH (127 mL), 2-methoxypropene (12.1 mL, 127 mmol, 20.0 equiv), and pyridinium *p*-toluenesulfonate (158 mg, 630 μmol, 0.100 equiv). The reaction mixture was stirred at ambient temperature for 4.5 h before a saturated aqueous sodium bicarbonate solution (250 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (250 mL), water (250 mL), and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a yellow syrup. The residue was purified by flash-column chromatography (silica gel, eluent: gradient, 5 → 15% EtOAc in hexanes) to afford acetonide (+)-**2.108** (3.38 g, 84%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.53–7.49 (m, 2 H), 7.42 (d, *J* = 7.4 Hz, 2 H), 7.24–7.15 (m, 5 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 6.07 (dd, *J* = 1.6, 10.3 Hz, 1 H), 5.84 (dd, *J* = 1.4, 10.3 Hz, 1 H), 4.96 (d, *J* = 11.9 Hz, 1 H), 4.72 (d, *J* = 11.9 Hz, 1 H), 4.11 (dd, *J* = 8.2, 11.0 Hz, 1 H), 4.09 (d, *J* = 6.2 Hz, 1 H), 3.99 (dd, *J* = 6.2, 11.2 Hz, 1 H), 2.37–2.26 (m, 3 H), 2.05–1.95 (m, 2 H), 1.78 (dtdd, *J* = 5.2, 7.2, 12.6, 19.9 Hz, 1 H), 1.69–1.57 (m, 1 H), 1.54–1.46 (m, 4 H), 1.29 (s, 3 H), 0.97 (s, 9 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.31 (s, 3 H), 0.31 (s, 3 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

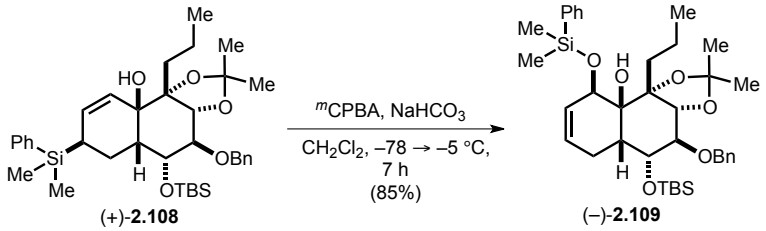
^{13}C NMR (125 MHz, C_6D_6) δ: 139.6, 137.8, 134.4, 131.4, 130.4, 129.5, 128.6, 128.3, 128.2, 127.5, 108.9, 87.5, 86.8, 80.6, 73.0, 72.6, 69.8, 43.0, 39.9, 27.6, 27.0, 26.4, 24.2, 20.8, 18.7, 18.6, 15.5, –4.1, –4.5, –4.9.

FTIR (thin film) cm^{-1}: 3467, 2958, 2930, 2860, 1639, 1461, 1380, 1252, 1208, 1114, 1032, 837, 774, 734, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{37}H_{56}O_5Si_2Na$ $[M+Na]^+$: 659.3559, found 659.3576.

$[\alpha]_D^{23}$: +12.3 (*c* = 1.18, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.63 (UV, CAM, anis).



Silyl Ether (–)-**2.109**:

A 250 mL round-bottomed flask was charged with (+)-**2.108** (3.32 g, 5.21 mmol, 1.00 equiv), CH_2Cl_2 (105 mL), and sodium bicarbonate (1.31 g, 15.6 mmol, 3.00 equiv), and cooled to –78 °C. A separate 25-mL round-bottomed flask was charged with 3-chloroperbenzoic acid (77 wt. %, 2.34 g, 10.4 mmol, 2.00 equiv) and CH_2Cl_2 (10 mL), and was transferred dropwise via cannula to the stirred reaction mixture over 5 min. The resultant inhomogeneous reaction mixture was warmed to –5 °C. After 7 h, a saturated aqueous sodium sulfite solution (100 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (400 mL), water (400 mL) and brine (400 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a colorless syrup. The syrup was purified by flash-column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford silyl ether (–)-**2.109** (2.88 g, 85%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.53–7.49 (m, 4 H), 7.22 (t, J = 7.6 Hz, 2 H), 7.19–7.15 (m, 3 H), 7.10 (t, J = 7.6 Hz, 1 H), 5.84–5.75 (m, 2 H), 5.10 (d, J = 11.7 Hz, 1 H), 4.81 (d, J = 11.7 Hz, 1 H), 4.71 (dd, J = 3.9, 9.3 Hz, 1 H), 4.57 (d, J = 3.7 Hz, 1 H), 4.38 (d, J = 5.1 Hz, 1 H), 3.93 (dd, J = 5.1, 9.3 Hz, 1 H), 3.88 (s, 1 H), 2.60–2.51 (m, 1 H), 2.43–2.34 (m, 2 H), 2.28 (ddd, J = 5.6, 12.0, 14.2 Hz, 1 H), 1.62–1.42 (m, 2 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.00 (s, 9 H), 0.84 (t, J = 7.2 Hz, 3 H), 0.31 (s, 3 H), 0.29 (s, 3 H), 0.20 (s, 3 H), 0.15 (s, 3 H).

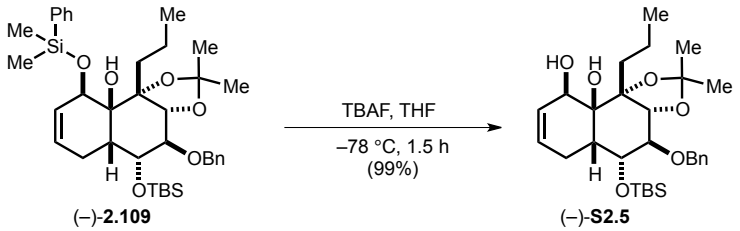
^{13}C NMR (125 MHz, C_6D_6) δ: 139.7, 137.4, 133.9, 130.3, 130.2, 128.6, 128.4, 128.3, 128.2, 127.5, 109.5, 89.0, 87.0, 83.0, 73.8, 73.1, 71.2, 68.1, 44.0, 41.3, 29.0, 28.5, 26.3, 25.5, 18.8, 18.4, 15.4, –0.7, –4.0, –4.6.

FTIR (thin film) cm^{-1}: 3490, 2956, 2929, 2894, 2856, 1456, 1429, 1378, 1254, 1234, 1118, 1038, 835, 787, 736, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{37}H_{56}O_6Si_2Na$ $[M+Na]^+$: 675.3508, found 675.3505.

$\mathbf{[\alpha]_D^{23}}$: –77.0 (*c* = 0.87, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.65 (UV, CAM, anis).



(–)-**2.109** (–)-**S2.5**

Allylic Alcohol (–)-S2.5:

A 250-mL round-bottomed flask was charged with (–)-**2.109** (2.83 g, 4.33 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (43 mL) was introduced, and the resultant solution was cooled to –78 °C. A solution of tetrabutylammonium fluoride in THF (1.0 M, 6.50 mL, 6.50 mmol, 1.50 equiv) was added dropwise via syringe to the stirred reaction mixture over 5 min. After 1.5 h, a saturated aqueous ammonium chloride solution (100 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a yellow gel. The gel was purified by flash-column chromatography (silica gel, eluent: gradient, 5 → 10% EtOAc in hexanes) to afford allylic alcohol (–)-**S2.5** (2.22 g, 99%) as a colorless gel.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.27 (m, 5 H), 5.72 (d, *J* = 9.6 Hz, 1 H), 5.38 (d, *J* = 9.8 Hz, 1 H), 4.77 (br. s., 1 H), 4.68 (d, *J* = 11.9 Hz, 1 H), 4.58 (d, *J* = 11.9 Hz, 1 H), 4.37 (br. s, 1 H), 4.04 (br. s., 1 H), 3.89 (br. s., 1 H), 3.70 (br. s., 1 H), 3.40 (br. s., 1 H), 2.69–2.59 (m, 1 H), 2.31 (d, *J* = 6.2 Hz, 1 H), 2.07 (dt, *J* = 3.4, 13.5 Hz, 1 H), 1.80–1.69 (m, 2 H), 1.63 (br. s., 1 H), 1.56 (s, 3 H), 1.52–1.44 (m, 1 H), 1.41 (s, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.84 (s, 9 H), –0.03 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 128.4, 127.8, 127.6, 127.3, 126.8, 107.4, 89.4, 79.8, 77.2, 75.5, 75.2, 72.3, 70.1, 38.04, 37.4, 27.6, 26.0, 25.9, 25.7, 18.0, 17.7, 15.0, –5.0, –5.2.

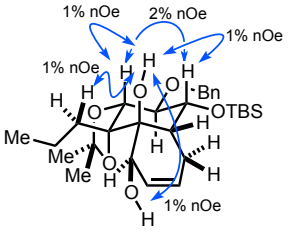
FTIR (thin film) cm^{-1}: 3493, 3029, 2958, 2906, 2858, 1462, 1383, 1252, 1210, 1072, 991, 856, 775, 738, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{29}H_{46}O_6SiNa$ $[M+Na]^+$: 541.2956, found 541.2973.

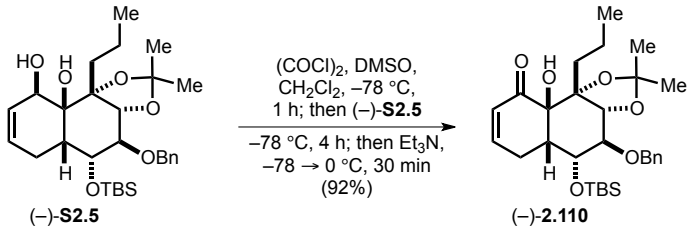
[α]$_D^{23}$: –43.6 (*c* = 0.77, C_6H_6).

TLC (15% EtOAc in hexanes), R_f: 0.46 (UV, CAM).

1D NOESY data (500 MHz, C_6D_6):



(–)-**S2.5**



C14-hydroxy *ent*-AB/HG-enone (–)-2.110:

A 250-mL round-bottomed flask was charged with dimethyl sulfoxide (4.73 mL, 66.6 mL, 16.0 equiv) and CH_2Cl_2 (45 mL), and cooled to –78 °C. A separate 25-mL round-bottomed flask was charged with a solution of oxalyl chloride (2.80 mL, 33.3 mmol, 8.00 equiv) and CH_2Cl_2 (5 mL), and was transferred dropwise via cannula to the 250-mL reaction vessel over 5 min. The resultant mixture was stirred for 1 h at –78 °C. A separate 50-mL round-bottomed flask was charged with (–)-**S2.5** (2.16 g, 4.16 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (20 mL) was introduced, and the resultant solution was cooled to –78 °C and transferred to the reaction mixture dropwise via dry-ice wrapped cannula over 5 min. After 4 h, triethylamine (18.6 mL, 133 mmol, 32.0 equiv) was added dropwise via syringe, down the wall of the reaction vessel, over 5 min. The reaction mixture was stirred at –78 °C for 5 min and was then allowed to warm to 0 °C over 30 min. A saturated aqueous solution of ammonium chloride (100 mL) and Et_2O (100 mL) were added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to furnish a colorless syrup. The syrup was purified by flash-column chromatography (silica gel, eluent: gradient, 5 → 15% EtOAc in hexanes) to afford the C14-hydroxy *ent*-AB/HG-enone (–)-**2.110** (1.97 g, 92%) as a colorless solid. Crystals suitable for X-ray diffraction were obtained by cooling a saturated solution of (–)-**2.110** in pentane to –20 °C for 48 h.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.1 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 2 H), 7.29–7.24 (m, J = 7.4, 7.4 Hz, 1 H), 6.97 (ddd, J = 2.2, 5.4, 9.9 Hz, 1 H), 6.20 (dd, J = 2.1, 10.1 Hz, 1 H), 4.91 (d, J = 11.7 Hz, 1

H), 4.71 (d, J = 11.5 Hz, 1 H), 4.25 (s, 1 H), 4.15 (dd, J = 4.9, 9.5 Hz, 1 H), 4.06 (d, J = 5.9 Hz, 1 H), 3.75 (dd, J = 5.9, 9.5 Hz, 1 H), 2.68 (tdd, J = 2.8, 11.2, 20.0 Hz, 1 H), 2.57 (td, J = 5.6, 20.0 Hz, 1 H), 2.32 (td, J = 5.6, 11.0 Hz, 1 H), 2.04 (ddd, J = 7.8, 10.0, 14.9 Hz, 1 H), 1.59–1.51 (m, 2 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.24–1.15 (m, 2 H), 0.91–0.86 (m, 9 H), 0.79 (t, J = 7.3 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.0, 151.3, 138.7, 128.1, 127.9, 127.6, 127.3, 110.1, 88.0, 85.9, 81.7, 76.0, 73.2, 70.1, 47.9, 37.8, 29.0, 28.4, 26.2, 25.9, 18.1, 16.1, 14.6, –4.5, –4.9.

FTIR (thin film) cm^{-1}: 3462, 2955, 2930, 2891, 2858, 1677, 1473, 1380, 1254, 1231, 1110, 1089, 1030, 853, 837, 777, 735, 697.

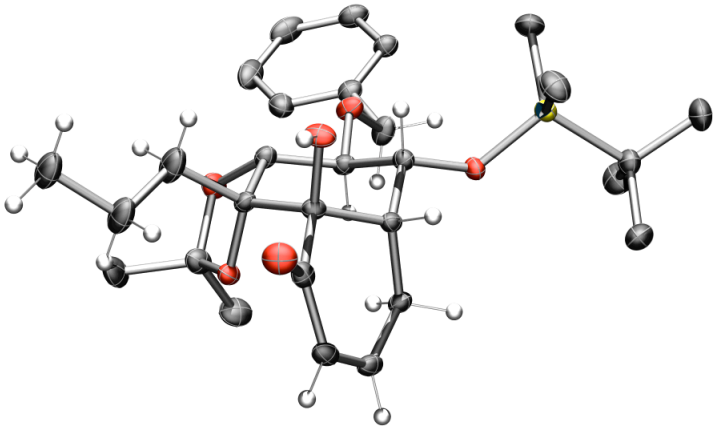
HRMS (ESI) (*m/z*) calc'd for $C_{29}H_{44}O_6SiNa$ $[M+Na]^+$: 539.2799, found 539.2796.

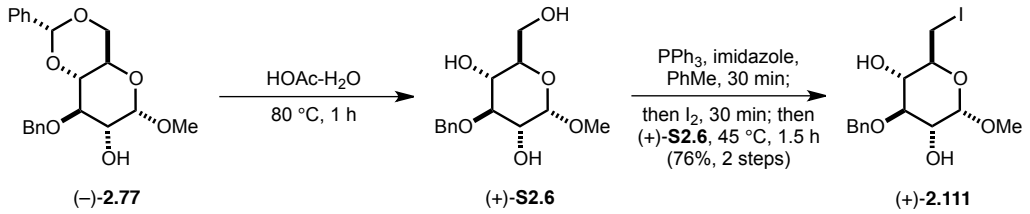
$[\alpha]_D^{23}$: –67.4 (*c* = 1.10, C_6H_6).

M.p.: 99.5 °C (pentane).

TLC (15% EtOAc in hexanes), R_f: 0.55 (UV, CAM).

X-Ray Crystal Structure:





Methyl 3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**2.111**):

A 1-L round-bottomed flask was charged with (–)-**2.77** (37.7 g, 101 mmol, 1.00 equiv), acetic acid (219 mL), and water (55 mL). The reaction vessel was sealed with a plastic cap and the heterogeneous reaction mixture was warmed to 80 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The resultant white solid (+)-**S2.6** was azeotropically dried with toluene (4 × 400 mL) and used immediately without further purification. An analytical sample of (+)-**S2.6** was obtained through purification by flash column chromatography (silica gel, eluent: 10% MeOH in CH_2Cl_2) to afford methyl 3-*O*-benzyl-α-D-glucopyranoside ((+)-**S2.6**) as a white crystalline solid.

A 2-L round-bottomed flask was charged with triphenylphosphine (34.5 g, 131 mmol, 1.30 equiv), imidazole (20.6 g, 303 mmol, 3.00 equiv), and PhMe (505 mL). The reaction mixture was vigorously stirred for 30 min to break-up the solids before iodine (33.4 g, 131 mmol, 1.30 equiv) was added in one portion. After 30 min, a solution of (+)-**S2.6** in CH_2Cl_2 (151 mL) was added via cannula to the stirred reaction mixture over 15 min. The resultant heterogeneous reaction mixture was warmed to 45 °C. After 1.5 h, the reaction mixture was allowed to cool to ambient temperature. Brine (700 mL) was added and the resultant mixture stirred for 15 min or until all of the solid material had fully dissolved. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant pale-yellow syrup was purified by flash column chromatography (silica gel, eluent: 30% EtOAc in hexanes) to afford methyl 3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**2.111**) (30.1 g, 76% over two steps) as a white crystalline solid.

Methyl 3-*O*-benzyl-α-D-glucopyranoside ((+)-**S2.6**):

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.32 (m, 4 H), 7.29 (t, *J* = 6.6 Hz, 1 H), 4.98 (d, *J* = 11.6 Hz, 1 H), 4.75 (d, *J* = 11.6 Hz, 1 H), 4.72 (d, *J* = 3.7 Hz, 1 H), 3.80 (dd, *J* = 3.4, 11.8 Hz, 1 H), 3.76 (dd, *J* = 4.0, 11.8 Hz, 1 H), 3.64 (dd, *J* = 3.7, 8.8 Hz, 1 H), 3.62–3.52 (m, 3 H), 3.41 (s, 3 H), 2.48 (br. s., 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.5, 128.6, 127.91, 127.88, 99.6, 82.6, 74.9, 72.7, 71.0, 70.0, 62.2, 55.3.

FTIR (thin film) cm^{-1}: 3407, 3011, 2934, 1497, 1455, 1407, 1360, 1216, 1193, 1150, 1117, 1036, 909, 841, 759, 701, 667.

HRMS (ESI) (*m/z*) calc'd for $C_{14}H_{20}NaO_6$ $[M+Na]^+$: 307.1158, found 307.1177.

$[\alpha]_D^{23}$: +95.1 (*c* = 1.16, $CHCl_3$).

M.p.: 85–86 °C ($CHCl_3$).

TLC (60% EtOAc in hexanes), R_f: 0.10 (UV, CAM).

Methyl 3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**2.111**):

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.34 (m, 4 H), 7.34–7.29 (m, 1 H), 5.02 (d, *J* = 11.5 Hz, 1 H), 4.76 (d, *J* = 3.9 Hz, 1 H), 4.69 (d, *J* = 11.5 Hz, 1 H), 3.69 (dt, *J* = 3.9, 9.3 Hz, 1 H), 3.59–3.53 (m, 2 H), 3.49 (s, 3 H), 3.43 (ddd, *J* = 2.3, 7.2, 9.5 Hz, 1 H), 3.32 (dt, *J* = 2.5, 9.0 Hz, 1 H), 3.27 (dd, *J* = 7.2, 10.6 Hz, 1 H), 2.36 (d, *J* = 2.7 Hz, 1 H), 2.21 (d, *J* = 9.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 128.7, 128.03, 127.95, 99.5, 82.3, 74.9, 73.2, 72.9, 70.1, 55.6, 6.8.

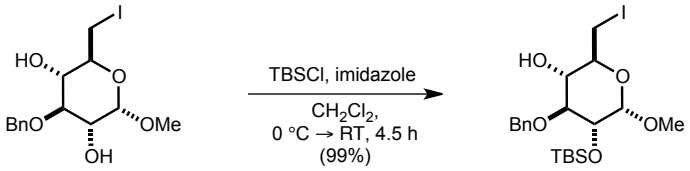
FTIR (thin film) cm^{-1}: 3448, 3028, 3009, 2908, 2838, 1497, 1454, 1408, 1363, 1216, 1197, 1146, 1122, 1051, 944, 891, 758, 699, 667.

HRMS (ESI) (*m/z*) calc'd for $C_{14}H_{19}INaO_5$ $[M+Na]^+$: 417.0169, found 417.0177.

$[\alpha]_D^{23}$: +60.7 (*c* = 2.27, $CHCl_3$).

M.p.: 80 °C ($CHCl_3$).

TLC (60% EtOAc in hexanes), R_f: 0.46 (UV, CAM).



(+)-**2.111** (+)-**S2.7**

Methyl 2-*O*-*t*-butyldimethylsilyloxy-3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**S2.7**):

A 1-L round-bottomed flask was charged with (+)-**2.111** (24.0 g, 61.0 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (305 mL) was introduced, and the resultant solution cooled to 0 °C. Imidazole (20.8 g, 305 mmol, 5.00 equiv) and *t*-butyldimethylsilyl chloride (18.4 g, 122 mmol, 2.00 equiv) were sequentially added to the stirred reaction mixture. After the addition was complete, the reaction mixture was allowed to warm to ambient temperature. After 4.5 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution (500 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford methyl 2-*O*-*t*-butyldimethylsilyloxy-3-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**S2.7**) (30.9 g, 99%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.28 (m, 5 H), 4.99 (d, *J* = 11.8 Hz, 1 H), 4.67 (d, *J* = 3.5 Hz, 1 H), 4.59 (d, *J* = 11.8 Hz, 1 H), 3.72 (dd, *J* = 3.5, 9.3 Hz, 1 H), 3.65 (t, *J* = 8.8 Hz, 2 H), 3.53 (dd, *J* = 2.6, 10.6 Hz, 1 H), 3.47 (s, 3 H), 3.43 (ddd, *J* = 2.3, 7.3, 9.4 Hz, 1 H), 3.29–3.23 (m, 2 H), 1.99 (d, *J* = 2.4 Hz, 1 H), 0.94 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H).

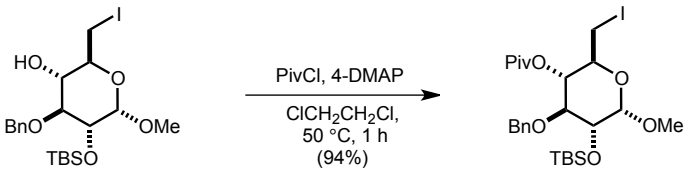
^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.6, 128.7, 128.0, 127.9, 100.3, 81.7, 75.4, 73.9, 73.6, 70.0, 55.5, 25.8, 18.1, 7.1, –4.5, –4.6.

FTIR (thin film) cm^{-1}: 3569, 3010, 2953, 2929, 2857, 1472, 1463, 1408, 1389, 1362, 1262, 1216, 1147, 1094, 1047, 861, 838, 759, 698, 668.

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{33}INaO_5Si$ $[M+Na]^+$: 531.1034, found 531.1046.

$[\alpha]_D^{23}$: +25.6 (*c* = 1.57, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.55 (UV, CAM).



(+)-**S2.7** (+)-**2.112**

Methyl 2-*O*-*t*-butyldimethylsilyloxy-3-*O*-benzyl-4-*O*-pivaloyl-6-deoxy-6-iodo-α-D-glucopy-ranoside ((+)-2.112):

A 1-L round-bottomed flask was charged with (+)-**S2.7** (42.2 g, 83.0 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before 1,2-dichloroethane (166 mL) was introduced. Trimethylacetyl chloride (12.8 mL, 104 mmol, 1.25 equiv) and 4-dimethylaminopyridine (15.2 g, 125 mmol, 1.50 equiv) were added to the stirred solution at ambient temperature. The reaction vessel was sealed with a plastic cap and the reaction mixture was warmed to 50 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature and poured into an aqueous solution of HCl (1.2 M, 250 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with saturated aqueous potassium carbonate solution (3 × 250 mL) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford methyl 2-*O*-*t*-butyldimethylsilyloxy-3-*O*-benzyl–4-*O*-pivaloyl-6-deoxy-6-iodo-α-D-glucopyranoside ((+)-**2.112**) (46.3 g, 94%) as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32–7.20 (m, 5 H), 4.86 (d, *J* = 11.6 Hz, 1 H), 4.84 (d, *J* = 9.3 Hz, 1 H), 4.70 (d, *J* = 3.0 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 3.85–3.77 (m, 2 H), 3.76 (dt, *J* = 2.3, 9.6 Hz, 1 H), 3.53 (s, 3 H), 3.20 (dd, *J* = 2.3, 10.7 Hz, 1 H), 3.08 (t, *J* = 10.2 Hz, 1 H), 1.13 (s, 9 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.2, 138.4, 128.1, 127.2, 126.7, 100.2, 79.5, 75.2, 73.8, 73.4, 69.6, 55.8, 38.8, 27.0, 25.7, 18.1, 4.4, –4.5, –4.8.

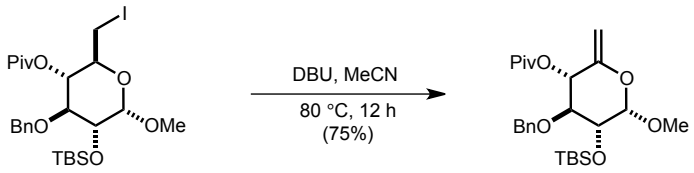
FTIR (thin film) cm^{-1}: 2957, 2905, 2858, 1738, 1704, 1473, 1462, 1397, 1362, 1254, 1205, 1158, 1135, 1106, 1038, 995, 958, 911, 863, 834, 779, 761, 697, 669.

HRMS (ESI) (*m/z*) calc'd for $C_{25}H_{41}INaO_6Si$ $[M+Na]^+$: 615.1609, found 615.1612.

$[\alpha]_D^{23}$: +34.2 (*c* = 0.97, $CHCl_3$).

M.**p**.: 82–83 °C ($CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.69 (UV, CAM).



(+)-**2.112** (+)-**2.113**

Enol ether (+)-**2.113**

A 1-L round-bottomed flask was charged with (+)-**2.112** (26.0 g, 43.9 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before MeCN (219 mL) was introduced. 1,8-Diazabicyclo[5.4.0]undec-7-ene (23.0 mL, 132 mmol, 3.00 equiv) was added via syringe to the stirred solution at ambient temperature. The reaction vessel was equipped with a reflux condenser and the reaction mixture was warmed to 80 °C. After 12 h, the reaction mixture was allowed to cool to ambient temperature and poured into saturated aqueous sodium bicarbonate solution (300 mL). The mixture was partitioned with EtOAc (250 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford enol ether (+)-**2.113** (15.2 g, 75%) as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.20 (m, 5 H), 5.43 (td, *J* = 2.1, 9.1 Hz, 1 H), 4.84 (d, *J* = 11.4 Hz, 1 H), 4.72 (d, *J* = 3.2 Hz, 1 H), 4.67 (d, *J* = 3.7 Hz, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 4.44 (t, *J* = 1.7 Hz, 1 H), 3.91 (dd, *J* = 3.3, 9.3 Hz, 1 H), 3.86 (t, *J* = 9.0 Hz, 1 H), 3.48 (s, 3 H), 1.19 (s, 9 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.9, 151.8, 138.4, 128.1, 127.2, 126.9, 101.0, 95.9, 79.6, 75.1, 73.4, 71.0, 55.7, 38.7, 27.1, 25.7, 18.1, –4.5, –4.8.

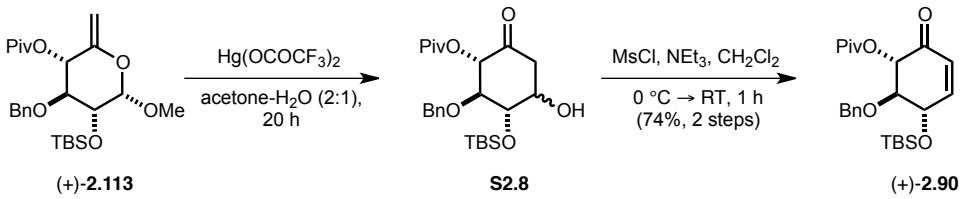
FTIR (thin film) cm^{-1}: 2957, 2931, 2858, 1742, 1667, 1613, 1530, 1463, 1355, 1279, 1255, 1217, 1168, 1138, 1097, 1044, 1025, 839, 762, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{25}H_{40}NaO_6Si$ $[M+Na]^+$: 487.2486, found 487.2498.

$[\alpha]_D^{23}$: +163.5 (*c* = 1.12, $CHCl_3$).

M.**p**. .: 52–53 °C ($CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.67 (UV, CAM).



(+)-**2.113** **S2.8** (+)-**2.90**

2-Cyclohexenone (+)-**2.90**:

A solution of mercury(II) trifluoroacetate (3.31 g, 7.76 mmol, 0.30 equiv) in water (86 mL) was added in one portion to a vigorously stirred solution of (+)-**2.113** (15.3 g, 25.9 mmol, 1.00 equiv) in acetone (173 mL) at ambient temperature. The resultant heterogeneous reaction mixture was sealed with a plastic cap. After 20 h the acetone was removed under reduced pressure and the resultant mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with 10% (w/v) aqueous potassium iodide solution (250 mL), 20% (w/v) aqueous sodium thiosulfate solution (250 mL), and brine (250 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield b-hydroxy ketone **S2.8** as a yellow oil, which was used without further purification.

A 1-L round-bottomed flask was charged with **S2.8** and azeotropically dried with three portions of benzene. CH_2Cl_2 (129 mL) was introduced, and the resultant solution cooled to 0 °C. Triethylamine (27.0 mL, 207 mmol, 8.00 equiv) and methanesulfonyl chloride (8.00 mL, 103 mmol, 4.00 equiv) were sequentially added dropwise via syringe to the stirred reaction mixture over 10 min. After 5 min, the resultant brown reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was poured into aqueous sulfuric acid solution (0.5 M, 200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 5% → 10% EtOAc in hexanes) to afford 2-cyclohexenone (+)-**2.90** (8.26 g, 74% over two steps) as a clear, colorless syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35–7.25 (m, 5 H), 6.76 (dd, *J* = 1.7, 10.4 Hz, 1 H), 6.05 (dd, *J* = 2.4, 10.4 Hz, 1 H), 5.42 (d, *J* = 11.1 Hz, 1 H), 4.80 (s, 2 H), 4.64 (td, *J* = 2.1, 8.0 Hz, 1 H), 3.93 (dd, *J* = 8.0, 11.2 Hz, 1 H), 1.24 (s, 9 H), 0.93 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

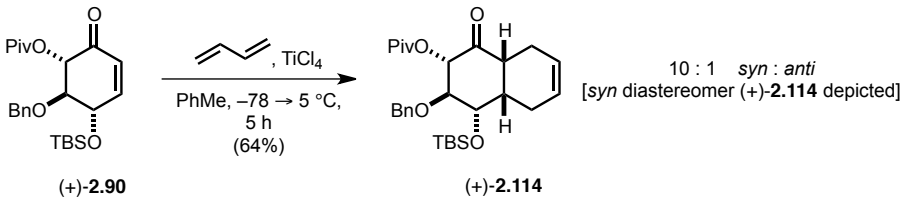
^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.2, 177.5, 151.5, 137.8, 128.2, 127.5, 127.2, 127.0 , 83.7, 77.1, 75.2, 72.9, 38.8, 27.2, 25.7, 18.0, –4.7, –4.9.

FTIR (thin film) cm^{-1}: 2957, 2897, 2858, 1740, 1704, 1480, 1383, 1360, 1282, 1254, 1216, 1154, 1136, 1104, 1046, 987, 961, 864, 839, 779, 761, 697, 670.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{37}O_5Si$ $[M+H]^+$: 433.2405, found 433.2410.

$[\alpha]_D^{23}$: +83.3 (*c* = 1.60, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



(+)-**2.90** (+)-**2.114**

***cis*-Decalin (+)-2.114 (*syn* diastereomer)**:

A 500-mL round-bottomed flask was charged with (+)-**2.90** (5.38 g, 12.5 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. PhMe (125 mL) was introduced, and the resultant solution cooled to –78 °C. A 25-mL round-bottomed flask was charged in a glove box with a solution of titanium(IV) chloride (2.36 g, 12.5 mmol, 1.00 equiv) in PhMe (13.0 mL), sealed with a rubber septum, and removed from the glove box. The solution of titanium(IV) chloride was then added dropwise via cannula to the stirred solution of (+)-**15** over 10 min. The resultant yellow solution was stirred for 1 h at –78 °C. 1,3-Butadiene (ca. 8.70 mL, 100 mmol, 8.00 equiv) was condensed at –78 °C in a 10-mL, two-necked, round-bottomed flask equipped with a dry-ice acetone condenser and a rubber septum. The cold, neat 1,3-butadiene was transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of (+)-**2.90** over 5 min. The resultant red reaction mixture was allowed to warm to 5 °C. After 5 h, a saturated aqueous sodium bicarbonate solution (150 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite, which was rinsed with water (100 mL) and EtOAc (2 × 100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant off-white solid (>10:1 mixture of *syn*:*anti* diastereomers by ^{1}H NMR analysis) was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford pure *cis*-decalin *syn* diastereomer (+)-**2.114** (3.85 g, 64%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.24 (m, 5 H), 5.70–5.61 (m, 2 H), 5.28 (d, *J* = 9.8 Hz, 1 H), 4.78 (d, *J* = 11.0 Hz, 1 H), 4.75 (d, *J* = 11.0 Hz, 1 H), 4.22 (dd, *J* = 4.8, 8.9 Hz, 1 H), 3.85 (t, *J* = 9.4 Hz, 1 H),

2.85 (t, J = 5.3 Hz, 1 H), 2.62–2.51 (m, 1 H), 2.42–2.27 (m, 2 H), 2.13–2.04 (m, 1 H), 1.69–1.55 (m, 1 H), 1.23 (s, 9 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.4, 177.6, 138.2, 128.2, 127.5, 127.3, 124.9, 124.4, 82.2, 79.4, 75.3, 74.9, 42.7, 38.7, 38.4, 27.2, 25.8, 23.0, 22.2, 18.0, –4.6, –4.7.

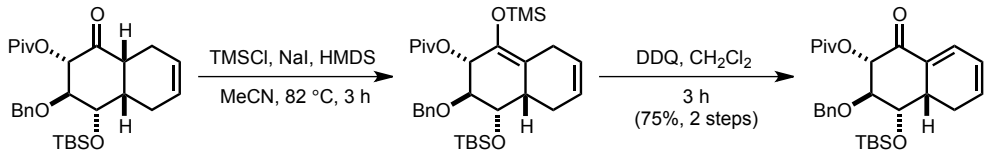
FTIR (thin film) cm^{-1}: 3030, 2950, 2930, 2907, 2888, 2857, 1747, 1731, 1472, 1396, 1360, 1287, 1251, 1216, 1159, 1106, 1072, 1031, 1012, 930, 838, 814, 777, 752, 700, 683, 633.

HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{43}O_5Si$ $[M+H]^+$: 487.2874, found 487.2859.

$[\alpha]_D^{23}$: +19.8 (c = 1.72, $CHCl_3$).

M.**p**.: 141–146°C ($CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.38 (UV, CAM).



(+)-**2.114** **S2.9** (–)-**2.115**

Dienone (–)-**2.115**:

A 350-mL, glass, round-bottomed, pressure vessel was charged with (+)-**2.114** (4.00 g, 8.23 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before MeCN (165 mL) was introduced. Hexamethyldisilazane (34.3 mL, 164 mmol, 20.0 equiv), sodium iodide (18.5 g, 124 mmol, 15.0 equiv), and chlorotrimethylsilane (10.5 mL, 82.3 mmol, 10.0 equiv) were added to the stirred solution at ambient temperature. The reaction vessel was sealed with a PTFE bushing and heated to 82 °C. After 3 h, the resultant orange reaction mixture was allowed to cool to ambient temperature and was then cautiously poured into a stirred saturated aqueous sodium bicarbonate solution (300 mL). The mixture was partitioned with EtOAc (200 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford silyl enol ether **S2.9** as a yellow syrup, which was used immediately without further purification.

A 500-mL round-bottomed flask was charged with **S2.9** and azeotropically dried with three portions of benzene before CH_2Cl_2 (165 mL) was introduced. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (5.60 g, 24.7 mmol, 3.00 equiv) was added in one portion to the stirred solution at ambient temperature to produce a dark-green, heterogeneous mixture. After 3 h, the reaction mixture was cautiously poured into a 1-L Erlenmeyer flask containing a stirred 1:1 mixture of saturated aqueous sodium bicarbonate solution (250 mL) and 1% (w/v) aqueous sodium bisulfite solution (250 mL). The mixture was diluted with EtOAc (250 mL), layers were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish an orange oil, which was purified by flash column chromatography (silica gel, eluent:

gradient, 7 → 10% EtOAc in hexanes) to afford dienone (–)-**2.115** (3.00 g, 75% over two steps) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.33 (m, 2 H), 7.32–7.28 (m, 3 H), 6.79 (tdd, *J* = 0.7, 3.1, 4.1 Hz, 1 H), 6.16–6.10 (m, 1 H), 6.05 (ddd, *J* = 3.3, 5.0, 9.4 Hz, 1 H), 5.43 (d, *J* = 2.5 Hz, 1 H), 4.68 (d, *J* = 11.9 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 3.82–3.79 (m, 1 H), 3.77 (t, *J* = 2.6 Hz, 1 H), 3.38 (dd, *J* = 8.5, 18.9 Hz, 1 H), 2.41 (tdd, *J* = 2.8, 17.1, 19.4 Hz, 1 H), 2.12 (ddd, *J* = 6.2, 8.4, 17.1 Hz, 1 H), 1.28 (s, 9 H), 0.80 (s, 9 H), 0.00 (s, 3 H), –0.06 (s, 3 H).

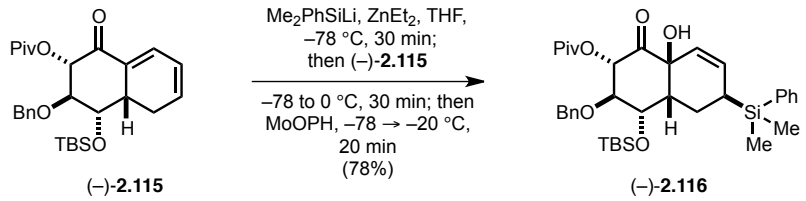
^{13}C NMR (125 MHz, $CDCl_3$) δ: 192.1, 177.2, 137.3, 132.9, 131.3, 129.6, 128.5, 128.0, 127.9, 124.0, 83.6, 77.1, 71.3, 70.2, 38.7, 36.5, 27.2, 25.7, 25.5, 17.9, –4.6, –4.8.

FTIR (thin film) cm^{-1}: 3034, 2957, 2931, 2899, 2859, 1737, 1704, 1637, 1567, 1479, 1462, 1397, 1364, 1256, 1218, 1149, 1119, 1094, 1075, 965, 922, 837, 776, 762, 700.

HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{40}NaO_5Si$ $[M+Na]^+$: 507.2543, found 507.2539.

$[\alpha]_D^{23}$: –79.7 (*c* = 2.36, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.46 (UV, CAM).



(–)-**2.115** (–)-**2.116**

α-Hydroxy ketone (–)-**2.116**:

A 250-mL, two-necked, round-bottomed flask, equipped with a Merlic solid addition adapter containing MoOPH (4.21 g, 9.69 mmol, 3.00 equiv), was flushed with argon and charged with THF (16 mL) and a solution of diethylzinc in PhMe (0.83 M, 5.84 mL, 4.85 mmol, 1.50 equiv) and cooled to –78 °C. A dark-purple solution of dimethylphenylsilyllithium in THF (0.56 M, 8.66 mL, 4.85 mmol, 1.50 equiv) was added dropwise via syringe to the stirred reaction mixture. The resultant red solution was stirred for 30 min at –78 °C before a solution of (–)-**2.115** (1.57 g, 3.23 mmol, 1.00 equiv) in THF (16 mL) was added dropwise via cannula over 10 min. The transfer was completed with two additional portions of THF (5 mL). The resultant yellow solution was allowed to warm to 0 °C over 30 min before being cooled to –78 °C. MoOPH was then slowly added via the solid addition adapter over 5 min to the vigorously stirred reaction mixture, which was subsequently allowed to warm to –20 °C over 20 min. A 1:1 mixture of saturated aqueous ammonium chloride solution (25 mL) and saturated aqueous sodium sulfite solution (25 mL) was then added to the tan, homogeneous reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was partitioned with EtOAc (100 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a yellow syrup. The product was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford α-hydroxy ketone (–)-**2.116** (1.60 g, 78%) as a clear, colorless gel.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.43–7.39 (m, 2 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.23–7.14 (m, 5 H), 7.07 (t, *J* = 7.7 Hz, 1 H), 6.25 (d, *J* = 10.2 Hz, 1 H), 5.81 (dd, *J* = 4.0, 10.0 Hz, 1 H), 5.40 (dd, *J* = 2.1, 10.0 Hz, 1 H), 4.84 (d, *J* = 11.4 Hz, 1 H), 4.76 (dd, *J* = 5.4, 9.5 Hz, 1 H), 4.73 (d, *J* = 11.7 Hz, 1 H), 3.72 (t, *J* = 9.7

Hz, 1 H), 2.56 (s, 1 H), 2.30–2.23 (m, 2 H), 1.77 (ddd, J = 2.5, 4.0, 6.8 Hz, 1 H), 1.26 (s, 9 H), 0.90 (s, 9 H), 0.28 (s, 3 H), 0.26 (s, 3 H), 0.01 (s, 6 H)

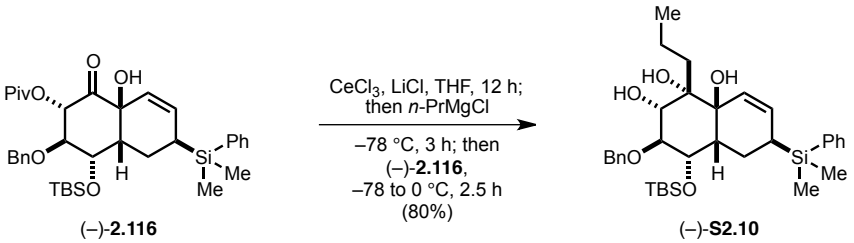
^{13}C NMR (125 MHz, C_6D_6) δ: 201.1, 177.6, 139.1, 137.8, 134.1, 132.1, 129.6, 128.6, 128.5, 127.6, 127.1, 126.3, 81.5, 78.2, 76.9, 75.3, 70.9, 44.6, 39.0, 27.4, 27.0, 26.3, 19.4, 18.1, –3.4, –3.5, –4.3.

FTIR (thin film) cm^{-1}: 3449, 3026, 2956, 2930, 2904, 2857, 1743, 1718, 1644, 1480, 1461, 1428, 1397, 1360, 1285, 1252, 1216, 1158, 1104, 1030, 1006, 985, 940, 892, 838, 815, 759, 700.

HRMS (ESI) (*m/z*) calc'd for $C_{36}H_{52}NaO_6Si_2$ $[M+Na]^+$: 659.3195, found 659.3197.

$[\alpha]_D^{23}$: –116.9 (c = 2.39, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.28 (UV, CAM).



Triol (–)-S2.10:

A 2-L round-bottomed flask was charged with anhydrous cerium(III) chloride (16.0 g, 65.1 mmol, 15.0 equiv) and lithium chloride (5.51 g, 130 mmol, 30.0 equiv), and heated to 145 °C under reduced pressure (0.05 Torr) for 2.5 h. The flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (651 mL) was introduced via cannula over 15 min. The resultant heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –78 °C before a solution of *n*-propylmagnesium chloride in Et_2O (1.75 M, 30.0 mL, 52.1 mmol, 12.0 equiv) was added dropwise via syringe over 10 min. The resultant yellow slurry was stirred for 3 h at –78 °C. A solution of (–)-**2.116** (2.76 g, 4.34 mmol, 1.00 equiv) in THF (22 mL) at –78 °C was then transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 10 min. The transfer was completed with two additional portions of THF (10 mL). The resultant mixture was gradually allowed to warm to 0 °C over 1 h and stirred at 0 °C for an additional 1.5 h. Saturated aqueous ammonium chloride solution (300 mL) was then cautiously added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (100 mL) and EtOAc (3 × 150 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow syrup was purified by flash column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford triol (–)-**S2.10** (2.07 g, 80%) as a colorless gel.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.54–7.48 (m, 2 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.27–7.20 (m, 3 H), 7.17 (t, *J* = 7.4 Hz, 2 H), 7.08 (t, *J* = 7.3 Hz, 1 H), 5.75 (dd, *J* = 3.6, 10.2 Hz, 1 H), 5.35 (dd, *J* = 2.6, 10.2 Hz, 1 H), 4.94 (d, *J* = 11.8 Hz, 1 H), 4.72 (d, *J* = 11.8 Hz, 1 H), 4.35 (dd, *J* = 5.8, 9.9 Hz, 1 H), 3.95 (dd, *J* = 4.8, 9.1 Hz, 1 H), 3.77 (t, *J* = 9.5 Hz, 1 H), 2.58 (dt, *J* = 8.5, 14.1 Hz, 1 H), 2.30 (dd, *J* = 4.5, 13.7 Hz, 1 H), 2.18 (dd, *J* = 2.3, 4.6 Hz, 1 H), 1.93 (td, *J* = 3.2, 8.3 Hz, 1 H), 1.88 (td, *J* = 5.1, 14.6 Hz, 1 H), 1.82 (dt, *J* = 2.1, 12.2 Hz, 1 H), 1.78–1.63 (m, 2 H), 1.56–1.44 (m, 1 H), 0.99 (s, 9 H), 0.93 (t, *J* = 7.1 Hz, 3 H), 0.34 (s, 3 H), 0.33 (s, 3 H), 0.15 (s, 3 H), 0.05 (s, 3 H).

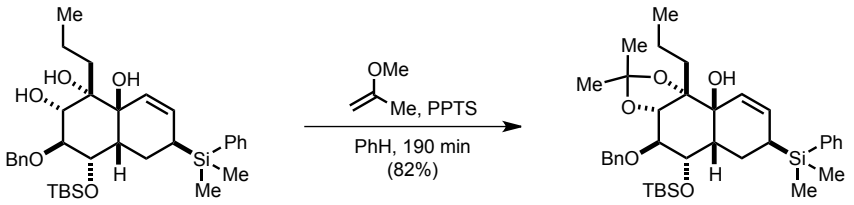
^{13}C NMR (125 MHz, C_6D_6) δ: 139.9, 138.3, 134.3, 133.7, 129.5, 128.7, 128.6, 128.2, 127.6, 127.5, 81.8, 78.4, 75.7, 75.6, 75.1, 72.1, 48.8, 39.3, 26.5, 26.4, 19.8, 18.9, 18.2, 15.6, –3.4, –3.7, –4.2, –4.2.

FTIR (thin film) cm^{-1}: 3461, 3069, 3024, 2957, 2931, 2895, 2857, 1471, 1428, 1253, 1217, 1115, 970, 836, 736, 701.

HRMS (ESI) (*m/z*) calc'd for $C_{34}H_{52}NaO_5Si_2$ $[M+Na]^+$: 619.3251, found 619.3264.

$[\alpha]_D^{23}$: –102.5 (*c* = 2.06, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.25 (UV, CAM).



(–)-**S2.10** (+)-**2.117**

Acetonide (+)-**2.117**:

A 100 mL round-bottomed flask was charged with (–)-**S2.10** (1.79 g, 3.00 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before dry benzene (60 mL) was introduced. 2-Methoxypropene (5.75 mL, 60.0 mmol, 20.0 equiv) and pyridinium *p*-toluenesulfonate (75.4 mg, 0.300 mmol, 0.100 equiv) were sequentially added to the vigorously stirred solution at ambient temperature. After 190 min, saturated aqueous sodium bicarbonate solution (30 mL) was added to the stirred reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (150 mL) and brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a yellow syrup. The product was purified by flash column chromatography (silica gel, eluent: gradient, 5 → 10% EtOAc in hexanes) to afford acetonide (+)-**2.117** (1.57 g, 82%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, C_6D_6) δ: 7.53–7.49 (m, 2 H), 7.43 (d, *J* = 7.0 Hz, 2 H), 7.25–7.16 (m, 5 H), 7.08 (t, *J* = 7.3 Hz, 1 H), 6.06 (dd, *J* = 2.0, 10.0 Hz, 1 H), 5.84 (dd, *J* = 1.9, 10.2 Hz, 1 H), 4.98 (d, *J* = 11.9 Hz, 1 H), 4.73 (d, *J* = 11.8 Hz, 1 H), 4.12 (dd, *J* = 8.1, 11.1 Hz, 1 H), 4.09 (d, *J* = 6.2 Hz, 1 H), 3.99 (dd, *J* = 6.1, 11.1 Hz, 1 H), 2.36–2.28 (m, 2 H), 2.05–1.97 (m, 2 H), 1.78 (dtdd, *J* = 5.2, 7.2, 12.6, 19.9 Hz, 1 H), 1.71–1.59 (m, 1 H), 1.52 (dd, *J* = 4.0, 14.3 Hz, 1 H), 1.48 (s, 3 H), 1.29 (s, 3 H), 0.97 (s, 9 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.32 (s, 3 H), 0.31 (s, 3 H), 0.15 (s, 3 H), 0.09 (s, 3 H).

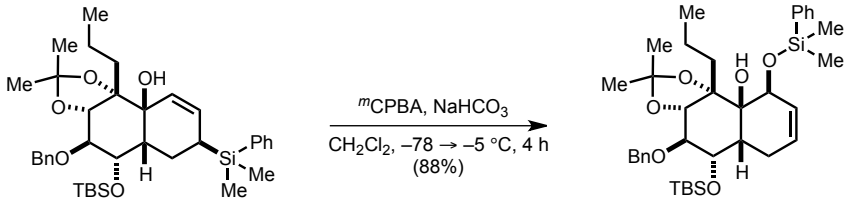
^{13}C NMR (125 MHz, C_6D_6) δ: 139.6, 137.8, 134.4, 131.4, 130.4, 129.5, 128.4, 128.3, 128.2, 127.5, 108.9, 87.5, 86.8, 80.6, 73.0, 72.6, 69.8, 43.0, 39.9, 27.6, 27.0, 26.4, 24.2, 20.8, 18.7, 18.6, 15.4, –4.08, –4.14, –4.5, –4.9.

FTIR (thin film) cm^{-1}: 3483, 3458, 3007, 2957, 2929, 2856, 1461, 1428, 1380, 1253, 1209, 1113, 1086, 1032, 871, 849, 835, 812, 760, 736, 700, 669.

HRMS (ESI) (*m/z*) calc'd for $C_{37}H_{56}NaO_5Si_2$ $[M+Na]^+$: 659.3558, found 659.3536.

$[\alpha]_D^{23}$: +10.2 (*c* = 1.13, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.63 (UV, CAM, anis).



(+)-**2.117** (+)-**2.118**

Silyl ether (+)-**2.118**:

A 200 mL round-bottomed flask was charged with (+)-**2.117** (1.73 g, 2.71 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before CH_2Cl_2 (54 mL) was introduced. Sodium bicarbonate (683 mg, 8.13 mmol, 3.00 equiv) was added to the stirred solution at ambient temperature, and the resultant heterogeneous mixture was cooled to –78 °C. A separate 25-mL round-bottomed flask was charged with *m*CPBA (77 wt. %, 1.22 g, 5.43 mmol, 2.00 equiv) and diluted with CH_2Cl_2 (10 mL). The resultant solution was then transferred dropwise via cannula to the stirred, cooled reaction mixture over 5 min. The transfer was completed with two additional portions of CH_2Cl_2 (5 mL). The resultant heterogeneous reaction mixture was warmed to –5 °C. After 4 h, saturated aqueous sodium sulfite solution (50 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (200 mL), water (200 mL), and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a colorless syrup. The product was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford silyl ether (+)-**2.118** (1.55 g, 88%) as a colorless flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61–7.57 (m, 2 H), 7.44–7.36 (m, 5 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 5.82 (dd, *J* = 3.6, 9.9 Hz, 1 H), 5.67 (ddd, *J* = 1.6, 3.3, 9.4 Hz, 1 H), 4.86 (d, *J* = 11.9 Hz, 1 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 4.34 (d, *J* = 4.7 Hz, 1 H), 4.26 (dd, *J* = 4.5, 9.4 Hz, 1 H), 4.05 (d, *J* = 5.6 Hz, 1 H), 3.65 (dd, *J* = 5.4, 9.4 Hz, 1 H), 3.53 (s, 1 H), 2.31 (td, *J* = 5.6, 18.7 Hz, 1 H), 2.20–2.10 (m,

1 H), 2.03–1.93 (m, 2 H), 1.59–1.51 (m, 1 H), 1.40–1.23 (m, 8 H), 0.90 (s, 9 H), 0.78 (t, J = 7.3 Hz, 3 H), 0.48 (s, 3 H), 0.45 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

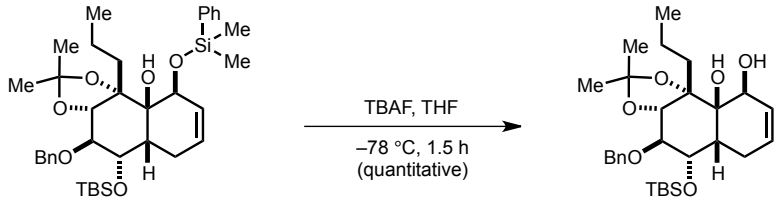
^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.0, 137.3, 133.5, 130.2, 129.9, 128.0, 127.94, 127.85, 127.09, 127.08, 109.3, 88.0, 86.4, 82.1, 73.2, 72.9, 70.5, 67.3, 43.1, 40.3, 29.0, 28.3, 25.9, 24.8, 18.2, 18.1, 15.0, –0.5, –0.7, –4.5, –4.8.

FTIR (thin film) cm^{-1}: 3504, 3027, 3006, 2956, 2930, 2892, 2856, 1461, 1429, 1378, 1368, 1291, 1254, 1234, 1118, 1102, 1060, 1040, 959, 918, 867, 852, 836, 760, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{37}H_{56}NaO_6Si_2$ $[M+Na]^+$: 675.3508, found 675.3514 .

$[\alpha]_D^{23}$: +79.8 (c = 1.19, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.65 (UV, CAM).



(+)-**2.118** (+)-**S2.11**

Allylic alcohol (+)-**S2.11**:

A 50-mL round-bottomed flask was charged with (+)-**2.118** (1.55 g, 2.37 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (24 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of tetrabutylammonium fluoride in THF (1.0 M, 3.56 mL, 3.56 mmol, 1.50 equiv) was added dropwise via syringe to the stirred, cooled reaction mixture over 5 min. After 1.5 h, saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a yellow oil. The product was purified by flash column chromatography (silica gel, eluent: gradient, 5 → 10% EtOAc in hexanes) to afford allylic alcohol (+)-**S2.11** (1.23 g, quantitative) as a colorless gel.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 5 H), 5.74–5.69 (m, 1 H), 5.40–5.36 (m, 1 H), 4.79–4.75 (m, 1 H), 4.68 (d, *J* = 11.9 Hz, 1 H), 4.58 (d, *J* = 12.1 Hz, 1 H), 4.39–4.36 (m, 1 H), 4.03 (d, *J* = 1.9 Hz, 1 H), 3.90–3.87 (m, 1 H), 3.70 (t, *J* = 2.1 Hz, 1 H), 3.40 (s, 1 H), 2.64 (ddd, *J* = 2.9, 6.9, 18.3 Hz, 1 H), 2.31 (dd, *J* = 2.1, 7.4 Hz, 1 H), 2.07 (ddd, *J* = 3.8, 12.5, 14.3 Hz, 1 H), 1.79–1.70 (m, 2 H), 1.62–1.55 (m, 4 H), 1.52–1.45 (m, 1 H), 1.41 (s, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.84 (s, 9 H), –0.03 (s, 3 H), –0.05 (s, 3 H).

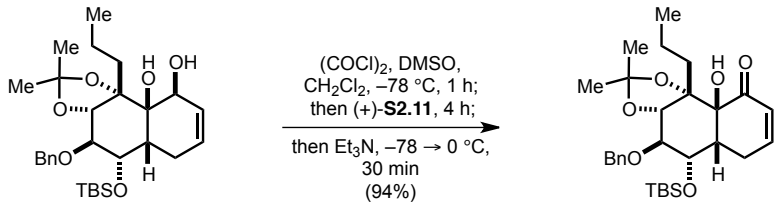
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 128.4, 127.8, 127.6, 127.3, 126.8, 107.3, 89.4, 79.8, 77.2, 75.4, 75.2, 72.3, 70.1, 38.0, 37.4, 27.6, 26.0, 25.9, 25.7, 17.9, 17.7, 15.0, –5.0, –5.2.

FTIR (thin film) cm^{-1}: 3517, 3498, 3028, 3008, 2951, 2929, 2901, 2858, 1429, 1384, 1336, 1298, 1215, 1110, 1072, 1030, 991, 939, 857, 837, 760, 670.

HRMS (ESI) (*m/z*) calc'd for $C_{29}H_{46}NaO_6Si$ $[M+Na]^+$: 541.2956, found 541.2930.

$[\alpha]_D^{23}$: +34.2 (*c* = 1.01, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.46 (UV, CAM).



Enone (+)-**2.119**:

A 100-mL round-bottomed flask was charged with dimethyl sulfoxide (2.70 mL, 37.9 mL, 16.0 equiv) and CH_2Cl_2 (26 mL), and cooled to –78 °C. A solution of oxalyl chloride (1.60 mL, 19.0 mmol, 8.00 equiv) in CH_2Cl_2 (3 mL) was added dropwise via cannula to the stirred reaction mixture. After 1 h, a solution of (+)-**2.11** (1.23 g, 2.37 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) was transferred dropwise via cannula to the stirred, cooled reaction mixture over 5 min. After 4 h, triethylamine (10.6 mL, 75.8 mmol, 32.0 equiv) was slowly added via syringe down the wall of the reaction vessel over 5 min. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 30 min, saturated aqueous ammonium chloride solution (30 mL) was added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was partitioned with EtOAc (50 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (250 mL) and brine (250 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a colorless syrup. The product was purified by flash column chromatography (silica gel, eluent: gradient, 5 → 10% EtOAc in hexanes) to afford enone (+)-**2.119** (1.15 g, 94%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 7.1 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 2 H), 7.26 (t, *J* = 7.4 Hz, 1 H), 6.97 (ddd, *J* = 2.3, 5.1, 10.1 Hz, 1 H), 6.20 (ddd, *J* = 0.9, 2.8, 10.2 Hz, 1 H), 4.91 (d, *J* = 11.8 Hz, 1 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.25 (s, 1 H), 4.16 (dd, *J* = 5.0, 9.4 Hz, 1 H), 4.06 (d, *J* = 5.7 Hz, 1 H), 3.75 (dd, *J* = 5.8, 9.6 Hz, 1 H), 2.68 (tdd, *J* = 2.6, 11.2, 19.9 Hz, 1 H), 2.57 (td, *J* = 6.0, 20.1 Hz, 1 H), 2.32 (td, *J* = 5.6, 10.9 Hz, 1 H), 2.04 (ddd, *J* = 7.9, 9.9, 15.0 Hz, 1 H), 1.55 (td, *J* = 7.9, 15.8 Hz, 1 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.21–1.14 (m, 2 H), 0.89 (s, 9 H), 0.80 (t, *J* = 7.4 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.9, 151.3, 138.7, 128.0, 127.9, 127.6, 127.2, 110.1, 88.0, 85.9, 81.6, 76.0, 73.1, 70.1, 47.9, 37.7, 29.0, 28.4, 26.2, 25.9, 18.0, 16.1, 14.6, –4.6, –4.9.

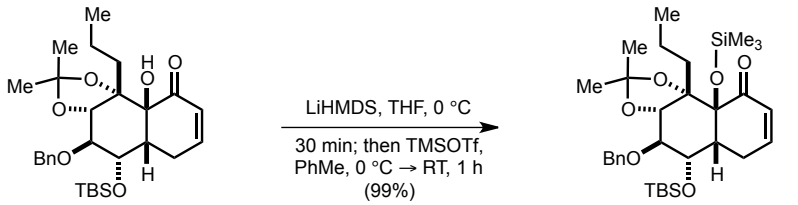
FTIR (thin film) cm^{-1}: 3465, 3006, 2955, 2930, 2889, 2856, 1678, 1460, 1380, 1255, 1231, 1214, 1110, 1031, 1006, 917, 854, 838, 761, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{29}H_{44}NaO_6Si$ $[M+Na]^+$: 539.2799, found 539.2797.

$[\alpha]_D^{23}$: +71.5 (*c* = 1.18, $CHCl_3$).

M.**p**.: 99–100 °C (Et_2O).

TLC (15% EtOAc in hexanes), R_f: 0.55 (UV, CAM).



(+)-**2.119** AB/HG-Enone (+)-**2.68**

AB/HG-Enone (+)-**2.68**:

A 100-mL round-bottomed flask was charged with (+)-**2.119** (1.15 g, 2.23 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (45 mL) was introduced, and the resultant solution cooled to 0 °C. A freshly prepared solution of lithium hexamethyldisilazide in THF (1.0 M, 4.45 mL, 4.45 mmol, 2.00 equiv) was added dropwise via syringe to the stirred reaction mixture over 2 min. After 30 min, a solution of trimethylsilyl trifluoromethanesulfonate (1.21 mL, 6.69 mmol, 3.00 equiv) in PhMe (6.7 mL) was added dropwise via cannula to the stirred, cooled reaction mixture over 5 min. After 30 min, the reaction was warmed to ambient temperature. After an additional 30 min, saturated aqueous ammonium chloride solution (25 mL) was added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to furnish a yellow oil. The product was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford AB/HG-enone (+)-**2.68** (1.30 g, 99%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.26 (t, *J* = 7.4 Hz, 1 H), 6.88 (ddd, *J* = 2.3, 5.1, 10.3 Hz, 1 H), 6.11 (dd, *J* = 2.1, 10.0 Hz, 1 H), 4.91 (d, *J* = 11.6 Hz, 1 H), 4.70 (d, *J* = 11.6 Hz, 1 H), 4.15 (dd, *J* = 5.0, 9.4 Hz, 1 H), 4.07 (d, *J* = 5.7 Hz, 1 H), 3.74 (dd, *J* = 5.7, 9.5 Hz, 1 H), 2.65 (tdd, *J* = 2.6, 11.0, 19.7 Hz, 1 H), 2.57 (td, *J* = 5.8, 19.9 Hz, 1 H), 2.34 (td, *J* = 5.7, 11.0 Hz, 1 H), 1.91 (ddd, *J* = 5.4, 12.3, 14.6 Hz, 1 H), 1.70 (ddd, *J* = 3.7, 12.8, 14.6 Hz, 1 H), 1.36 (s, 6 H), 1.24–1.14 (m, 2 H), 0.90 (s, 9 H), 0.80 (t, *J* = 7.4 Hz, 3 H), 0.16 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

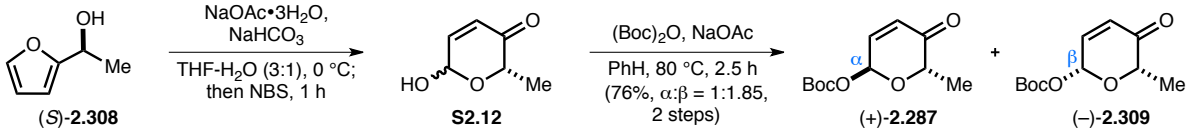
^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.3, 149.1, 138.7, 129.4, 128.1, 128.0, 127.3, 109.9, 87.1, 86.2, 82.0, 81.1, 73.3, 70.4, 49.1, 38.3, 28.9, 28.4, 26.7, 25.9, 18.1, 16.7, 14.6, 2.2, –4.5, –4.6.

FTIR (thin film) cm^{-1}: 3010, 2955, 2931, 2897, 2857, 1689, 1462, 1380, 1251, 1231, 1126, 1034, 925, 851, 761.

HRMS (ESI) (*m/z*) calc'd for $C_{32}H_{52}NaO_6Si_2$ $[M+Na]^+$: 611.3195, found 611.3223.

$[\alpha]_D^{23}$: +72.2 (*c* = 1.09, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.69 (UV, CAM).



α-Boc-pyranone (+)-2.287 and β-Boc-pyranone (–)-2.309:

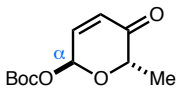
A 2-L round-bottomed flask was charged with (*S*)-1-(furan-2-yl)ethanol (**2.308**)[232] and diluted with THF (455 mL) and H_2O (155 mL). The resultant solution was cooled to 0 °C and sodium bicarbonate (65.1 g, 775 mmol, 1.83 equiv), sodium acetate trihydrate (106 g, 779 mmol, 1.84 equiv), and *N*-bromosuccinimide (76.8 g, 432 mmol, 1.02 equiv) were sequentially added in single portions to the reaction vessel. The resultant inhomogeous yellow reaction mixture stirred for 1 h at 0 °C open to the air. Saturated aqueous sodium bicarbonate solution (800 mL) was then added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 600 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford (2*S*)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (**S2.12**)[233] as yellow oil, which was used immediately without further purification.

A 2-L round-bottomed flask was charged with **S2.12** and azeotropically dried with three portions of benzene. Benzene (846 mL), di-*tert*-butyl dicarbonate (141 g, 648 mmol, 1.53 equiv), and anhydrous sodium acetate (38.5 g, 470 mmol, 1.11 equiv) were introduced. The reaction vessel was equipped with a reflux condenser and the reaction mixture was warmed to 80 °C. After 2.5 h, the reaction mixture was allowed to cool to ambient temperature and poured into saturated aqueous sodium bicarbonate solution (1 L). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 600 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 7%

[232] (*S*)-1-(furan-2-yl)ethanol (**2.308**) was prepared in 90-g batches through the reported procedure: Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2,* 1749–1751.

[233] For spectroscopic and physical characterization, see: Shan, S.; Xing, Y.; O'Doherty, G. A. *J. Org. Chem.*, **2009**, *74*, 5961–596

EtOAc in hexanes) to afford α-Boc-pyranone (+)-**2.287** (25.7 g, 27%) and β-Boc-pyranone (–)-**2.309** (47.7 g, 49%) as a colorless solids.



(+)-**2.287**

α-Boc-pyranone (+)-2.287:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 3.7, 10.2 Hz, 1 H), 6.34 (d, *J* = 3.6 Hz, 1 H), 6.20 (d, *J* = 10.2 Hz, 1 H), 4.65 (q, *J* = 6.7 Hz, 1 H), 1.52 (s, 9 H), 1.41 (d, *J* = 6.7 Hz, 3 H).

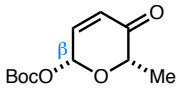
^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.7, 151.8, 140.9, 128.3, 89.1, 83.6, 72.1, 27.6, 15.2.

FTIR (thin film) cm^{-1}: 2985, 2941, 2878, 1751, 1703, 1476, 1454, 1396, 1372, 1333, 1278, 1258, 1159, 1105, 1091, 1058, 1030, 944, 860, 842, 759.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{16}NaO_5$ $[M+Na]^+$: 251.0890, found 251.0896.

$[\alpha]_D^{23}$: +89.1 (*c* = 1.38, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.45 (UV, CAM).



(–)-**2.309**

β-Boc-pyranone (–)-2.309:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.89 (dd, *J* = 2.6, 10.4 Hz, 1 H), 6.37 (s, 1 H), 6.21 (d, *J* = 10.4 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 1 H), 1.55–1.49 (m, 12 H).

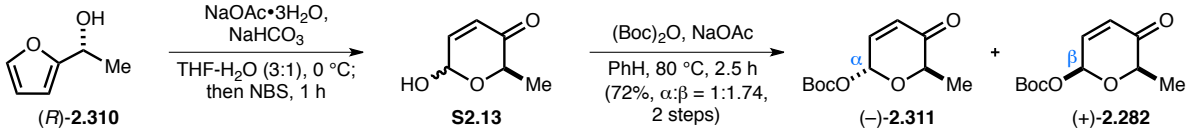
^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.9, 151.7, 142.8, 128.2, 89.9, 83.6, 75.7, 27.6, 18.6.

FTIR (thin film) cm^{-1}: 2986, 2940, 2878, 1754, 1703m 1477, 1454, 1372, 1278, 1256, 1162, 1128, 1069, 1033, 940, 855, 761, 667.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{16}NaO_5$ $[M+Na]^+$: 251.0890, found 251.0897.

$[\alpha]_D^{23}$: –41.8 (*c* = 1.08, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.38 (UV, CAM).



α-Boc-pyranone (–)-2.311 and β-Boc-pyranone (+)-2.282:

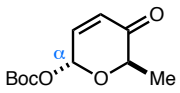
A 2-L round-bottomed flask was charged with (*R*)-1-(furan-2-yl)ethanol (**2.310**)[234] and diluted with THF (547 mL) and H_2O (186 mL). The resultant solution was cooled to 0 °C and sodium bicarbonate (78.2 g, 931 mmol, 1.83 equiv), sodium acetate trihydrate (127 g, 936 mmol, 1.84 equiv), and *N*-bromosuccinimide (92.3 g, 519 mmol, 1.02 equiv) were sequentially added in single portions to the reaction vessel. The resultant inhomogeous yellow reaction mixture stirred for 1 h at 0 °C open to the air. Saturated aqueous sodium bicarbonate solution (800 mL) was then added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 600 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford (2*R*)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (**S2.13**)[235] as yellow oil, which was used immediately without further purification.

A 2-L round-bottomed flask was charged with **S2.13** and azeotropically dried with three portions of benzene. Benzene (1.02 L), di-*tert*-butyl dicarbonate (170 g, 778 mmol, 1.53 equiv), and anhydrous sodium acetate (46.3 g, 565 mmol, 1.11 equiv) were introduced. The reaction vessel was equipped with a reflux condenser and the reaction mixture was warmed to 80 °C. After 2.5 h, the reaction mixture was allowed to cool to ambient temperature and poured into saturated aqueous sodium bicarbonate solution (1 L). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 600 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 7%

[234] (*R*)-1-(furan-2-yl)ethanol (**2.310**) was prepared in 90-g batches through the reported procedure: Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2,* 1749–1751.

[235] For spectroscopic and physical characterization see: Shan, S.; Xing, Y.; O'Doherty, G. A. *J. Org. Chem.*, **2009**, *74*, 5961–596.

EtOAc in hexanes) to afford α-Boc-pyranone (–)-**2.311** (30.5 g, 26%) and β-Boc-pyranone (+)-**2.282** (53.1 g, 46%) as a colorless solids.



(–)-**2.311**

α-Boc-pyranone (–)-**2.311**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 3.7, 10.2 Hz, 1 H), 6.34 (d, *J* = 3.7 Hz, 1 H), 6.20 (d, *J* = 10.2 Hz, 1 H), 4.65 (q, *J* = 6.8 Hz, 1 H), 1.53 (s, 9 H), 1.42 (d, *J* = 6.8 Hz, 3 H).

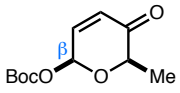
^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.7, 151.8, 140.9, 128.4, 89.2, 83.6, 72.2, 27.6, 15.2.

FTIR (thin film) cm^{-1}: 2985, 2942, 2877, 1751, 1703, 1476, 1451, 1396, 1372, 1333, 1278, 1257, 1159, 1106, 1090, 1058, 1030, 945, 861, 841, 760.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{16}NaO_5$ $[M+Na]^+$: 251.0890, found 251.0889.

$[\alpha]_D^{23}$: –100.5 (*c* = 1.15, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.45 (UV, CAM).



(+)-**2.282**

β-Boc-pyranone (+)-**2.282**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.89 (dd, *J* = 2.6, 10.4 Hz, 1 H), 6.37 (s, 1 H), 6.21 (d, *J* = 10.4 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 1 H), 1.55–1.49 (m, 12 H).

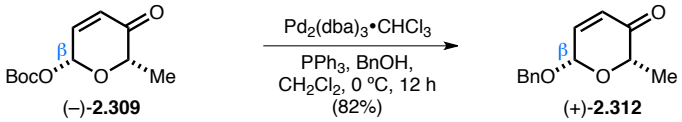
^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.9, 151.7, 142.8, 128.2, 89.9, 83.6, 75.7, 27.6, 18.6.

FTIR (thin film) cm^{-1}: 2985, 2941, 2877, 1753, 1703, 1477, 1454, 1372, 1277, 1255, 1161, 1128, 1068, 1032, 1007, 941, 855, 791, 761.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{16}NaO_5$ $[M+Na]^+$: 251.0890, found 251.0884.

$[\alpha]_D^{23}$: +44.5 (*c* = 1.54, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.38 (UV, CAM).



β-Benzyl acetal (+)-**2.312**:

A 500-mL round-bottomed flask was charged with β-Boc-pyranone ((–)-**2.309**) (20.0 g, 87.6 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (88 mL) and benzyl alcohol (18.1 mL, 175 mmol, 2.0 equiv) were introduced and the resultant solution cooled to 0 °C. A separate 100-mL round-bottomed flask was charged with tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (1.13 g, 1.10 mmol, 0.0125 equiv) and triphenylphosphine (1.15 g, 4.38 mmol, 0.05 equiv) and the flask was evacuated and then backfilled with argon. The process was repeated three times before CH_2Cl_2 (56 ml) was introduced. The resultant red reaction mixture was cooled to 0 °C and transferred dropwise via cannula to the 500-mL reaction vessel over 10 min. After 12 h, saturated aqueous sodium bicarbonate solution (200 mL) was added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 8% EtOAc in hexanes) to afford β-benzyl acetal (+)-**2.312** (15.7 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.29 (m, 5 H), 6.91 (dd, J = 1.7, 10.3 Hz, 1 H), 6.14 (dd, J = 1.0, 10.3 Hz, 1 H), 5.40 (s, 1 H), 4.95 (d, J = 11.7 Hz, 1 H), 4.69 (d, J = 11.7 Hz, 1 H), 4.24 (q, J = 6.8 Hz, 1 H), 1.53 (d, J = 6.9 Hz, 3 H).

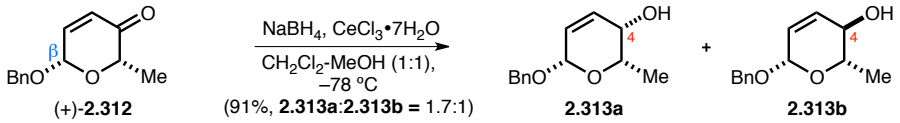
^{13}C NMR (125 MHz, $CDCl_3$) δ:196.8, 146.5, 136.8, 128.5, 128.1, 128.03, 127.99, 94.3, 75.2, 70.1, 17.2.

FTIR (thin film) cm^{-1}: 3385, 3064, 3032, 2987, 2939, 2873, 2825, 1698, 1498, 1455, 1374, 1302, 1223, 1165, 1148, 1116, 1099, 1058, 1036, 1024, 907, 803, 755, 736, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{14}NaO_3$ $[M+Na]^+$: 241.0835, found 241.0830.

$[\alpha]_D^{23}$: +32.0 (*c* = 1.71, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.375 (UV, CAM).



Allylic alcohol 2.313a/2.313b:

A 500-mL round-bottomed flask was charged with (+)-**2.312** (19.0 g, 87.2 mmol, 1.00 equiv), CH_2Cl_2 (90 mL), MeOH (90 mL) and cerium(III) chloride heptahydrate (13.0 g, 34.9 mmol, 0.40 equiv). The resultant yellow mixture was stirred at ambient temperature until homogeneous and then cooled to –78 °C. Sodium borohydride (4.95 g, 131 mmol, 1.50 equiv) was added to the stirred reaction mixture in a single portion. After 3 h, saturated aqueous sodium bicarbonate solution (250 mL) was carefully added to the cold reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (100 mL) and Et_2O (3 × 50 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow syrup was purified by flash column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford an inseparable mixture of allylic alcohols **2.313a** and **2.313b** (17.5 g, 91%, **2.313a**:**2.313b** = 1.7:1) as a colorless oil.[236]

^{1}H NMR (400 MHz, $CDCl_3$) allylic alcohol **2.313a** δ: 7.42–7.27 (m, 5 H), 6.17 (ddd, *J* = 1.3, 5.1, 10.0 Hz, 1 H), 5.87 (d, *J* = 10.1 Hz, 1 H), 5.13 (d, *J* = 1.1 Hz, 1 H), 4.92 (d, *J* = 11.9 Hz, 1 H), 4.66 (d, *J* = 11.9 Hz, 1 H), 3.75 (dq, *J* = 2.1, 6.5 Hz, 1 H), 3.71–3.68 (m, 1 H), 1.74 (d, *J* = 11.1 Hz, 1 H), 1.34 (d, *J* = 6.5 Hz, 3 H); allylic alcohol **2.313b** δ: 7.42–7.27 (m, 5 H), 5.98 (td, *J* = 2.1, 10.2 Hz, 1 H), 5.82 (td, *J* = 1.4, 10.2 Hz, 1 H), 5.19 (q, *J* = 1.6 Hz, 1 H), 4.87 (d, *J* = 11.8 Hz, 1 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 3.97–3.89 (m, 1 H), 3.68–3.64 (m, 1 H), 1.69 (d, *J* = 7.9 Hz, 1 H), 1.40 (d, *J* = 6.4 Hz, 3 H).

[236] Stereochemical assignment based on previous report: Iyer, A. K. V.; Zhou, M.; Azad, N.; Elbaz, H.; Wang, L.; Rogalsky, D. K.; Rojanasakul, Y.; O' Doherty, G. A.; Langenhan, J. M. *ACS Med. Chem. Lett.*, **2010**, *1*, 326–330.

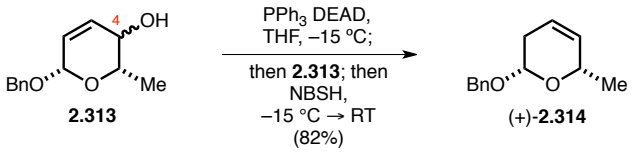
^{13}C NMR (100 MHz, $CDCl_3$) allylic alcohol **2.313a** δ: 137.4, 131.3, 130.5, 128.4 (2C), 127.9 (2C), 127.7, 96.9, 71.4, 69.9, 64.7, 16.6; allylic alcohol **2.313b** δ: 137.6, 132.1, 128.6, 128.3 (2C), 127.9 (2C), 127.6, 95.5, 74.3, 69.2, 68.2, 18.4.

FTIR (thin film) cm^{-1}: 3410, 3064, 3033, 2980, 2935, 2871, 1498, 1454, 1408, 1379, 1320, 1254, 1172, 1136, 1109, 1053, 1025, 1010, 983, 909, 868, 790, 736, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{16}NaO_3$ $[M+Na]^+$: 243.0992, found 243.1008.

$[\alpha]_D^{23}$: +32.0 (*c* = 1.71, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.20 (UV, CAM).



Dihydropyran (+)-**2.314**:

A 500-mL round-bottomed flask was charged with triphenylphosphine (17.9 g, 68.2 mmol, 1.5 equiv) and THF (91 mL) and cooled to –15 °C. A solution of diethyl azodicarboxylate in PhMe (40 wt. (silica gel, eluent:, 29.0 mL, 27.7 g, 63.6 mmol, 1.40 equiv) was added via dropwise via syringe over 5 min. A separate 100-mL round-bottomed flask was charged with **2.313** and azeotropically dried with three portions of benzene. THF (35 mL) was introduced and the resultant solution was added dropwise to the cooled reaction mixture via cannula over 5 min. The transfer was completed with two additional portions of THF (5 mL). After 15 min a solution of 2-nitrobenzenesulfonylhydrazide[237] (14.8 g, 68.2 mmol, 1.50 equiv) in THF (74 mL), prepared in a separate 250-mL round-bottomed flask, was added dropwise to the cooled reaction mixture via cannula over 15 min. The reaction mixture stirred for 1 h at –15 °C and then was allowed to warm to ambient temperature over 12 h. The solvent was removed under reduced pressure to furnish a brown residue, which was dissolved in MeOH (100 mL) and H_2O (100 mL) and extracted with pentanes (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford dihydropyran (+)-**2.314** (9.12 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.27 (m, 5 H), 5.68 (tdd, *J* = 2.3, 4.9, 7.4 Hz, 1 H), 5.63–5.55 (m, 1 H), 4.94 (d, *J* = 12.1 Hz, 1 H), 4.74 (dd, *J* = 3.5, 7.8 Hz, 1 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.41–4.27 (m, 1 H), 2.32–2.22 (m, 1 H), 2.22–2.12 (m, 1 H), 1.32 (d, *J* = 6.8 Hz, 3 H) .

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.8, 130.8, 128.3, 127.9, 127.6, 122.4, 97.7, 70.6, 69.7, 30.9, 21.1.

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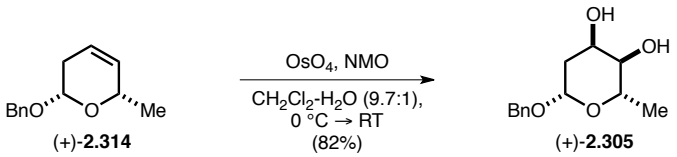
[237] 2-Nitrobenzenesulfonylhydrazide was prepared according to the reported procedure: Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

FTIR (thin film) cm^{-1}: 3034, 2977, 2931, 2911, 2836, 1498, 1455, 1432, 1392, 1365, 1312, 1204, 1158, 1107, 1081, 1028, 881, 780, 752, 698, 681, 619.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{16}NaO_2$ $[M+Na]^+$: 227.1043, found 227.1000.

$[\alpha]_D^{23}$: +127.1 (*c* = 1.18, $CHCl_3$).

TLC (5% EtOAc in hexanes), R_f: 0.33 (UV, CAM).



Diol (+)-2.305:

A 100-mL round-bottomed flask was charged with dihydropyran (+)-**2.314** (3.0 g, 14.7 mmol, 1.00 equiv), CH_2Cl_2 (29.4 mL) and a solution of NMO in H_2O (50% wt., 6.09 mL, 6.88 g, 29.4 mmol, 2.00 equiv) and cooled to 0 °C. OsO_4 (38.1 mg, 15.0 μmol, 0.01 equiv) was added in a single portion and the resultant yellow solution warmed to ambient temperature. After 6 h, a mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (10:1, 40 mL) and Florisil (5 g) were added to the stirred reaction mixture. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with Et_2O (3 × 50 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography (silica gel, eluent: gradient, 35 → 40% EtOAc in hexanes) to afford diol (+)-**2.305** (3.69 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 5 H), 4.91 (dd, *J* = 1.8, 9.2 Hz, 1 H), 4.90 (d, *J* = 11.7 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.14 (br. s., 1 H), 3.76 (qd, *J* = 6.2, 9.1 Hz, 1 H), 3.40–3.31 (m, 1 H), 2.26–2.18 (m, 1 H), 2.14 (d, *J* = 13.9 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.85–1.76 (m, 1 H), 1.61–1.55 (m, 1 H), 1.35 (d, *J* = 6.2 Hz, 3 H).

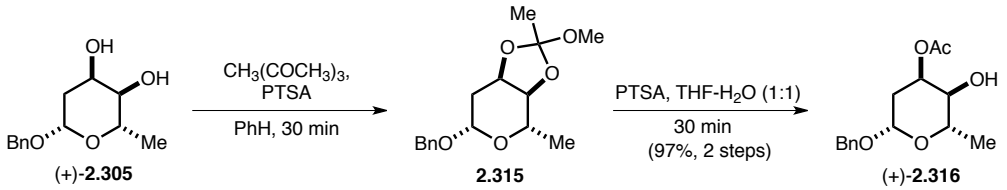
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.5, 128.3, 127.9, 127.7, 96.9, 72.9, 70.5, 69.5, 67.8, 37.6, 18.1.

FTIR (thin film) cm^{-1}: 3416, 2973, 2933, 2884, 1639, 1454, 1365, 1216, 1163, 1137, 1074, 1006, 910, 867, 822, 757, 699, 666.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097, found 261.1074.

$[\alpha]_D^{23}$: +70.3 (*c* = 1.55, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.12 (UV, CAM).



Alcohol (+)-2.316:

A 100-mL round-bottomed flask was charged with a solution of diol (+)-**2.305** (2.38 g, 9.45 mmol, 1.00 equiv) and benzene (19 mL). Trimethyl orthoformate (6.04 mL, 47.3 mmol, 5.00 equiv) and *para*-toluenesulfonic acid monohydrate (90.0 mg, 0.473 mmol, 0.05 equiv) were sequentially introduced to the stirred reaction mixture at ambient tempurature. After 30 min, the solvent was removed under reduced pressure to afford orthoester **2.315** as a tan residue, which was immediately dissolved in THF (11.3 mL) and H_2O (11.3 mL). *para*-Toluenesulfonic acid monohydrate (4.49 g, 23.6 mmol, 2.50 equiv) was introduced in a single portion to the stirred reaction mixture at ambient temperature. After 30 min, saturated aqueous sodium bicarbonate (50 mL) was added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 35 → 45% EtOAc in hexanes) to afford alcohol (+)-**2.316** (2.58 g, 97%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 4.3 Hz, 5 H), 5.30 (q, *J* = 3.2 Hz, 1 H), 4.91 (d, *J* = 11.9 Hz, 1 H), 4.83 (dd, *J* = 2.0, 9.4 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 3.73 (qd, *J* = 6.3, 9.2 Hz, 1 H), 3.47 (ddd, *J* = 3.3, 6.0, 9.1 Hz, 1 H), 2.15 (td, *J* = 2.4, 14.2 Hz, 1 H), 2.11 (s, 3 H), 1.99–1.92 (m, 1 H), 1.88 (ddd, *J* = 3.0, 9.6, 14.3 Hz, 1 H), 1.36 (d, *J* = 6.2 Hz, 3 H).

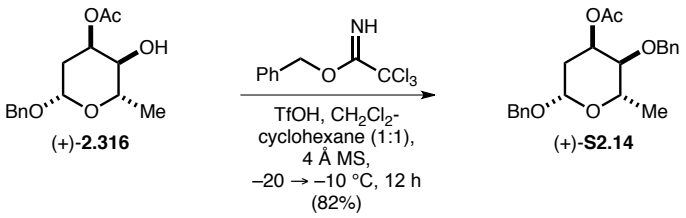
^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2, 137.5, 128.3, 127.7, 127.6, 96.9, 72.0, 70.8, 70.4, 70.2, 35.5, 21.0, 18.0.

FTIR (thin film) cm^{-1}: 3460, 3012, 2981, 2935, 2879, 2739, 1498, 1454, 1372, 1246, 1217, 1164, 1143, 1078, 1007, 867, 758, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{15}H_{20}NaO_5$ $[M+Na]^+$: 303.1203, found 303.1182.

$[\alpha]_D^{23}$: +47.3 (*c* = 1.06, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.24 (UV, CAM).



Benzyl ether (+)-S2.14:

A 25-mL round-bottomed flask was charged with alcohol (+)-**2.316** (429 mg, 1.53 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (10.2 mL), cyclohexane (5.1 mL), benzyl 2,2,2-trichloroacetimidate (854 µL, 4.59 mmol, 3.00 equiv), and 4 Å MS (100 mg) were introduced and the resultant mixture stirred at ambient temperature. After 1 h, the reaction mixture was cooled to –20 °C and freshly distilled trifluoromethanesulfonic acid (108 µL, 1.22 mmol, 0.80 equiv) was added dropwise via syringe. The resultant reaction mixture was allowed to warm to –10 °C. After 12 h, a saturated aqueous sodium bicarbonate solution (10 mL) was added and the resultant mixture was subsequently allowed to warm to ambient temperature, filtered through a pad of Celite, and rinsed with hexanes (3 × 20 mL). The layers of the filtrate were separated and the aqueous layer was extracted with hexanes (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10 → 15% EtOAc in hexanes) to afford an benzyl ether (+)-**S2.14** (464 mg, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 10 H), 5.61 (q, J = 2.6 Hz, 1 H), 4.91 (d, J = 11.8 Hz, 1 H), 4.87 (dd, J = 1.6, 9.5 Hz, 1 H), 4.67 (d, J = 11.2 Hz, 1 H), 4.57 (d, J = 11.8 Hz, 1 H), 4.40 (d, J = 11.2 Hz, 1 H), 3.87 (qd, J = 6.2, 9.2 Hz, 1 H), 3.18 (dd, J = 2.9, 9.3 Hz, 1 H), 2.15–2.06 (m, 4 H), 1.82 (ddd, J = 2.8, 9.7, 14.1 Hz, 1 H), 1.31 (d, J = 6.2 Hz, 3 H).

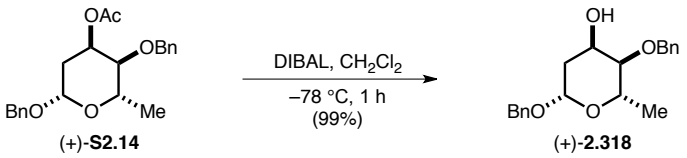
^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 137.6, 137.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 97.1, 78.5, 71.5, 70.5, 69.3, 66.0, 35.8, 21.1, 18.3.

FTIR (thin film) cm^{-1}: 3478, 3031, 3009, 2972, 2932, 2876, 1741, 1497, 1455, 1365, 1308, 1241, 1216, 1165, 1150, 1089, 1028, 1008, 910, 866, 755, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{22}H_{26}NaO_5$ $[M+Na]^+$: 393.1672, found 393.1659.

$[\alpha]_D^{23}$: +26.4 (*c* = 1.52, $CHCl_3$).

TLC (15% EtOAc in hexanes), R_f: 0.32 (UV, CAM).



Alcohol (+)-2.318:

A 50-mL round-bottomed flask was charged with a solution of benzyl ether (+)-**S2.14** (1.0 g, 2.70 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (13.5 mL) was introduced and the resultant solution was cooled to –78 °C. A freshly prepared solution of diisobutylaluminum hydride in CH_2CH_2 (1.0 M, 5.40 mL, 5.40 mmol, 2.00 equiv) was added dropwise via syringe to the stirred reaction mixture. After 1 h, saturated aqueous sodium bicarbonate solution (15 mL) was added to the cold reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (25 mL) and Et_2O (3 × 20 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 25 → 30% EtOAc in hexanes) to afford alcohol (+)-**2.318** (880 mg, 99%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.26 (m, 10 H), 4.93 (dd, *J* = 1.6, 9.5 Hz, 1 H), 4.89 (d, *J* = 11.8 Hz, 1 H), 4.64 (d, *J* = 11.5 Hz, 1 H), 4.57 (d, *J* = 6.8 Hz, 1 H), 4.54 (d, *J* = 6.5 Hz, 1 H), 4.24 (d, *J* = 2.8 Hz, 1 H), 3.84 (qd, *J* = 6.2, 9.2 Hz, 1 H), 3.17 (dd, *J* = 2.8, 9.3 Hz, 1 H), 2.39 (d, *J* = 1.2 Hz, 1 H), 2.25–2.16 (m, 1 H), 1.77–1.67 (m, 1 H), 1.33 (d, *J* = 6.2 Hz, 3 H).

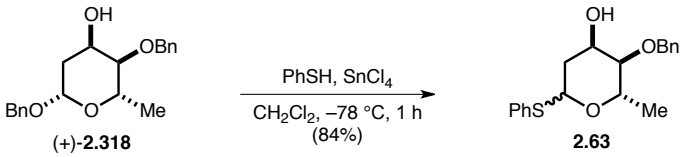
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.7, 137.4, 128.5, 128.3, 128.1, 127.91, 127.86, 127.6, 97.0, 80.5, 71.7, 70.6, 68.1, 64.6, 36.7, 18.2.

FTIR (thin film) cm^{-1}: 3031, 2974, 2934, 2875, 1741, 1498, 1455, 1370, 1317, 1242, 1218, 1167, 1153, 1093, 1073, 1030, 1014, 945, 912, 866, 756, 700, 667.

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{24}NaO_4$ $[M+Na]^+$: 351.1567, found 351.1551.

$[\alpha]_D^{23}$: +17.0 (*c* = 1.32, $CHCl_3$).

TLC (30% EtOAc in hexanes), R_f: 0.24 (UV, CAM).



Thiophenyl glycoside (2.63):

A 100-mL round-bottomed flask was charged with alcohol (+)-**2.318** (880 mg, 2.68 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (26.8 mL) and thiophenol (5.50 mL, 53.6 mmol, 20.0 equiv) were introduced and the resultant solution was cooled to –78 °C. A freshly prepared solution of tin(IV) tetrachloride in CH_2CH_2 (1.0 M, 4.02 mL, 4.02 mmol, 1.5 equiv) was added dropwise via syringe to the stirred reaction mixture over 5 min. After 1 h, saturated aqueous sodium bicarbonate solution (30 mL) was added to the cold reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (25 mL) and Et_2O (3 × 30 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers washed with brine (100 mL) and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography (silica gel, eluent: gradient, 20 → 30% EtOAc in hexanes) to afford an anomeric mixture of thiophenyl glycosides **2.63** (746 mg, 84%, α:β = 2:1), as a colorless oil. α- and β-thiophenyl glycosides **2.63a** and **2.63b** were inseparable by silica gel chromatography.[238]

^{1}H NMR (500 MHz, $CDCl_3$) α-thiophenyl glycoside **2.63a** δ: 7.51–7.18 (m, 8 H), 5.44 (d, *J* = 6.2 Hz, 1 H), 4.68 (d, *J* = 11.8 Hz, 1 H), 4.58 (d, *J* = 11.8 Hz, 1 H), 4.50 (qd, *J* = 6.3, 9.3 Hz, 1 H), 4.28–4.24 (m, 1 H), 3.19 (dd, *J* = 3.0, 9.3 Hz, 1 H), 2.59 (s, 1 H), 2.39 (dd, *J* = 2.9, 14.9 Hz, 1 H), 2.32–2.24 (m, 1 H), 1.29 (d, *J* = 6.3 Hz, 3 H); β-thiophenyl glycoside **2.63b** δ: 7.51–7.17 (m, 8 H), 5.19 (dd, *J* = 1.8, 11.8 Hz, 1 H), 4.66–4.61 (m, 1 H), 4.54 (d, *J* = 11.6 Hz, 1 H), 4.23 (q, *J* = 2.9 Hz, 1 H), 3.84 (qd, *J* = 6.3, 9.5 Hz, 1

[238] Stereochemical assignment of anomeric position based on $J_{DG1\text{-}DG2}$.

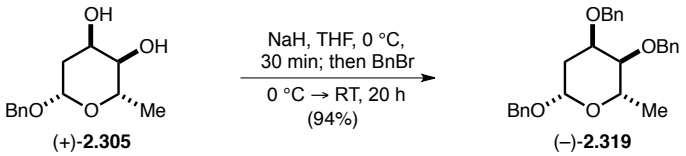
H), 3.16 (dd, *J* = 2.9, 9.5 Hz, 1 H), 2.43 (s, 1 H), 2.3 –2.24 (m, 1 H), 1.87 (tdd, *J* = 2.3, 11.9, 14.0 Hz, 1 H), 1.31 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) α-thiophenyl glycoside **2.63a** δ: 137.9, 137.5, 130.2, 128.7, 128.5, 128.0, 127.8, 126.4, 82.5, 80.1, 71.2, 63.5, 63.0, 36.4, 17.8; β-thiophenyl glycoside **2.63b** δ:137.3, 134.3, 131.1, 128.7, 128.5, 128.1, 127.9, 127.0, 80.0, 79.3, 71.5, 70.9, 64.4, 37.1, 18.4.

FTIR (thin film) cm^{-1}: 3056, 3045, 3032, 3015, 2872, 1564, 1481, 1454, 1439, 1086, 1076, 1027, 987, 972, 911, 857, 739, 692, 656.

HRMS (ESI) (*m/z*) calc'd for $C_{19}H_{22}NaO_3S$ $[M+Na]^+$: 353.1182, found 353.1215.

TLC (30% EtOAc in hexanes), R_f: 0.43 (UV, CAM).



Tribenzyl ether (–)-2.319:

100-mL round-bottomed flask was charged with diol (+)-**2.305** (909 mg, 3.62 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (36.2 mL) was introduced and the resultant solution was cooled to 0 °C. A dispersion of sodium hydride (60% wt. in mineral oil, 724 mg, 18.1 mmol, 5.00 equiv) was added in a single portion to the stirred reaction mixture. After 30 min, benzyl bromide, was added dropwise via syringe. After an additional 30 min, the reaction mixture was allowed to warm to ambient temperature. After 20 h, the reaction mixture was poured into a 250-mL Erlenmeyer flask containing saturated aqueous ammonium chloride solution (50 mL) and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant tan residue was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford tribenzyl ether (–)-**2.319** (1.43 g, 94%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41–7.23 (m, 15 H), 4.95 (d, *J* = 9.4 Hz, 1 H), 4.90 (d, *J* = 11.7 Hz, 1 H), 4.66 (d, *J* = 12.6 Hz, 1 H), 4.63 (d, *J* = 12.3 Hz, 1 H), 4.60–4.52 (m, 2 H), 4.43 (d, *J* = 11.7 Hz, 1 H), 4.09–4.02 (m, 1 H), 4.00 (br. s., 1 H), 3.16 (d, *J* = 9.1 Hz, 1 H), 2.24 (dd, *J* = 1.7, 13.8 Hz, 1 H), 1.61 (dd, *J* = 10.6, 12.6 Hz, 1 H), 1.33 (d, *J* = 5.9 Hz, 3 H).

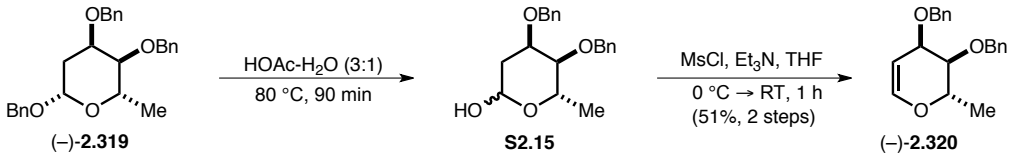
^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.5, 138.0, 137.8, 128.3, 127.85, 127.79, 127.69, 127.66, 127.55, 127.54, 97.3, 80.7, 71.5, 71.3, 71.1, 70.5, 69.1, 35.2, 18.4.

FTIR (thin film) cm^{-1}: 3028, 2929, 2868, 1496, 1453, 1362, 1344, 1316, 1207, 1164, 1148, 1088, 1056, 1026, 1000, 735, 696.

HRMS (ESI) (*m/z*) calc'd for $C_{27}H_{30}NaO_4$ $[M+Na]^+$: 441.2036, found 441.2058.

$[\alpha]_D^{23}$: –20.0 (*c* = 1.75, CH_2Cl_2).

TLC (20% EtOAc in hexanes), R_f: 0.48 (UV, CAM).



Glycal (–)-2.320:

A 250-mL round-bottomed flask was charged with a solution of tribenzyl ether (–)-**2.319** (1.33 g, 3.18 mmol, 1.00 equiv), water (16 mL), and acetic acid (48 mL). The reaction vessel was sealed with a plastic cap and heated to 80 °C for 1.5 h. The reaction mixture was allowed to cool to ambient temperature and concentrated under reduced pressure. The resultant colorless syrup was filtered through pad of silica (eluent: 50% EtOAc in hexanes) and the filtrate was concentrated under reduced pressure to yield the hemiacetal **S2.15** (1.04 g) as a colorless oil, which was used immediately without further purification.

A 100-mL round-bottomed flask was charged with hemiacetal **S2.15** and azeotropically dried with three portions of benzene. THF (125 mL) was introduced, and the resultant solution cooled to 0 °C. Et_3N (2.20 mL, 15.8 mmol, 5.00 equiv) and methanesulfonyl chloride (733 μL, 9.46 mmol, 3.00 equiv) were sequentially added dropwise via syringe to the stirred reaction solution and subsequently allowed to warm to ambient temperature. After 1 h, saturated aqueous ammonium chloride solution (30 mL) was added and the mixture was diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant tan residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford glycal (–)-**2.320** (501 mg, 51% over two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.27 (m, 10 H), 6.41 (d, *J* = 6.0 Hz, 1 H), 4.90 (t, *J* = 5.8 Hz, 1 H), 4.76–4.71 (m, 1 H), 4.69 (d, *J* = 11.8 Hz, 1 H), 4.64 (d, *J* = 12.2 Hz, 1 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.25 (qd, *J* = 6.3, 10.2 Hz, 1 H), 3.97 (dd, *J* = 3.7, 5.5 Hz, 1 H), 3.35 (dd, *J* = 3.5, 10.0 Hz, 1 H), 1.39 (d, *J* = 6.3 Hz, 3 H).

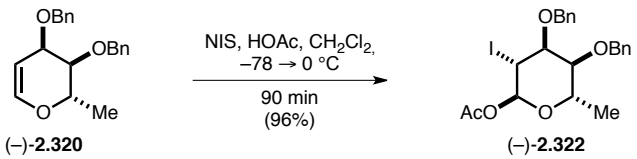
^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.7, 138.7, 137.9, 128.3, 128.0, 127.9, 127.7, 127.6, 98.2, 78.6, 71.1, 70.24, 70.16, 65.3, 17.7.

FTIR (thin film) cm^{-1}: 3062, 3029, 2932, 2864, 1640, 1496, 1453, 1274, 1235, 1206, 1173, 1119, 1090, 1064, 1027, 886, 801, 735, 697, 616, 597, 515, 439.

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{22}NaO_3$ $[M+Na]^+$: 333.1461, found 333.1475.

$[\alpha]_D^{23}$: –307 (*c* = 1.13, CH_2Cl_2).

TLC (10% EtOAc in hexanes), R_f: 0.43 (UV, CAM).



(–)-**2.320** (–)-**2.322**

Glycosyl acetate (–)-2.322:

A 100-mL round-bottomed flask was charged with glycal (–)-**2.320** and azeotropically dried with three portions of benzene. CH_2Cl_2 (31 mL) was introduced, and the resultant solution cooled to –78 °C. Acetic acid (211 μL, 3.68 mmol, 2.00 equiv) and *N*-iodosuccinamide (688 mg, 3.06 mmol, 1.66 equiv) were sequentially added to the stirred reaction solution. The reaction mixture was subsequently allowed to warm to 0 °C over 90 min. Saturated aqueous sodium thiosulfate solution (30 mL) was added and the mixture was diluted with EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford glycosyl acetate (–)-**2.322** (872 mg, 96%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.28 (m, 10 H), 6.12 (s, 1 H), 4.63 (d, J = 11.8 Hz, 1 H), 4.57 (d, J = 12.3 Hz, 1 H), 4.55–4.47 (m, 3 H), 4.40 (qd, J = 6.3, 8.5 Hz, 1 H), 4.03 (t, J = 2.9 Hz, 1 H), 3.88 (dd, J = 2.6, 8.9 Hz, 1 H), 2.02 (s, 3 H), 1.31 (d, J = 6.3 Hz, 3 H).

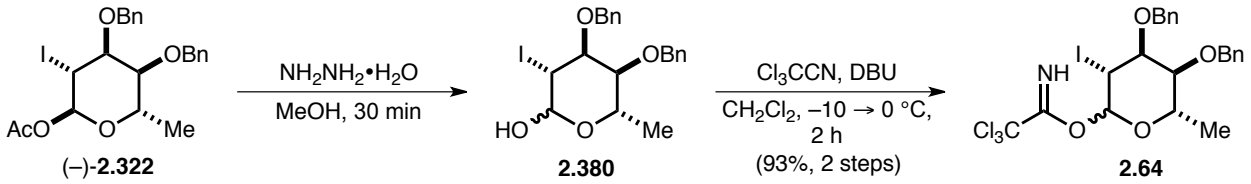
^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.5, 137.6, 137.5, 128.42, 128.40, 128.0, 127.92, 127.89, 127.8, 94.9, 76.1, 75.2, 72.1, 71.6, 66.8, 23.9, 20.9, 17.6.

FTIR (thin film) cm^{-1}: 3029, 2975, 2932, 2869, 1737, 1614, 14961454, 1371, 1220, 1144, 1087, 1066, 1027, 1005, 949, 923, 736, 696, 600, 470.

HRMS (ESI) (*m/z*) calc'd for $C_{22}H_{25}INaO_5$ $[M+Na]^+$: 519.0639, found 519.0648.

$[\alpha]_D^{23}$: –37.4 (c = 1.02, CH_2Cl_2).

TLC (20% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



Glycosyl trichloroacetimidate 2.64:

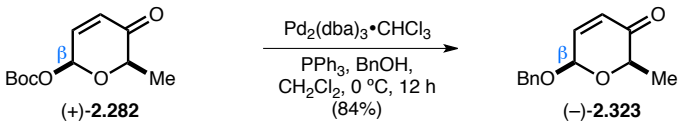
A 5-mL round-bottomed flask was charged with a solution of (–)-**2.322** (49.5 mg, 100 μmol, 1.00 equiv) and MeOH (1 mL). Hydrazine monohydrate (19.0 μL, 250 μmol, 2.50 equiv) was added dropwise via syringe to the stirred reaction solution. After 30 min, the reaction mixture was poured into 25-mL Erlenmeyer flask containing saturated aqueous sodium bicarbonate solution (5 mL) and diluted with EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant tan residue was filtered through pad of silica gel (eluent: 30% EtOAc in hexanes) and the filtrate was concentrated to yield the hemiacetal **2.380** (45.0 mg) as a colorless oil, which was used immediately without further purification.

A 5-mL round-bottomed flask was charged with hemiacetal **2.380** and azeotropically dried with three portions of benzene. CH_2Cl_2 (1 mL) and freshly distilled trichloroacetonitrile (100 μL, 1.00 mmol, 10.0 equiv) were introduced, and the resultant solution cooled to –10 °C. DBU (3.0 μL, 20.0 μmol, 0.20 equiv) was added via syringe. After 1h, the reaction mixture was allowed to warm to 0 °C. After an additional 1 h the reaction mixture was concentrated under reduced pressure. The resultant tan residue filtered through a pad of neutral alumina (eluent: 25% EtOAc in hexanes) to afford glycosyl trichloroacetimidate **2.64** (56 mg, 93% over two steps, 3:1 anomeric mixture, ca. 95% purity) as a tan oil that was used immediately without further purification.

Partial data for the 3:1 mixture glycosyl trichloroacetimidates **2.64**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.62 (s, 1 H), 7.40–7.27 (m, 10 H), 6.32 (s, 1 H), 5.58 (d, J = 1.3 Hz, 1 H), 4.76 (dd, J = 1.9, 4.4 Hz, 1 H), 4.74 (d, J = 11.7 Hz, 1 H), 4.67–4.63 (m, 1 H), 4.53 (d, J = 11.7 Hz, 1 H),

4.48 (d, *J* = 11.9 Hz, 1 H), 4.21 (qd, *J* = 6.4, 8.5 Hz, 1 H), 4.12–4.09 (m, 1 H), 3.96 (dd, *J* = 2.7, 8.6 Hz, 1 H), 1.36 (d, *J* = 6.5 Hz, 3 H).



β-Benzyl acetal (–)-2.323:

A 500-mL round-bottomed flask was charged with β-Boc-pyranone (+)-**2.282** (20.0 g, 87.6 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (88 mL) and benzyl alcohol (18.1 mL, 175 mmol, 2.0 equiv) were introduced and the resultant solution cooled to 0 °C. A separate 100-mL round-bottomed flask was charged with tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (1.13 g, 1.10 mmol, 0.0125 equiv) and triphenylphosphine (1.15 g, 4.38 mmol, 0.05 equiv) and the flask was evacuated and then backfilled with argon. The process was repeated three times before CH_2Cl_2 (56 ml) was introduced. The resultant red reaction mixture was cooled to 0 °C and transferred dropwise via cannula to the 500-mL reaction vessel over 10 min. After 12 h, saturated aqueous sodium bicarbonate solution (200 mL) was then added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: 8% EtOAc in hexanes) to afford β-benzyl acetal (–)-**2.323** (16.0 g, 84%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.29 (m, 5 H), 6.91 (dd, J = 1.9, 10.3 Hz, 1 H), 6.14 (dd, J = 1.4, 10.3 Hz, 1 H), 5.40 (s, 1 H), 4.95 (d, J = 11.8 Hz, 1 H), 4.69 (d, J = 11.8 Hz, 1 H), 4.24 (q, J = 6.8 Hz, 1 H), 1.53 (d, J = 6.9 Hz, 3 H).

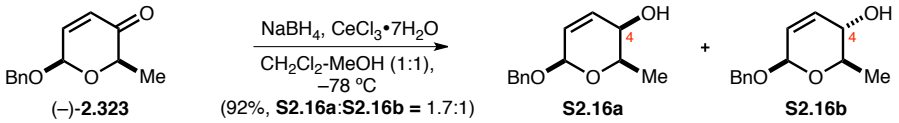
^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.8, 146.5, 136.8, 128.5, 128.1, 128.04, 128.00, 94.3, 75.2, 70.1, 17.2.

FTIR (thin film) cm^{-1}: 3360, 3065, 3032, 2987, 2939, 2873, 2833, 1699, 1498, 1455, 1374, 1339, 1323, 1302, 1259, 1221, 1165, 1149, 1116, 1099, 1058, 1024, 907, 803, 757, 699, 668.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{14}NaO_3$ $[M+Na]^+$: 241.0835, found 241.0828.

$[\alpha]_D^{23}$: –33.7 (*c* = 1.71, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.375 (UV, CAM).



Allylic alcohol S2.16a/S2.16b:

A 1-L round-bottomed flask was charged with (–)-**2.323** (42.4 g, 194 mmol, 1.00 equiv), CH_2Cl_2 (194 mL), MeOH (194 mL) and cerium(III) chloride heptahydrate (28.9 g, 77.7 mmol, 0.40 equiv). The resultant yellow mixture was stirred at ambient temperature until homogeneous and then cooled to –78 °C. Sodium borohydride (11.0 g, 291 mmol, 1.50 equiv) was added to the stirred reaction mixture in a single portion. After 3 h, saturated aqueous sodium bicarbonate solution (500 mL) was carefully added to the cold reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (200 mL) and Et_2O (3 × 100 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow syrup was purified by flash column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford an inseparable mixture of allylic alcohols **S2.16a** and **S2.16b** (17.5 g, 91%, **S2.16a**:**S2.16b** = 1.7:1) as a colorless oil.[236]

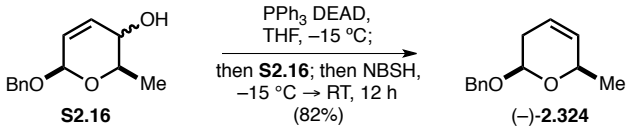
^{1}H NMR (500 MHz, $CDCl_3$) allylic alcohol **S2.16a** δ: 7.39–7.27 (m, 5 H), 6.17 (dd, *J* = 5.1, 10.0 Hz, 1 H), 5.87 (d, *J* = 10.1 Hz, 1 H), 5.15–5.12 (m, 1 H), 4.91 (d, *J* = 11.8 Hz, 1 H), 4.66 (d, *J* = 11.8 Hz, 1 H), 3.75 (dq, *J* = 2.1, 6.4 Hz, 1 H), 3.72–3.68 (m, 1 H), 1.72 (d, *J* = 11.1 Hz, 1 H), 1.34 (d, *J* = 6.4 Hz, 3 H); allylic alcohol **S2.16b** δ: 7.40–7.27 (m, 5 H), 6.01–5.96 (m, 1 H), 5.82 (dd, *J* = 1.1, 10.2 Hz, 1 H), 5.21–5.18 (m, 1 H), 4.87 (d, *J* = 11.8 Hz, 1 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 3.93 (t, *J* = 6.6 Hz, 1 H), 3.68–3.65 (m, 1 H), 1.68 (d, *J* = 7.6 Hz, 1 H), 1.40 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) allylic alcohol **S2.16a** δ: 137.4, 131.3, 130.4, 128.3(2C), 127.9 (2C), 127.7, 96.9, 71.4, 69.9, 64.6, 16.6; allylic alcohol **S2.16b** δ: 137.6, 132.2, 128.5 (2C), 128.3, 127.9 (2C), 127.6, 95.5, 74.3, 69.2, 68.2, 18.3.

FTIR (thin film) cm^{-1}: 3410, 3033, 2980, 2935, 2872, 1656, 1498, 1454, 1408, 1379, 1320, 1253, 1211, 1172, 1136, 1109, 1053, 1010, 983, 909, 868, 790, 736, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{16}NaO_3$ $[M+Na]^+$: 243.0992, found 243.0997.

TLC (20% EtOAc in hexanes), R_f: 0.20 (UV, CAM).



Dihydropyran (–)-2.324:

A 2-L, two-necked, round-bottomed flask was equipped with an internal thermocouple, a 250-mL graduated addition funnel, and a rubber septa. The reaction flask was charged with triphenylphosphine (69.8 g, 266 mmol, 1.5 equiv) and THF (350 mL) and cooled to –15 °C. A solution of diethyl azodicarboxylate in PhMe (40% wt., 113 mL, 108 g, 248 mmol, 1.40 equiv) was added via dropwise via graduated addition funnel over 15 min. A separate 250-mL round-bottomed flask was charged with **S2.16** and azeotropically dried with three portions of benzene. THF (120 mL) was introduced and the resultant solution was added dropwise to the cooled reaction mixture via cannula over 10 min. The transfer was completed with three additional portions of THF (10 mL). After 15 min a solution of 2-nitrobenzenesulfonylhydrazide[237] (57.8 g, 266 mmol, 1.50 equiv) in THF (250 mL), prepared in a separate 500-mL round-bottomed flask, was added dropwise to the cooled reaction mixture via cannula over 15 min. The reaction mixture stirred for 1 h at –15 °C and then was allowed to warm to ambient temperature over 12 h. The solvent was removed under reduced pressure to furnish a brown residue, which was dissolved in MeOH (200 mL) and H_2O (200 mL) and extracted with pentanes (3 × 350 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 5% EtOAc in hexanes) to afford dihydropyran (–)-**2.324** (29.7 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.27 (m, 5 H), 5.72–5.64 (m, 1 H), 5.59 (dd, J = 1.0, 10.1 Hz, 1 H), 4.94 (d, J = 12.1 Hz, 1 H), 4.74 (dd, J = 3.4, 8.0 Hz, 1 H), 4.62 (d, J = 12.1 Hz, 1 H), 4.38–4.29 (m, 1 H), 2.31–2.22 (m, 1 H), 2.22–2.14 (m, 1 H), 1.32 (d, J = 6.8 Hz, 3 H).

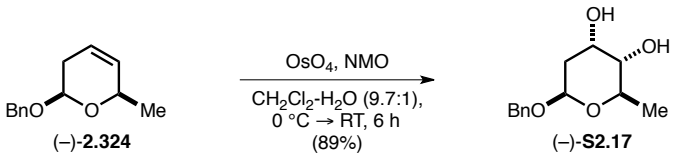
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 130.9, 128.3, 127.9, 127.5, 122.4, 97.7, 70.6, 69.7, 30.9, 21.1.

FTIR (thin film) cm^{-1}: 3033, 2978, 2931, 2937, 1498, 1455, 1432, 1392, 1366, 1313, 1205, 1184, 1158, 1135, 1107, 1080, 1045, 1028, 970, 881, 780, 753, 698, 680, 619.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{16}NaO_2$ $[M+Na]^+$: 227.1043, found 227.1000.

$[\alpha]_D^{23}$: –134 (*c* = 1.12, $CHCl_3$).

TLC (5% EtOAc in hexanes), R_f: 0.33 (UV, CAM).



Diol (–)-S2.17:

A 250-mL round-bottomed flask was charged with dihydropyran (–)-**2.324** (5.0 g, 24.5 mmol, 1.00 equiv), CH_2Cl_2 (49.0 mL) and a solution of NMO in H_2O (50% wt., 10.2 mL, 11.5 g, 49.0 mmol, 2.00 equiv) and cooled to 0 °C. OsO_4 (63.0 mg, 256 μmol, 0.01 equiv) was added in a single portion and the resultant yellow solution warmed to ambient temperature. After 6 h, a mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (10:1, 50 mL) and Florisil (5 g) were added to the stirred reaction mixture. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with Et_2O (3 × 50 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography (silica gel, eluent: gradient, 35 → 40% EtOAc in hexanes) to afford diol (–)-**S2.17** (5.45 g, 89%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40–7.27 (m, 5 H), 4.91 (dd, *J* = 1.7, 9.2 Hz, 1 H), 4.90 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.16–4.09 (m, 1 H), 3.75 (qd, *J* = 6.1, 9.2 Hz, 1 H), 3.40–3.31 (m, 0 H), 2.26 (br. s., 1 H), 2.14 (d, *J* = 13.9 Hz, 1 H), 2.07 (br. s., 1 H), 1.80 (ddd, *J* = 2.8, 9.4, 13.9 Hz, 1 H), 1.34 (d, *J* = 6.2 Hz, 1 H).

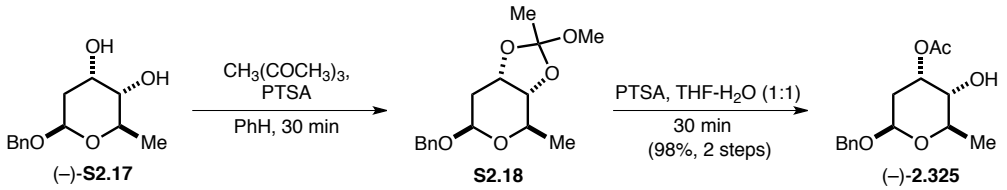
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.4, 128.3, 127.9, 127.7, 96.9, 72.8, 70.5, 69.4, 67.7, 37.5, 18.1.

FTIR (thin film) cm^{-1}: 3418, 3032, 3014, 2973, 2933, 2883, 1498, 1454, 1365, 1216, 1164, 1137, 1075, 1007, 910, 867, 822, 758, 699, 667.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{18}NaO_4$ $[M+Na]^+$: 261.1097, found 261.1099.

$[\alpha]_D^{23}$: –69.0 (*c* = 1.17, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.12 (UV, CAM).



Alcohol (–)-2.325:

A 100-mL round-bottomed flask was charged with a solution of diol (–)-**S2.17** (5.06 g, 20.1 mmol, 1.00 equiv) and benzene (40.3 mL). Trimethyl orthoformate (12.9 mL, 101 mmol, 5.00 equiv) and *para*-toluenesulfonic acid monohydrate (192 mg, 1.01 mmol, 0.05 equiv) were sequentially introduced to the stirred reaction mixture at ambient temperature. After 30 min, the solvent was removed under reduced pressure to afford orthoester **S2.18** as a tan residue, which was immediately dissolved in THF (24.0 mL) and H_2O (24.0 mL). *para*-Toluenesulfonic acid monohydrate (9.60 g, 50.4 mmol, 2.50 equiv) was introduced in a single portion to the stirred reaction mixture at ambient temperature. After 30 min, saturated aqueous sodium bicarbonate (100 mL) was added to the reaction mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 30 → 45% EtOAc in hexanes) to afford alcohol (–)-**2.325** (5.51 g, 98%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 5 H), 5.30 (q, *J* = 3.2 Hz, 1 H), 4.92 (d, *J* = 11.8 Hz, 1 H), 4.83 (dd, *J* = 2.0, 9.5 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 3.73 (qd, *J* = 6.2, 9.2 Hz, 1 H), 3.47 (ddd, *J* = 3.2, 6.0, 9.2 Hz, 1 H), 2.15 (qd, *J* = 2.3, 14.4 Hz, 1 H), 2.11 (s, 3 H), 2.00–1.95 (m, 1 H), 1.88 (ddd, *J* = 2.9, 9.5, 14.3 Hz, 1 H), 1.36 (d, *J* = 6.3 Hz, 3 H).

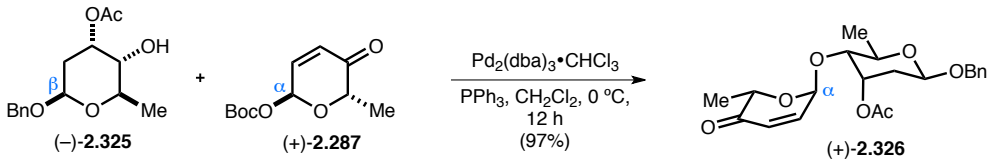
^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2, 137.5, 128.3, 127.8, 127.7, 96.9, 72.1, 70.9, 70.4, 70.3, 35.6, 21.1, 18.0.

FTIR (thin film) cm^{-1}: 3436, 2974, 2934, 2879, 1740, 1454, 1372, 1244, 1217, 1164, 1137, 1076, 1006, 947, 912, 867, 757, 699, 666.

HRMS (ESI) (*m/z*) calc'd for $C_{15}H_{20}KO_5$ $[M+K]^+$: 319. 0942, found 319. 0943.

$[\alpha]_D^{23}$: –45.6 (*c* = 1.03, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.24 (UV, CAM).



Disaccharide (+)-2.326:

A 100-mL round-bottomed flask was charged with (–)-**2.325** (7.81 g, 27.9 mmol, 1.00 equiv) and α-Boc-pyranone (+)-**2.287** (12.7 g, 55.8 mmol, 2.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (28 mL) was introduced and the resultant solution cooled to 0 °C. A separate 10-mL round-bottomed flask was charged with tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (361 mg, 349 μmol, 0.0125 equiv) and triphenylphosphine (366 mg, 1.39 mmol, 0.05 equiv) and the flask was evacuated and then backfilled with argon. The process was repeated three times before CH_2Cl_2 (3.5 ml) was introduced. The resultant red reaction mixture was cooled to 0 °C and transferred dropwise via cannula to the 100-mL reaction vessel over 2 min. After 12 h, saturated aqueous sodium bicarbonate solution (30 mL) was then added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 10 → 30% EtOAc in hexanes) to afford disaccharide (+)-**2.326** (10.5 g, 97%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.27 (m, 5 H), 6.77 (dd, *J* = 3.4, 10.2 Hz, 1 H), 6.09 (d, *J* = 10.2 Hz, 1 H), 5.49 (q, *J* = 3.2 Hz, 1 H), 5.27 (d, *J* = 3.4 Hz, 1 H), 4.91 (d, *J* = 11.8 Hz, 1 H), 4.84 (dd, *J* = 2.1, 9.4 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.50 (q, *J* = 6.8 Hz, 1 H), 3.94 (qd, *J* = 6.3, 9.2 Hz, 1 H), 3.51 (dd, *J* = 3.1, 9.3 Hz, 1 H), 2.20–2.12 (m, 1 H), 2.06 (s, 3 H), 1.38–1.34 (m, 6 H).

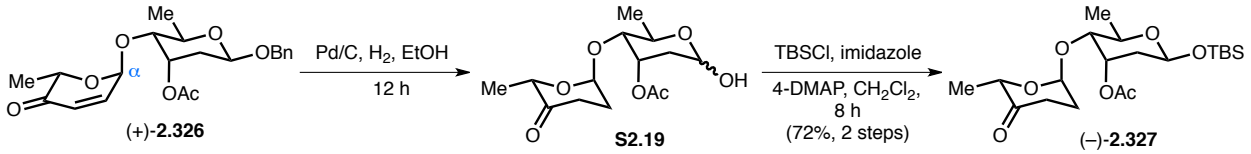
^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.4, 170.0, 142.0, 137.4, 128.3, 127.74, 127.68, 127.5, 97.0, 95.3, 80.4, 70.7, 70.5, 69.6, 69.0, 36.0, 21.1, 18.1, 14.9.

FTIR (thin film) cm^{-1}: 2982, 2936, 2881, 1741, 1701, 1454, 1400, 1373, 1316, 1241, 1165, 1089, 1054, 1010, 846, 755, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{21}H_{26}NaO_7$ $[M+Na]^+$: 413.1571, found 413.1565.

$[\alpha]_D^{23}$: +23.0 (*c* = 1.53, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.375 (UV, CAM).



Ketone (–)-2.327:

A 100-mL round-bottomed flask was charged with enone (+)-**2.326** (2.30 g, 5.89 mmol, 1.00 equiv) and EtOH (58.9 mL). Palladium on carbon (10 wt. % loading (dry basis), 1.13 g, 1.06 mmol, 0.18 equiv) was added in a single portion to the stirred solution, which was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen gas. After 12 h, the balloon was removed and the stirred reaction mixture was sparged with argon gas. After 5 min, the reaction mixture was filtered through a pad of Celite and rinsed with EtOAc (3 × 25 mL). The filtrate was concentrated under reduced pressure to yield the hemiacetal **S2.19** as a colorless oil, which was used immediately without further purification.

A 250-mL round-bottomed flask was charged with hemiacetal **S2.19** and azeotropically dried with three portions of benzene. CH_2Cl_2 (58.9 mL) was introduced and the resultant solution stirred at ambient temperature. *tert*-Butyldimethylsilyl chloride (2.66 g, 17.7 mmol, 3.00 equiv), imidazole (2.00 g, 29.5 mmol, 5.00 equiv), and 4-(dimethylamino)pyridine (144 mg, 1.18 mmol, 0.20 equiv) were sequentially added to the reaction vessel in single portions. After 8 h, saturated aqueous sodium bicarbonate solution (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient, 15 → 20% EtOAc in hexanes) to afford ketone (–)-**2.327** (1.77 g, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.41 (q, *J* = 3.1 Hz, 1 H), 5.07 (t, *J* = 5.8 Hz, 1 H), 5.04 (dd, *J* = 1.9, 9.3 Hz, 1 H), 4.28 (q, *J* = 6.8 Hz, 1 H), 3.87 (qd, *J* = 6.3, 9.5 Hz, 1 H), 3.46 (dd, *J* = 3.1, 9.6 Hz, 1 H), 2.40 (d, *J* = 7.7 Hz, 1 H), 2.39 (d, *J* = 7.9 Hz, 1 H), 2.30 (qd, *J* = 5.7, 14.3 Hz, 1 H), 2.10 (s, 3 H), 2.04 (ddd, *J* =

2.1, 3.5, 14.2 Hz, 1 H), 1.94 (dtd, *J* = 5.8, 8.0, 14.2 Hz, 1 H), 1.80 (ddd, *J* = 2.7, 9.3, 14.3 Hz, 1 H), 1.28 (d, *J* = 3.8 Hz, 3 H), 1.26 (d, *J* = 3.2 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H).

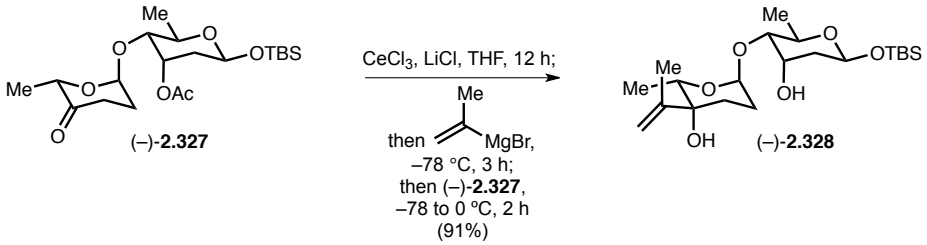
^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.7, 170.1, 99.1, 92.7, 78.6, 71.3, 70.4, 69.3, 38.6, 33.3, 28.0, 25.7, 21.1, 18.07, 18.05, 14.6, –4.2, –5.2.

FTIR (thin film) cm^{-1}: 2956, 2934, 2885, 2859, 1739, 1392, 1370, 1319, 1244, 1217, 1175, 1154, 1117, 1093, 1069, 1012, 941, 857, 839, 781, 761, 692, 668.

HRMS (ESI) (*m/z*) calc'd for $C_{20}H_{36}NaO_7Si$ $[M+Na]^+$: 439.2123, found 439.2102.

$[\alpha]_D^{23}$: –75.2 (*c* = 1.02, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.63 (UV, CAM).



Allylic Alcohol (–)-2.328:

A 2-L round-bottomed flask was charged with anhydrous cerium(III) chloride (15.7 g, 63.8 mmol, 15.0 equiv) and lithium chloride (5.40 g, 128 mmol, 30.0 equiv), and heated to 145 °C under reduced pressure (0.05 Torr) for 2.5 h. The flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (640 mL) was introduced via cannula over 15 min. The resultant heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –78 °C before a solution of isopropenylmagnesium bromide in THF (0.5 M, 102 mL, 51.0 mmol, 12.0 equiv) was added dropwise via syringe over 15 min. The resultant yellow slurry was stirred for 3 h at –78 °C. A solution of (–)-**2.327** (1.77 g, 4.25 mmol, 1.00 equiv) in THF (9.0 mL) at –78 °C was then transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled reaction mixture over 10 min. The transfer was completed with two additional portions of THF (5.0 mL). The resultant mixture was gradually allowed to warm to 0 °C over 30 min and stirred at 0 °C for an additional 1.5 h. Saturated aqueous ammonium chloride solution (300 mL) was then cautiously added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (100 mL) and EtOAc (3 × 150 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow syrup was purified by flash column chromatography (silica gel, eluent: 20% EtOAc in hexanes) to afford allylic alcohol (–)-**2.328** (1.61 g, 91%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.18–5.10 (m, 2 H), 4.96 (d, *J* = 3.3 Hz, 1 H), 4.91 (s, 1 H), 4.14 (s, 1 H), 4.09 (q, *J* = 6.5 Hz, 1 H), 3.83 (qd, *J* = 6.3, 9.5 Hz, 1 H), 3.34 (dd, *J* = 3.0, 9.6 Hz, 1 H), 2.32 (s, 1 H), 2.17–1.99 (m, 4 H), 1.76 (s, 5 H), 1.51 (ddd, *J* = 2.8, 3.7, 13.3 Hz, 1 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 0.90 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H).

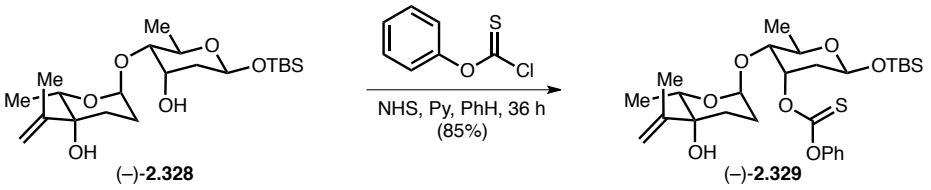
^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.2, 111.2, 98.6, 92.5, 80.4, 73.3, 68.6, 68.3, 67.9, 39.6, 29.7, 25.8, 25.6, 19.5, 18.14, 18.11, 14.2, –4.2, –5.2.

FTIR (thin film) cm^{-1}: 3492, 2955, 2932, 2896, 1448, 1383, 1308, 1252, 1213, 1176, 1124, 1090, 1078, 1030, 996, 978, 929, 861, 839, 782, 757, 669.

HRMS (ESI) (*m/z*) calc'd for $C_{21}H_{40}NaO_6Si$ $[M+Na]^+$: 439.2486, found 439.2462.

$[\alpha]_D^{23}$: –43.4 (*c* = 1.44, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.49 (UV, CAM).



Phenylthionocarbonate (–)-2.329:

A 25-mL round-bottomed flask was charged with allylic alcohol (–)-**2.328** (591 mg, 1.42 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Benzene (7.1 mL) was introduced and the resultant solution stirred at ambient temperature. *N*-Hydroxysuccinimide (49.0 mg, 43.0 μmol, 0.30 equiv), pyridine (689 μL, 8.52 mmol, 6.00 equiv), and *O*-phenyl chlorothionoformate (558 μL, 5.68 mmol, 4.00 equiv) were sequentially added to the reaction vessel. After 24 h, additional *N*-hydroxysuccinimide (24.5 mg, 21.5 μmol, 0.15 equiv), pyridine (345 μL, 4.26 mmol, 3.00 equiv), and *O*-phenyl chlorothionoformate (279 μL, 2.84 mmol, 2.00 equiv) were sequentially added to the reaction mixture. After an additional 12 h, saturated aqueous sodium bicarbonate solution (10 mL) was added to the stirred reaction mixture. The mixture was diluted with EtOAc (25 mL), and the layers were separated. the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (2 × 50 mL), and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 30% EtOAc in hexanes) to afford phenylthionocarbonate (–)-**2.329** (668 mg, 85%) as a yellow foam.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 (t, *J* = 8.1 Hz, 2 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 7.8 Hz, 2 H), 5.59 (q, *J* = 2.7 Hz, 1 H), 5.02 (s, 1 H), 4.93 (dd, *J* = 1.8, 9.2 Hz, 1 H), 4.81 (d, *J* = 3.4 Hz, 1 H), 4.78–4.75 (m, 1 H), 4.05 (q, *J* = 6.4 Hz, 1 H), 3.77 (qd, *J* = 6.2, 9.6 Hz, 1 H), 3.39 (dd, *J* = 2.9, 9.5 Hz, 1 H), 2.32 (qd, *J* = 2.1, 14.8 Hz, 1 H), 2.09 (dt, *J* = 4.6, 13.7 Hz, 1 H), 1.99–1.88 (m, 2 H), 1.74 (ddd, *J* = 2.4, 9.3, 14.6 Hz, 1 H), 1.65–1.61 (m, 1 H), 1.38 (ddd, *J* = 1.9, 4.5, 13.5 Hz, 1 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 0.89 (d, *J* = 6.4 Hz, 3 H), 0.80 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

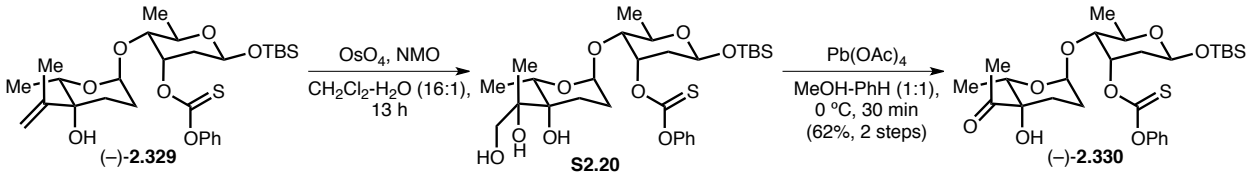
^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.9, 153.1, 147.4, 129.5, 126.6, 121.7, 111.0, 99.7, 92.6, 81.3, 78.8, 73.5, 69.8, 68.3, 37.3, 29.6, 25.74, 25.66, 19.7, 18.10, 18.08, 14.2, –4.2, –5.2.

FTIR (thin film) cm^{-1}: 3500, 2955, 2933, 2897, 2858, 1762, 1643, 1592, 1491, 1446, 1360, 1296, 1263, 1198, 1174, 1128, 1071, 1028, 1004, 978, 928, 905, 853, 840, 804, 782, 756, 690.

HRMS (ESI) (*m/z*) calc'd for $C_{28}H_{44}NaO_7SSi$ $[M+Na]^+$: 575.2469, found 575.2440.

$[\alpha]_D^{23}$: –40.7 (*c* = 1.60, $CHCl_3$).

TLC (70% EtOAc in hexanes), R_f: 0.47 (UV, CAM).



α-Hydroxy ketone (–)-2.330:

A 10-mL round-bottomed flask was charged with phenylthionocarbonate (–)-**2.329** (318 mg, 575 μmol, 1.00 equiv), CH_2Cl_2 (2.90 mL), and a solution of NMO in H_2O (50 wt. %, 358 μL, 405 mg, 1.73 mmol, 3.00 equiv). OsO_4 (38.1 mg, 15.0 μmol, 0.01 equiv) was added in a single portion to the stirred reaction mixture at ambient temperature. After 13 h, a mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (10:1, 5 mL) and Florisil (1 g) were added to the stirred reaction mixture. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with Et_2O (3 × 10 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow oil was filtered through pad of silica gel (eluent: 3% MeOH in CH_2Cl_2) and the filtrate was concentrated to yield triol **S2.20** (305 mg) as a brown oil, which was used immediately without further purification.

A 25-mL round-bottomed flask was charged with triol **S2.20** and azeotropically dried with three portions of benzene. MeOH (2.6 mL) and benzene (2.6 mL) were introduced and the resultant solution cooled to 0 °C. Lead(IV) acetate (346 mg, 780 μmol, 1.50 equiv) was added in a single portion to the stirred, cooled reaction mixture. After 30 min, the reaction mixture was diluted with Et_2O (20 mL) and filtered through a pad of Celite and rinsed with Et_2O (3 × 25 mL). The filtrate was concentrated under reduced pressure to yield a tan residue that was purified by flash column chromatography (silica gel, eluent: gradient, 10% → 12% EtOAc in CH_2Cl_2) to afford α-hydroxy ketone (–)-**2.330** (197 mg, 62%) as a colorless foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44 (t, *J* = 8.3 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 5.76 (q, *J* = 2.6 Hz, 1 H), 5.04 (dd, *J* = 1.3, 9.0 Hz, 1 H), 4.99 (d, *J* = 2.9 Hz, 1 H), 4.36 (q, *J* = 6.3 Hz,

1 H), 3.88 (qd, *J* = 6.2, 9.5 Hz, 1 H), 3.73 (s, 1 H), 3.55 (dd, *J* = 2.9, 9.5 Hz, 1 H), 2.40 (td, *J* = 2.3, 14.5 Hz, 1 H), 2.30 (dt, *J* = 4.5, 13.3 Hz, 1 H), 2.23 (s, 3 H), 2.10 (tt, *J* = 4.1, 13.7 Hz, 1 H), 1.88 (ddd, *J* = 2.3, 9.3, 14.5 Hz, 1 H), 1.82–1.74 (m, 1 H), 1.51 (ddd, *J* = 2.0, 4.0, 12.8 Hz, 1 H), 1.29 (d, *J* = 6.2 Hz, 3 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H).

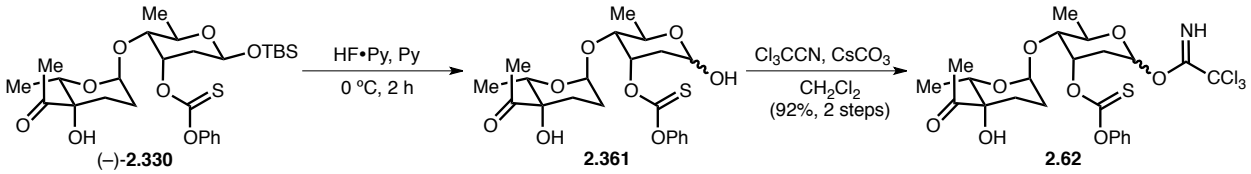
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.9, 194.1, 153.1, 129.6, 126.7, 121.7, 99.4, 92.7, 81.5, 78.7, 78.5, 69.8, 66.8, 37.5, 27.7, 25.8, 24.9, 24.7, 18.2, 18.1, 14.9, –4.1, –5.1.

FTIR (thin film) cm^{-1}: 3472, 2933, 2894, 2882, 2858, 1706, 1490, 1354, 1295, 1261, 1220, 1196, 1174, 1128, 1090, 1070, 1019, 994, 930, 852, 838, 782, 690.

HRMS (ESI) (*m/z*) calc'd for $C_{27}H_{42}NaO_8SSi$ $[M+Na]^+$: 577.2262, found 577.2234.

$[\alpha]_D^{23}$: –32.2 (*c* = 0.55, $CHCl_3$).

TLC (10% EtOAc in CH_2Cl_2), R_f: 0.23 (UV, CAM).



Glycosyl trichloroacetimidate 2.62:

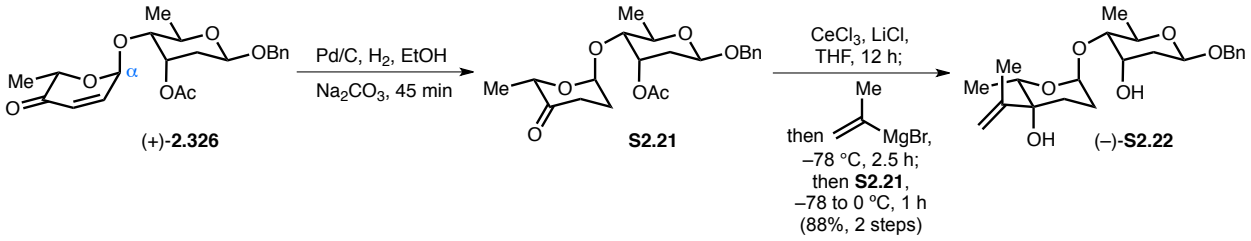
Hydrogen fluoride pyridine (197 μL) was slowly added to a stirred solution of α-hydroxy ketone (–)-**2.330** (54.6 mg, 98.0 μmol, 1.00 equiv) in pyridine (1.5 mL) in a polyethylene vessel at 0 °C. After 2 h, the reaction mixture was cautiously poured into a vigorously stirred mixture of saturated aqueous sodium bicarbonate solution (10 mL), EtOAc (20 mL), and ice at 0 °C. After gas evolution ceased, the layers were separated. The organic layer was washed with a saturated aqueous sodium bicarbonate solution (3 × 10 mL), and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluent: 65% EtOAc in hexanes) to afford hemiacetal **2.361** as an colorless foam, which was used without further purification.

A 2-mL vial was charged with **2.361** and azeotropically dried with three portions of benzene. CH_2Cl_2 (930 μL), freshly distilled trichloroacetonitrile (93 μL, 930 μmol, 10.0 equiv), and cesium carbonate (6.0 mg, 18.6 μmol, 0.20 equiv) were sequential introduced. The vial was sealed with a PTFE coated cap and the resultant solution stirred at ambient temperature. After 12 h, the tan reaction mixture was diluted with CH_2Cl_2 (1 mL), filtered through a pad of Celite, and with CH_2Cl_2 (3 × 2 mL). The filtrate was concentrated under reduced pressure to afford glycosyl trichloroacetimidate **2.62** (52.7 mg, 92% over two steps, 10:1 anomeric mixture, ca. 95% purity) as a tan foam that was used immediately without further purification.

Partial data for the 10:1 mixture glycosyl trichloroacetimidates **2.62**:

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 8.64 (s, 1 H), 7.45 (t, *J* = 7.4 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 6.22 (dd, *J* = 2.5, 7.5 Hz, 1 H), 5.89 (td, *J* = 2.9, 6.0 Hz, 1 H), 5.02 (d, *J* = 3.1 Hz, 1 H), 4.41 (q, *J* = 6.4 Hz, 1 H), 4.15 (quin, *J* = 6.7 Hz, 1 H), 3.82 (dd, *J* = 2.8, 7.4 Hz, 1 H), 3.62 (s, 1 H), 2.70

(ddd, J = 2.6, 6.0, 14.0 Hz, 1 H), 2.33 (dt, J = 4.5, 13.4 Hz, 1 H), 2.25–2.17 (m, 4 H), 2.07 (tt, J = 4.1, 13.6 Hz, 1 H), 1.83–1.74 (m, 1 H), 1.55–1.47 (m, 1 H), 1.40 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 6.3 Hz, 3 H).



Alyllic Alcohol (–)-S2.22:

A 5-mL round-bottomed flask was charged with enone (+)-**2.326** (50 mg, 127 μmol, 1.00 equiv) and EtOH (1.3 mL). Palladium on carbon (5 wt. % loading (dry basis), 244 mg, 5.7 μmol, 0.04 equiv) was added in a single portion to the stirred solution, which was subsequently sparged with hydrogen gas for 5 min. The stirred reaction mixture was maintained under a balloon of hydrogen gas. After 45 min, the balloon was removed and the stirred reaction mixture was sparged with argon gas. After 5 min, the reaction mixture was filtered through a pad of Celite and rinsed with EtOAc (3 × 5 mL). The filtrate was concentrated under reduced pressure to yield the ketone **S2.21** as a colorless oil, which was used without further purification.

A 10-mL round-bottomed flask was charged with anhydrous cerium(III) chloride (188 mg, 0.76 mmol, 6.00 equiv) and lithium chloride (32.0 mg, 0.76 mmol, 6.00 equiv), and heated to 145 °C under reduced pressure (0.05 Torr) for 2.5 h. The flask was allowed to cool to ambient temperature and flushed with argon. The flask was further cooled to 0 °C before THF (3.8 mL) was introduced via syringe over 2 min. The resultant heterogeneous, off-white slurry was allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –78 °C before a solution of isopropenylmagnesium bromide in THF (0.5 M, 1.66 mL, 0.70 mmol, 5.50 equiv) was added dropwise via syringe over 15 min. The resultant yellow slurry was stirred for 3 h at –78 °C. A solution of **S2.21** in THF (0.6 mL) at –78 °C was then transferred dropwise via syringe. The transfer was completed with two additional portions of THF (0.3 mL). The resultant mixture was gradually allowed to warm to 0 °C over 30 min and stirred at 0 °C for an additional 30 min. Saturated aqueous ammonium chloride solution (3 mL) was then added to the reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (10 mL) and EtOAc (3 × 10 mL). The

layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow syrup was purified by flash column chromatography (silica gel, eluent: gradient, 30% → 35% EtOAc in hexanes) to afford allylic alcohol (–)-**S2.22** (43.6 mg, 88%) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.27 (m, 5 H), 5.12 (s, 1 H), 4.97 (d, *J* = 3.2 Hz, 1 H), 4.93 (dd, *J* = 1.7, 9.6 Hz, 1 H), 4.92–4.87 (m, 2 H), 4.57 (d, *J* = 11.9 Hz, 1 H), 4.17 (q, *J* = 2.4 Hz, 1 H), 4.09 (q, *J* = 6.4 Hz, 1 H), 3.85 (qd, *J* = 6.2, 9.3 Hz, 1 H), 3.37 (dd, *J* = 2.9, 9.3 Hz, 1 H), 2.33 (br. s., 1 H), 2.21–2.01 (m, 4 H), 1.81 (ddd, *J* = 2.6, 9.3, 12.9 Hz, 1 H), 1.76 (s, 4 H), 1.54–1.48 (m, 1 H), 1.30 (d, *J* = 6.3 Hz, 3 H), 1.02 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.2, 137.7, 128.3, 127.9, 127.6, 111.2, 98.6, 96.9, 80.5, 73.3, 70.5, 68.6, 68.3, 67.5, 37.0, 29.6, 25.5, 19.5, 18.1, 14.2.

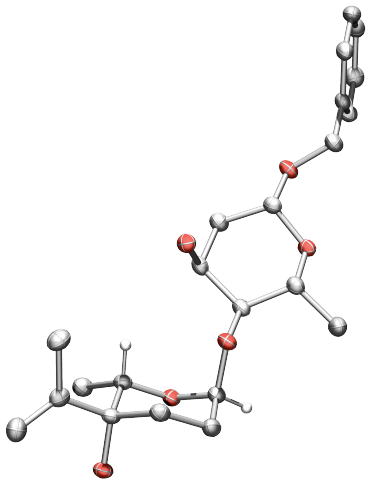
FTIR (thin film) cm^{-1}: 3556, 3495, 2986, 2936, 1498, 1453, 1383, 1364, 1308, 1275, 1214, 1166, 1124, 1086, 1055, 1029, 999, 978, 932, 906, 866, 847, 758, 699.

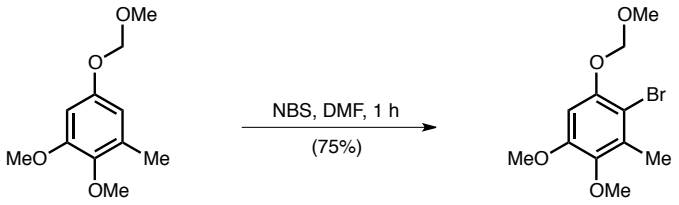
HRMS (ESI) (*m/z*) calc'd for $C_{22}H_{32}NaO_6$ $[M+Na]^+$: 415.2091, found 415.2117.

$[\alpha]_D^{23}$: –98.4 (*c* = 1.45, $CHCl_3$).

TLC (40% EtOAc in hexanes), R_f: 0.24 (UV, CAM).

X-Ray Crystal Structure:





2.339 **2.340**

Aryl bromide 2.340:

A 50-mL round-bottomed flask was charged with **2.339**[239] (1.55 g, 7.30 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. DMF (14.6 mL) was introduced, and the resultant solution stirred at ambient temperature. *N*-Bromosuccinamide (1.43 g, 8.00 mmol, 1.10 equiv) was added to the reaction mixture in a single portion. After 1 h, saturated aqueous sodium sulfite solution (15 mL) and Et_2O (15 mL) were added to the yellow reaction mixture. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 25 mL). The combined organic layers were then washed with H_2O (4 × 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 15% EtOAc in hexanes) to afford aryl bromide **2.340** (1.59 g, 75%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.69 (s, 1 H), 5.20 (s, 2 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.54 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.1, 150.3, 142.8, 132.8, 106.4, 99.6, 95.8, 60.5, 56.3, 55.9, 16.3.

FTIR (thin film) cm^{-1}: 2995, 2934, 2827, 1579, 1475, 1421, 1331, 1233, 1214, 1194, 1151, 1087, 1040, 1015, 999, 935, 817, 793.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{15}BrNaO_4$ $[M+Na]^+$: 313.0046, found 313.0061.

M.**p**.: 61 °C (EtOAc).

TLC (30% EtOAc in hexanes), R_f: 0.44 (UV, CAM).

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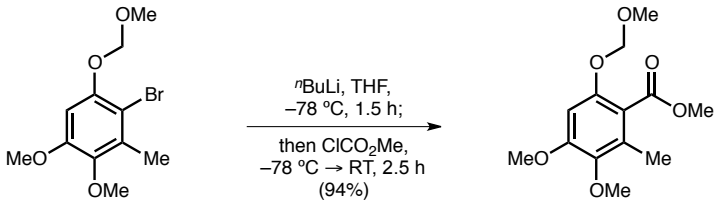
[239] Trialkoxytoluene **2.339** was prepared from vanillin in five steps on multigram scale following literature procedures: (a) Sinhababu, A. K.; Borchardt, R. T. *Syn. Comm.* **1983***, 13*, 677–683. (b) Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.,* **2012**, *134*, 16765–16772.



***ortho*-Toluate 2.341**:

A 200-mL round-bottomed flask was charged with **2.340** (1.59 g, 5.46 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (55 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of *n*-butyllithium in hexanes (2.53 M, 2.48 mL, 6.28 mmol, 1.15 equiv) was then added dropwise via syringe to the stirred reaction mixture. After 1.5 h, methyl chloroformate (633 μL, 8.19 mmol, 1.50 equiv) was added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to gradually warm to ambient temperature over 2.5 h. Saturated aqueous sodium bicarbonate solution (50 mL) and Et_2O (100 mL) were then added to the reaction mixture. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 30% EtOAc in hexanes) to afford *ortho*-toluate **2.341** (1.39 g, 94%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.62 (s, 1 H), 5.13 (s, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.73 (s, 3 H), 3.48 (s, 3 H), 2.21 (s, 3 H).

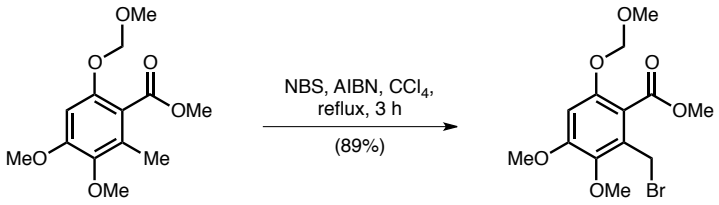
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.1, 154.1, 150.8, 142.1, 130.1, 117.7, 98.6, 95.5, 60.3, 56.1, 55.8, 52.0, 12.8.

FTIR (thin film) cm^{-1}: 2995, 2949, 2828, 1725, 1597, 1489, 1453, 1330, 1266, 1212, 1152, 1087, 1043, 1003, 938, 840, 894, 794, 772.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{18}KO_6$ $[M+K]^+$: 309.0735, found 309.0740.

M.p.: 44–45 °C (Et_2O).

TLC (30% EtOAc in hexanes), R_f: 0.44 (UV, CAM).



2.341 **2.342**

Benzylic bromide 2.342:

A 200-mL round-bottomed flask was charged with **2.341** (1.49g, 5.51 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CCl_4 (55 mL), *N*-bromosuccinamide (1.18 g, 6.62 mmol, 1.20 equiv), and 2,2′-azobis(2-methylpropionitrile) (181 mg, 1.10 mmol, 0.20 equiv) were introduced, and the resultant stirred solution was heated to reflux. After 3 h the stirred reaction mixture was allowed to cool to ambient temperature before triethylamine (2.30 ml, 16.5 mmol, 3.00 equiv) was added to the reaction mixture which was subsequently concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 30% EtOAc in hexanes) to afford benzylic bromide **2.342** (1.46 g, 76%) as a white flocculent solid.

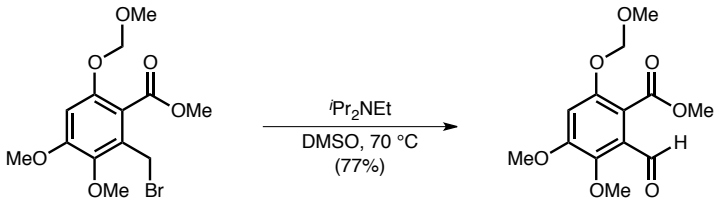
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.75 (s, 1 H), 5.14 (s, 2 H), 4.64 (s, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.50 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.0, 154.4, 151.6, 142.2, 130.2, 116.6, 101.5, 95.7, 61.0, 56.2, 55.9, 52.3, 23.8.

FTIR (thin film) cm^{-1}: 2947, 1720, 1595, 1488, 1453, 1431, 1402, 1333, 1269, 1236, 1215, 1195, 1152, 1102, 1089, 1048, 1024, 980, 947.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{17}BrNaO_6$ $[M+Na]^+$: 371.0101, found 371.0082.

TLC (30% EtOAc in hexanes), R_f: 0.26 (UV, CAM).



Aldehyde 2.343:

A 200-mL round-bottomed flask was charged with **2.342** (1.00 g, 2.86 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene before dimethyl sulfoxide (57.2 mL) was introduced. Diisopropylamine (1.47 mL, 8.59 mmol, 3.00 equiv) was added dropwise via syringe to the stirred solution at ambient temperature, which was subsequently warmed to 70 °C. After 2 h, the reaction mixture was cooled to ambient temperature before a saturated aqueous ammonium chloride solution (100 mL) was cautiously added to the stirred reaction mixture. The mixture was partitioned with EtOAc (100 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 75 mL) and the combined organic layers were then washed with saturated aqueous ammonium chloride solution (3 × 200 mL), water (3 × 200 mL), and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 30% → 40% → 50% EtOAc in hexanes) to afford aldehyde **2.343** (625 mg, 77%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.36 (s, 1 H), 7.02 (s, 1 H), 5.16 (s, 2 H), 3.96–3.89 (m, 9 H), 3.49 (s, 3 H).

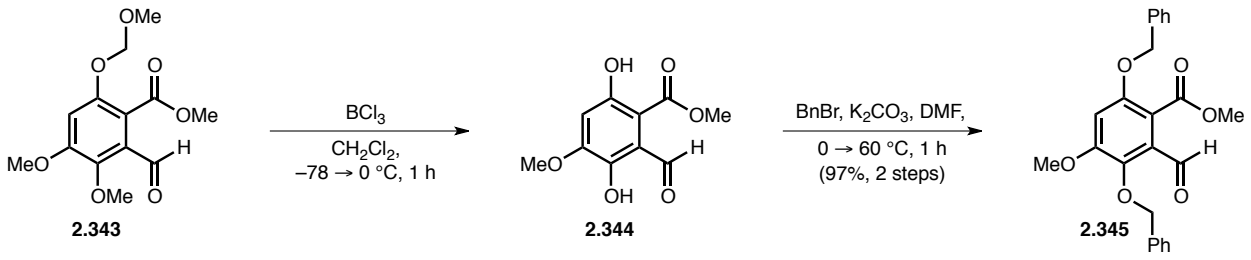
^{13}C NMR (125 MHz, $CDCl_3$) δ: 188.9, 167.3, 154.4, 150.6, 147.4, 127.2, 115.2, 106.4, 95.5, 62.6, 56.3, 56.2, 52.6.

FTIR (thin film) cm^{-1}: 3006, 2952, 2911, 2883, 2860, 2833, 1729, 1682, 1593, 1491, 1433, 1381, 1330, 1289, 1262, 1239, 1212, 1192, 1165, 1150, 1102, 1085, 1032, 979, 943, 918, 839, 810, 772, 612.

HRMS (ESI) (*m/z*) calc'd for $C_{13}H_{16}NaO_7$ $[M+Na]^+$: 307.0788, found 307.0803.

M.**p**.: 79–80 °C (EtOAc).

TLC (40% EtOAc in hexanes), R_f: 0.23 (UV, CAM).



Dibenzyl-protected aldehyde 2.345:

A 200-mL round-bottomed flask was charged with **2.343** (625 mg, 2.20 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (44 mL) was introduced, and the resultant solution cooled to –78 °C. A solution of boron trichloride in CH_2Cl_2 (1.0 M, 6.60 mL, 6.60 mmol, 3.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C. After 1 h, water (100 mL) and Et_2O (50 mL) were added to the stirred reaction mixture, which was subsequently warmed to ambient temperature. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with water (3 × 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford crude hydroquinone **2.344** as a yellow flocculent solid**,** which was used without further purification.

A 100-mL round-bottomed flask was charged with **2.344** and azeotropically dried with three portions of benzene. DMF (22.0 mL) was introduced, and the resultant solution cooled to 0 °C. Benzyl bromide (2.62 mL, 22.0 mmol, 10.0 equiv) and potassium carbonate (4.26 g, 30.8 mmol, 14.0 equiv) were then sequentially added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature and then heated to 60 °C. After 1 h the stirred reaction mixture was allowed to cool to ambient temperature before saturated aqueous ammonium chloride solution (50 mL) and Et_2O (50 mL) were added. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with saturated aqueous ammonium chloride solution (2 × 100 mL), water (3 × 100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography

(silica gel, eluent: gradient, 30% → 40% EtOAc in hexanes) to afford dibenzyl-protected aldehyde **2.345** (863 mg, 97% over two steps) as a colorless oil.

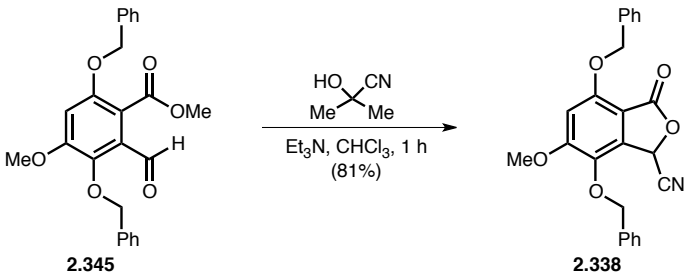
^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.18 (s, 1 H), 7.42–7.29 (m, 10 H), 6.76 (s, 1 H), 5.13 (s, 2 H), 5.06 (s, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.0, 167.4, 154.4, 152.0, 145.0, 136.1, 136.0, 128.6, 128.54, 128.51, 128.48, 128.0, 127.8, 127.0, 114.9, 104.8, 76.7, 71.7, 56.2, 52.5.

FTIR (thin film) cm^{-1}: 3029, 2946, 2872, 1730, 1691, 1593, 1491, 1442, 1366, 1333, 1263, 1197, 1168, 1073, 1024, 948, 829, 777, 740, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{22}NaO_6$ $[M+Na]^+$: 429.1309, found 429.1303.

TLC (40% EtOAc in hexanes), R_f: 0.39 (UV, CAM).



2.345 **2.338**

Cyanophthalide 2.338:

A 100-mL round-bottomed flask was charged with **2.345** (572 mg, 1.41 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. Chloroform (28 mL) was introduced, and the resultant solution stirred at ambient temperature. Triethylamine (392 μL, 2.81 mmol, 2.00 equiv) and acetone cyanohydrin (257 μL, 2.81 mmol, 2.00 equiv) were sequentially added to the reaction vessel dropwise via syringe. After 1 h, saturated aqueous ammonium chloride solution (30 mL) was added to the reaction mixture, which was stirred vigorously for 10 min. The layers were then separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 30% → 40% EtOAc in hexanes) to afford cyanophthalide **2.338** (458 g, 81%) as a white flocculent solid.

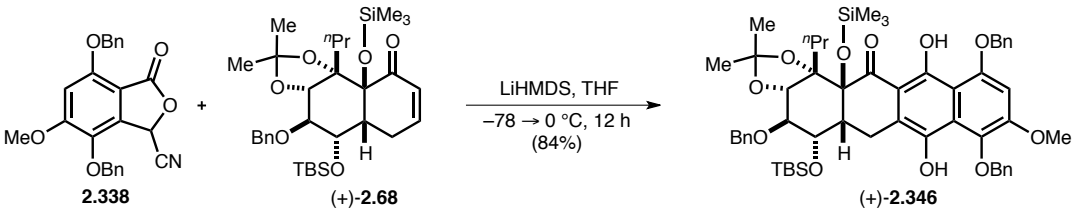
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 (d, J = 7.4 Hz, 2 H), 7.45–7.31 (m, 8 H), 6.61 (s, 1 H), 5.32 (s, 2 H), 5.10 (s, 2 H), 3.92 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.9, 159.6, 155.1, 136.44, 136.40, 135.5, 135.2, 128.82, 128.78, 128.77, 128.7, 128.3, 126.9, 113.9, 104.0, 101.0, 75.0, 71.5, 62.9, 56.6.

FTIR (thin film) cm^{-1}:2947, 2843, 1724, 1598, 1492, 1451, 1431, 1417, 1376, 1337, 1265, 1235, 1198, 1165, 1087, 1073, 1053, 995, 985, 855, 821, 776, 741, 699.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{19}NNaO_5$ $[M+Na]^+$: 424.1155, found 424.1136.

TLC (40% EtOAc in hexanes), R_f: 0.31 (UV, CAM).



Tetracycle (+)-**2.346**:

A 10-mL Schlenk tube was charged with **2.338** (67.7 mg, 169 μmol, 1.50 equiv) and AB-/HG-enone (+)-**2.68** (66.2 mg, 112 μmol, 1.00 equiv), which were then azeotropically dried with five portions of benzene. THF (2.25 mL) was then introduced, and the resultant solution was deoxygenated and then cooled to –78 °C. A solution of freshly prepared deoxygenated lithium hexamethyldisilazide in THF (1.0 M, 506 μL, 506 μmol, 4.50 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 30 min. After 12 h, a solution of acetic acid (100 μL) in THF (600 μL) was added via syringe rapidly down the vessel-wall to the vigorously stirred purple reaction mixture. After the reaction mixture turned fluorescent orange, a saturated aqueous ammonium chloride solution (2 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (10 mL) and water H_2O (10 mL), and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL), dried over anhydrous so sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 20% → 25% EtOAc in hexanes) to afford tetracycle (+)-**2.346**[240] (91.0 mg, 84%) as an orange flocculent solid.

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 14.36 (s, 1 H), 9.58 (s, 1 H), 7.65 (d, *J* = 7.5 Hz, 2 H), 7.55–7.32 (m, 12 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 6.72 (s, 1 H), 5.26 (s, 3 H), 5.11 (s, 3 H), 4.88 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 11.5 Hz, 1 H), 4.25 (dd, *J* = 4.6, 8.9 Hz, 1 H), 4.20 (d, *J* = 4.3 Hz, 1 H), 4.03 (s, 3 H), 3.91 (dd, *J* = 4.3, 8.9 Hz, 1 H), 3.31 (dd, *J* = 6.1, 17.9 Hz, 1 H), 2.99 (dd, *J* = 13.5, 17.9 Hz, 1 H), 2.40 (td, *J* = 5.4, 13.0 Hz,

[240] Minor oxidation of (+)-**2.346** occurs during purification and handling. Purification of highly oxygenated naphthalenes by flash column chromatography is difficult due to their adherence to silica gel (streaking).

1 H), 1.98 (ddd, *J* = 3.8, 12.6, 14.1 Hz, 1 H), 1.86 (ddd, *J* = 5.0, 12.1, 14.3 Hz, 1 H), 1.58–1.48 (m, 1 H), 1.43–1.29 (m, 1 H), 1.25 (s, 3 H), 1.19 (s, 3 H), 0.92 (s, 9 H), 0.86 (t, *J* = 7.3 Hz, 3 H), 0.19 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

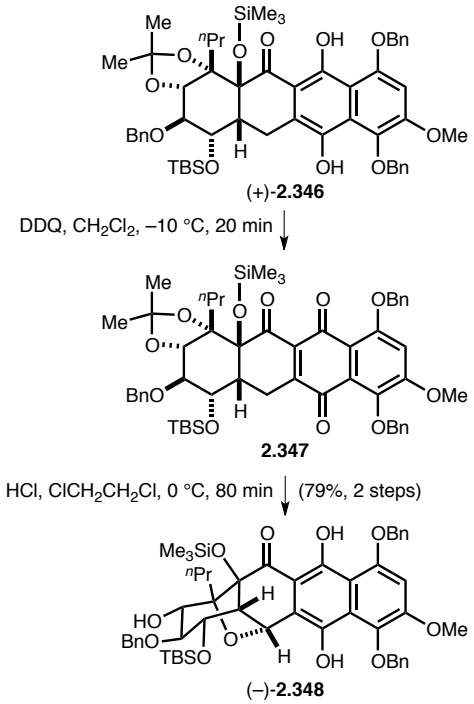
^{13}C NMR (125 MHz, CD_2Cl_2) δ: 203.1, 159.3, 157.6, 152.5, 140.1, 139.4, 137.2, 136.1, 134.8, 129.6, 129.2, 129.0, 128.9, 128.5, 128.20, 128.18, 127.63, 127.58, 124.9, 120.1, 111.6, 111.1, 109.8, 97.2, 87.4, 86.8, 83.4, 81.5, 77.5, 73.4, 72.1, 71.7, 56.8, 47.8, 40.2, 28.2, 27.6, 26.1, 21.4, 18.4, 17.8, 15.0, 2.3, –4.2, –4.5.

FTIR (thin film) cm^{-1}: 3327, 2954, 2935, 2896, 2856, 1712, 1602, 1499, 1457, 1440, 1401, 1378, 1343, 1311, 1250, 1231, 1216, 1168, 1116, 1082, 1035, 961, 912, 847, 803, 755, 698, 668.

HRMS (ESI) (*m/z*) calc'd for $C_{55}H_{70}NaO_{11}Si_2$ $[M+Na]^+$: 985.4349, found 985.4334.

$[\alpha]_D^{23}$: +93.9 (*c* = 1.85, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.45 (UV, CAM).



Pentacycle (–)-**2.348**:

A 10-mL round-bottomed flask was charged with (+)-**2.346** (91.0 mg, 94.0 μmol, 1.00 equiv) and was azeotropically dried with three portions of benzene. CH_2Cl_2 (1.88 mL) was introduced and the resultant solution was cooled to –10 °C. A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (32.2 mg, 142 μmol, 1.5 equiv) in CH_2Cl_2 (500 μL) was added dropwise via cannula to the stirred reaction mixture. The transfer was completed with two additional portions of CH_2Cl_2 (100 μL). After 20 min, a 1:1 mixture of 1% (w/v) aqueous sodium bisulfite solution (0.1 M, 2.5 mL) and saturated aqueous sodium bicarbonate solution (2.5 mL) was added to the reaction mixture. The mixture was diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with a 1:1 mixture of 1% (w/v) aqueous sodium bisulfite solution (0.1 M) and saturated aqueous sodium bicarbonate solution (2 × 10 mL), saturated aqueous sodium bicarbonate solution (10 mL), and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford naphthazarin **2.347**, which was used immediately without further purification.

A 250-mL round-bottomed flask was charged with **2.347** and azeotropically dried with five portions of benzene. 1,2-dichloroethane was then introduced (91.0 mL), and the resultant solution was cooled to 0 °C. A solution of anhydrous HCl in Et_2O (2.0 M, 2.35 mL, 4.70 mmol, 50.0 equiv) was added dropwise via syringe to the stirred solution. After 80 min, saturated aqueous sodium bicarbonate solution (50 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (2 × 100 mL), and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 20% → 25% EtOAc in hexanes) to afford pentacycle (–)-**2.348** (68.3 mg, 79% over two steps) as an orange film.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 13.93 (s, 1 H), 9.68 (s, 1 H), 7.66 (d, *J* = 7.4 Hz, 2 H), 7.55 (d, *J* = 6.1 Hz, 2 H), 7.51–7.34 (m, 10 H), 7.30 (t, *J* = 7.3 Hz, 1 H), 6.81 (s, 1 H), 5.86 (s, 1 H), 5.28 (s, 2 H), 5.14 (d, *J* = 10.3 Hz, 1 H), 5.11 (d, *J* = 10.2 Hz, 1 H), 4.94 (d, *J* = 11.6 Hz, 1 H), 4.90 (d, *J* = 11.5 Hz, 1 H), 4.18 (dd, *J* = 3.8, 7.5 Hz, 1 H), 4.10 (d, *J* = 6.1 Hz, 1 H), 4.05 (s, 3 H), 3.75 (t, *J* = 7.7 Hz, 1 H), 2.43 (d, *J* = 3.7 Hz, 1 H), 1.92–1.75 (m, 1 H), 1.72–1.56 (m, 1 H), 1.27–1.15 (m, 1 H), 1.02 (dt, *J* = 3.7, 13.2 Hz, 1 H), 0.95 (s, 9 H), 0.81 (t, *J* = 7.3 Hz, 3 H), 0.27 (s, 9 H), 0.14 (s, 3 H), 0.07 (s, 3 H).

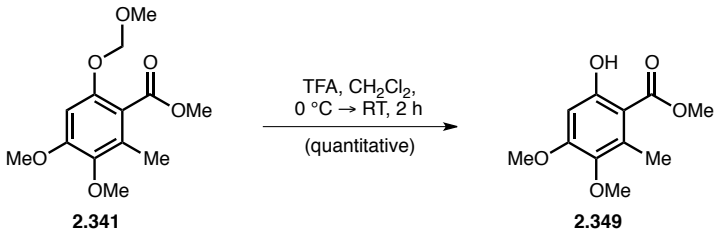
^{13}C NMR (125 MHz, CD_2Cl_2) δ: 202.6, 160.3, 157.9, 153.5, 140.1, 139.3, 137.2, 136.2, 136.1, 129.9, 129.6, 129.3, 129.1, 128.8, 128.5, 128.2, 127.9, 127.8, 125.5, 122.3, 112.2, 108.4, 98.5, 88.2, 87.6, 85.1, 77.8, 75.5, 74.5, 72.6, 72.4, 69.9, 58.3, 57.0, 35.8, 26.2, 18.4, 16.8, 15.2, 2.1, –4.0, –4.1.

FTIR (thin film) cm^{-1}: 3319, 2955, 2931, 2857, 1714, 1650, 1624, 1598, 1498, 1464, 1442, 1402, 1376, 1317, 1253, 1232, 1217, 1094, 1065, 1026, 954, 888, 841, 756, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{52}H_{64}NaO_{11}Si_2$ $[M+Na]^+$: 943.3879, found 943.3835.

$[\alpha]_D^{23}$: –20.6 (*c* = 2.31, CH_2Cl_2).

TLC (30% EtOAc in hexanes), R_f: 0.52 (UV, CAM).



2.341 **2.349**

Phenol 2.349:

A 250-mL round-bottomed flask was charged with **2.341** (1.38 g, 5.10 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (102 mL) was introduced, and the resultant solution cooled to 0 °C. Trifluoroacetic acid (1.95 mL, 25.5 mmol, 5.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. After 2 h, saturated aqueous sodium bicarbonate solution (100 mL) was added to the stirred reaction mixture. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford phenol **2.349** (1.15 g, quantitatve) as a white flocculent solid, which was used without further purification.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 11.56 (s, 1 H), 6.37 (s, 1 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.68 (s, 3 H), 2.45 (s, 3 H).

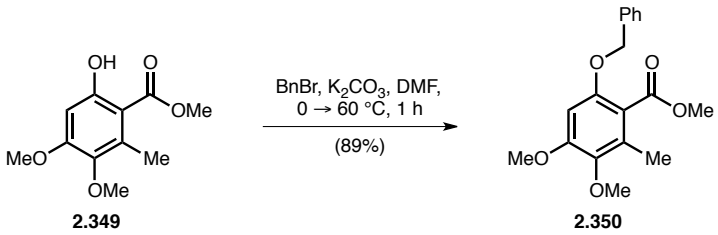
^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.3, 154.0, 152.3, 141.5, 136.8, 130.5, 128.5, 127.8, 127.0, 117.2, 97.0, 71.4, 60.4, 55.8, 52.0, 12.9.

FTIR (thin film) cm^{-1}: 2942, 2839, 1725, 1596, 1491, 1450, 1415, 1385, 1335, 1266, 1229, 1197, 1163, 1111, 1060, 1005, 943, 852, 842, 791, 773, 740, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{18}H_{20}NaO_5$ $[M+Na]^+$: 339.1203, found 339.1198.

M.p.: 64–65 °C (Et_2O).

TLC (30% EtOAc in hexanes), R_f: 0.40 (UV, CAM).



Benzyl Ether 2.350:

A 100-mL round-bottomed flask was charged with **2.349** (1.15 g, 5.08 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. DMF (51 mL) was introduced, and the resultant solution cooled to 0 °C. Benzyl bromide (3.00 mL, 25.4 mmol, 5.00 equiv) and potassium carbonate (4.91 g, 35.6 mmol, 7.00 equiv) were then sequentially added to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature and then heated to 60 °C. After 1 h the stirred reaction mixture was allowed to cool to ambient temperature before saturated aqueous ammonium chloride solution (25 mL) and Et_2O (25 mL) were added. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 50 mL). The combined organic layers were then washed with saturated aqueous ammonium chloride solution (2 × 100 mL), water (3 × 100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 30% EtOAc in hexanes) to afford benzyl ether **2.350** (1.44 g, 89%) as a white flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.34 (m, 4 H), 7.33–7.28 (m, 1 H), 6.40 (s, 1 H), 5.08 (s, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.72 (s, 3 H), 2.23 (s, 3 H).

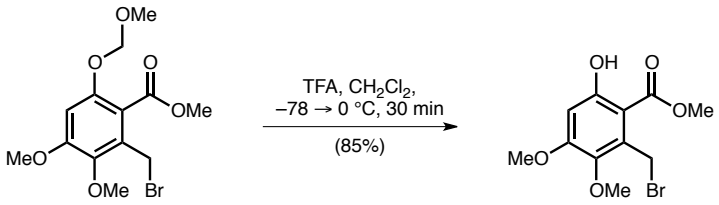
^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 161.1, 158.2, 140.6, 133.9, 104.6, 98.3, 60.5, 55.7, 51.9, 14.7.

FTIR (thin film) cm^{-1}: 2945, 2843, 1647, 1600, 1481, 1446, 1373, 1326, 1249, 1222, 1165, 1067, 1042, 953, 823, 797, 778, 669, 609, 453.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{14}NaO_5$ $[M+Na]^+$: 249.0733, found 249.0740.

M.**p**.: 60–61 °C (Et_2O).

TLC (30% EtOAc in hexanes), R_f: 0.44 (UV, CAM).



2.342 **2.353**

Phenol 2.353:

A 100-mL round-bottomed flask was charged with **2.342** (502 mg, 1.44 mmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (28.8 mL) was introduced, and the resultant solution cooled to –78 °C. Trifluoroacetic acid (550 µL, 7.18 mmol, 5.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C. After 30 min, saturated aqueous sodium bicarbonate solution (30 mL) was added to the stirred reaction mixture. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 30% EtOAc in hexanes) to afford phenol **2.353** (374 mg, 85%) as a white flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.63 (s, 1 H), 6.49 (s, 1 H), 5.00 (s, 2 H), 4.00 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H).

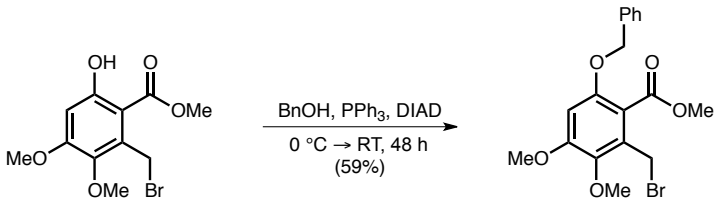
^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 161.5, 158.2, 141.4, 132.4, 102.8, 101.4, 61.1, 55.9, 52.3, 26.0.

FTIR (thin film) cm^{-1}: 2953, 1651, 1602, 1487, 1446, 1428, 1389, 1338, 1298, 1258, 1233, 1053, 1016, 967, 956, 859, 816, 804, 778, 676, 610, 593, 535, 460, 430.

HRMS (ESI) (*m/z*) calc'd for $C_{11}H_{13}BrNaO_5$ $[M+Na]^+$: 326.9839, found 326.9826.

M.**p**.: 114–116 °C (Et_2O).

TLC (30% EtOAc in hexanes), R_f: 0.56 (UV, CAM).



2.353 **2.354**

Benzyl ether 3.354:

A 25-mL round-bottomed flask was charged with **3.353** (274 mg, 898 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. THF (4.5 mL), benzyl alcohol (372 μL, 3.59 mmol, 4.00 equiv), and triphenylphosphine (942 mg, 3.59 mmol, 4.00 equiv) were introduced, and the resultant solution cooled to 0 °C. Diisopropyl azodicarboxylate (744 μL, 3.59 mmol, 4.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. After 48 h, brine (8 mL) and Et_2O (8 mL) were added to the stirred reaction mixture. The layers were separated, and the aqueous layer was further extracted with Et_2O (3 × 15 mL). The combined organic layers were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified through two flash column chromatography operations (silica gel, eluent: gradient, 25% → 30% EtOAc in hexanes) and (silica gel, eluent: 5% EtOAc in CH_2Cl_2) to afford benzyl ether **3.354** (210 mg, 59%) as a white flocculent solid.

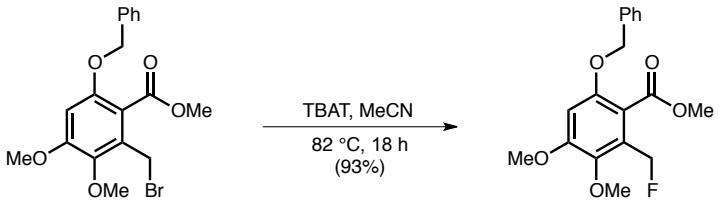
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.35 (m, 4 H), 7.32 (t, *J* = 6.9 Hz, 1 H), 6.51 (s, 1 H), 5.09 (s, 2 H), 4.66 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.83 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.1, 154.4, 153.1, 141.6, 136.5, 130.6, 128.5, 128.0, 127.0, 116.2, 99.9, 71.7, 61.1, 55.9, 52.3, 23.8.

FTIR (thin film) cm^{-1}: 2920, 2851, 1721, 1594, 1490, 1451, 1431, 1413, 1383, 1337, 1268, 1234, 1221, 1199, 1142, 1086, 1072, 1030, 950.

HRMS (ESI) (*m/z*) calc'd for $C_{18}H_{19}BrNaO_5$ $[M+Na]^+$: 417.0308, found 417.0295.

TLC (30% EtOAc in hexanes), R_f: 0.375 (UV, CAM).



2.354 **2.355**

Benzyl fluoride 2.355:

A 25-mL round-bottomed flask was charged with **2.354** (360 mg, 910 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. The flask was equipped with a reflux condenser and then purged with argon before MeCN (9.1 mL) was introduced. Tetrabutylammonium difluorotriphenylsilicate (1.48 g, 2.73 mmol, 3.00 equiv) was then added in a single portion to the stirred reaction mixture, which was subsequently heated to 82 °C. After 18 h, the reaction mixture was allowed to cool to ambient temperature and saturated aqueous sodium bicarbonate solution (7 mL) and Et_2O (7 mL) were added. The layers were separated, and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 20% EtOAc in hexanes) to afford benzyl fluoride **2.355** (283 mg, 93%) as a colorless oil.

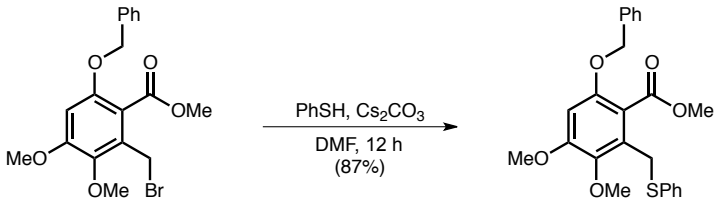
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.35 (m, 4 H), 7.31 (t, *J* = 6.8 Hz, 1 H), 6.57 (s, 1 H), 5.55 (s, 1 H), 5.45 (s, 1 H), 5.10 (s, 2 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.2, 154.3 (*J* = 1.8 Hz), 152.8 (*J* = 2.3 Hz), 142.0 (*J* = 4.1 Hz), 136.5, 128.5, 128.2 (*J* = 15.6 Hz), 127.9, 127.0, 116.6 (*J* = 2.7 Hz), 100.5 (*J* = 3.2 Hz), 77.0 (*J* = 164 Hz), 71.7, 61.8, 55.9, 52.3.

FTIR (thin film) cm^{-1}: 3064, 3033, 3019, 2983, 2941, 2892, 1795, 1629, 1609, 1514, 1456, 1440, 1358, 1337, 1264, 1236, 1202, 1159, 1093, 1057, 1014, 997, 984, 968, 908, 836, 758, 729, 704, 650, 551, 452.

HRMS (ESI) (*m/z*) calc'd for $C_{18}H_{19}FNaO_5$ $[M+Na]^+$: 357.1109, found 357.1101.

TLC (40% EtOAc in hexanes), R_f: 0.50 (UV, CAM).



2.354 **2.357**

Thioether 2.357:

A 5-mL vial was charged with benzyl ether **2.354** (210 mg, 531 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. DMF (2.7 mL), freshly distilled thiophenol (71 μL, 691 μmol, 1.30 equiv), and cesium carbonate (225 mg, 691 μmol, 1.30 equiv) were sequential introduced. The vial was sealed with a PTFE coated cap and the resultant solution stirred at ambient temperature. After 12 h, the reaction mixture was diluted with Et_2O (10 mL), washed with H_2O (3 × 5 mL) and brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 20% → 30% EtOAc in hexanes) to afford thioether **2.357** (196 mg, 87%) as a colorless oil.

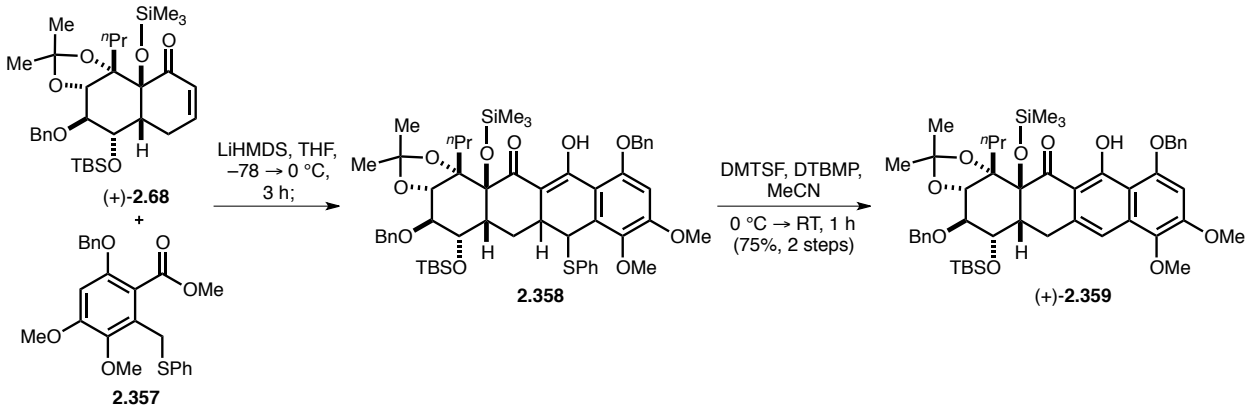
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.35 (m, 6 H), 7.31 (t, *J* = 7.2 Hz, 1 H), 7.26 (t, *J* = 7.2 Hz, 2 H), 7.18 (t, *J* = 7.0 Hz, 1 H), 6.46 (s, 1 H), 5.08 (s, 2 H), 4.30 (s, 2 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.70 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.6, 154.2, 153.0, 141.6, 136.7, 136.6, 130.8, 130.4, 128.7, 128.4, 127.8, 127.0, 126.4, 116.3, 98.7, 71.6, 61.3, 55.8, 52.1, 30.6.

FTIR (thin film) cm^{-1}: 2943, 2836, 1717, 1594, 1487, 1450, 1430, 1335, 1268, 1239, 1198, 1150, 1070, 1031, 741, 696.

HRMS (ESI) (*m/z*) calc'd for $C_{24}H_{24}NaO_5S$ $[M+Na]^+$: 447.1237, found 447.1231.

TLC (30% EtOAc in hexanes), R_f: 0.40 (UV, CAM).



Naphthalene (+)-**2.359**:

A 10-mL round-bottomed flask was charged with **2.357** (133 mg, 314 μmol, 3.00 equiv) and AB-/HG-enone (+)-**2.68** (61.7 mg, 105 μmol, 1.00 equiv), which were then azeotropically dried with three portions of benzene. THF (2.1 mL) was then introduced, and the resultant solution cooled to –78 °C. A solution of freshly prepared lithium hexamethyldisilazide in THF (1.0 M, 630 μL, 630 μmol, 6.00 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 30 min. After 3 h, a saturated aqueous ammonium chloride solution (3 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with EtOAc (10 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (20 mL), and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 1% → 2% → 4% EtOAc in CH_2Cl_2-hexanes (1:1)) to afford impure tetracycle **2.358**[241,242] (97.5 mg) as an orange flocculent solid and recovered **2.357** (78.2 mg) as a colorless oil.

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[241] Minor oxidation of **2.358** occurs during purification and handling. Purification of highly oxygenated naphthalenes by flash column chromatography is difficult due to their adherence to silica gel (streaking).

[242] A significant loss of material is observed upon purification of highly oxygenated naphthalenes utilizing preparatory thin-layer chromatography, therefore **2.358** was carried forward to remove the minor impurities more easily at a subsequent stage without severe detriment to the overall yield.

A 25-mL round-bottomed flask was charged with **2.358** (97.5 mg, 99.3 μmol, 1.00 equiv) and 2,6-di-*t*-butyl-4-methylpyridine (40.8 mg, 199 μmol, 2.00 equiv) and was then azeotropically dried with three portions of benzene. MeCN (9.93 mL) was introduced, and the resultant solution cooled to 0 °C. A solution of dimethyl(methylthio)sulfonium tetrafluoroborate (21.4 mg, 109 μmol, 1.10 equiv) in MeCN (300 μL) was then added dropwise via syringe to the stirred reaction mixture. The transfer was completed with two additional portions of MeCN (200 μL). After 30 min, the stirred reaction mixture was allowed to warm to ambient temperature over 1 h before saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was partitioned with EtOAc (20 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 15% → 20% EtOAc in hexanes) to afford naphthalene (+)-**2.359**[243] (27.0 mg, 75% over two steps) as an orange film.

^{1}H NMR (500 MHz, CD_2Cl_2) δ: 15.00 (s, 1 H), 7.65 (d, *J* = 7.4 Hz, 2 H), 7.49–7.40 (m, 4 H), 7.36 (t, *J* = 7.6 Hz, 3 H), 7.29 (t, *J* = 7.1 Hz, 1 H), 7.23 (s, 1 H), 6.65 (s, 1 H), 5.24 (s, 2 H), 4.88 (d, *J* = 11.7 Hz, 1 H), 4.69 (d, *J* = 11.7 Hz, 1 H), 4.28–4.21 (m, 2 H), 3.97 (s, 3 H), 3.87–3.80 (m, 4 H), 3.48 (t, *J* = 15.4 Hz, 1 H), 3.20 (dd, *J* = 5.1, 16.9 Hz, 1 H), 2.46 (td, *J* = 4.9, 13.7 Hz, 1 H), 2.13 (ddd, *J* = 3.9, 12.1, 14.3 Hz, 1 H), 1.81 (ddd, *J* = 5.1, 12.2, 14.3 Hz, 1 H), 1.65–1.50 (m, 1 H), 1.49–1.35 (m, 1 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 0.93 (s, 9 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.18 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ: 203.2, 167.2, 157.0, 153.7, 139.5, 139.2, 137.6, 136.4, 135.4, 129.1, 128.7, 128.4, 128.3, 127.9, 127.7, 111.8, 110.7, 109.8, 109.6, 97.1, 87.8, 86.3, 83.4, 81.9, 73.3, 72.1, 71.7, 61.3, 56.8, 49.3, 40.9, 28.0, 27.7, 27.5, 26.3, 18.6, 18.4, 15.3, 2.3, –4.1, –4.2.

FTIR (thin film) cm^{-1}: 2958, 2932, 2855, 1621, 1598, 1580, 1462, 1371, 1306, 1250, 1109, 1076, 1032, 843, 779, 741, 700, 561.

HRMS (ESI) (*m/z*) calc'd for $C_{49}H_{67}O_{10}Si_2$ $[M+H]^+$: 871.4267, found 871.4285.

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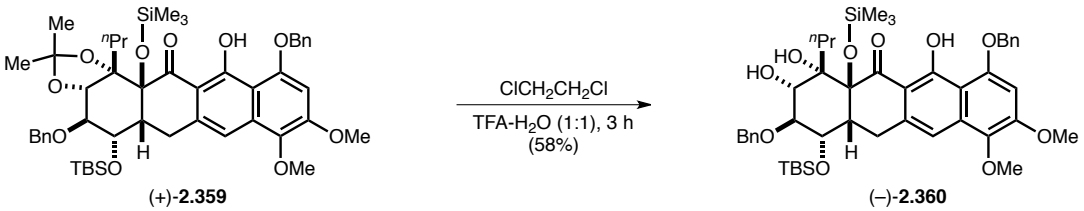
[243] Minor oxidation of (+)-**2.359** occurs during purification and handling.

$[\alpha]_D^{23}$: +60.0 (*c* = 0.97, CH_2Cl_2).

TLC (20% EtOAc in hexanes), R_f: 0.37 (UV, CAM).



(+)-**2.359** (–)-**2.360**

Triol (–)-**2.360**:

A 50-mL Schlenk tube was charged with (+)-**2.359** (73.5 mg, 84.4 μmol, 1.00 equiv) and 1,2-dichloroethane (15.0 mL) and the resultant solution was deoxygenated. A freshly deoxygenated solution of trifluoroacetic acid (3.75 mL) and H_2O (3.75 mL) was added to the reaction vessel via syringe. The Schlenk tube was sealed and the resultant reaction mixture was vigorously stirred at ambient temperature. After 3 h, saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was partitioned with EtOAc (20 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (40 mL) and brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resultant orange film was purified by semi-preparatory HPLC on a Agilent Prep-Sil column [10 μm, 30.0 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: EtOAc, solvent B: hexanes, gradient elution with 10% → 30% A over 35 min, flow rate: 30.0 mL/min]. Fractions eluting at 24–26 min concentrated under reduced pressure to afford triol (–)-**2.360** (40.8 mg, 58%) as a orange film.

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 15.19 (s, 1 H), 7.64 (d, *J* = 7.6 Hz, 2 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.42–7.34 (m, 5 H), 7.31 (t, *J* = 7.0 Hz, 1 H), 7.25 (s, 1 H), 6.65 (s, 1 H), 5.24 (s, 2 H), 5.03 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.26 (t, *J* = 6.5 Hz, 1 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 3.83 - 3.78 (m, 2 H), 3.67 (t, *J* = 15.2 Hz, 1 H), 3.22 (dd, *J* = 5.6, 17.0 Hz, 1 H), 2.59 (td, *J* = 5.6, 13.2 Hz, 1 H), 2.24 (br. s., 1 H), 2.09 (br. s., 1 H), 1.86 (dt, *J* = 4.6, 13.3 Hz, 1 H), 1.72 (dt, *J* = 4.3, 13.4 Hz, 1 H), 1.50 (ddd, *J* = 6.4, 12.8, 18.8 Hz, 1 H), 1.21 (ddd, *J* = 6.4, 12.4, 19.0 Hz, 1 H), 1.00 (s, 9 H), 0.84 (t, *J* = 7.2 Hz, 3 H), 0.19 - 0.15 (m, 12 H), 0.13 (s, 3 H).

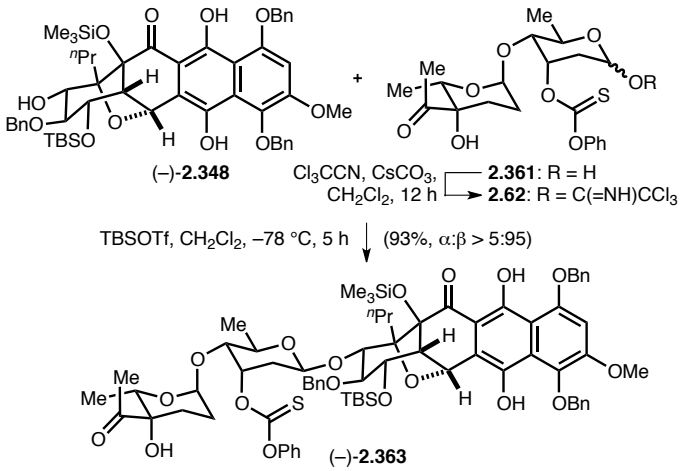
^{13}C NMR (125 MHz, CD_2Cl_2) δ: 203.5, 167.4, 157.0, 153.8, 140.1, 139.7, 137.6, 136.4, 135.4, 129.12, 129.08, 128.5, 128.4, 128.3, 127.8, 112.1, 110.5, 110.0, 97.2, 82.4, 82.0, 80.1, 76.0, 75.1, 72.8, 72.1, 61.3, 56.8, 49.5, 38.5, 28.5, 26.4, 18.7, 18.6, 15.2, 2.3, –3.9, –4.2.

FTIR (thin film) cm^{-1}: 3219, 2951, 2927, 2906, 2882, 2835, 1566, 1467, 1443, 1410, 1318, 1300, 1251, 1209, 1165, 1106, 1065, 1037, 915, 806, 744, 699, 676, 649, 584, 548, 479, 454.

HRMS (ESI) (*m/z*) calc'd for $C_{46}H_{63}O_{10}Si_2$ $[M+H]^+$: 831.3954, found 831.3913.

$[\alpha]_D^{23}$: –2.3 (*c* = 1.46, CH_2Cl_2).

TLC (20% EtOAc in hexanes), R_f: 0.42 (UV, CAM).



2-Deoxy-β-glycoside (–)-**2.363**:

A 2-mL vial was charged with hemiacetal **2.361** (28.0 mg, 64.0 μmol, 2.5 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (640 μL), freshly distilled trichloroacetonitrile (64.2 μL, 640 μmol, 25.0 equiv), and cesium carbonate (4.2 mg, 12.8 μmol, 0.50 equiv) were sequential introduced. The vial was sealed with a PTFE coated cap and the resultant solution stirred at ambient temperature. After 12 h, the tan reaction mixture was diluted with CH_2Cl_2 (1 mL), filtered through a pad of Celite, and with CH_2Cl_2 (3 × 2 mL). The filtrate was concentrated under reduced pressure to afford glycosyl trichloroacetimidate **2.62** as a tan foam that was used immediately without further purification.

A 1-mL vial was charged with freshly prepared glycosyl trichloroacetimidate **2.62** and pentacyle (–)-**2.348** (24.0 mg, 25.0 μmol, 1.00 equiv) and azeotropically dried with four portions of benzene. CH_2Cl_2 was then introduced (500 μL), and the resultant solution was cooled to –78 °C. A freshly prepared solution of distilled *tert*-butyldimethylsilyl trifluoromethanesulfonate in CH_2Cl_2 (1.0 M, 64.0 μL, 64.0 μmol, 2.50 equiv) was added to the stirred reaction mixture dropwise via syringe. After 5 h, triethylamine (100 μL, 717 μmol, 28.7 equiv) was added to the stirred, dark green reaction mixture. After 5 min, a saturated aqueous sodium bicarbonate solution (400 μL) was added and the resultant mixture was allowed to warm to ambient temperature. The mixture was diluted with aqueous sodium bicarbonate solution (5 mL) and EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 ×

5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 2% → 5% → 20% EtOAc in CH_2Cl_2) to afford 2-iodo-β-glycoside (–)-**2.363** (31.0 mg, 93%) as an orange film.

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 13.90 (s, 1 H), 9.64 (s, 1 H), 7.65 (d, *J* = 7.6 Hz, 2 H), 7.53 (d, *J* = 6.9 Hz, 2 H), 7.49–7.40 (m, 10 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.35–7.29 (m, 3 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 6.80 (s, 1 H), 5.88 (s, 1 H), 5.72 (q, *J* = 3.0 Hz, 1 H), 5.30–5.24 (m, 2 H), 5.16 (d, *J* = 11.3 Hz, 1 H), 5.14–5.09 (m, 2 H), 4.91 (d, *J* = 3.4 Hz, 1 H), 4.87 (dd, *J* = 1.6, 9.7 Hz, 1 H), 4.83 (d, *J* = 11.3 Hz, 1 H), 4.30–4.24 (m, 2 H), 4.15 (dd, *J* = 3.9, 7.6 Hz, 1 H), 4.05 (s, 3 H), 3.89 (t, *J* = 7.6 Hz, 1 H), 3.80 (qd, *J* = 6.1, 9.7 Hz, 1 H), 3.56 (s, 1 H), 3.46 (dd, *J* = 3.0, 9.7 Hz, 1 H), 2.46 (ddd, *J* = 2.1, 3.4, 14.9 Hz, 1 H), 2.41 (d, *J* = 3.9 Hz, 1 H), 2.25 (dt, *J* = 4.5, 13.4 Hz, 1 H), 2.19 (s, 3 H), 2.04–1.97 (m, 2 H), 1.92 (ddd, *J* = 2.4, 9.8, 14.7 Hz, 1 H), 1.74 (t, *J* = 12.9 Hz, 3 H), 1.47 (ddd, *J* = 2.6, 4.3, 13.1 Hz, 1 H), 1.19–1.05 (m, 2 H), 0.99 (d, *J* = 6.2 Hz, 3 H), 0.90 (s, 9 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.84 (t, *J* = 6.9 Hz, 3 H), 0.29 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H).

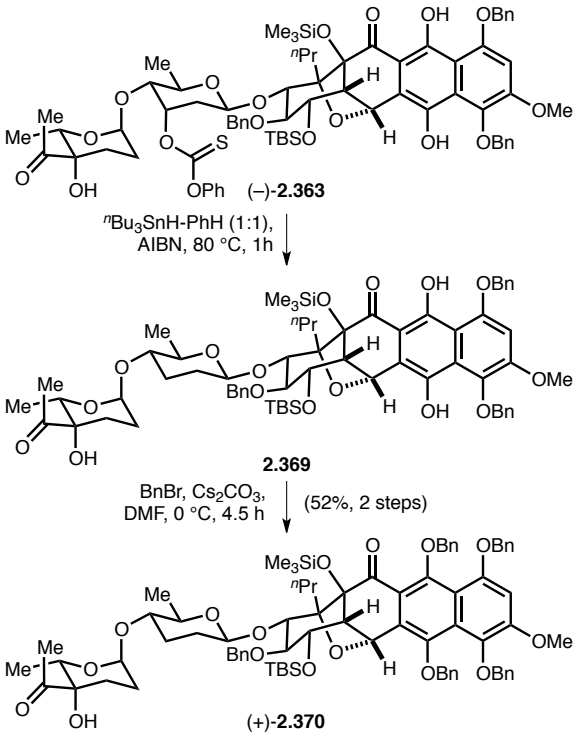
^{13}C NMR (125 MHz, CD_2Cl_2) δ: 210.6, 202.2, 194.8, 160.0, 157.7, 153.6, 153.3, 140.7, 139.2, 137.0, 136.1, 135.9, 129.9, 129.7, 129.4, 129.1, 128.9, 128.3, 128.1, 127.6, 127.1, 127.0, 126.8, 125.4, 122.1, 122.0, 112.0, 108.3, 100.0, 99.1, 98.3, 87.6, 85.7, 85.2, 82.2, 82.0, 79.3, 78.9, 77.6, 74.7, 72.6, 72.2, 70.2, 69.9, 67.2, 57.9, 56.8, 36.1, 35.9, 28.2, 25.9, 25.3, 25.0, 18.2, 17.8, 16.8, 15.1, 15.0, 2.0, –4.2, –4.4.

FTIR (thin film) cm^{-1}: 3480, 3320, 3066, 3033, 2955, 2933, 2858, 1709, 1623, 1597, 1491, 1471, 1402, 1374, 1318, 1265, 1213, 1198, 1123, 1075, 1075, 1021, 957, 888, 845, 775, 760, 735, 696, 608, 559, 498, 464.

HRMS (ESI) (*m/z*) calc'd for $C_{73}H_{91}O_{18}SSi_2$ $[M+Na]^+$: 1343.5459, found 1343.5429.

$[\alpha]_D^{23}$: –48.2 (*c* = 0.58, CH_2Cl_2).

TLC (20% EtOAc in CH_2Cl_2), R_f: 0.75 (UV, CAM).



Pentabenzyl-protected monomer (+)-**2.370**:

A 10-mL Schlenk tube was charged 2-iodo-β-glycoside (–)-**2.363** (126 mg, 93.8 μmol, 1.00 equiv) and 2,2′-azobis(2-methylpropionitrile) (308 mg, 1.88 mmol, 20.0 equiv) and azeotropically dried with three portions of benzene. Benzene (2.0 mL) and tributyltin hydride (2.0 mL) were introduced, and the resultant solution was deoxygenated. The reaction vessel was then sealed, and the stirred reaction mixture was warmed to 80 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature and was then quickly passed through a plug of silica gel (eluent: gradient, 15% → 100% EtOAc in CH_2Cl_2) to afford impure 2,3-dideoxy-β-glycoside **2.369** as an orange film, which was used without further purification.

A 10-mL Schlenk tube was charged **2.369** and azeotropically dried with three portions of benzene. DMF (4.77 mL) and freshly distilled benzyl bromide (176 μL, 1.48 μmol, 15.8 equiv) were introduced, and the resultant solution was deoxygenated. The reaction vessel was sealed, and place in the liquid nitrogen cooled well of a glovebox until the reaction mixture was frozen. Cesium carbonate (723 mg, 2.22 mmol, 23.7 equiv) was quickly introduced in one portion. The reaction vessel was sealed then

immediately removed from the glovebox and placed in an ice-water bath. After 3 h, H_2O (2 mL) and EtOAc (2 mL) were added to the vigorously stirred reaction mixture, which was subsequently allowed to warm to ambient temperature. The mixture was further diluted with H_2O (10 mL) and EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, eluent: gradient, 10% → 20% → 100% EtOAc in CH_2Cl_2) to afford penta-benzyl protected monomer (+)-**2.370** (66.7 mg, 52%) as an orange film.

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 7.62 (dd, *J* = 1.8, 7.6 Hz, 2 H), 7.46 (d, *J* = 7.6 Hz, 4 H), 7.39–7.26 (m, 14 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.22–7.18 (m, 1 H), 7.16–7.13 (m, 4 H), 6.80 (s, 1 H), 6.14 (s, 1 H), 5.20–5.15 (m, 3 H), 5.04–4.96 (m, 3 H), 4.90 (d, *J* = 10.3 Hz, 1 H), 4.86–4.79 (m, 3 H), 4.67 (d, *J* = 10.0 Hz, 1 H), 4.58 (dd, *J* = 1.8, 9.1 Hz, 1 H), 4.32 (d, *J* = 7.6 Hz, 1 H), 4.24 (q, *J* = 6.5 Hz, 1 H), 4.19 (dd, *J* = 3.8, 7.6 Hz, 1 H), 3.93 (d, *J* = 7.6 Hz, 1 H), 3.82 (s, 3 H), 3.47 (s, 1 H), 3.24 (qd, *J* = 6.1, 9.1 Hz, 1 H), 3.12 (dt, *J* = 4.7, 9.7 Hz, 1 H), 2.49 (d, *J* = 3.8 Hz, 1 H), 2.22–2.18 (m, 4 H), 1.94–1.89 (m, 2 H), 1.88–1.82 (m, 1 H), 1.65–1.55 (m, 3 H), 1.39 (s, 1 H), 0.99 (d, *J* = 5.9 Hz, 3 H), 0.91–0.85 (m, 4 H), 0.84–0.78 (m, 12 H), 0.30 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

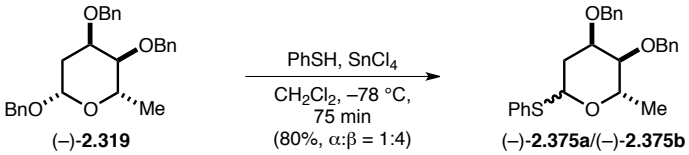
^{13}C NMR (125 MHz, CD_2Cl_2) δ: 211.3, 195.5, 158.6, 156.1, 154.2, 144.7, 140.9, 138.4, 138.1, 138.0, 137.3, 136.8, 135.8, 129.6, 129.4, 129.1, 128.7, 128.61, 128.58, 128.5, 128.4, 128.3, 128.2, 128.1, 128.06, 128.05, 127.5, 127.0, 118.7, 118.5, 102.9, 101.3, 99.3, 88.9, 86.1, 85.1, 81.2, 80.0, 79.2, 78.7, 77.9, 77.8, 75.5, 74.8, 73.2, 72.8, 71.2, 67.0, 57.9, 56.8, 36.1, 32.0, 30.4, 28.4, 26.1, 25.45, 25.39, 18.4, 18.3, 17.0, 15.1, 15.0, 2.4, –4.1, –4.2.

FTIR (thin film) cm^{-1}: 3475, 3065, 3033, 2952, 2934, 2857, 1691, 1596, 1557, 1498, 1455, 1374, 1338, 1253, 1121, 1100, 1056, 1022, 986, 889, 846, 777, 735, 698, 553, 493, 465.

HRMS (ESI) (*m/z*) calc'd for $C_{80}H_{98}NaO_{16}Si_2$ $[M+Na]^+$: 1393.6286, found 1393.6289.

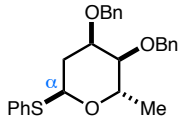
$[\alpha]_D^{23}$: +39.5 (*c* = 1.30, CH_2Cl_2).

TLC (10% EtOAc in CH_2Cl_2), R_f: 0.62 (UV, CAM).



Thiophenyl Glycoside (–)-2.375a and (–)-2.375b:

A 25-mL round-bottomed flask was charged with alcohol (–)-**2.319** (197 mg, 471 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (4.71 mL) and thiophenol (83 μL, 707 μmol, 20.0 equiv) were introduced and the resultant solution was cooled to –78 °C. A freshly prepared solution of tin(IV) tetrachloride in CH_2CH_2 (1.0 M, 83 μL, 707 μmol, 1.5 equiv) was added dropwise via syringe to the stirred reaction mixture. After 75 min, saturated aqueous sodium bicarbonate solution (5 mL) was added to the cold reaction mixture, which was subsequently allowed to warm to ambient temperature. The resultant heterogeneous mixture was filtered through a pad of Celite and rinsed with water (15 mL) and Et_2O (3 × 10 mL). The layers of the filtrate were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers washed with brine (50 mL) and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resultant yellow oil was purified by flash column chromatography (silica gel, eluent: gradient, 5 → 10 → 50% EtOAc in hexanes) to afford α-thiophenyl glycoside (–)-**2.375a** (32 mg, 16%) and β-thiophenyl glycoside (–)-**2.375b** (126 mg, 64%) as a colorless oils.[244]



(–)-**2.375a**

α-Thiophenyl Glycoside (–)-2.375a:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.50 (d, *J* = 7.8 Hz, 2 H), 7.48 (d, *J* = 7.3 Hz, 2 H), 7.39–7.25 (m, 10 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 5.44 (d, *J* = 6.2 Hz, 1 H), 4.87 (d, *J* = 12.3 Hz, 1 H), 4.69 (qd, *J* = 6.3, 9.1 Hz, 1 H), 4.60 (d, *J* = 12.5 Hz, 1 H), 4.55 (d, *J* = 11.9 Hz, 1 H), 4.40 (d, *J* = 11.9 Hz, 1 H), 4.01–3.93 (m, 1 H),

[244] Stereochemical assignment of anomeric position based on $J_{DG1'\text{-}DG2'}$.

3.15 (dd, *J* = 2.7, 9.3 Hz, 1 H), 2.52 (dd, *J* = 3.2, 14.7 Hz, 1 H), 2.12 (ddd, *J* = 2.4, 6.3, 14.7 Hz, 1 H), 1.32 (d, *J* = 6.3 Hz, 3 H).

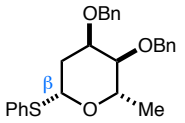
^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.4, 138.3, 138.1, 130.4, 128.7, 128.3, 128.0, 127.7, 127.6, 127.5, 126.5, 83.4, 80.3, 70.9, 70.8, 69.5, 64.5, 34.2, 18.1.

FTIR (thin film) cm^{-1}: 3060, 3029, 2927, 2857, 1453, 1223, 1159, 1099, 1087, 1027, 1007, 739, 696.

HRMS (ESI) (*m/z*) calc'd for $C_{26}H_{28}NaO_3S$ $[M+Na]^+$: 443.1651, found 443.1669.

$[\alpha]_D^{23}$: –293 (*c* = 1.60, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.32 (UV, CAM).



(–)-**2.375b**

β-Thiophenyl glycoside (–)-2.375b:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 7.3 Hz, 2 H), 7.40–7.22 (m, 13 H), 4.69 (d, *J* = 12.3 Hz, 1 H), 4.64 (d, *J* = 12.2 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.08 (qd, *J* = 6.2, 9.4 Hz, 1 H), 4.01–3.97 (m, 1 H), 3.14 (dd, *J* = 2.6, 9.5 Hz, 1 H), 2.35–2.27 (m, 1 H), 1.76 (ddd, *J* = 2.3, 12.0, 13.8 Hz, 1 H), 1.33 (d, *J* = 6.2 Hz, 3 H).

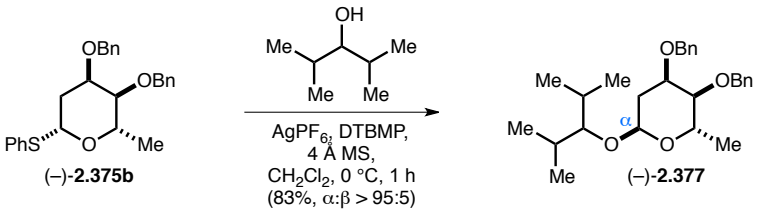
^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 137.9, 134.5, 130.8, 128.7, 128.3, 127.8, 127.75, 127.71, 127.6, 126.9, 80.6, 79.4, 71.8, 71.5, 71.2, 71.0, 35.7, 18.6.

FTIR (thin film) cm^{-1}: 3028, 2920, 2872, 1496, 1479, 1453, 1439, 1379, 1367, 1356, 1306, 1292, 1090, 1027, 1006, 917, 740, 698.

HRMS (ESI) (*m/z*) calc'd for $C_{26}H_{28}NaO_3S$ $[M+Na]^+$: 443.1656, found 443.1669.

$[\alpha]_D^{23}$: –56.5 (*c* = 1.41, CH_2Cl_2).

TLC (15% EtOAc in hexanes), R_f: 0.47 (UV, CAM).



Model DG/DG' α-glycoside (–)-2.377:

A 5-mL round-bottomed flask was charged with (–)-**2.375b** (16.6 mg, 39.5 μmol, 1.00 equiv) and 2,6-di-*t*-butyl-4-methylpyridine (36.5 mg, 158 μmol, 4.5 equiv) and was then azeotropically dried with three portions of benzene. CH_2Cl_2 (790 μL), 2,4-dimethyl-3-pentanol (8.3 μL, 59.2 μmol, 1.50 equiv), and 4 Å MS (100 mg) were introduced, the resultant solution cooled to 0 °C, and the reaction vessel was wrapped with aluminum foil. After 30 min, silver hexafluorophosphate (39.9 mg, 158 μmol, 4.00 equiv) was then added in a single portion to the stirred reaction mixture. After 1 h, pyridine (160 μL, 1.98 mmol, 50.0 equiv) was added to the stirred reaction mixture. After 30 min, the heterogeneous mixture was filtered through a plug of Celite and rinsed with EtOAc (3 × 5 mL). The filtrate was concentrated under reduced pressure and the resultant residue was purified by flash column chromatography (silica gel, eluent: 10% EtOAc in hexanes) to afford model DG/DG' α-glycoside (–)-**2.377** (14.0 mg, 83%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 7.2 Hz, 2 H), 7.35–7.30 (m, 6 H), 7.29–7.26 (m, 2 H), 4.82–4.78 (m, 2 H), 4.63 (d, *J* = 11.9 Hz, 1 H), 4.55 (d, *J* = 12.3 Hz, 1 H), 4.48–4.41 (m, 2 H), 3.91 (q, *J* = 3.1 Hz, 1 H), 3.14 (dd, *J* = 2.9, 9.1 Hz, 1 H), 3.06 (t, *J* = 5.0 Hz, 1 H), 2.40 (ddd, *J* = 1.0, 3.9, 14.6 Hz, 1 H), 1.91–1.78 (m, 2 H), 1.63 (ddd, *J* = 3.1, 4.7, 14.7 Hz, 1 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 0.98–0.88 (m, 12 H).

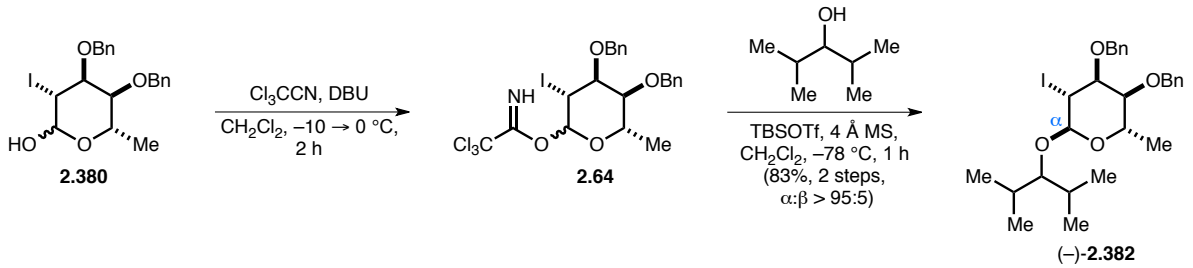
^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.8, 138.4, 128.3, 128.2, 127.9, 127.8, 127.5, 127.3, 97.6, 89.3, 80.0, 70.5, 69.9, 69.0, 63.7, 31.5, 31.0, 30.1, 20.6, 20.4, 18.5, 17.9, 17.8.

FTIR (thin film) cm^{-1}: 2958, 2929, 2870, 1496, 1453, 1383, 1365, 1339, 1226, 1204, 1147, 1097, 1005, 735, 697.

HRMS (ESI) (*m/z*) calc'd for $C_{27}H_{38}NaO_4$ $[M+Na]^+$: 449.2662, found 449.2653.

$[\alpha]_D^{23}$: –138.6 (*c* = 1.63, CH_2Cl_2).

TLC (10% EtOAc in hexanes), R_f: 0.39 (UV, CAM).



2-Iodo glycoside (–)-2.382:

A 5-mL round-bottomed flask was charged with hemiacetal **2.380** (31.3 mg, 69.0 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (690 μL) and freshly distilled trichloroacetonitrile (69 μL, 690 μmol, 10.0 equiv) were introduced, and the resultant solution cooled to –10 °C. DBU (2.0 μL, 13.8 μmol, 0.20 equiv) was added via syringe. After 1h, the reaction mixture was allowed to warm to 0 °C. After an additional 1 h the reaction mixture was concentrated under reduced pressure. The resultant tan residue filtered through a plug of neutral alumina (eluent: 25% EtOAc in hexanes) to afford glycosyl trichloroacetimidate **2.64** as a tan oil that was used immediately without further purification.

A 5-mL round-bottomed flask was charged with **2.64** and was azeotropically dried with three portions of benzene. CH_2Cl_2 (1.38 mL), 2,4-dimethyl-3-pentanol (14.5 μL, 104 μmol, 1.50 equiv), and 4 Å MS (100 mg) were introduced, and the resultant solution stirred at ambient temperature. After 30 min, the reaction mixture was cooled to –78 °C and a freshly prepared solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate in CH_2Cl_2 (1.0 M, 69.0 μL, 69 μmol, 1.00 equiv) was added dropwise via syringe to the cooled, stirred reaction mixture. After 1 h, triethylamine (100 μL, 717 μmol, 10.4 equiv) was added to the stirred reaction mixture. After 5 min, a saturated aqueous sodium bicarbonate solution (3 mL) was added and the heterogeneous mixture was filtered through a pad of Celite and rinsed with H_2O (10 mL) and EtOAc (3 × 5 mL). The layers of the filtrate were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was

then purified by flash column chromatography (silica gel, eluent: 3% EtOAc in hexanes) to afford 2-iodo-α-glycoside (–)-**2.382** (31.6 mg, 83%) as a white flocculent solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.27 (m, 10 H), 5.08 (s, 1 H), 4.74 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 2.4 Hz, 1 H), 4.58–4.51 (m, 2 H), 4.49–4.41 (m, 2 H), 4.01 (t, *J* = 3.1 Hz, 1 H), 3.85 (dd, *J* = 2.9, 9.2 Hz, 1 H), 3.06 (t, *J* = 4.9 Hz, 1 H), 1.93–1.76 (m, 2 H), 1.25 (d, *J* = 6.3 Hz, 3 H), 0.96–0.86 (m, 12 H).

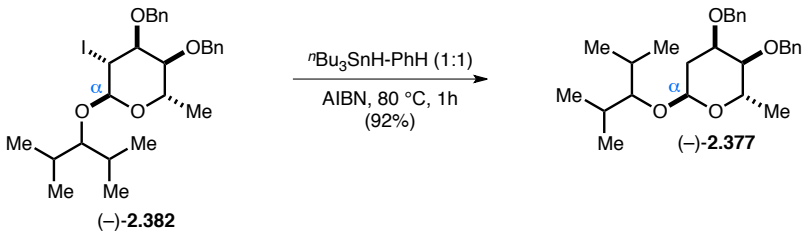
^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 137.9, 128.33, 128.28, 128.1, 128.0, 127.74, 127.66, 102.8, 90.5, 76.0, 75.9, 71.5, 71.4, 64.3, 30.9, 30.1, 26.8, 20.5, 20.3, 18.3, 17.8, 17.6.

FTIR (thin film) cm^{-1}: 2958, 2928, 2871, 1496, 1453, 1384, 1364, 1098, 1069, 1006, 735, 697.

HRMS (ESI) (*m/z*) calc'd for $C_{27}H_{37}INaO_4$ $[M+Na]^+$: 575.1629, found 575.1632.

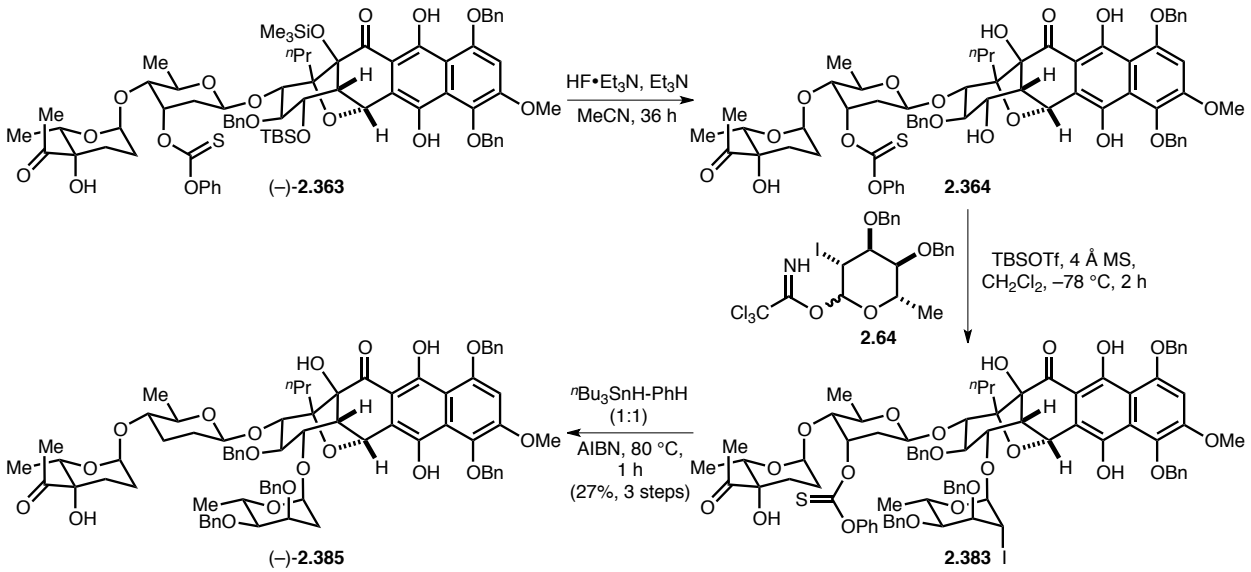
$[\alpha]_D^{23}$: –49.8 (*c* = 1.41, CH_2Cl_2).

TLC (10% EtOAc in hexanes), R_f: 0.47 (UV, CAM).



Model DG/DG' α-glycoside (–)-**2.377**:

A 5-mL Schlenk tube was charged with 2-iodo-α-glycoside (–)-**2.382** (30.6 mg, 55.4 μmol) and 2,2′-azobis(2-methylpropionitrile) (90.0 mg, 554 μmol, 10.0 equiv) and azeotropically dried with three portions of benzene. Benzene (550 μL) and tributyltin hydride (550 μL) were introduced, the reaction vessel was sealed, and the stirred reaction mixture was warmed to 80 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature and was then directly purified by flash column chromatography (silica gel, eluent: gradient, 1% → 5% EtOAc in hexanes) to afford model DG/DG' α-glycoside (–)-**2.377** (21.7 mg, 92%) as a colorless oil.



Bis-glycosylated monomer (–)-**2.385**:

A 10-mL Schlenk tube was charged 2-iodo-β-glycoside (–)-**2.363** (32.8 mg, 24.4 μmol, 1.00 equiv) and azeotropically dried with three portions of benzene. MeCN (300 μL) was introduced, and the resultant solution was deoxygenated. The solvent was then removed under reduced pressure. A second 10-mL Schlenk tube was charged sequentially with MeCN (4.4 mL), triethylamine trihydrofluoride (795 μL, 4.88 mmol, 200 equiv), and triethylamine (130 μL, 1.27 mmol, 52.1 equiv). The resultant solution was deoxygenated and transferred to the reaction vessel containing (–)-**2.363** via syringe. The reaction vessel was sealed and the resultant orange reaction mixture stirred at ambient temperature. After 36 h, aqueous potassium sodium phosphate pH 7.00 buffered solution (0.05 M, 5.0 mL) was added to the reaction mixture. The resultant mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was quickly passed through a plug of silica gel (eluent: gradient, 30% → 40% → 50% EtOAc in hexanes) to afford impure pentaol **2.364** (19.8 mg, 17.1 μmol) as an orange film that was used without further purification.

A 5-mL round-bottomed flask was charged with **2.364** and azeotropically dried with three portions of benzene. CH_2Cl_2 (700 μL) and 4 Å MS (60 mg) were introduced and the resultant mixture

stirred at ambient temperature. After 15 min, the reaction mixture was cooled to –78 °C and a freshly prepared solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate in CH_2Cl_2 (1.0 M, 64.0 μL, 64 μmol, 1.00 equiv) was added dropwise via syringe to the cooled, stirred reaction mixture. A separate 1-mL vial was charged with freshly prepared glycosyl trichloroacetimidate **2.64** (38.2 mg, 63.8 μmol, 3.73 equiv) and azeotropically dried with three portions of benzene. CH_2Cl_2 (382 μL) was introduced and the resultant solution was transferred dropwise to the reaction vessel containing **2.364** via syringe over 1 h. After an additional 30 min, triethylamine (250 μL, 1.79 mmol, 105 equiv) was added to the reaction mixture. After 5 min, a saturated aqueous sodium bicarbonate solution (1.0 mL) was added and the resultant mixture was allowed to warm to ambient temperature. The mixture was diluted with aqueous sodium bicarbonate solution (5 mL) and EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was quickly passed through a plug of silica gel (eluent: gradient, 20% → 30% → 50% EtOAc in hexanes) to afford impure 2-iodo-α-glycoside **2.383** (15.2 mg, 9.54 μmol) as an orange film that was used without further purification.

A 5-mL Schlenk tube was charged with 2-iodo-α-glycoside **2.383** and 2,2′-azobis(2-methylpropionitrile) (31.0 mg, 191 μmol, 20.0 equiv) and azeotropically dried with three portions of benzene. Benzene (300 μL) and tributyltin hydride (300 μL) were introduced, and the resultant solution was deoxygenated. The reaction vessel was then sealed, and the stirred reaction mixture was warmed to 80 °C. After 1 h, the reaction mixture was allowed to cool to ambient temperature and was then quickly passed through a plug of silica gel (eluent: gradient, 30% → 50% EtOAc in hexanes) to afford impure 2,3-dideoxy-α-glycoside (–)-**2.385**. The residue was further purified by preparatory thin-layer

chromatography (eluent: 50% EtOAc in hexanes) to afford bis-glycosylated monomer (–)-**2.385** (8.5 mg, 27% over three steps).[245]

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 13.24 (s, 1 H), 9.67 (s, 1 H), 7.63 (d, *J* = 7.2 Hz, 2 H), 7.48–7.30 (m, 15 H), 7.30–7.23 (m, 3 H), 7.22–7.16 (m, 5 H), 6.80 (s, 1 H), 5.87 (s, 1 H), 5.28 (d, *J* = 11.9 Hz, 1 H), 5.26 (d, *J* = 11.9 Hz, 1 H), 5.13 (d, *J* = 11.4 Hz, 1 H), 5.09 (d, *J* = 10.1 Hz, 1 H), 5.05 (d, *J* = 10.3 Hz, 1 H), 4.97 (dd, *J* = 1.6, 4.5 Hz, 1 H), 4.87 (d, *J* = 3.4 Hz, 1 H), 4.78 (d, *J* = 12.2 Hz, 1 H), 4.74 (d, *J* = 11.4 Hz, 1 H), 4.54 (dd, *J* = 1.9, 9.3 Hz, 1 H), 4.50 (d, *J* = 11.7 Hz, 1 H), 4.47 (d, *J* = 12.2 Hz, 1 H), 4.34 (d, *J* = 11.9 Hz, 1 H), 4.27 (d, *J* = 7.7 Hz, 1 H), 4.25 (q, *J* = 6.4 Hz, 1 H), 4.20 (qd, *J* = 6.5, 8.7 Hz, 1 H), 4.12 (s, 1 H), 4.08 (dd, *J* = 3.7, 8.5 Hz, 1 H), 4.03 (s, 3 H), 3.99 (t, *J* = 8.2 Hz, 1 H), 3.84 (q, *J* = 3.2 Hz, 1 H), 3.47 (s, 1 H), 3.30 (qd, *J* = 6.1, 9.0 Hz, 1 H), 3.18 (ddd, *J* = 4.8, 9.2, 10.4 Hz, 1 H), 3.07 (dd, *J* = 2.9, 8.7 Hz, 1 H), 2.66 (d, *J* = 4.0 Hz, 1 H), 2.23–2.16 (m, 5 H), 2.15–2.10 (m, 1 H), 1.95 (td, *J* = 4.0, 13.5 Hz, 1 H), 1.94–1.89 (m, 1 H), 1.74 (dt, *J* = 2.6, 13.4 Hz, 1 H), 1.68–1.60 (m, 2 H), 1.59–1.52 (m, 2 H), 1.51–1.45 (m, 1 H), 1.43 (ddd, *J* = 2.4, 4.5, 13.0 Hz, 1 H), 1.22–1.15 (m, 1 H), 1.14–1.07 (m, *J* = 6.1 Hz, 4 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.80 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ: 211.3, 201.5, 160.0, 158.0, 153.8, 140.8, 140.0, 139.6, 139.1, 137.1, 136.3, 136.0, 129.7, 129.3, 129.2, 129.1, 128.8, 128.76, 128.68, 128.6, 128.5, 128.24, 128.21, 127.9, 127.8, 127.4, 126.0, 122.1, 111.9, 107.4, 102.8, 99.3, 99.2, 98.4, 85.3, 84.6, 84.3, 81.1, 80.4, 80.0, 79.2, 79.0, 77.7, 75.51, 75.46, 72.4, 71.0, 70.5, 70.0, 67.0, 64.5, 57.0, 55.9, 35.4, 32.5, 31.8, 30.4, 28.4, 25.43, 25.40, 18.5, 18.1, 17.2, 15.2, 15.0.[246]

FTIR (thin film) cm^{-1}: 3466, 3318, 3064, 3031, 2961, 1932, 2871, 1705, 1653, 1598, 1497, 1455, 1374, 1322, 1256, 1219, 1164, 1123, 1076, 1056, 1020, 987, 918, 736, 698, 553.

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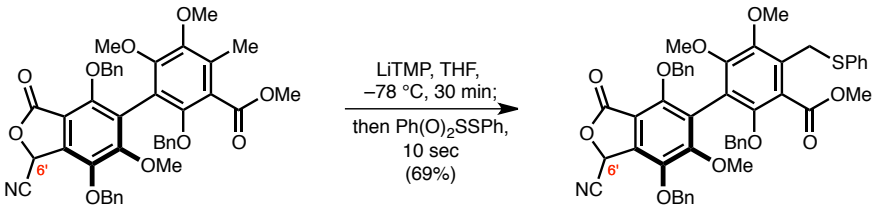
[245] Data for anomeric positions of bis-glycosylated monomer (–)-**2.385**: ^{1}H NMR (600 MHz, CD_2Cl_2): AM1' δ = 4.54 (dd, $J_{1,2a}$ = 9.3, $J_{1,2b}$ = 1.9, 1 H); DG1' δ = 4.97 (dd, $J_{1,2a}$ = 4.5, $J_{1,2b}$ = 1.6, 1 H). ^{13}C NMR (125 MHz, CD_2Cl_2): AM1' δ = 102.76; DG1' δ = 99.24. Reported data for anomeric positions of hibarimicin B: ^{1}H NMR (400 MHz, $CDCl_3$): AM1' δ = 4.460 (dd, $J_{1,2a}$ = 9.0, $J_{1,2b}$ = 1.8, 1 H); DG1' δ = 5.350 (dd, $J_{1,2a}$ = 3.0, $J_{1,2b}$ = <1.0, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): AM1' δ = 103.24; DG1' δ = 98.95.

[246] Due to the presence of multiple benzyl groups, one carbon resonance of (–)-**2.385** is unresolved as determined by comparison with related structures.

HRMS (ESI) (*m/z*) calc'd for $C_{77}H_{87}O_{19}$ $[M+H]^+$: 1315.5836, found 1315.5811.

$[\alpha]_D^{23}$: –30.0 (*c* = 0.35, CH_2Cl_2).

TLC (50% EtOAc in hexanes), R_f: 0.40 (UV, CAM).



2.388a **2.67a**
~2:1 mixture of C6'-epimers

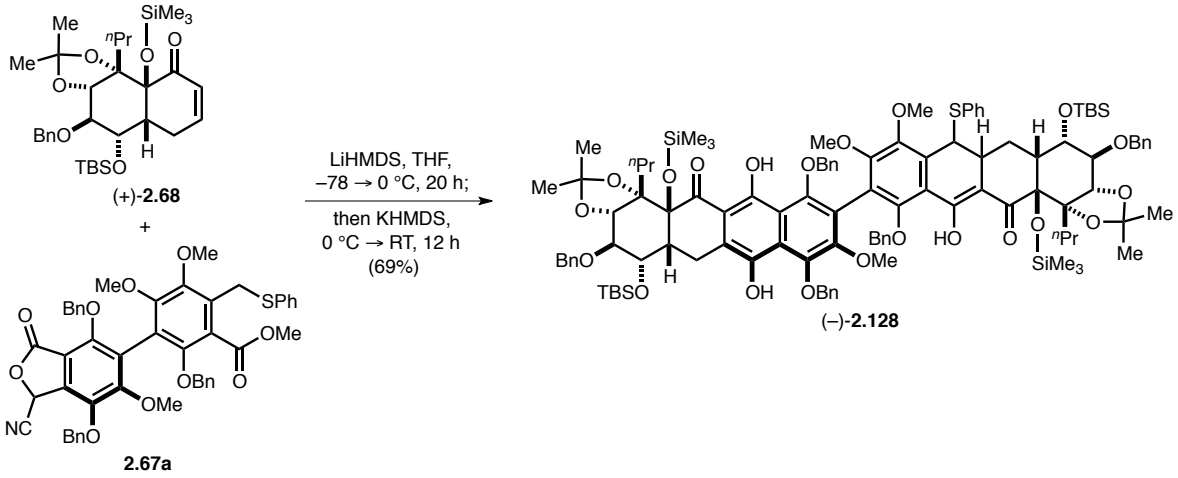
Unsymmetrical biaryl (±)-34:

A 50-mL round-bottomed flask was charged with **2.388a**[247] (210 mg, 291 μmol, 1.00 equiv) and azeotropically dried with four portions of benzene. THF (10 mL) was introduced, and the resultant solution cooled to –78 °C. In a separate 10-mL round-bottomed flask, a solution of *n*-butyllithium in hexanes (2.73 M, 266 μL, 727 μmol, 2.50 equiv) was added dropwise via syringe to a stirred solution of 2,2,6,6-tetramethylpiperidine (135 μL, 800 μmol, 2.75 equiv) in THF (1.2 mL) at 0 °C. After 30 min, the resultant solution of lithium 2,2,6,6-tetramethylpiperidide was cooled to –78 °C and transferred dropwise via a dry-ice wrapped cannula to the stirred, cooled solution of **2.388a** over 5 min. The transfer was completed with an additional portion of THF (1 mL). After 30 min, a solution of *S*-phenyl benzenethiosulfonate (76.5 mg, 306 μmol, 1.05 equiv) in THF (1.5 mL) was added via syringe rapidly down the vessel wall to the vigorously stirred deep red reaction mixture, whereupon the reaction mixture quickly turns yellow. After 10 sec, a solution of acetic acid (50 μL) in THF (1.0 mL) was rapidly added to the reaction mixture, followed immediately by addition of saturated aqueous ammonium chloride solution (5 mL). The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (20 mL) and EtOAc (20 mL) and the layers were separated. The combined organic layers were then washed with saturated aqueous ammonium chloride solution (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was

[247] Racemic (±)-**2.388** was prepared according to the procedures described in ref. 239b. The enantiomers were separated by chiral semi-preparatory HPLC on a RegisCell column [5 μm, 21.1 × 250 mm, UV detection at 254 nm, 23 ± 2 °C column temperature, solvent A: isopropyl alcohol, solvent B: hexanes, sample concentration 0.14 M (isopropyl alcohol:hexanes, 1:1), injection volume 0.70 mL, gradient elution with 40% A (0 → 25 min) and 70% (25 → 40 min), flow rate: 10.0 mL/min]. Fractions eluting at 12–16 min were concentrated under reduced pressure to afford **2.388a** and fractions eluting at 21–28 min were concentrated under reduced pressure to afford **2.388b**.

then purified by flash column chromatography (silica gel, eluent: gradient, 1% → 2% EtOAc in 9:1 benzene/hexanes) to afford unsymmetrical biaryl **2.67a** (165 mg, 69%) as a white flocculent solid (inseparable ~2:1 mixture of C6'-epimers).[248]

[248] Spectroscopic data was identical to the racemate ((±)-**2.388**). CD spectra for **2.388a** and **2.67a** were not recorded.

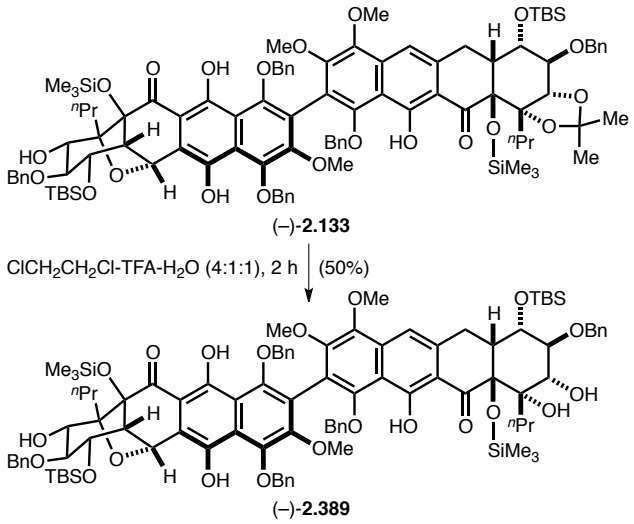


Octacycle (–)-**2.128**:

A 10-mL Schlenk tube was charged with **2.67a** (68.8 mg, 83.5 μmol, 1.00 equiv) and AB-/HG-enone (+)-**2.68** (148 mg, 251 μmol, 3.01 equiv), which were then azeotropically dried with five portions of benzene. THF (2.78 mL) was then introduced, and the resultant solution was deoxygenated and then cooled to –78 °C. A solution of freshly prepared deoxygenated lithium hexamethyldisilazide in THF (1.0 M, 835 μL, 835 μmol, 10.0 equiv) was then added dropwise via syringe to the stirred reaction mixture, which was subsequently allowed to warm to 0 °C over 30 min. After 20 h, a solution of deoxygenated potassium hexamethyldisilazide in THF (1.0 M, 2.09 mL, 2.09 mmol, 25.0 equiv) was added dropwise via cannula to the vigorously stirred purple reaction mixture, which was subsequently allowed to warm to ambient temperature. After 12 h, the reaction mixture was cooled to –50 °C before a solution of acetic acid (200 μL) in THF (1.0 mL) was added via syringe rapidly down the vessel-wall to the vigorously stirred purple reaction mixture. After the reaction mixture turned fluorescent orange, a saturated aqueous ammonium chloride solution (2 mL) was added. The resultant mixture was subsequently allowed to warm to ambient temperature. The mixture was diluted with Et_2O (20 mL), hexanes (20 mL) and saturated aqueous ammonium chloride solution (10 mL), and the layers were separated. The organic layers were then washed with saturated aqueous ammonium chloride solution (20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography

(silica gel, eluent: gradient, 5% → 6% → 10% EtOAc in hexanes) to afford octacycle (–)-**2.128**[249] (111.8 mg, 69%) as an orange flocculent solid.

[249] For spectroscopic and physical characterization of octacycle (–)-**2.128**, see Ref. 239b.



Pentaol (–)-**2.389**:

A 10-mL Schlenk tube was charged with (–)-**2.133**[250] (15.5 mg, 8.8 μmol, 1.00 equiv) and 1,2-dichloroethane (3.0 mL) and the resultant solution was deoxygenated. A freshly deoxygenated solution of trifluoroacetic acid (750 μL) and H_2O (750 μL) was added to the reaction vessel via syringe. The Schlenk tube was sealed and the resultant reaction mixture was vigorously stirred at ambient temperature. After 2 h, saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was partitioned with EtOAc (5 mL) and the layers were separated. The aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with saturated aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparatory thin-layer chromatography (eluent: 50% EtOAc in hexanes) to afford pentaol (–)-**2.389** (7.7 mg, 50%).

^{1}H NMR (600 MHz, CD_2Cl_2) δ: 15.07 (s, 1 H), 13.73 (s, 1 H), 9.59 (s, 1 H), 7.51–7.28 (m, 17H), 7.14–7.08 (m, 6 H), 7.08–7.03 (m, 2 H), 5.89 (s, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.08 (d, *J* = 3.6 Hz, 1 H), 5.06 (d, *J* = 5.1 Hz, 1 H), 5.02 (d, *J* = 10.3 Hz, 1 H), 5.00 (d, *J* = 10.6 Hz, 1 H), 5.00–4.94 (m, 2 H), 4.94–4.87 (m, 3 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.29 (dd, *J* = 5.3, 8.9 Hz, 1 H), 4.17 (dd, *J* = 3.9, 7.6 Hz, 1 H), 4.10 (t, *J* = 7.7 Hz, 1 H), 3.90 (s, 3 H), 3.87–3.81 (m, 8 H), 3.8–3.71 (m, 2 H), 3.31 (dd, *J* = 5.8, 17.0 Hz, 1 H),

[250] (–)-**2.133** was prepared from (–)-**2.128** following the protocol detailed in Ref. 239b.

2.64 (td, J = 5.5, 13.5 Hz, 1 H), 2.44 (d, J = 3.6 Hz, 1 H), 2.27 (d, J = 1.8 Hz, 1 H), 2.15 (s, 1 H), 1.95–1.84 (m, 2 H), 1.74 (ddd, J = 4.2, 12.4, 14.2 Hz, 1 H), 1.69–1.59 (m, 1 H), 1.58–1.48 (m, 1 H), 1.36–1.18 (m, 4 H), 1.07 (dt, J = 4.1, 13.1 Hz, 1 H), 1.02 (s, 9 H), 0.94 (s, 9 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.81 (t, J = 7.4 Hz, 3 H), 0.25 (s, 9 H), 0.19 (s, 3 H), 0.18 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (125 MHz, CD_2Cl_2) δ: 204.9, 203.7, 165.7, 158.5, 154.6, 153.3, 152.7, 143.8, 143.0, 140.3, 140.1, 140.0, 139.7, 138.6, 138.4, 135.8, 135.7, 129.9, 129.7, 129.5, 129.2, 128.8, 128.7, 128.52, 128.47, 128.33, 128.26, 128.0, 127.93, 127.91, 127.86, 127.8, 125.3, 125.0, 122.6, 121.7, 118.7, 116.1, 113.3, 110.7, 109.9, 88.1, 87.9, 85.1, 82.6, 82.0, 80.3, 78.1, 76.4, 76.2, 76.0, 75.5, 75.0, 74.5, 72.8, 72.6, 69.9, 61.8, 61.3, 61.2, 58.6, 49.8, 38.6, 35.8, 30.3, 28.6, 26.4, 26.2, 18.8, 18.6, 18.4, 16.8, 15.19, 15.16, 2.3, 2.1, –3.9, –4.0, –4.1, –4.2.

FTIR (thin film) cm^{-1}: 3457, 3346, 3032, 2955, 2931, 2857, 1617, 1588, 1559, 1497, 1455, 1409, 1372, 1308, 1252, 1211, 1173, 1116, 1078, 886, 839, 751, 697.

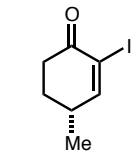
HRMS (ESI) (*m/z*) calc'd for $C_{98}H_{125}O_{21}Si_4$ $[M+H]^+$: 1749.7785, found 1749.7732.

$[\alpha]_D^{23}$: –258.6 (c = 0.46, CH_2Cl_2).

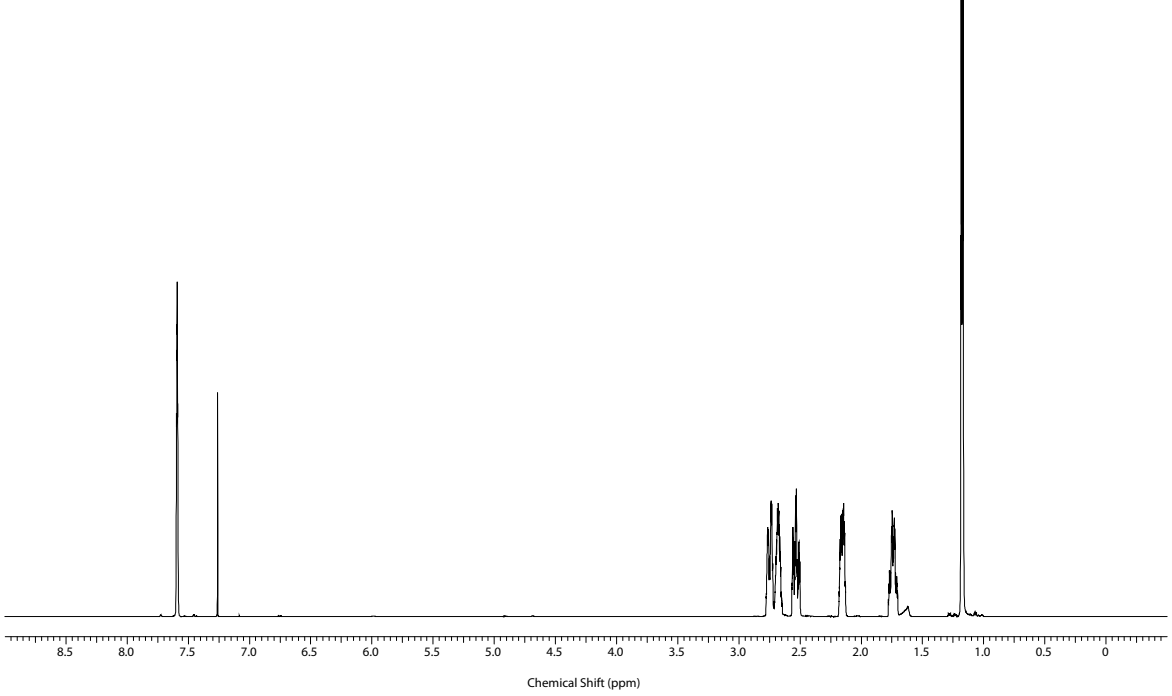
TLC (30% EtOAc in hexanes), R_f: 0.64 (UV, CAM).

Appendix A

Catalog of Spectra


O
I
Me

(±)-**1.133**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2.5
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1.5
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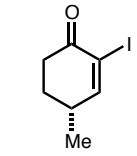
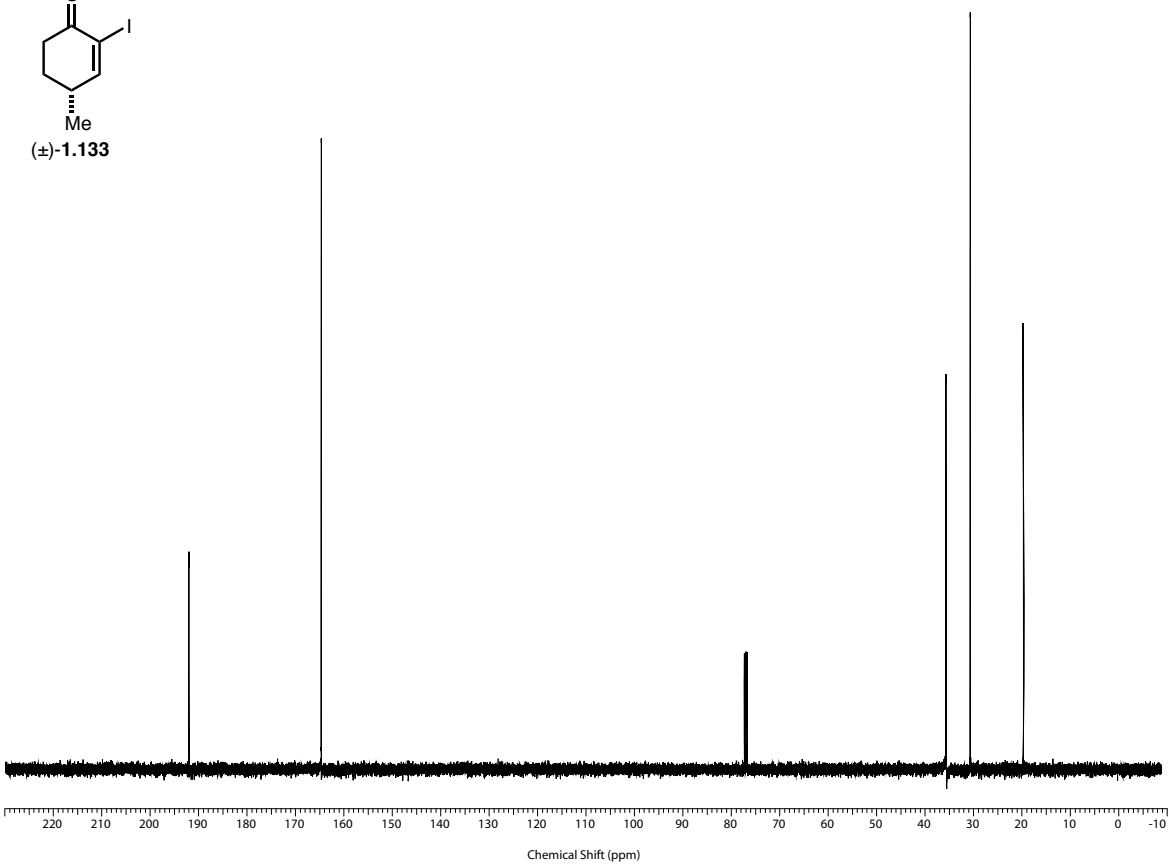
0.5
0
Chemical Shift (ppm)


O
I
Me

(±)-**1.133**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200
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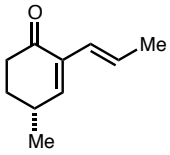
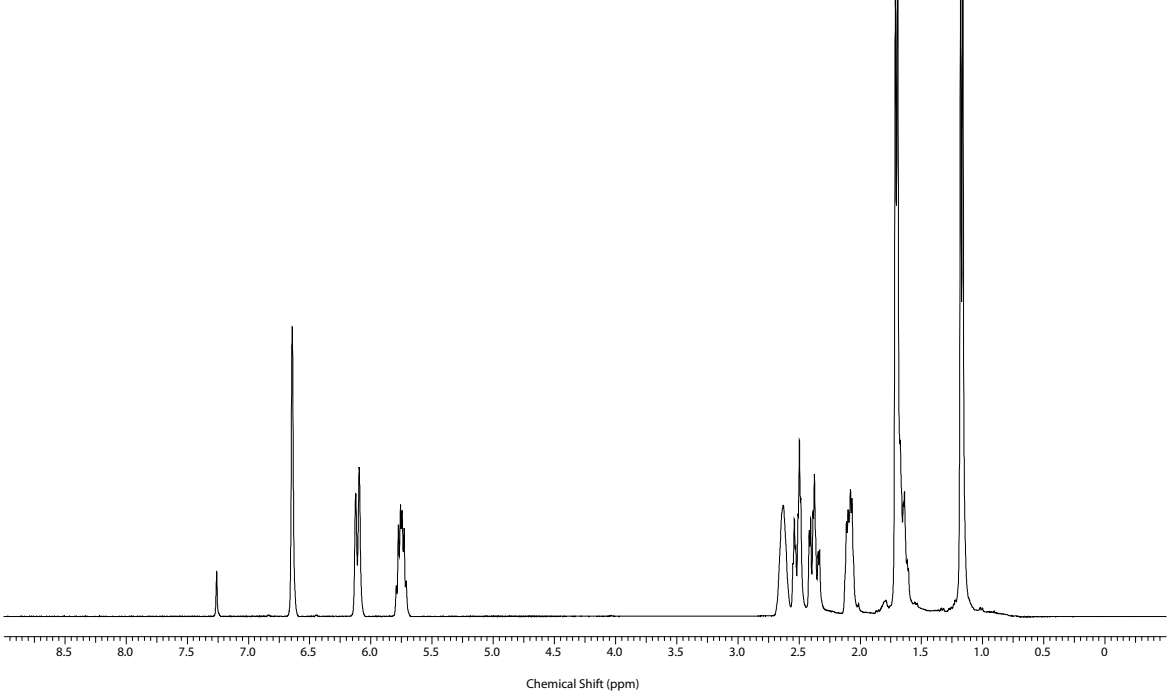
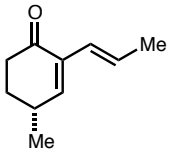
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

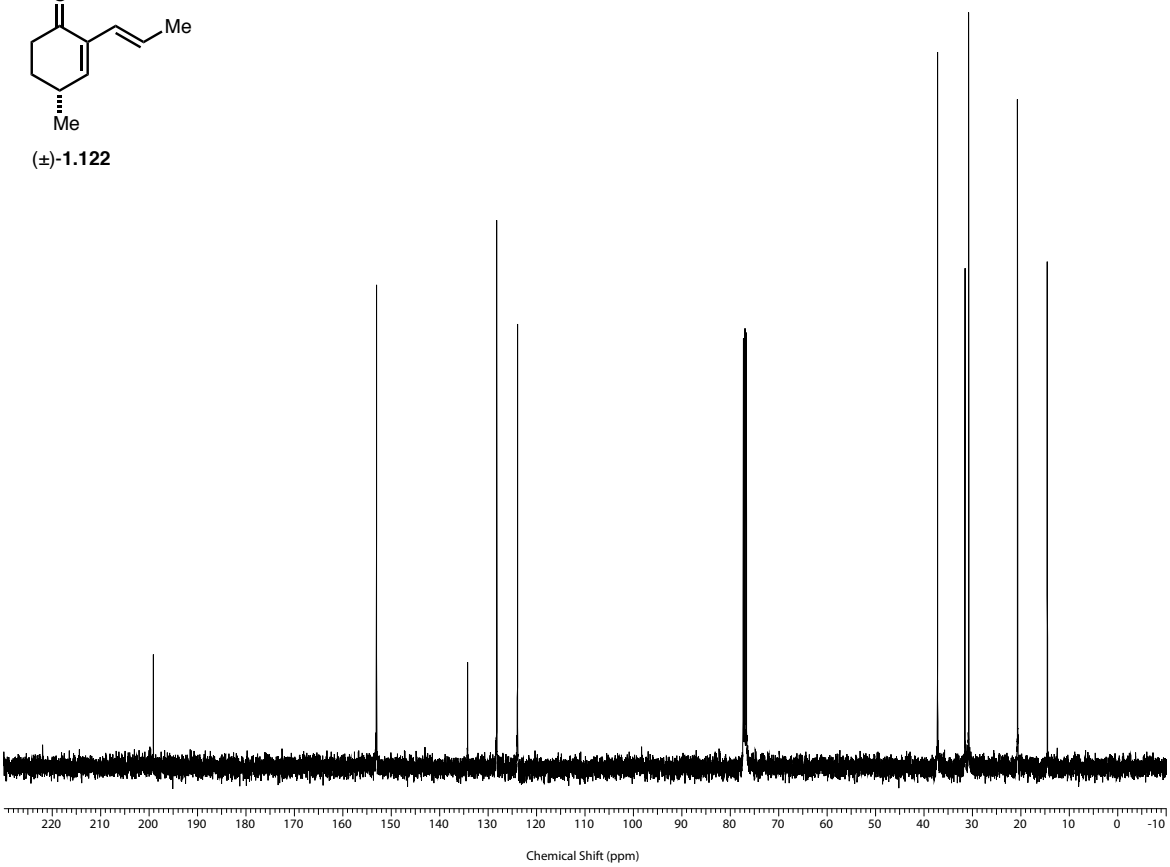

O
Me
Me

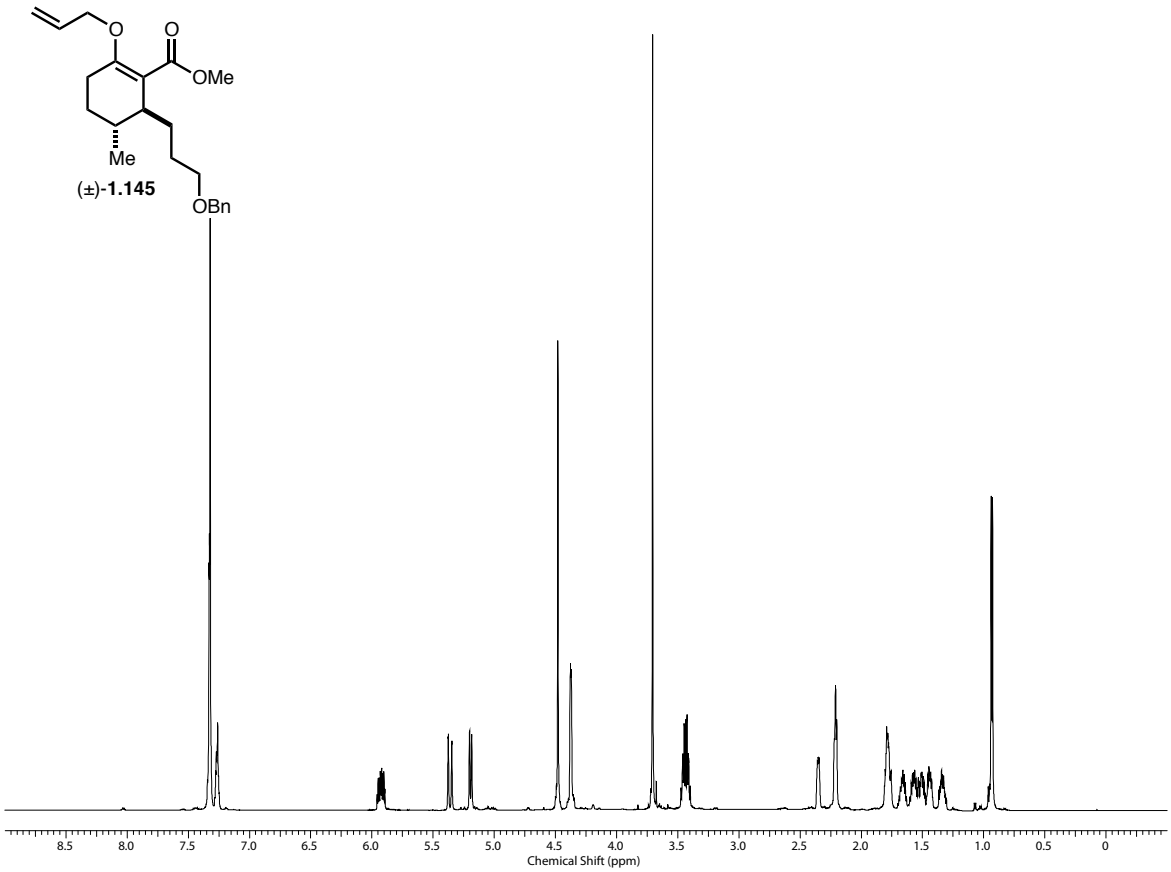
(±)-**1.122**

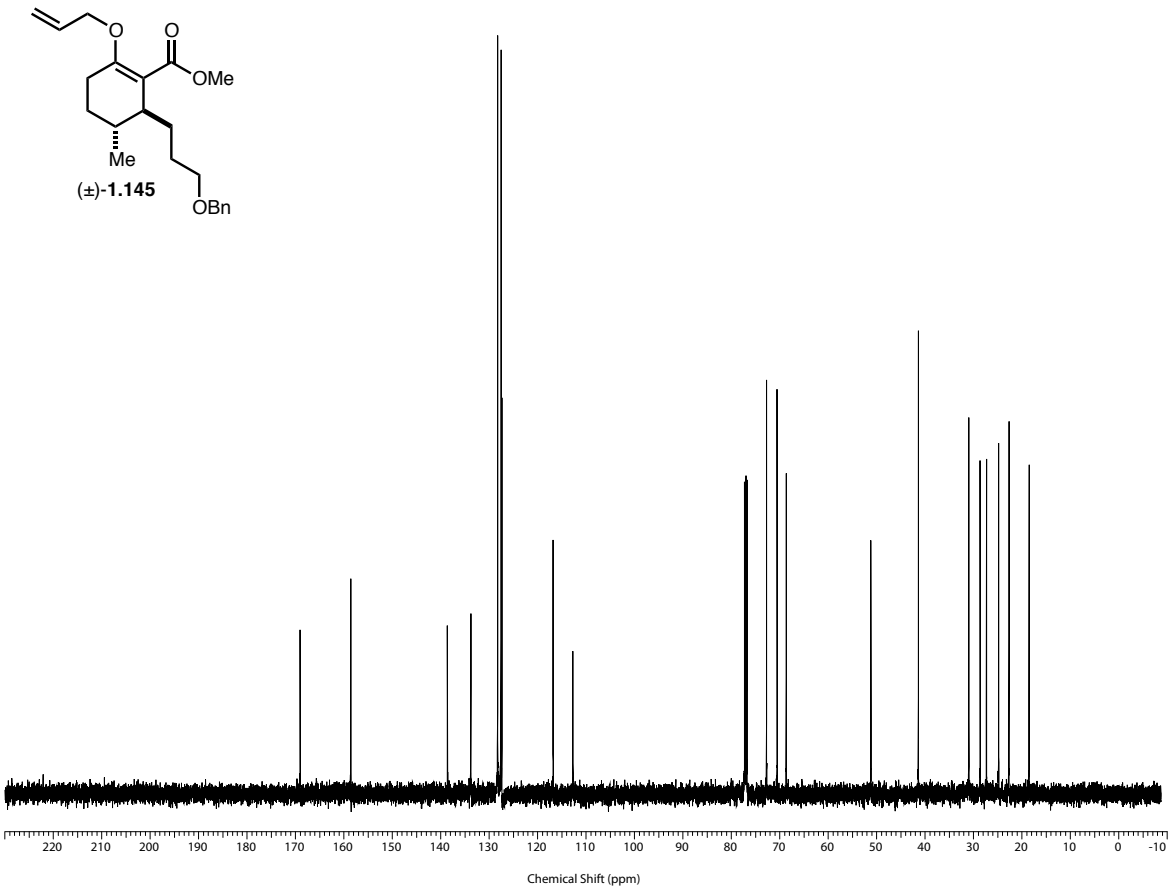

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

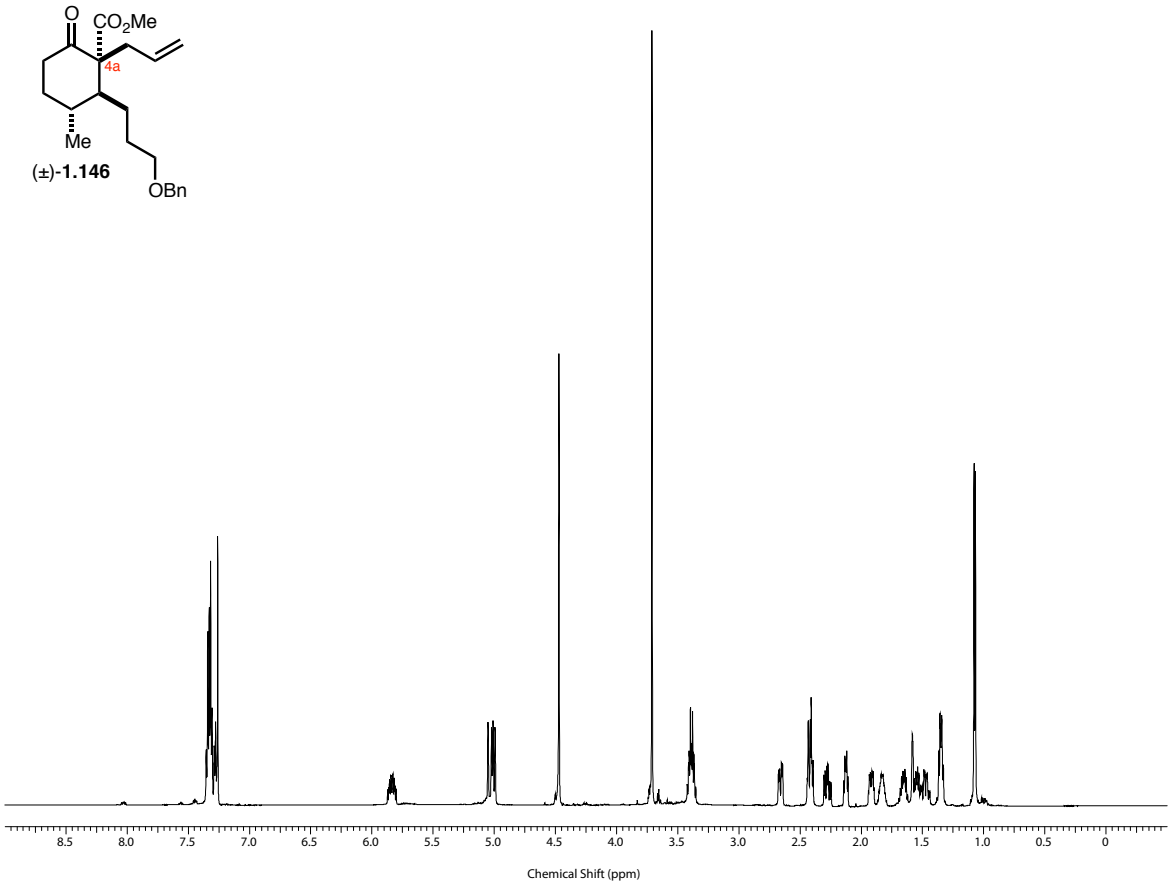

O
Me
Me

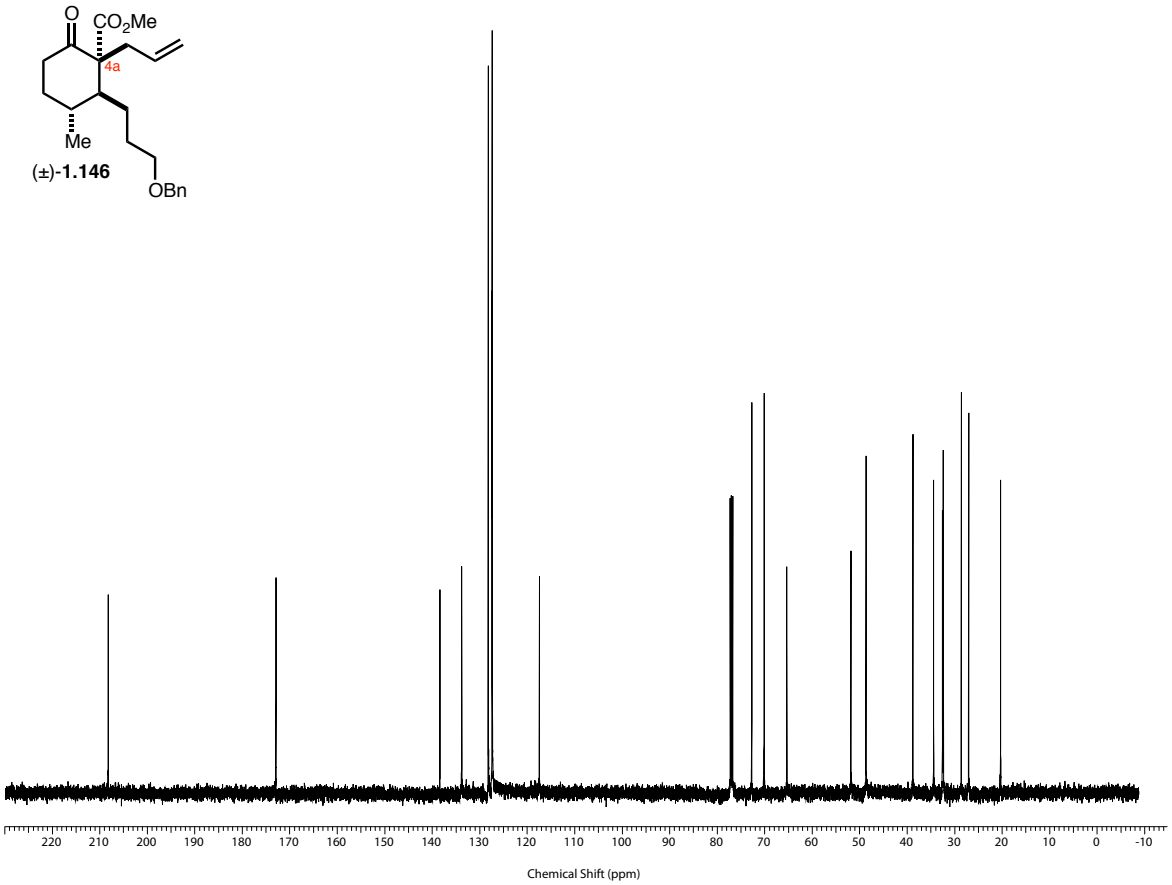
(±)-**1.122**

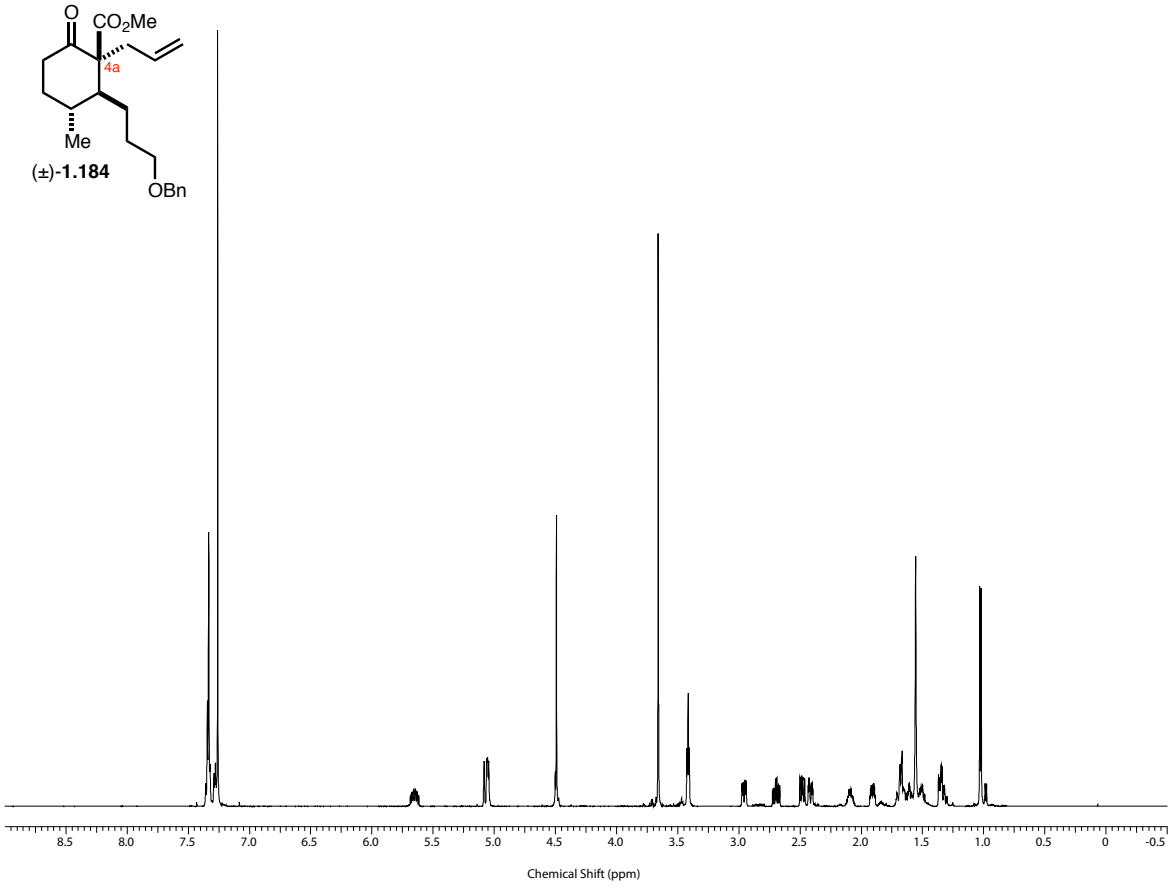

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

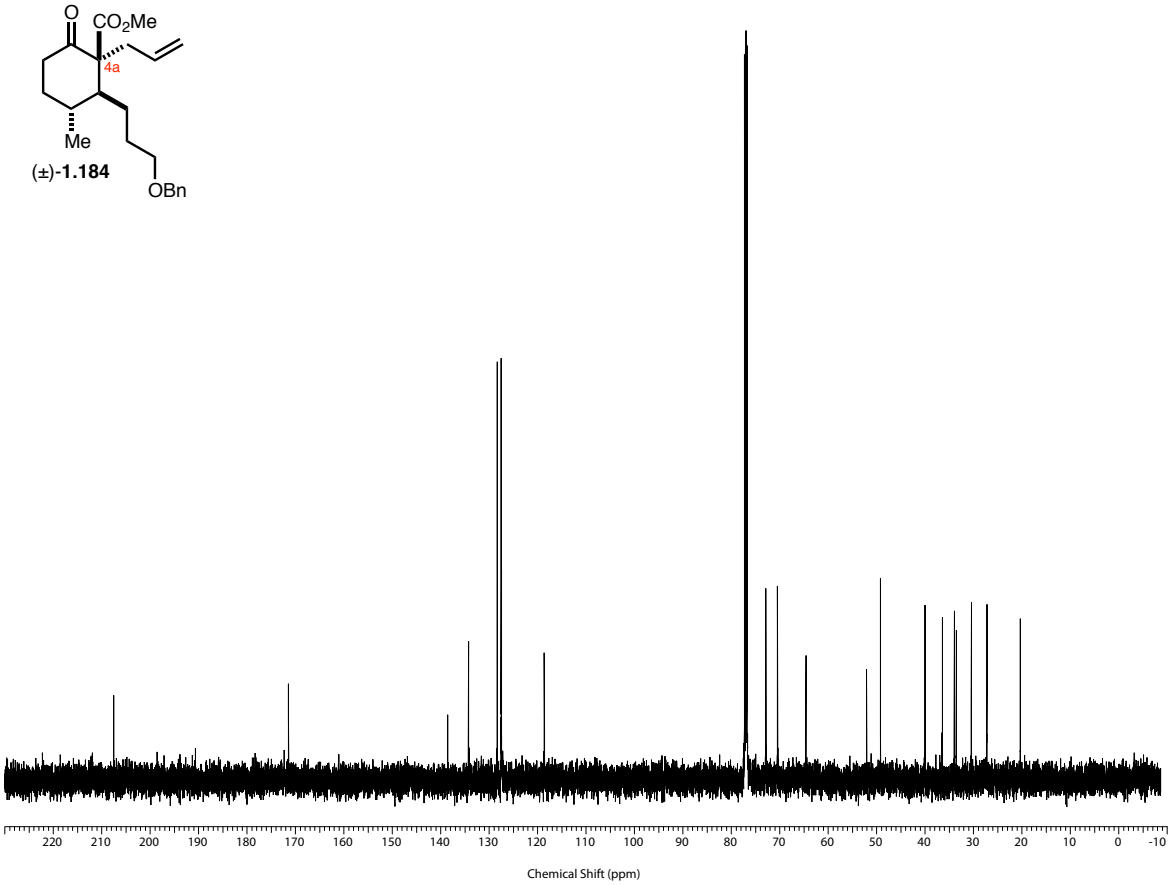

O
O
OMe
Me
OBn
(±)-1.145
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

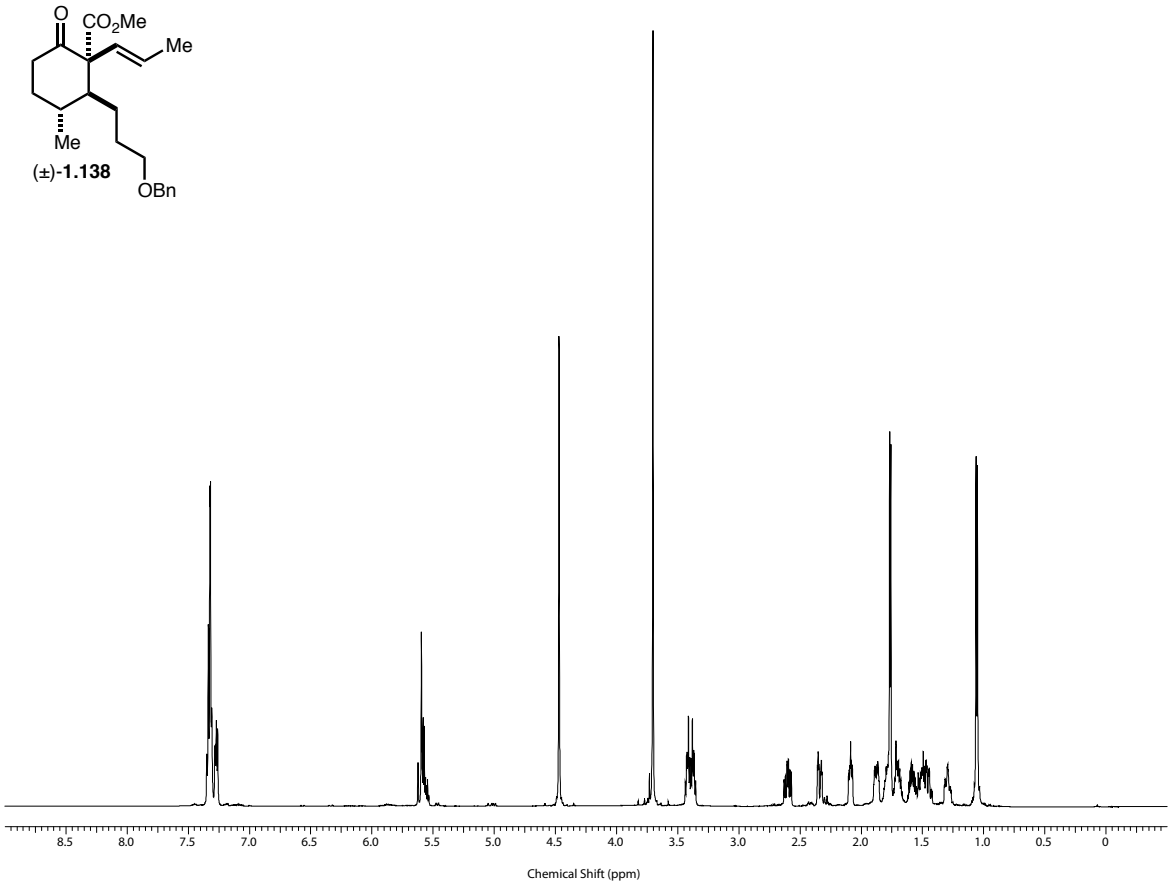

O
O
OMe
Me
OBn
(±)-1.145
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

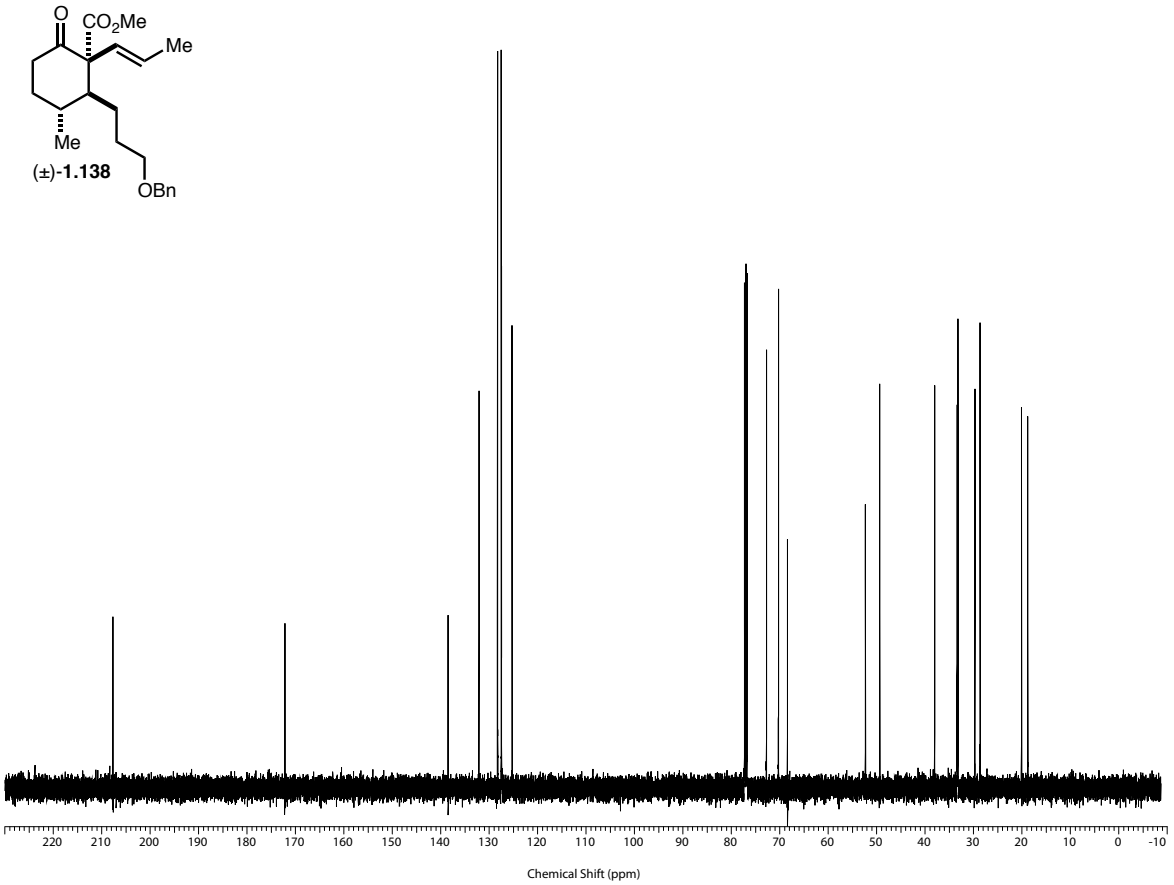

O
CO2Me
4a
Me
OBn
(±)-1.146
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

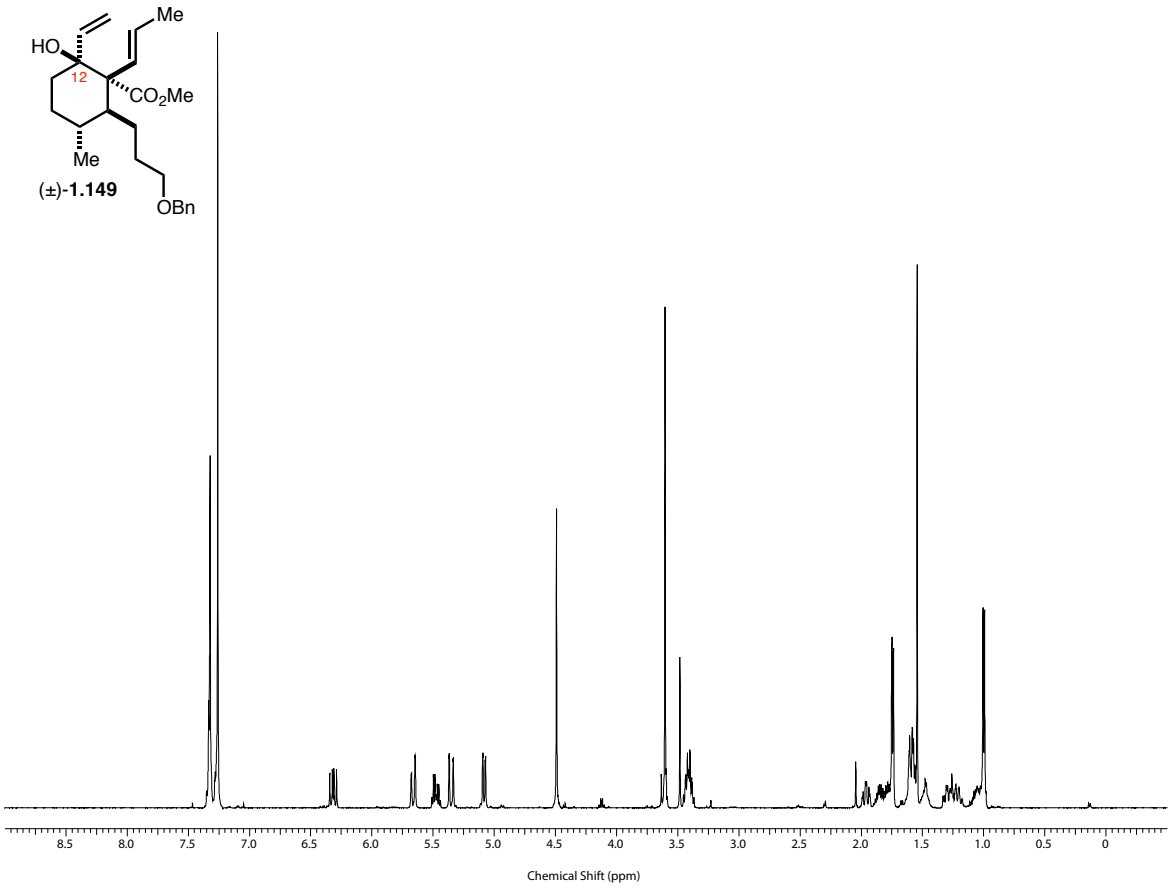

O
CO2Me
4a
Me
OBn
(±)-1.146
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

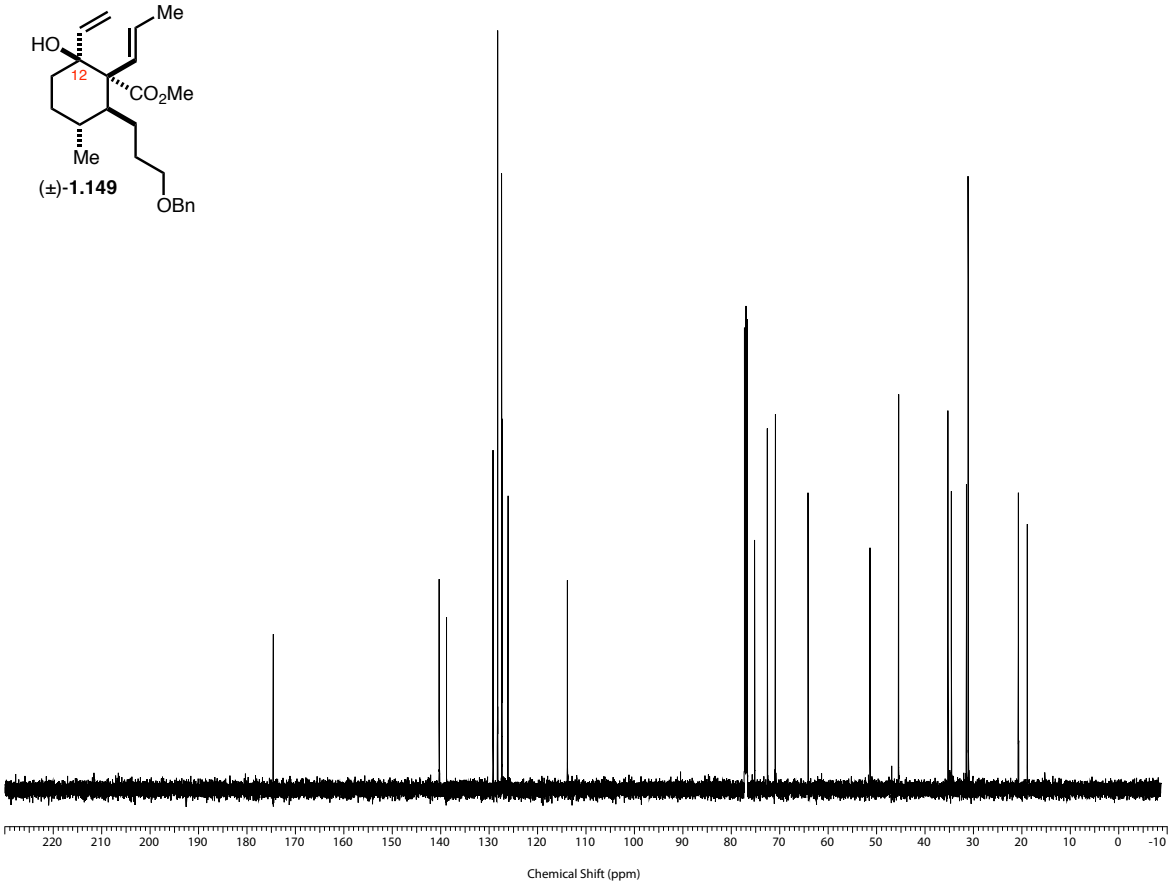

O
CO2Me
4a
Me
(±)-1.184
OBn
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


O
CO2Me
4a
Me
(±)-1.184
OBn
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


O
CO2Me
Me
Me
(±)-1.138
OBn
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

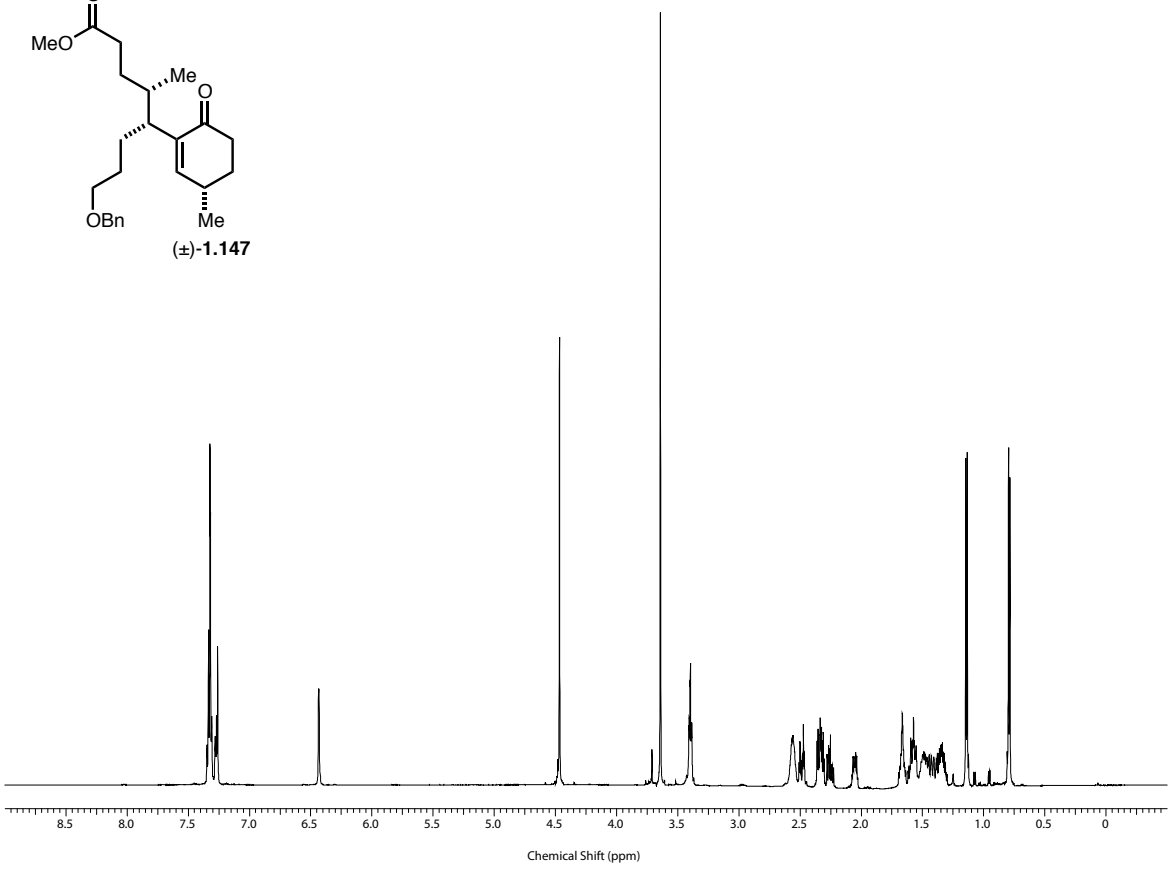

O
CO2Me
Me
Me
(±)-1.138
OBn
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


HO
12
Me
CO2Me
Me
OBn
(±)-1.149
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


HO
12
Me
CO2Me
Me
OBn
(±)-1.149
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

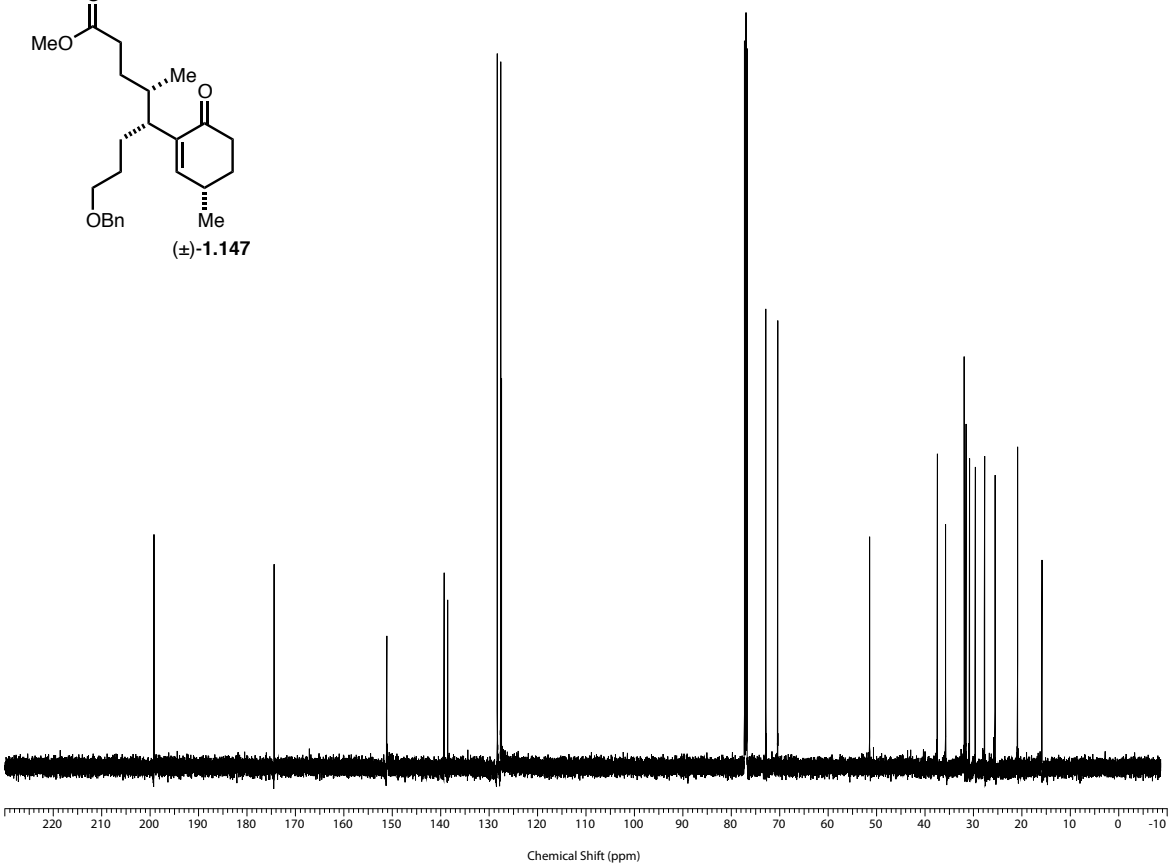
O
MeO
Me
O
OBn
Me

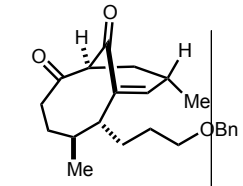
(±)-**1.147**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

O
MeO
Me
O
OBn
Me

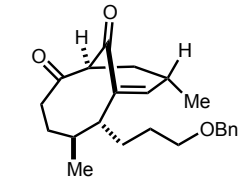
(±)-**1.147**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

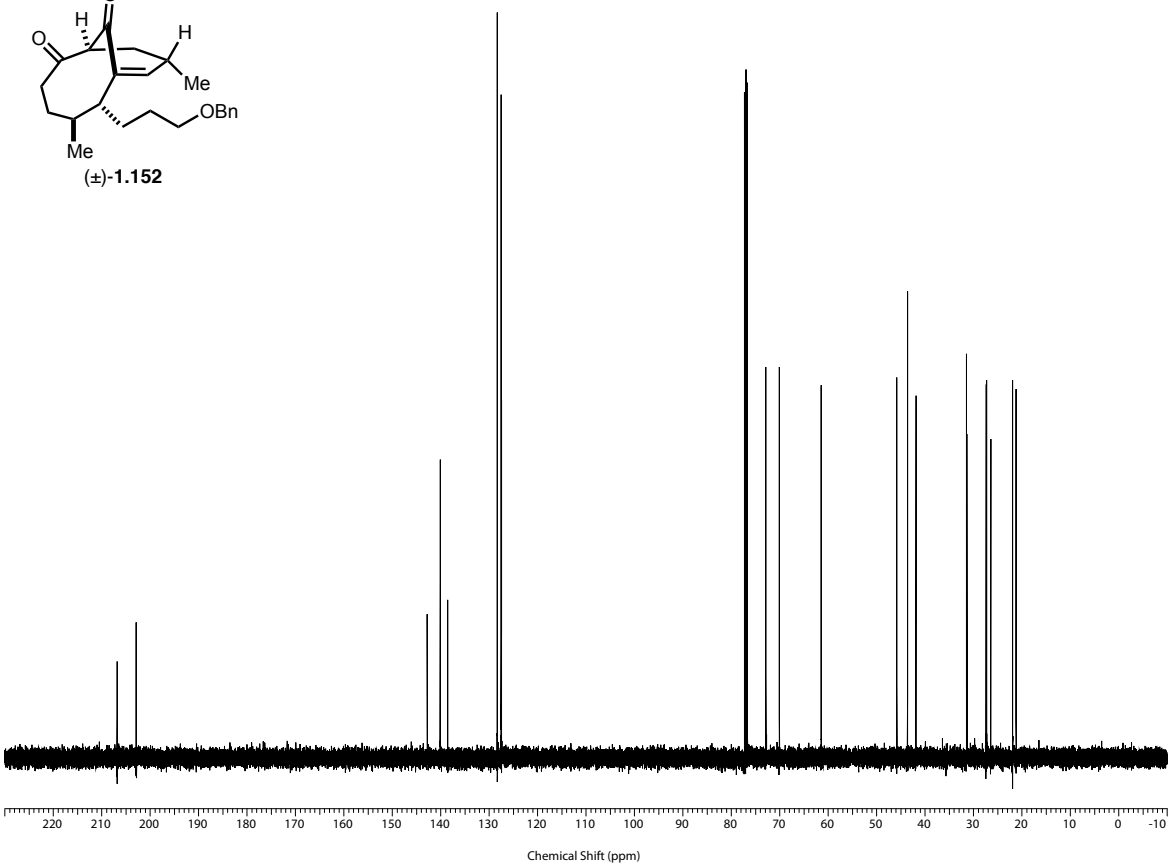

O
H
O
H
Me
OBn
Me

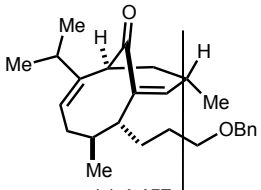
(±)-**1.152**

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

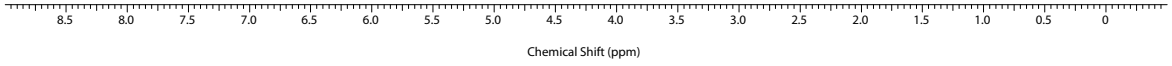

O
H
O
H
Me
OBn
Me

(±)-**1.152**

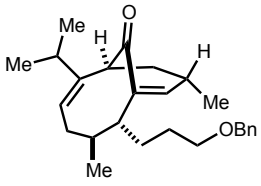

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



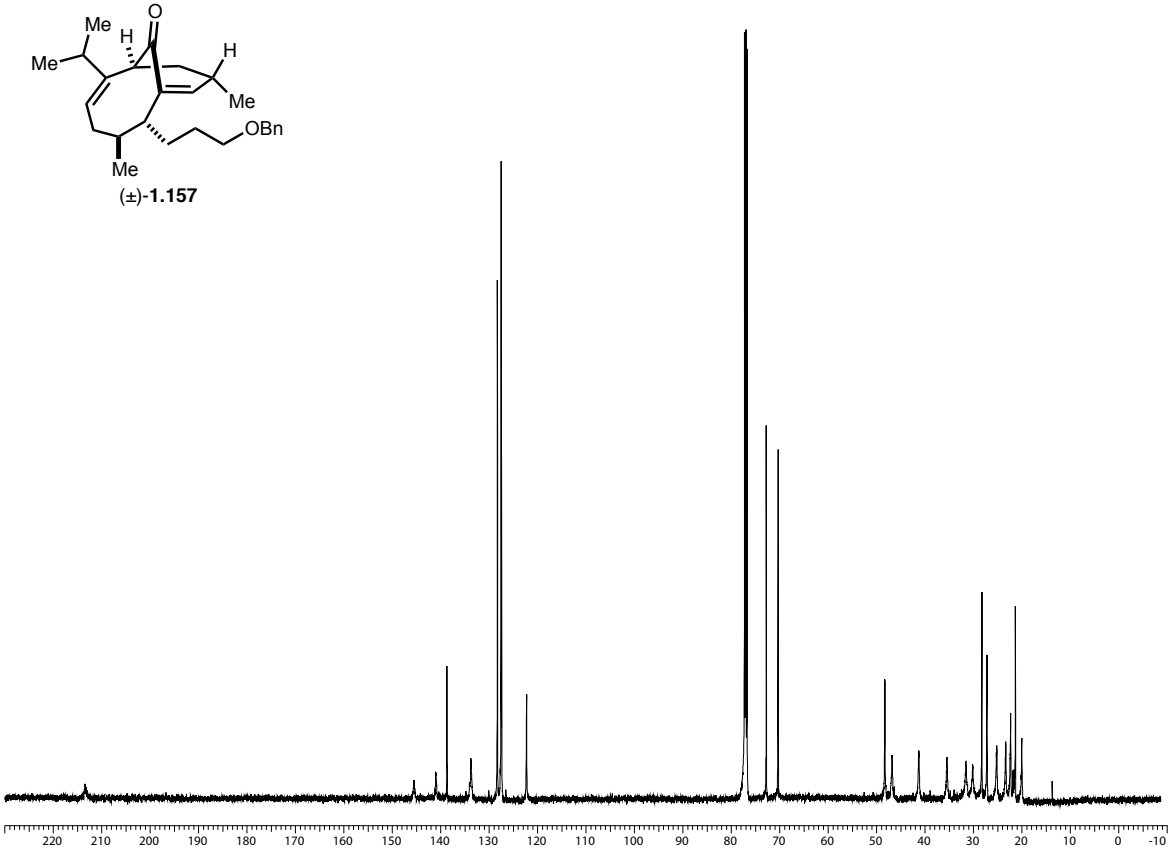
(±)-**1.157**



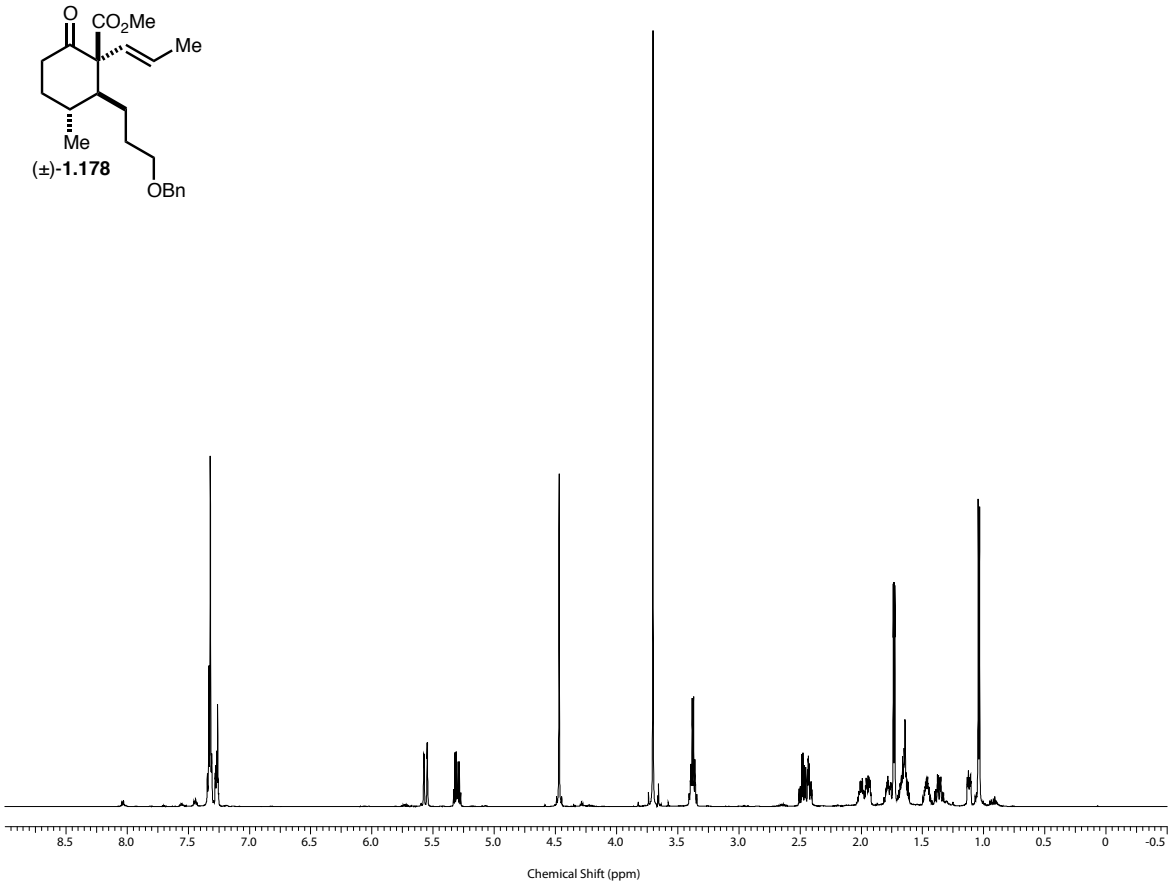
Chemical Shift (ppm)

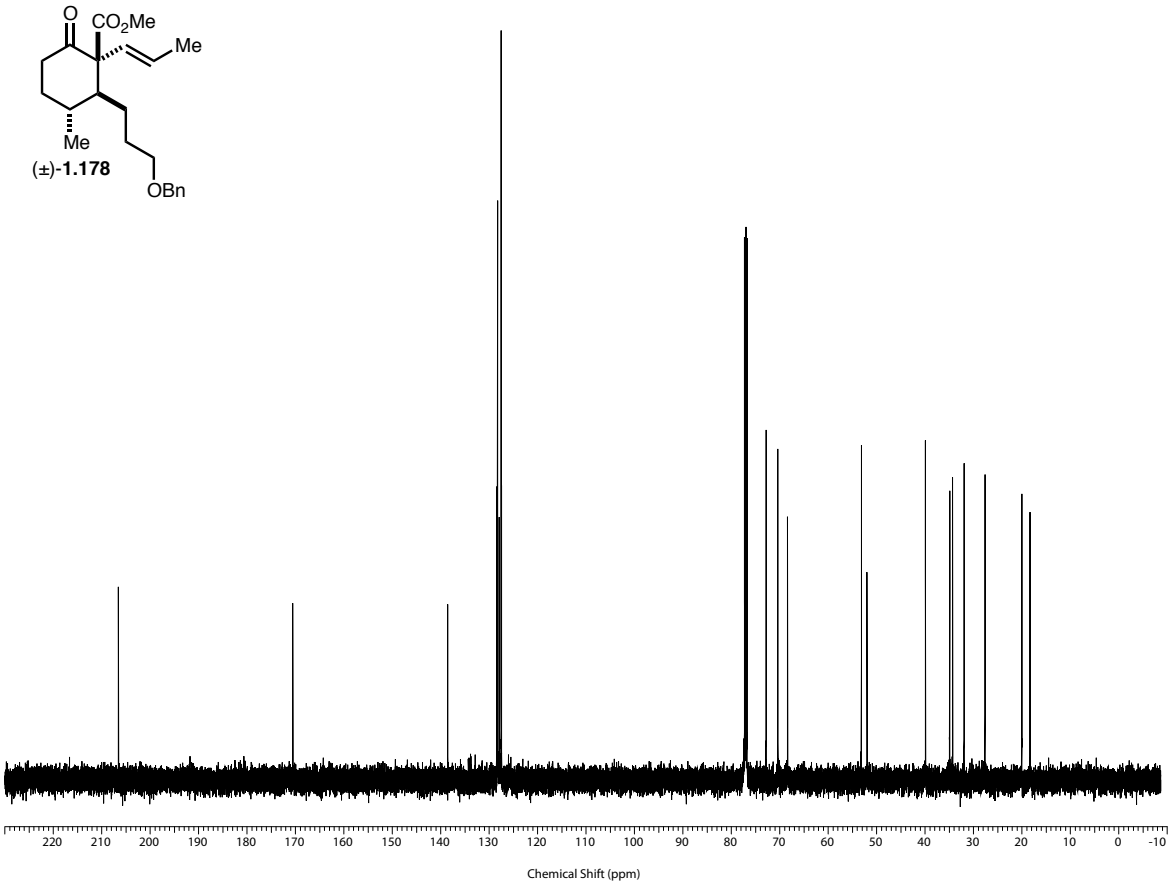


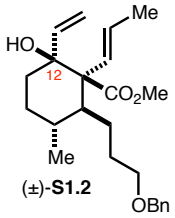
(±)-**1.157**



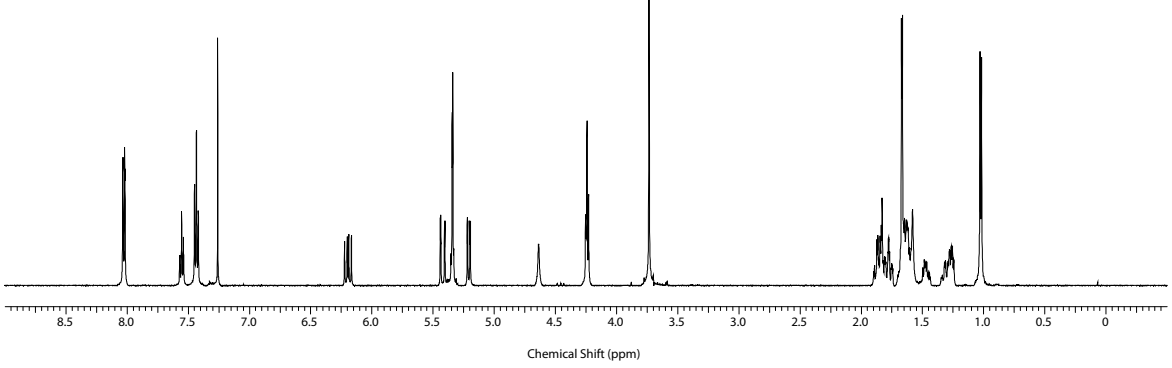
Chemical Shift (ppm)

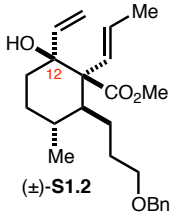

O
CO2Me
Me
Me
(±)-1.178
OBn
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


O
CO2Me
Me
Me
(±)-1.178
OBn
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

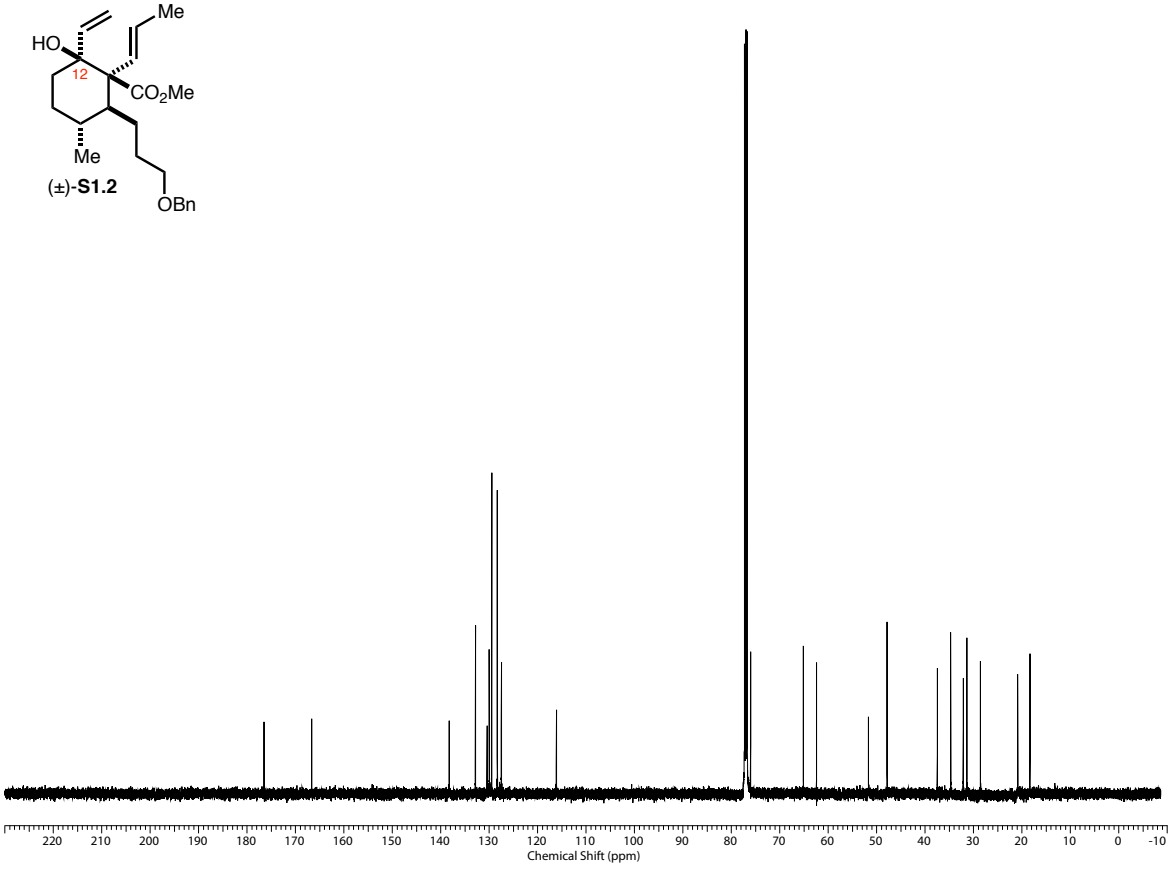

Me
HO
12
CO2Me
Me
OBn

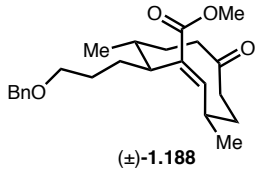
(±)-**S1.2**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

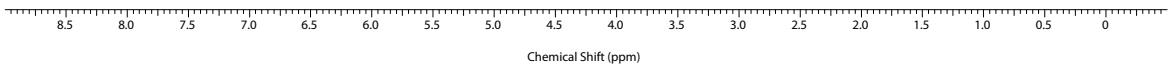

Me
HO
12
CO2Me
Me
OBn

(±)-**S1.2**

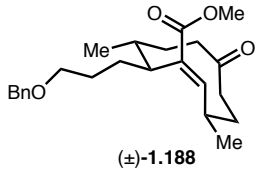

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



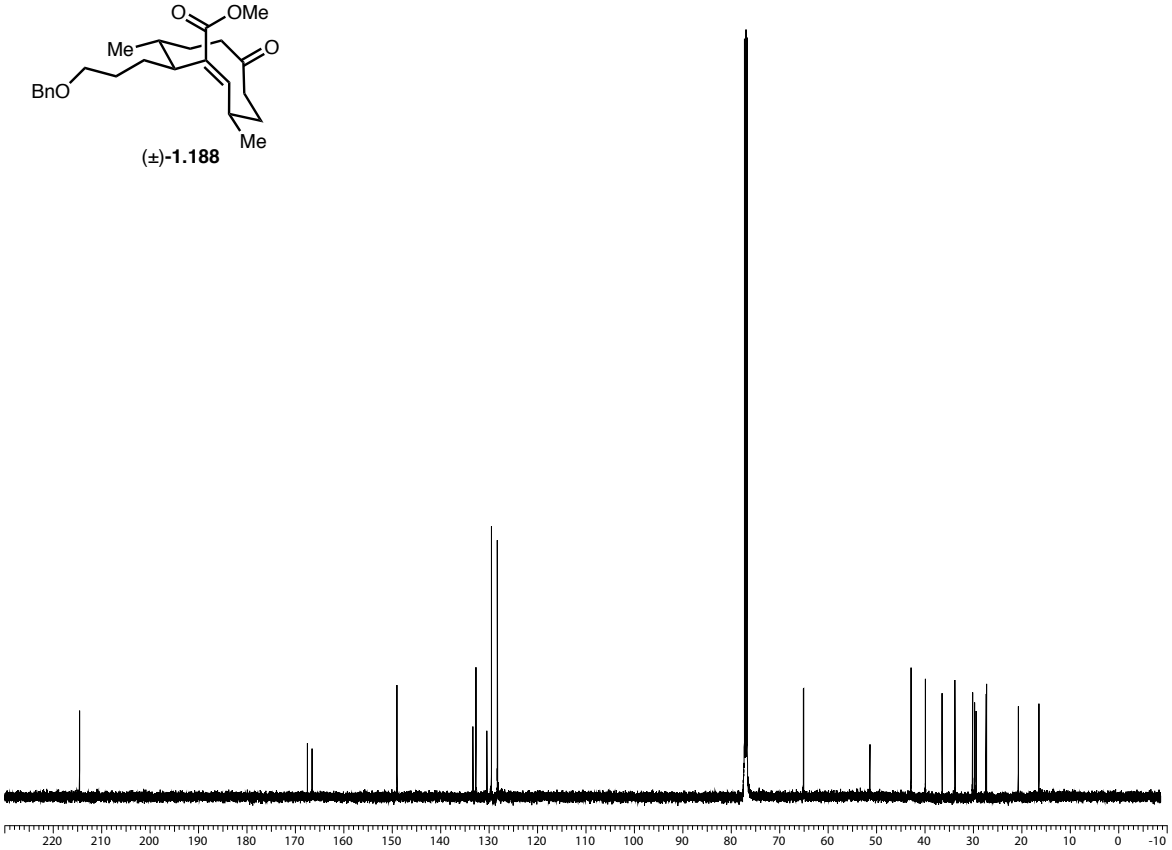
(±)-**1.188**



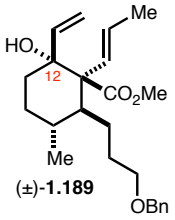
Chemical Shift (ppm)



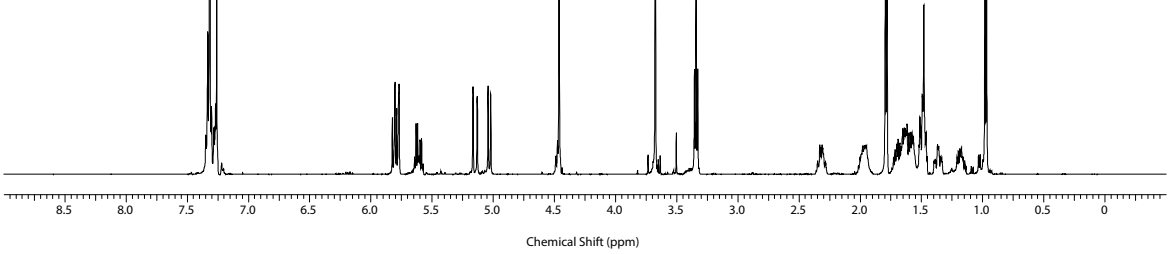
(±)-**1.188**

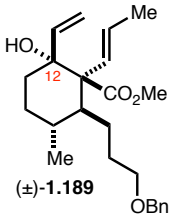


Chemical Shift (ppm)

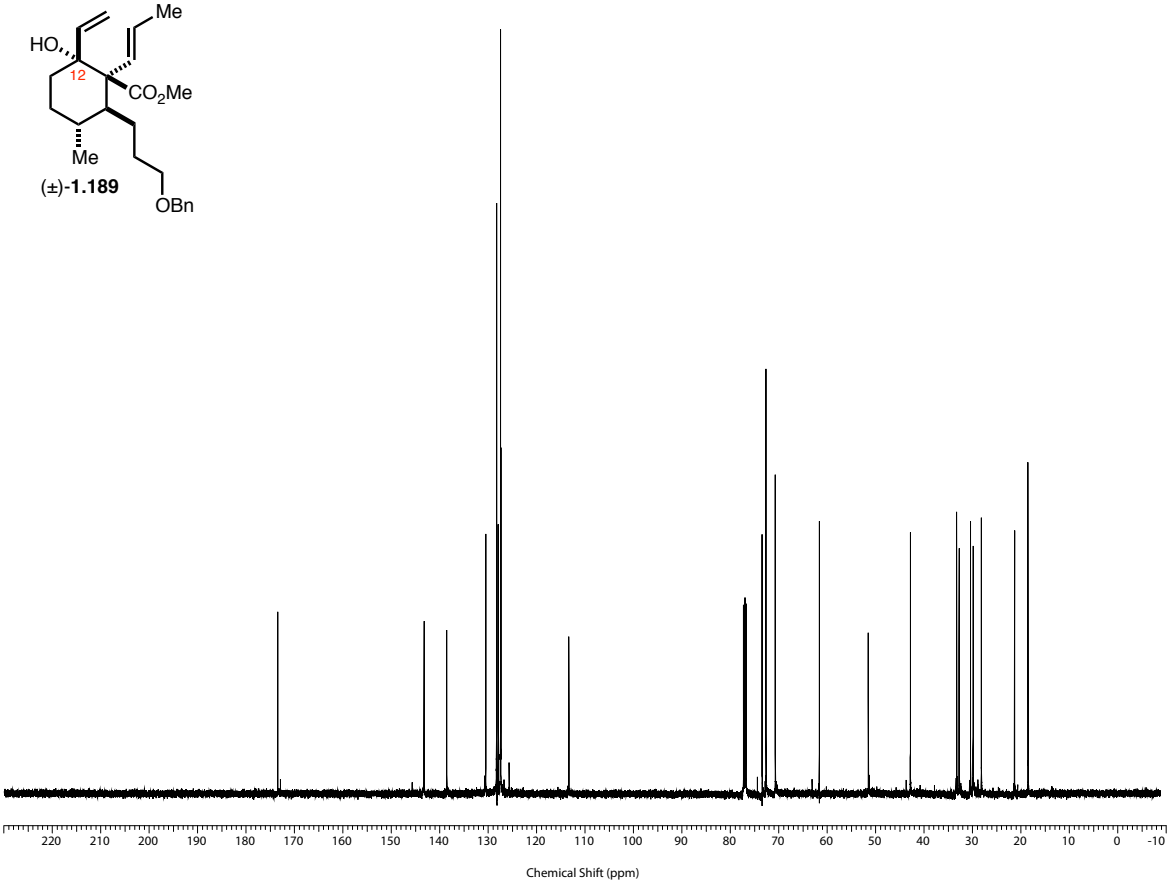

Me
HO
12
CO2Me
Me
OBn

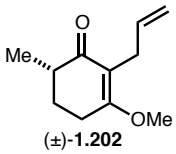
(±)-**1.189**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

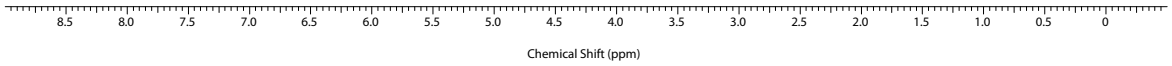

Me
HO
12
CO2Me
Me
OBn

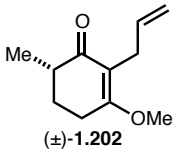
(±)-**1.189**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

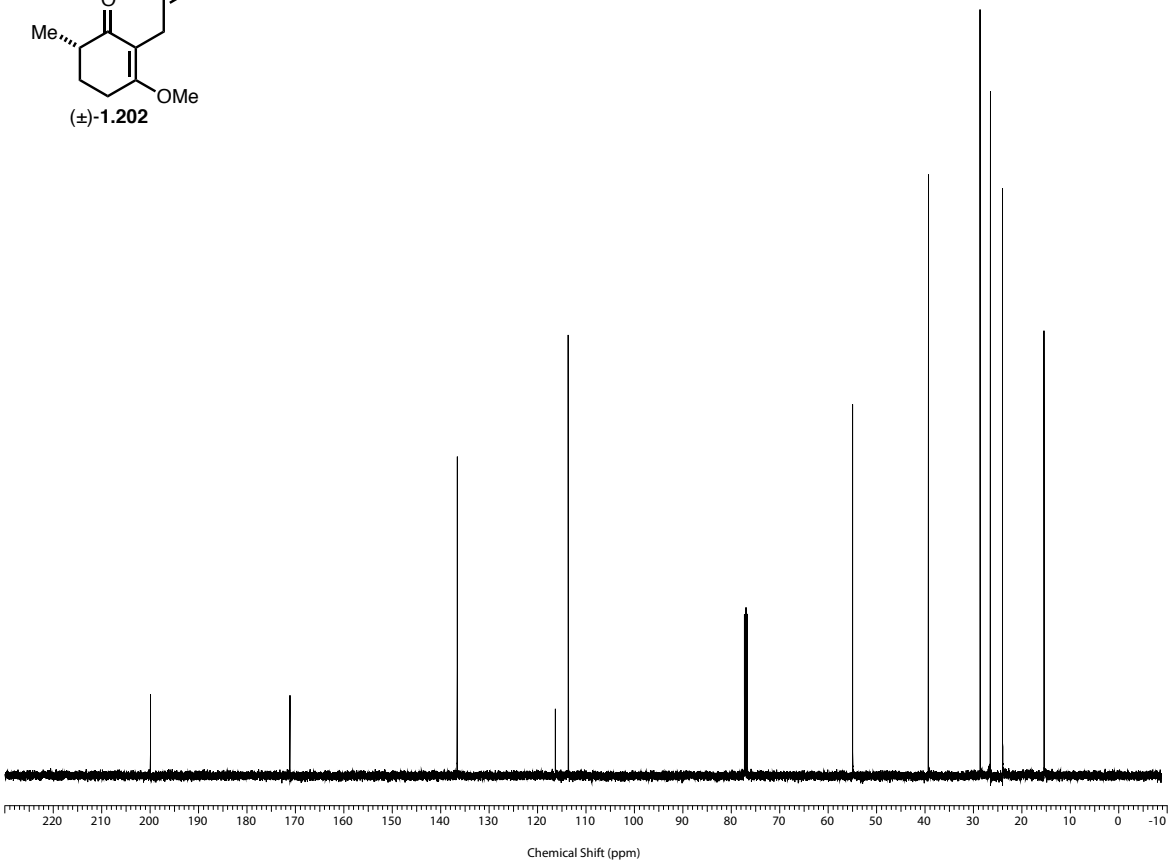

O
Me
OMe

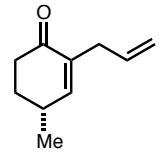
(±)-**1.202**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

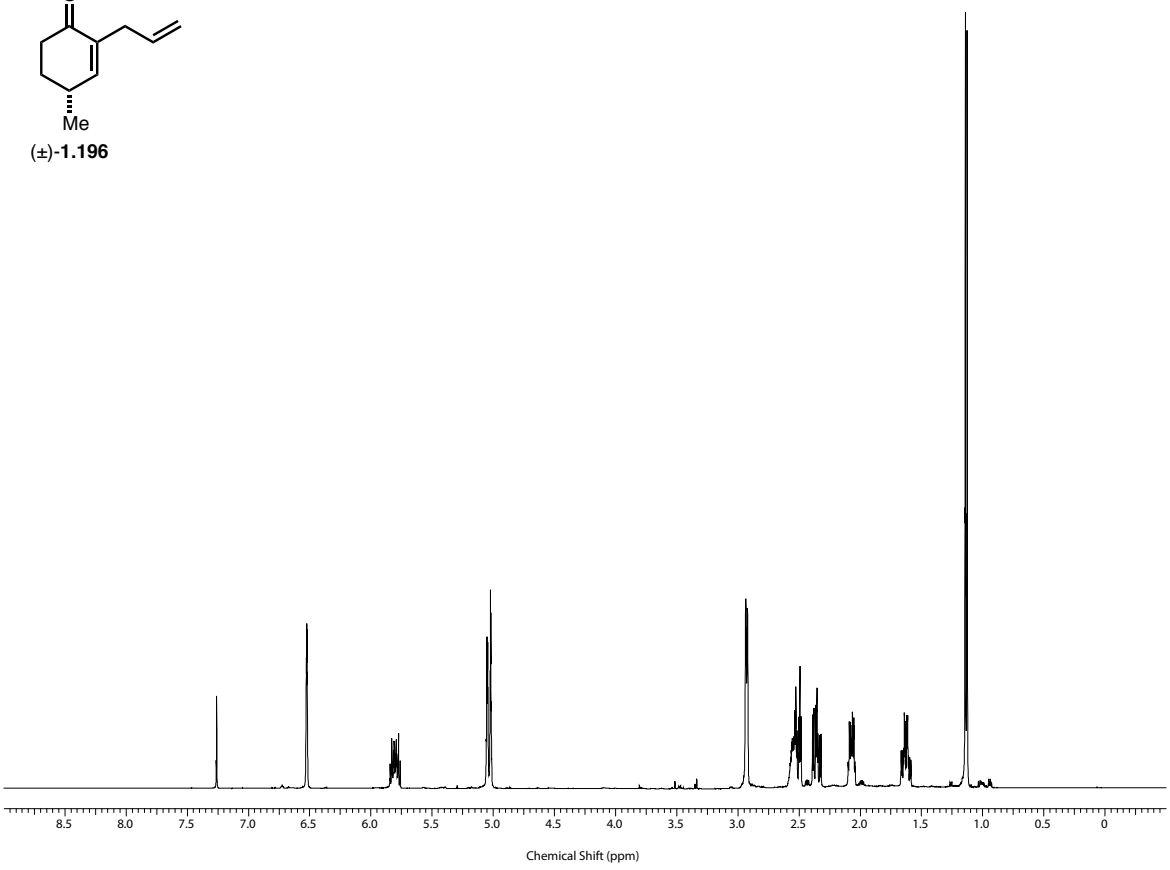

O
Me
OMe

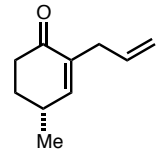
(±)-**1.202**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

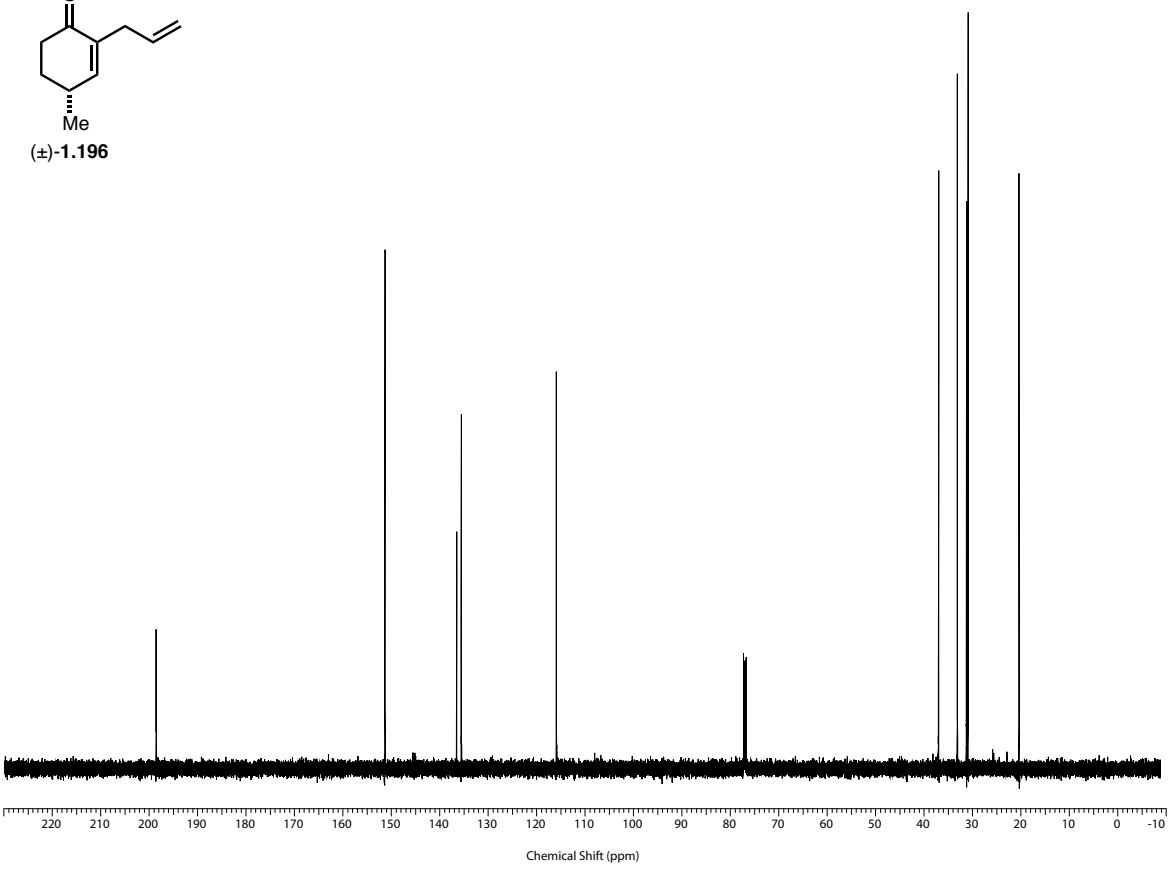

O
Me

(±)-**1.196**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
Me

(±)-**1.196**


220
210
200
190
180
170
160
150
140
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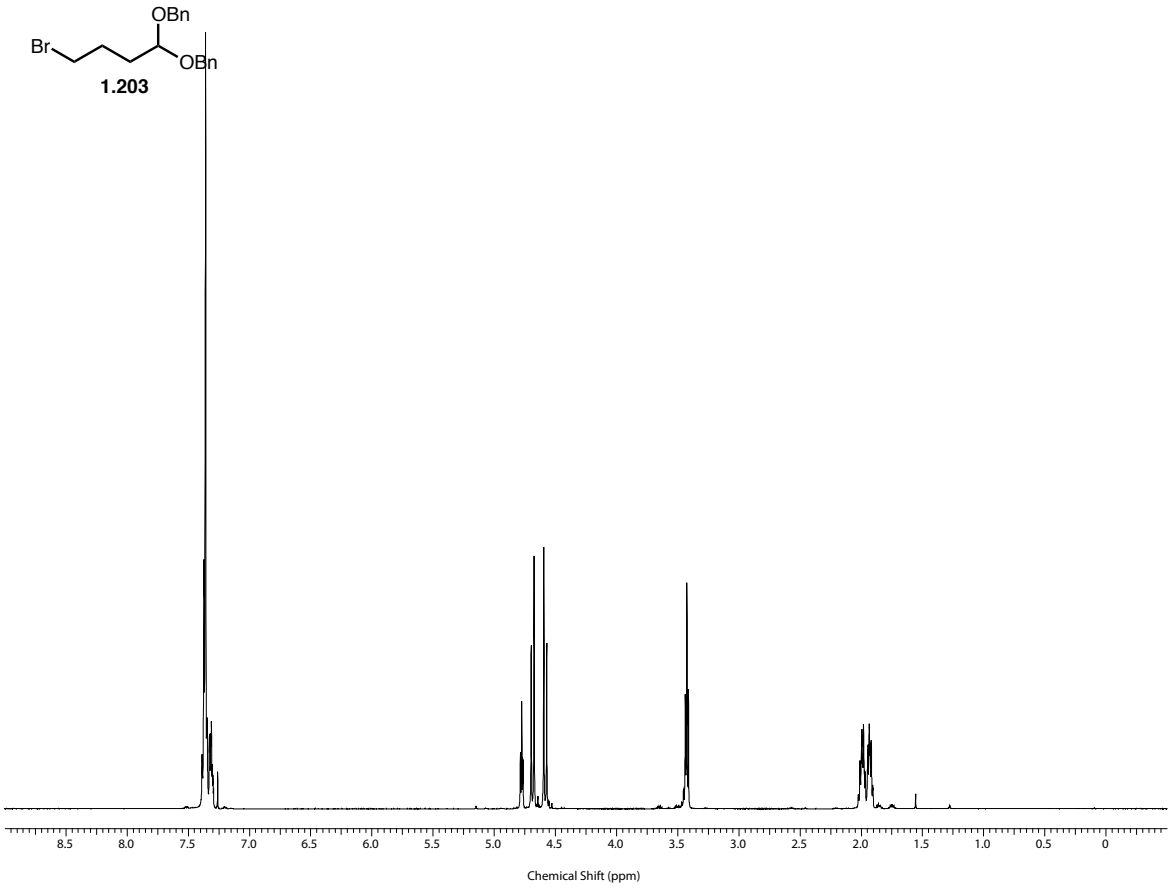
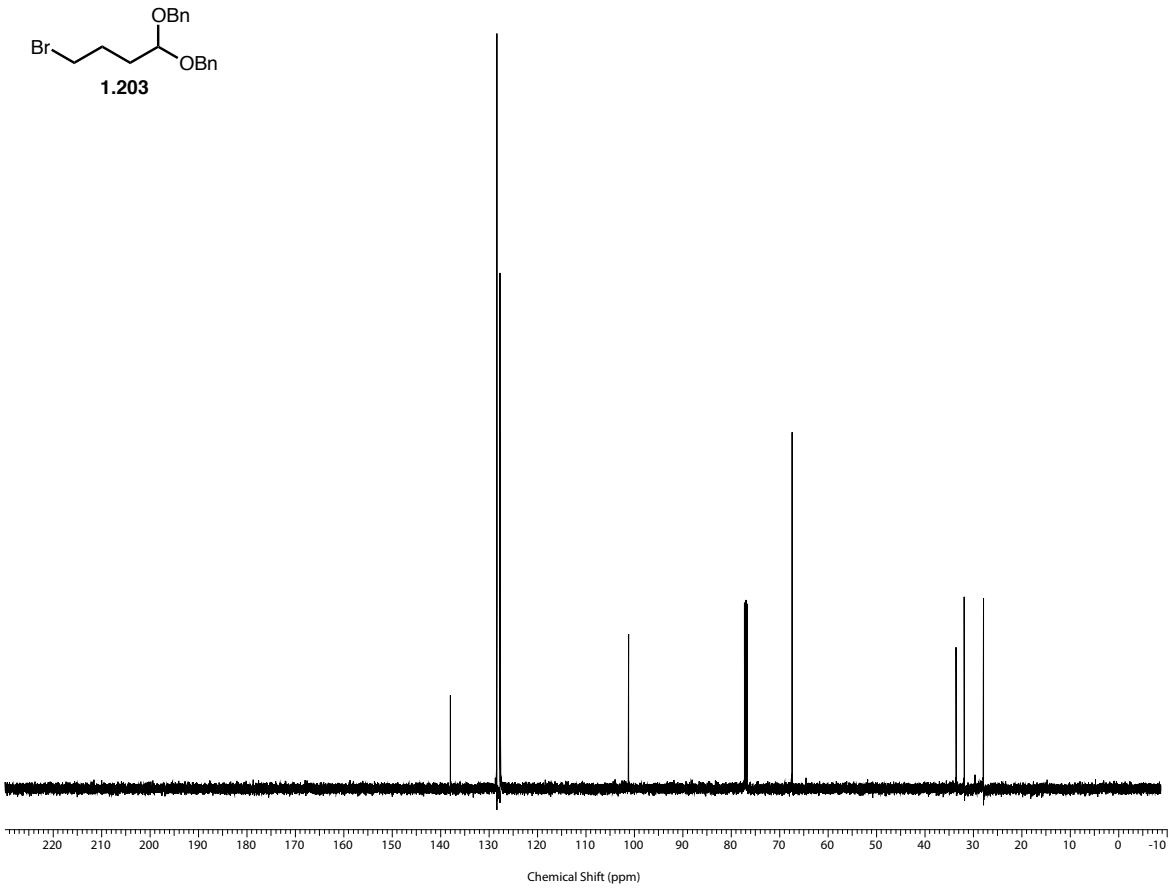
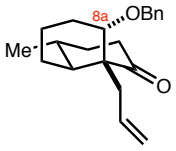
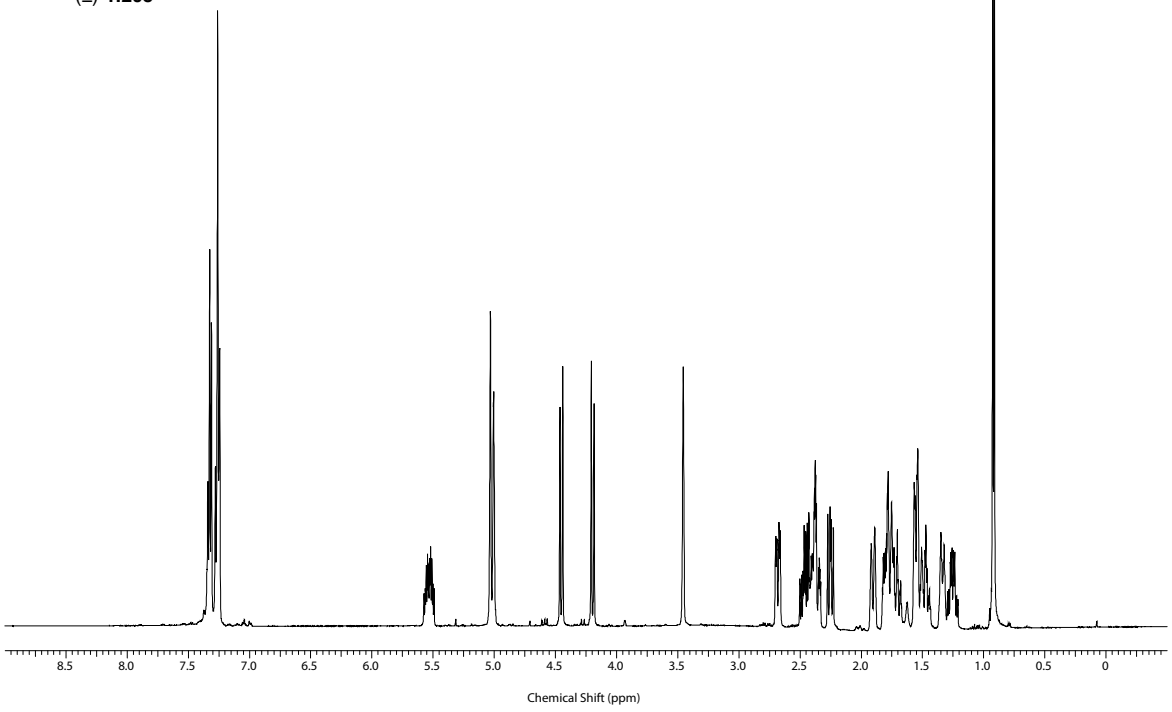
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OBn
Br
OBn
1.203
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


OBn
Br
OBn
1.203
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


8a
OBn
Me
O

(±)-**1.205**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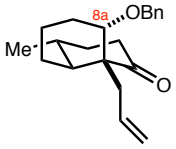
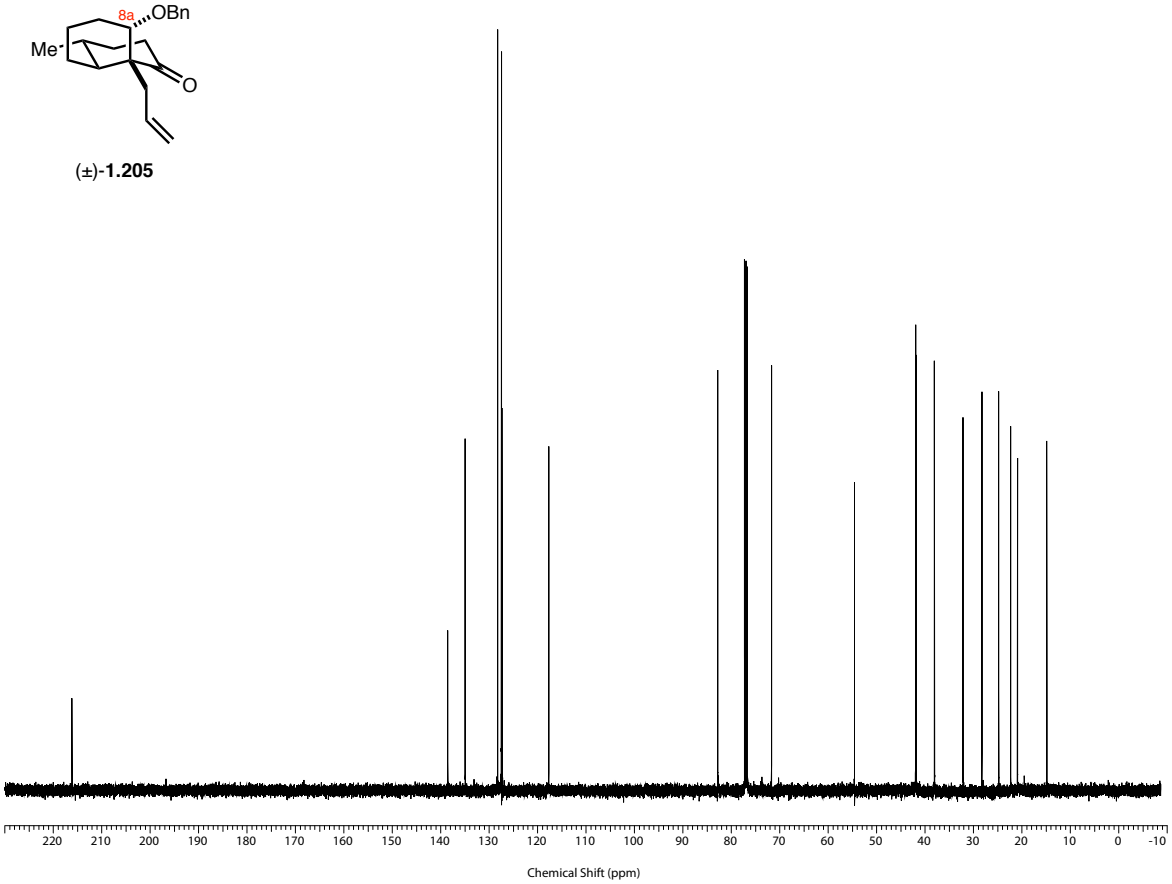
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


8a
OBn
Me
O

(±)-**1.205**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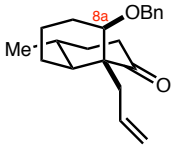
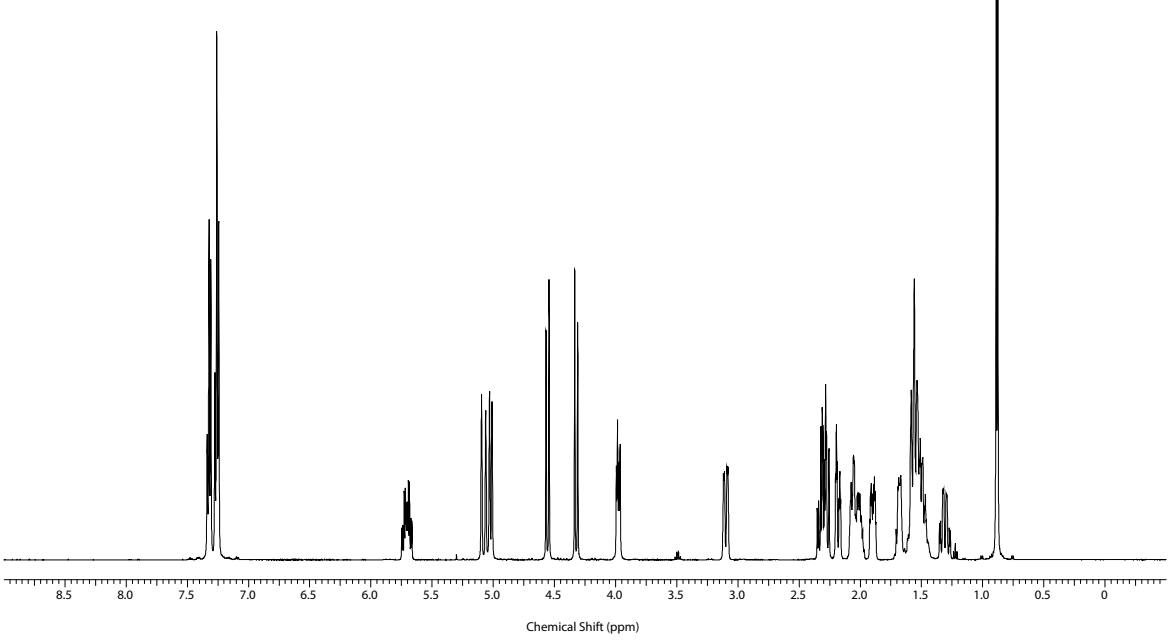
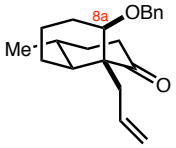
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

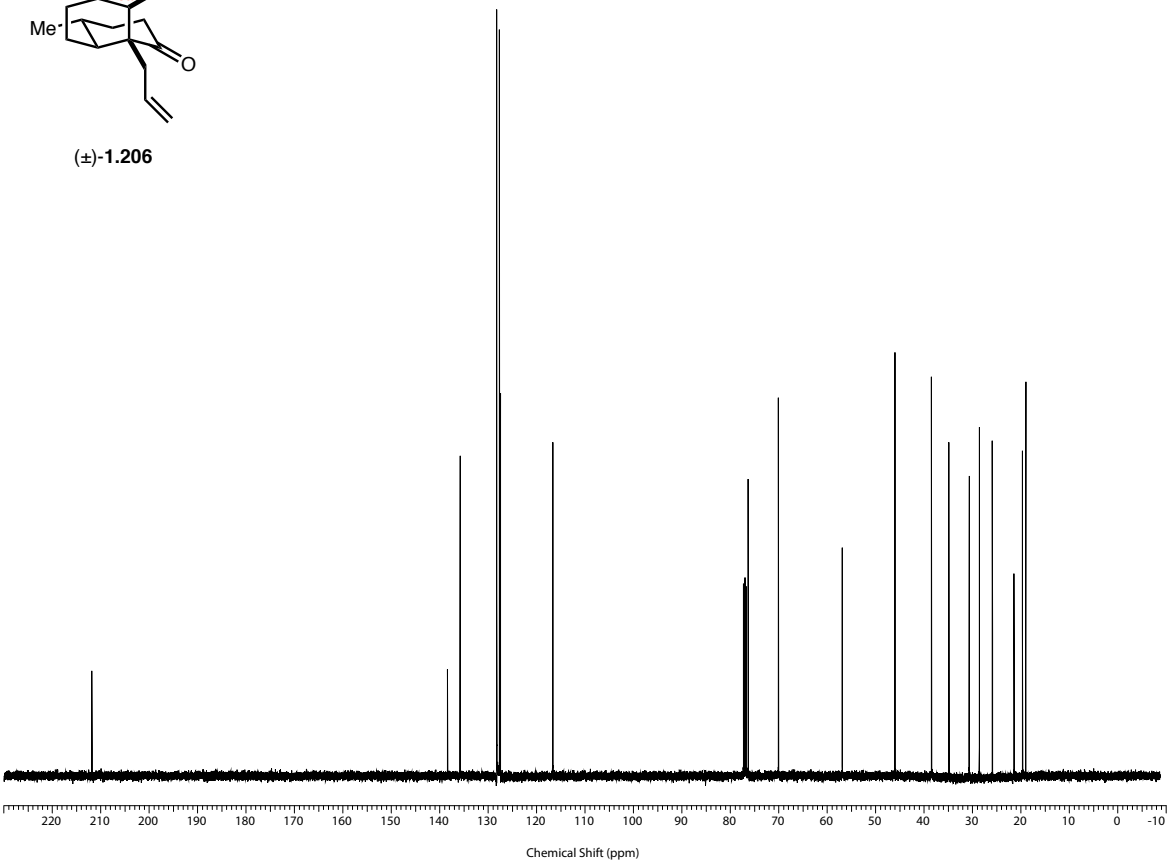

8a
OBn
Me
O

(±)-**1.206**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


8a
OBn
Me
O

(±)-**1.206**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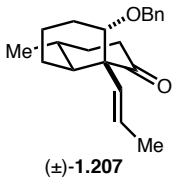
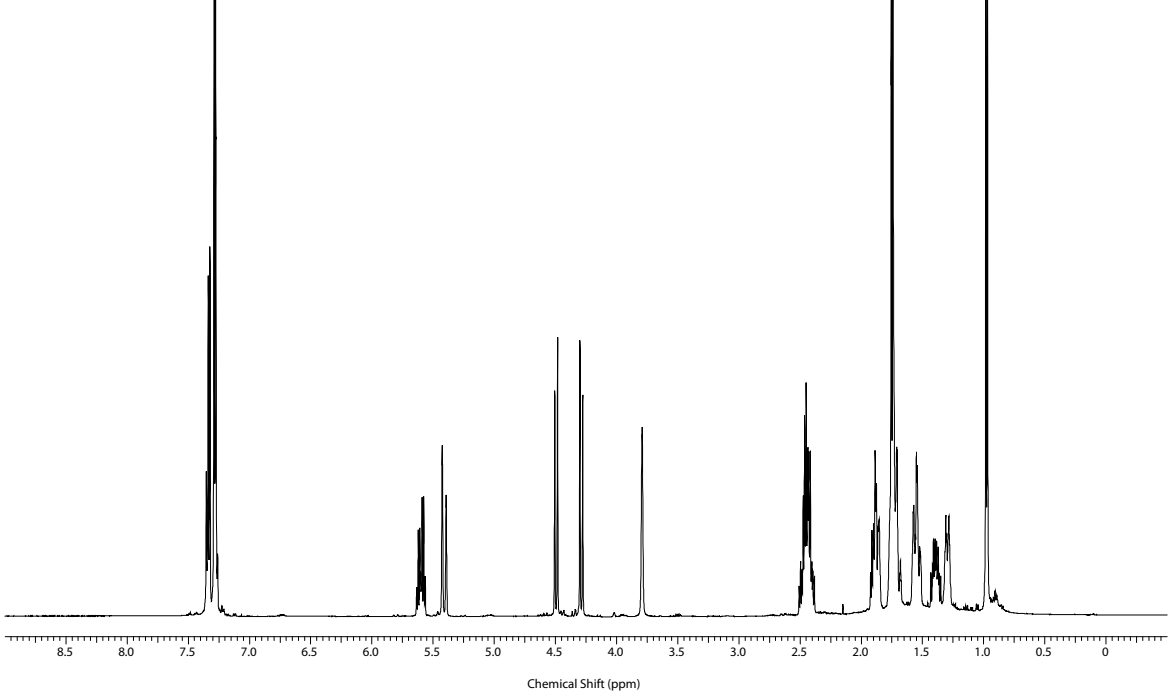
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OBn
Me
O
Me

(±)-**1.207**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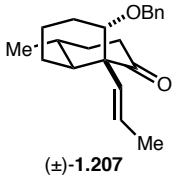
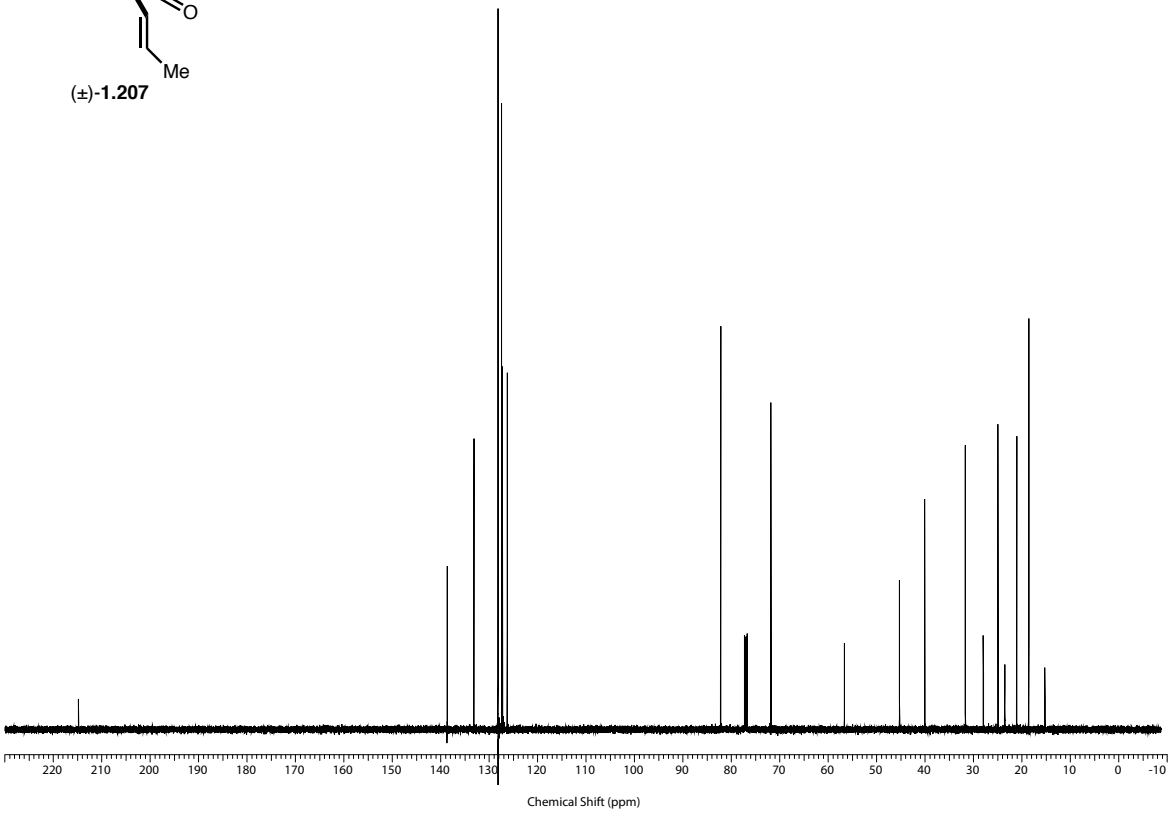
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
O
Me

(±)-**1.207**


220
210
200
190
180
170
160
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140
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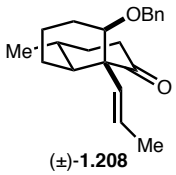
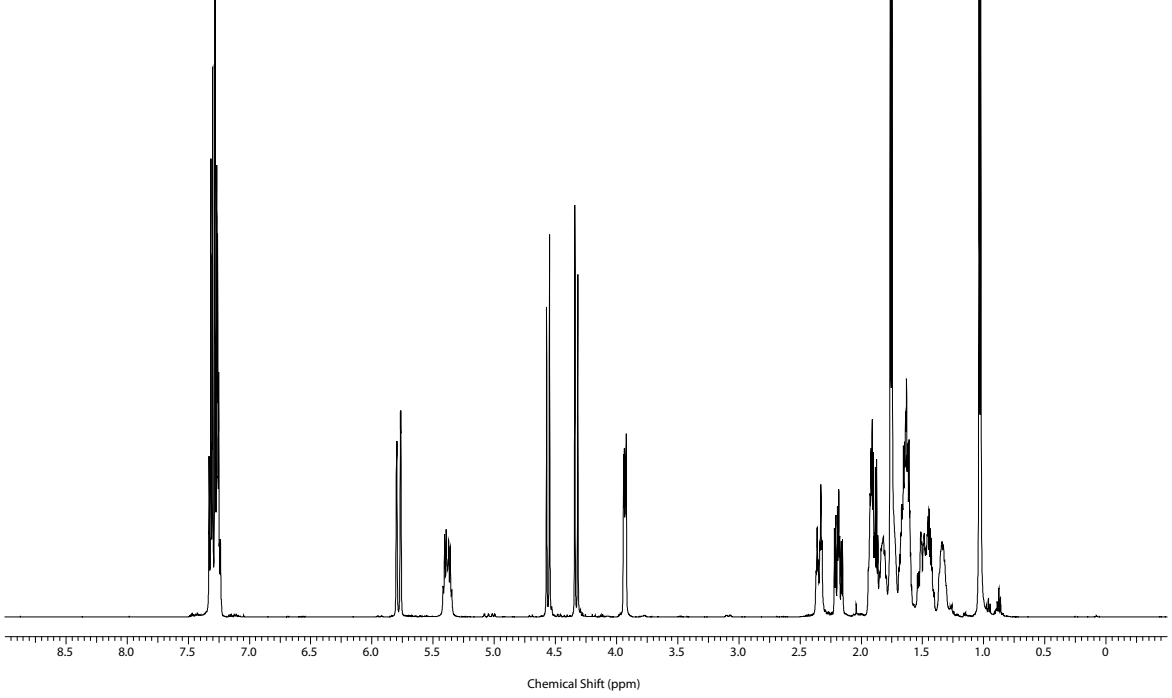
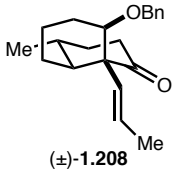
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

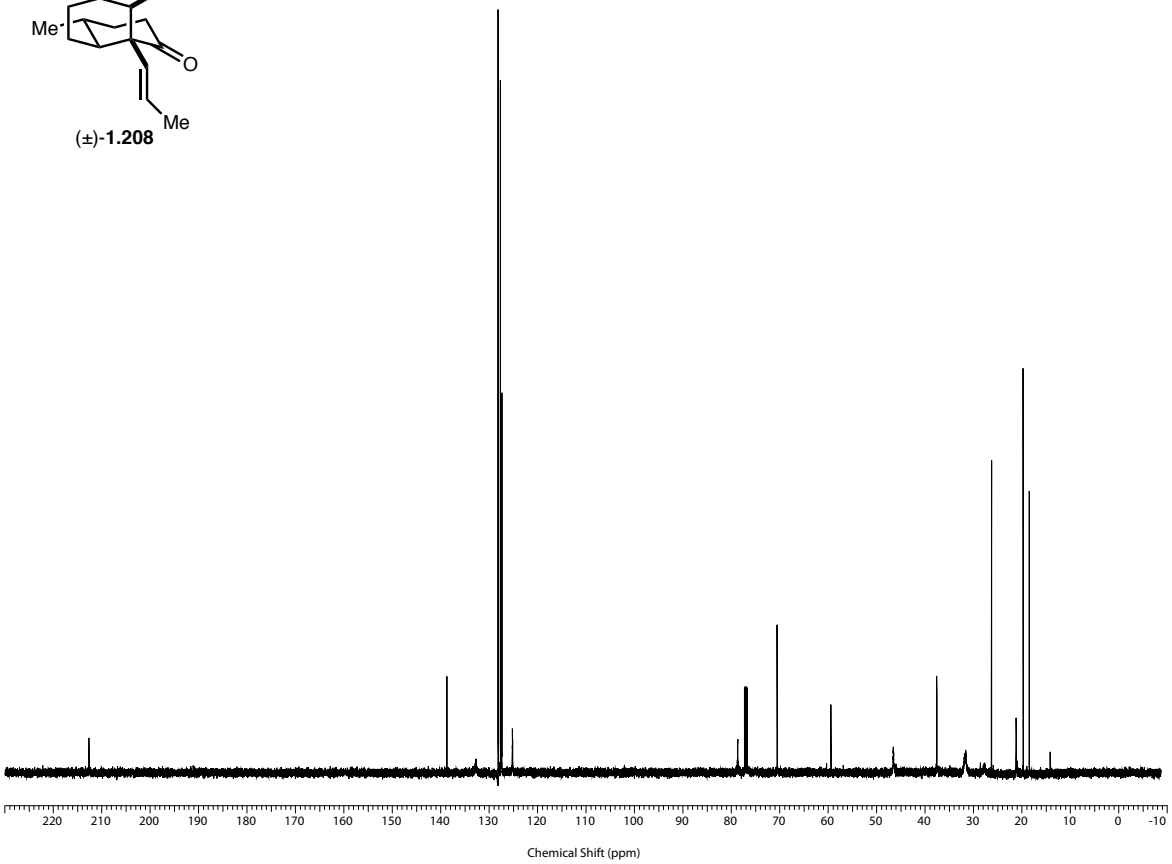

OBn
Me
O
Me

(±)-**1.208**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
O
Me

(±)-**1.208**


220
210
200
190
180
170
160
150
140
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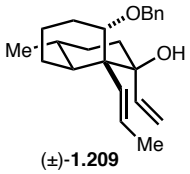
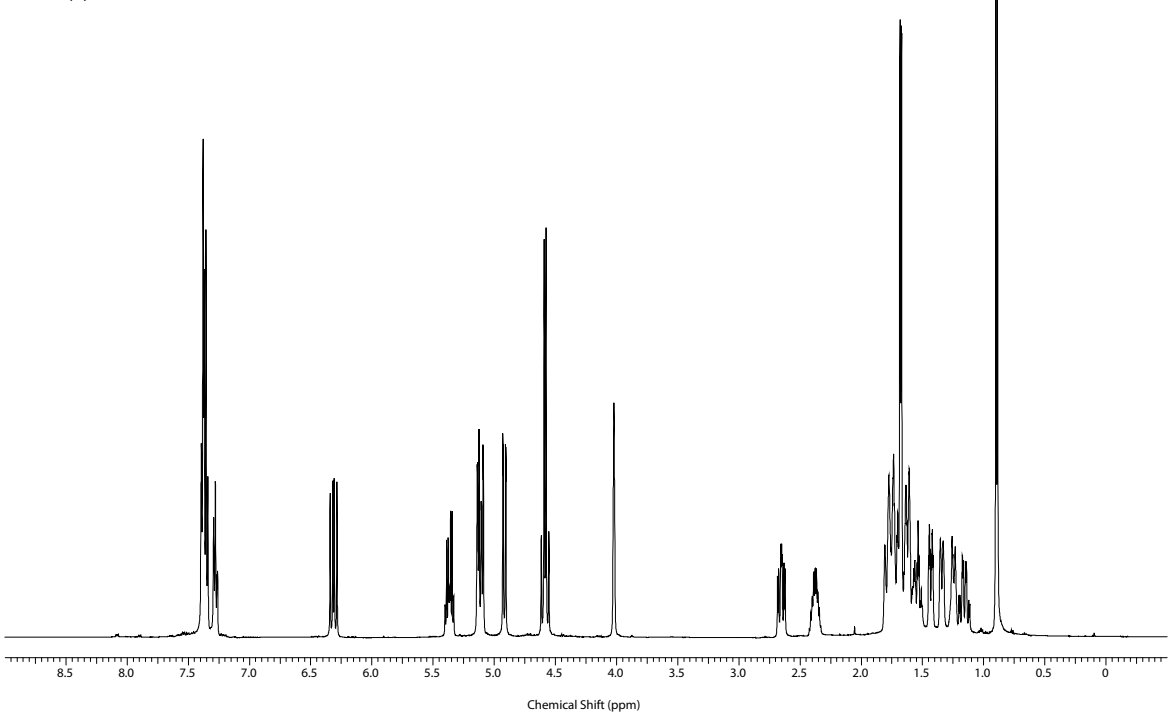
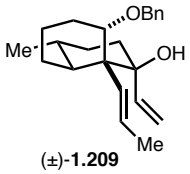
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

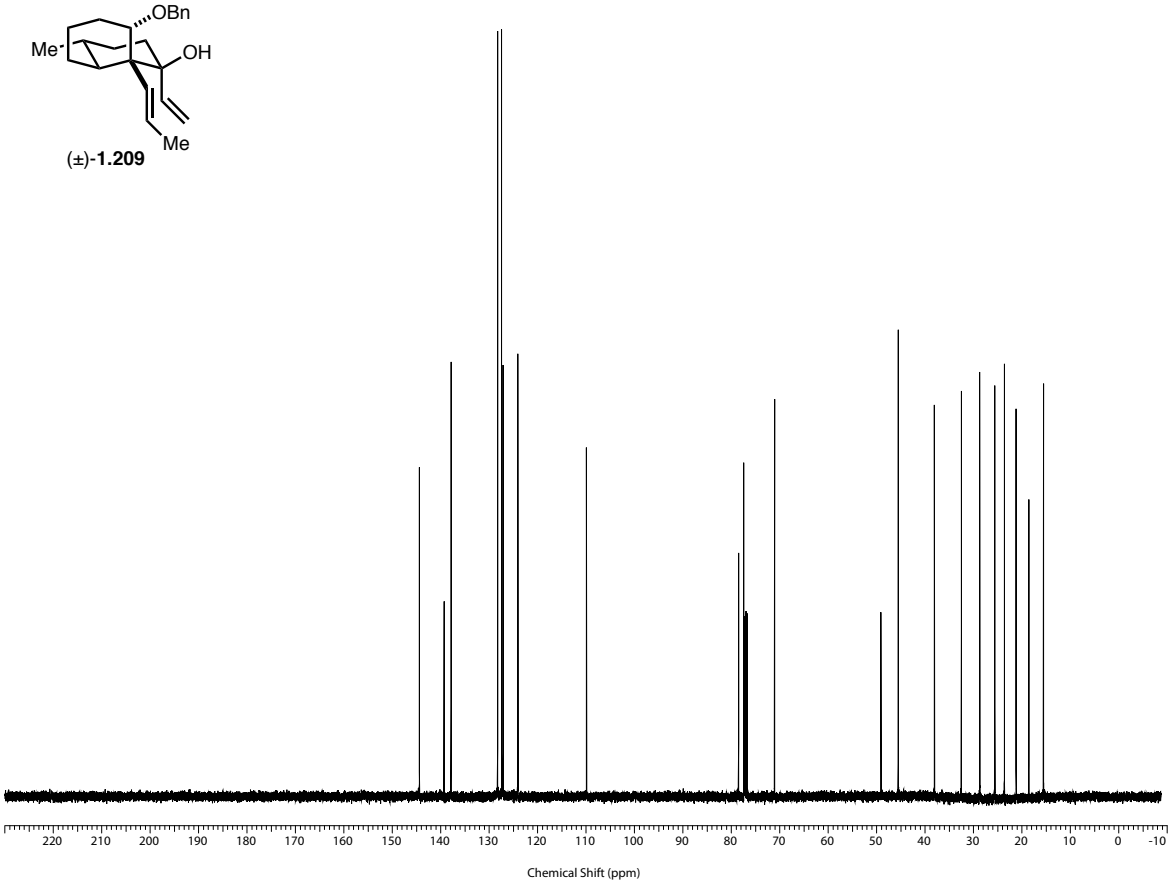

OBn
Me
OH
Me

(±)-**1.209**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
OH
Me

(±)-**1.209**


220
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190
180
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160
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140
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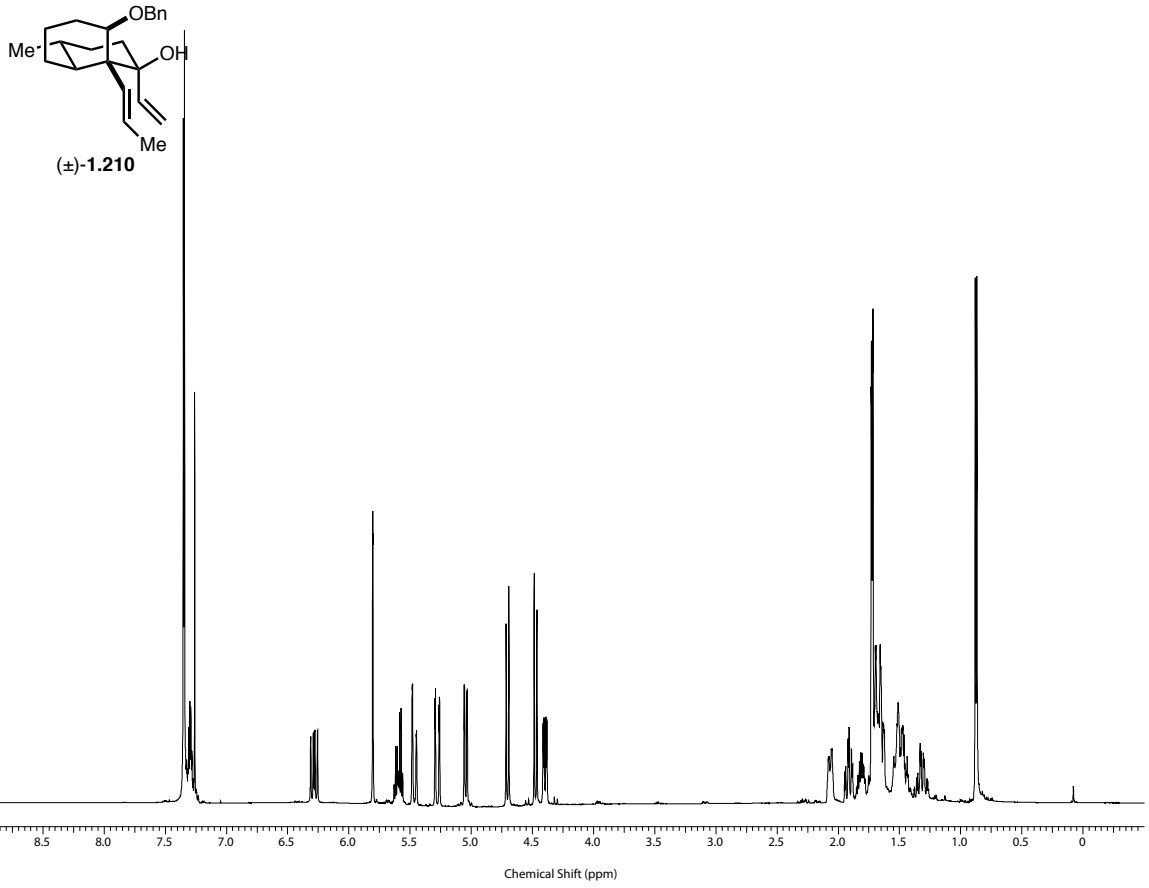
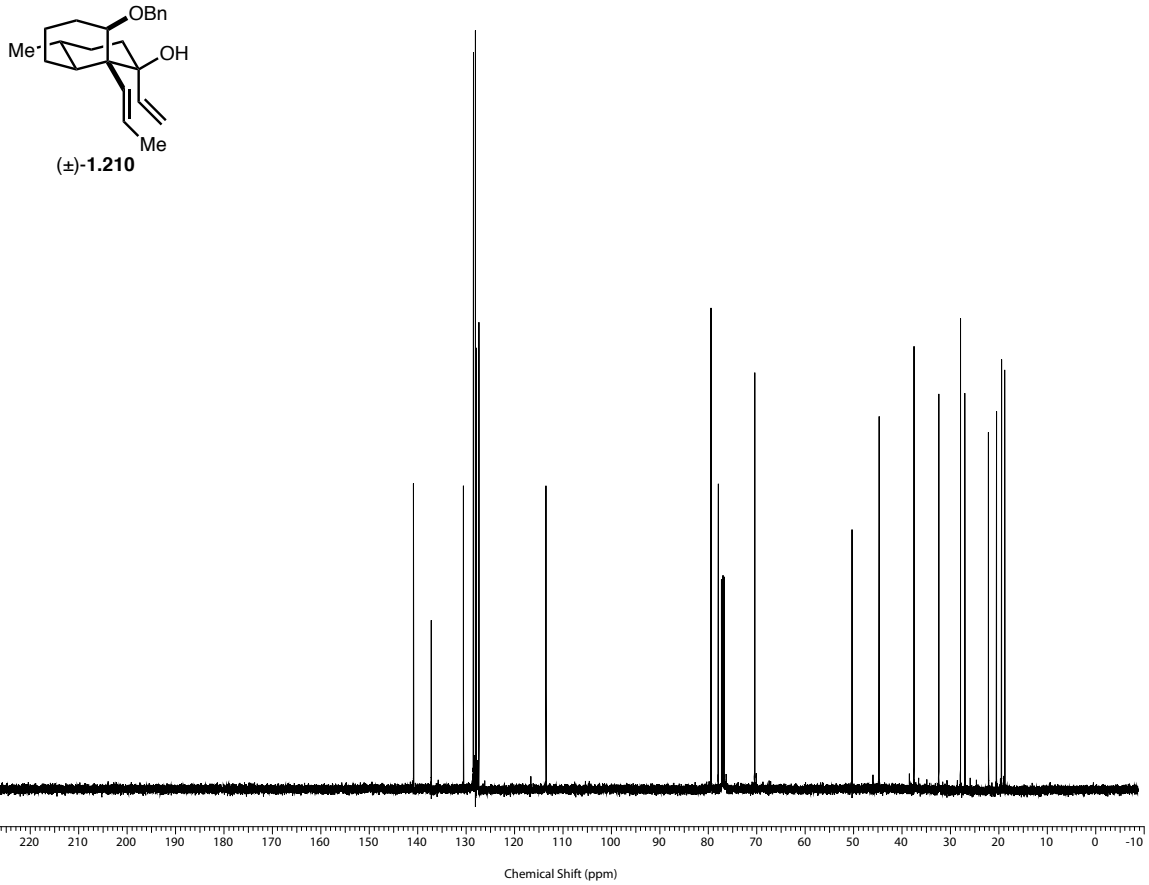
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OBn
Me
OH
Me
(±)-1.210
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
OH
Me
(±)-1.210
220
210
200
190
180
170
160
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140
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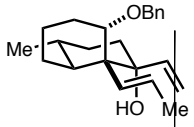
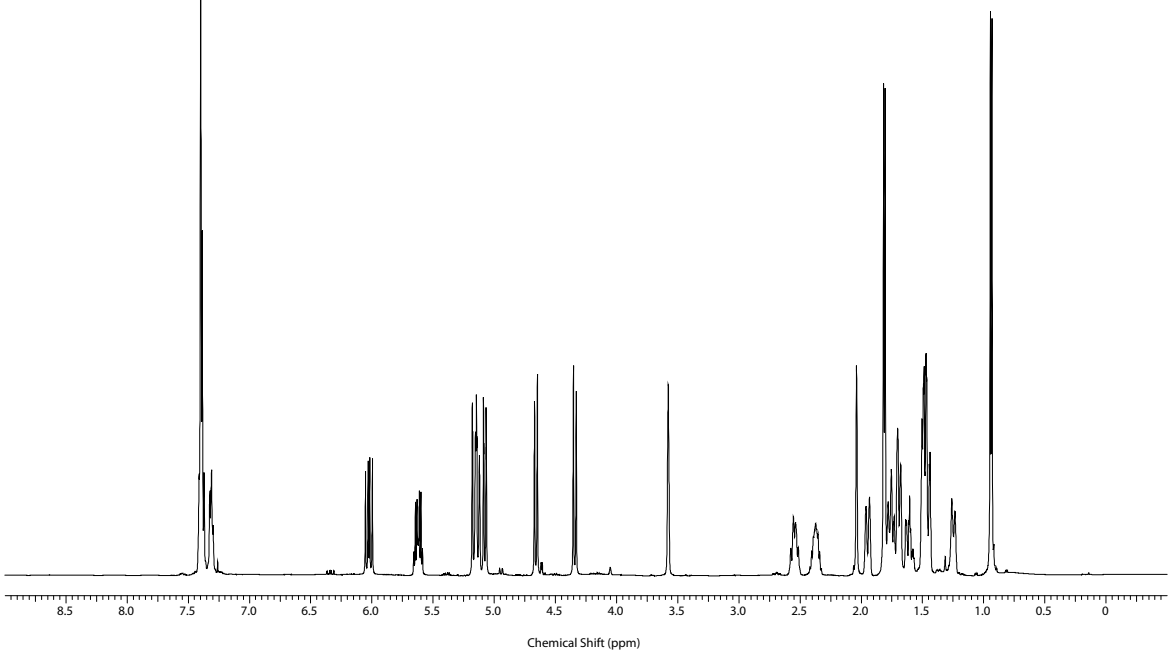
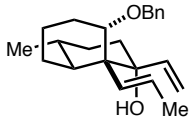
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

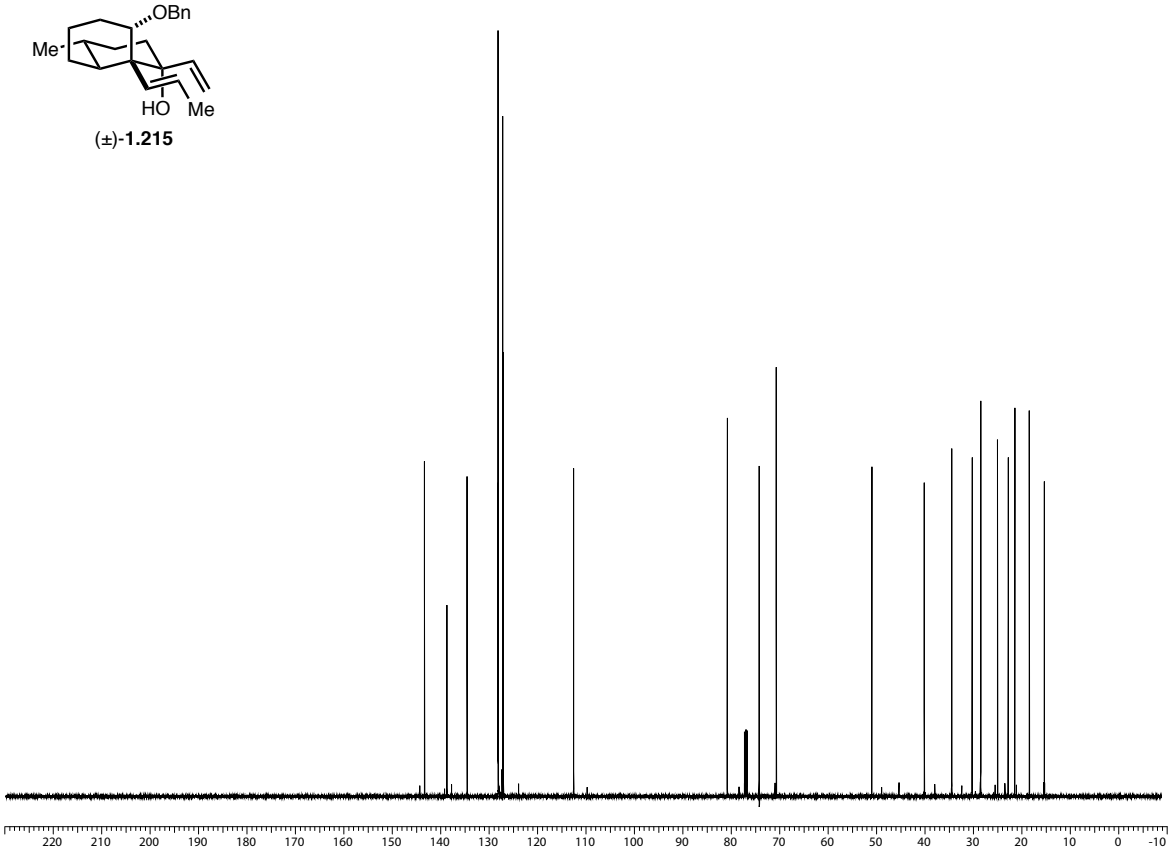

OBn
Me
HO
Me

(±)-**1.215**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
HO
Me

(±)-**1.215**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190
180
170
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140
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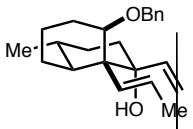
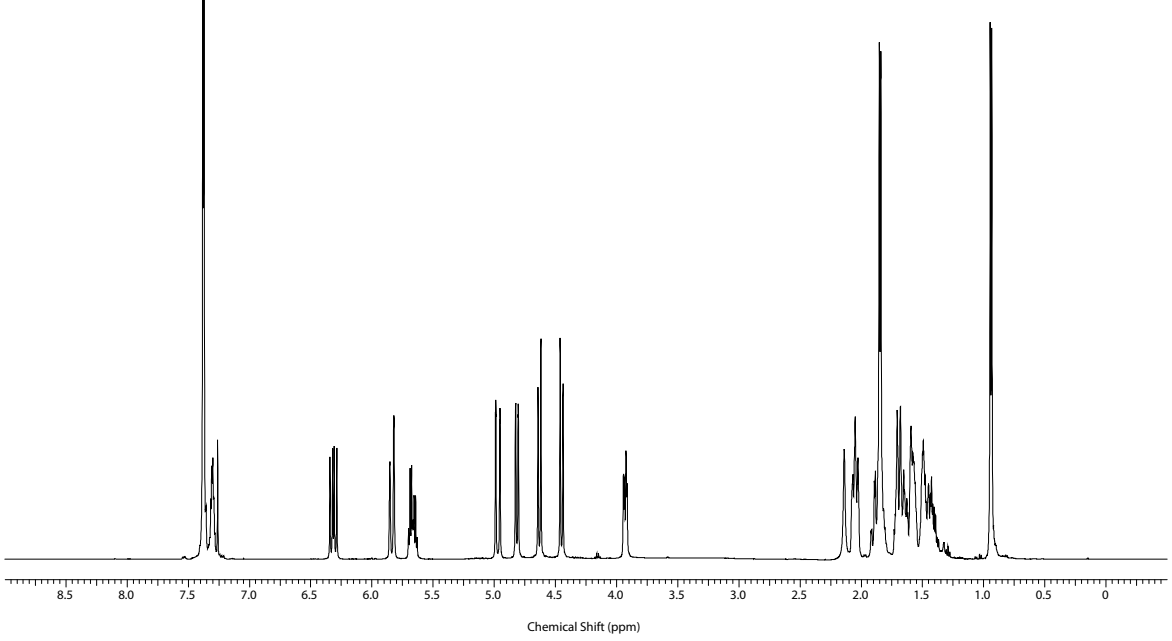
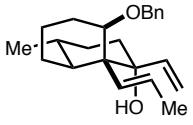
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

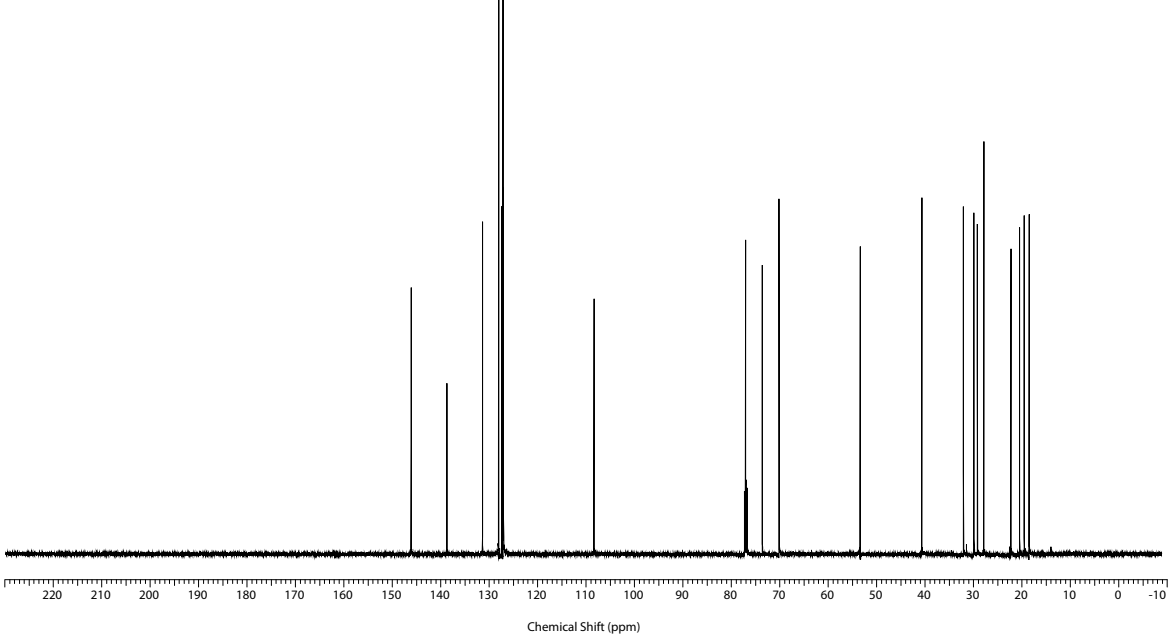

OBn
Me
HO
Me

(±)-**1.216**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
HO
Me

(±)-**1.216**


220
210
200
190
180
170
160
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140
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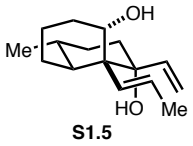
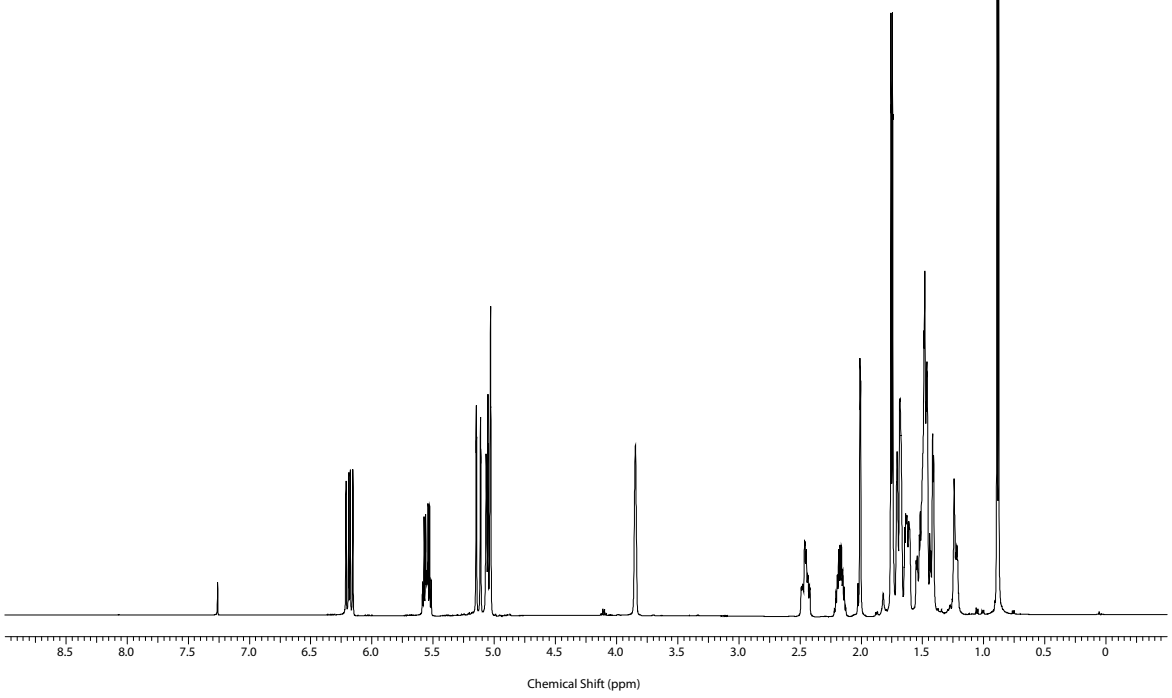
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OH
Me
HO
Me

S1.5


8.5
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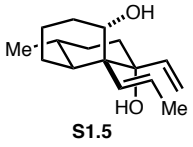
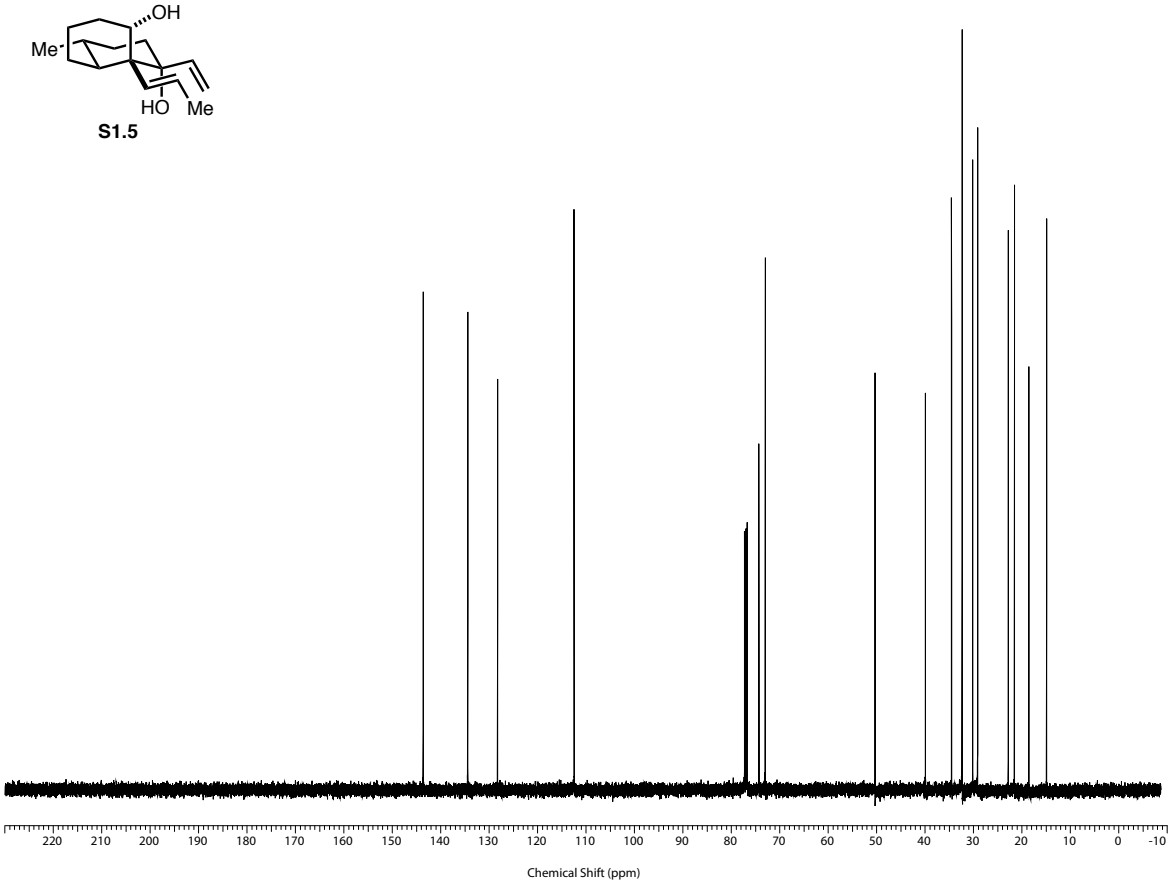
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OH
Me
HO
Me

S1.5


220
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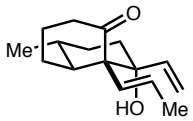
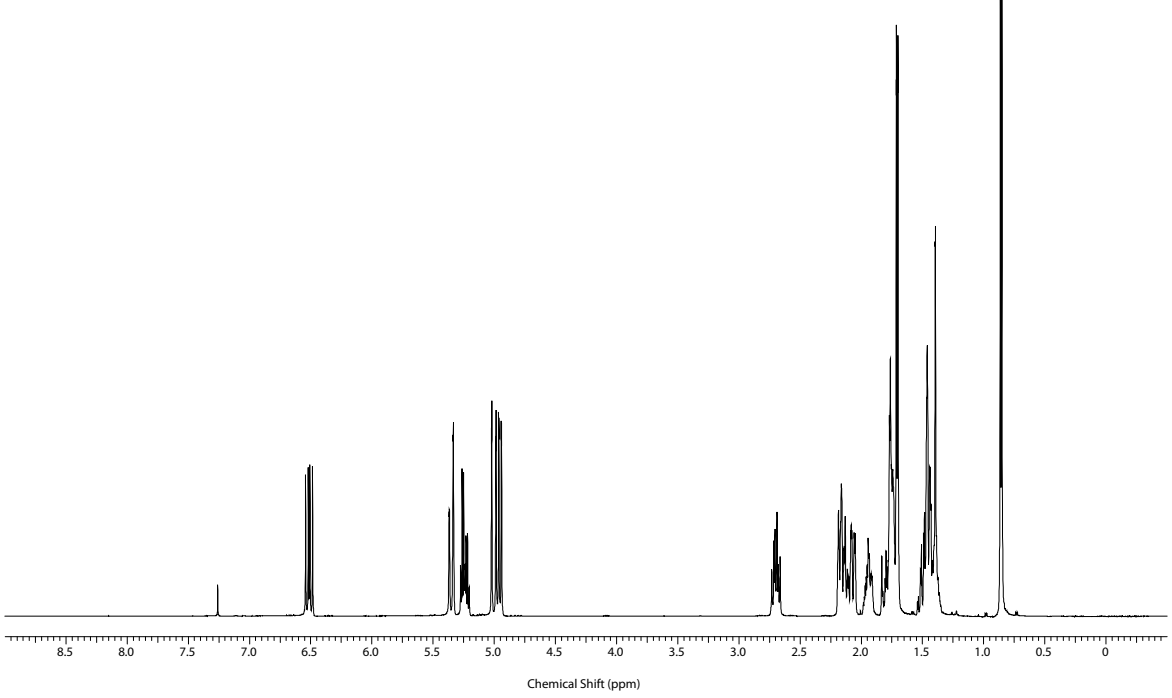
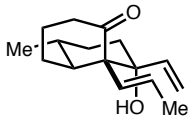
20
10
0
-10
Chemical Shift (ppm)

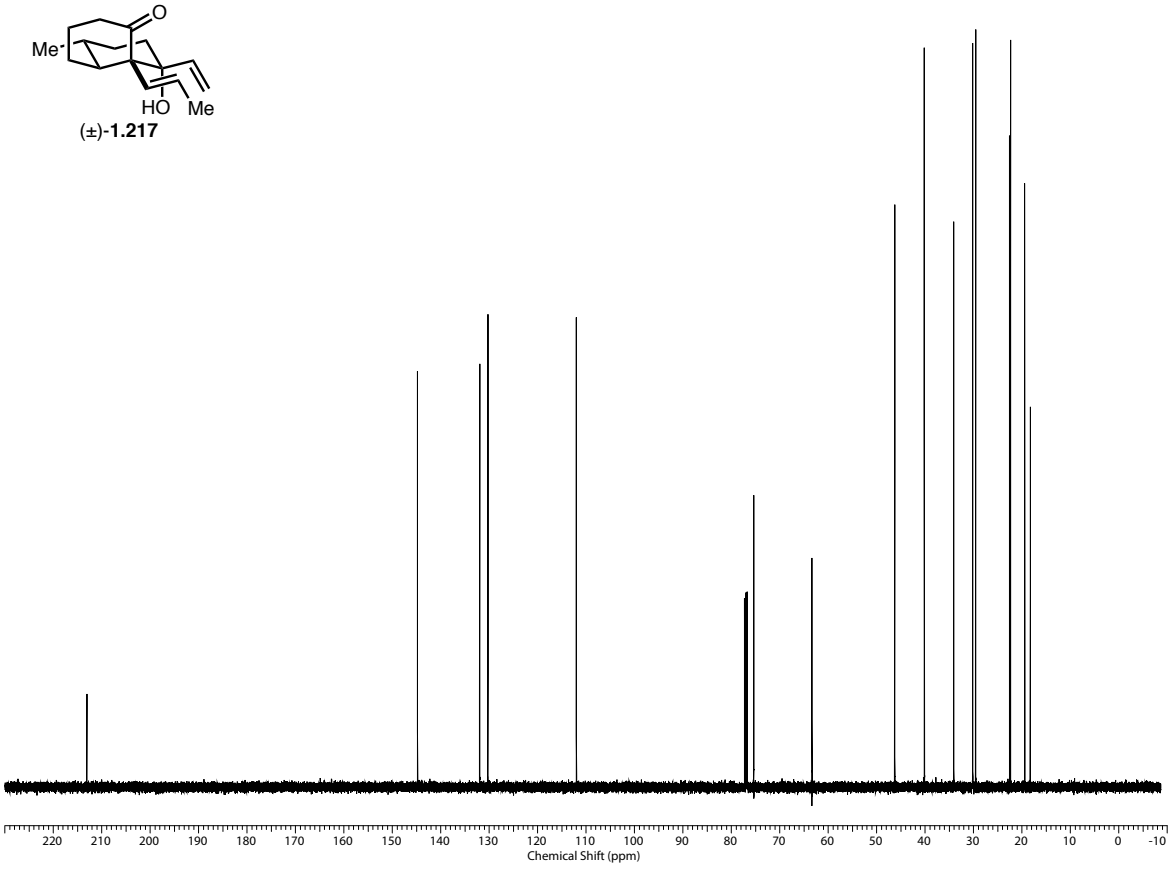

O
Me
HO
Me

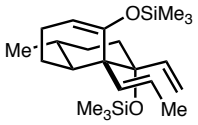
(±)-**1.217**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

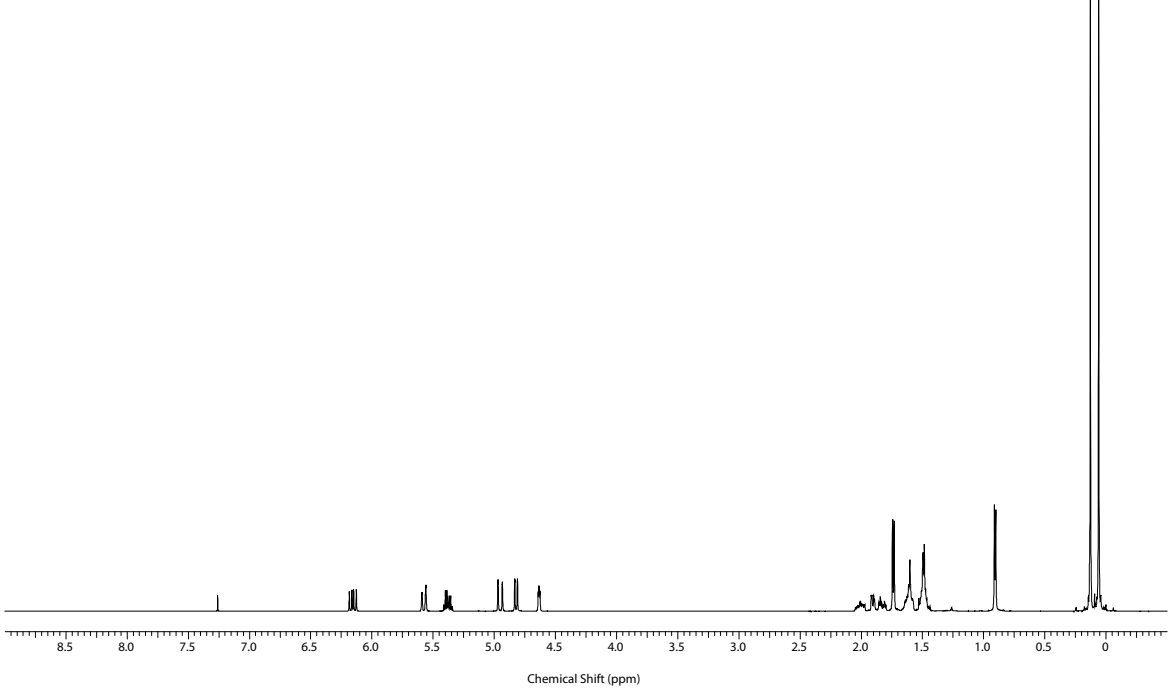

O
Me
HO
Me

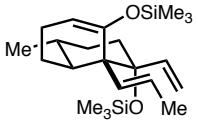
(±)-**1.217**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

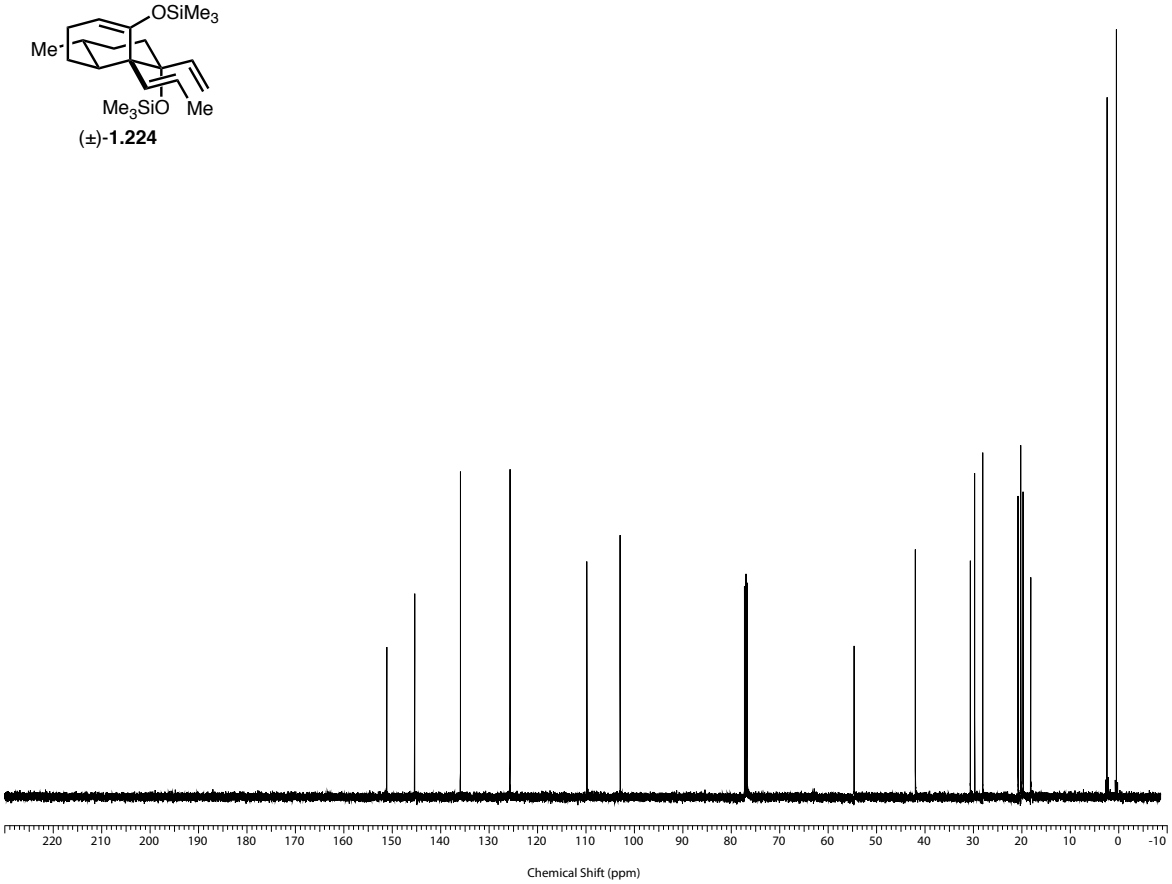

OSiMe3
Me
Me3SiO
Me

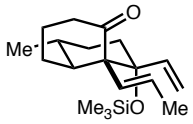
(±)-**1.224**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

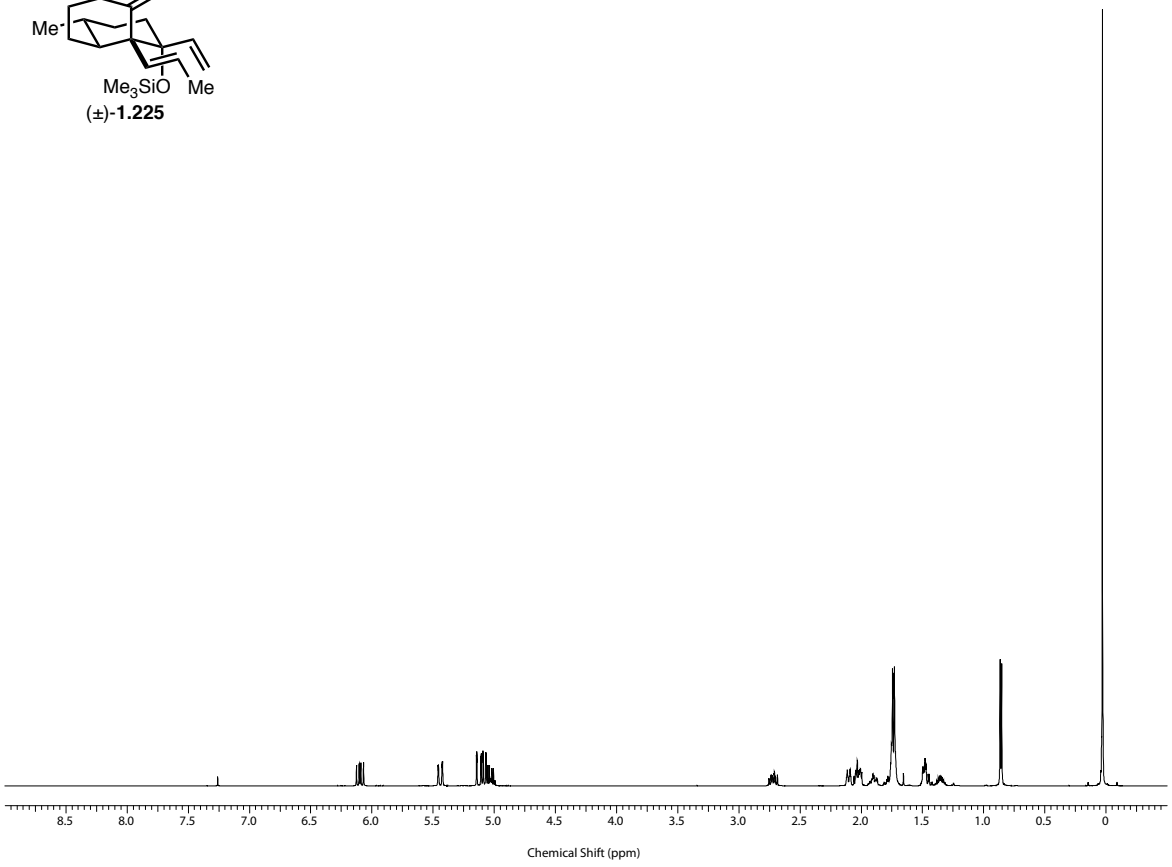

OSiMe3
Me
Me3SiO
Me

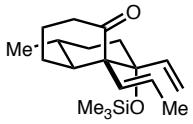
(±)-**1.224**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

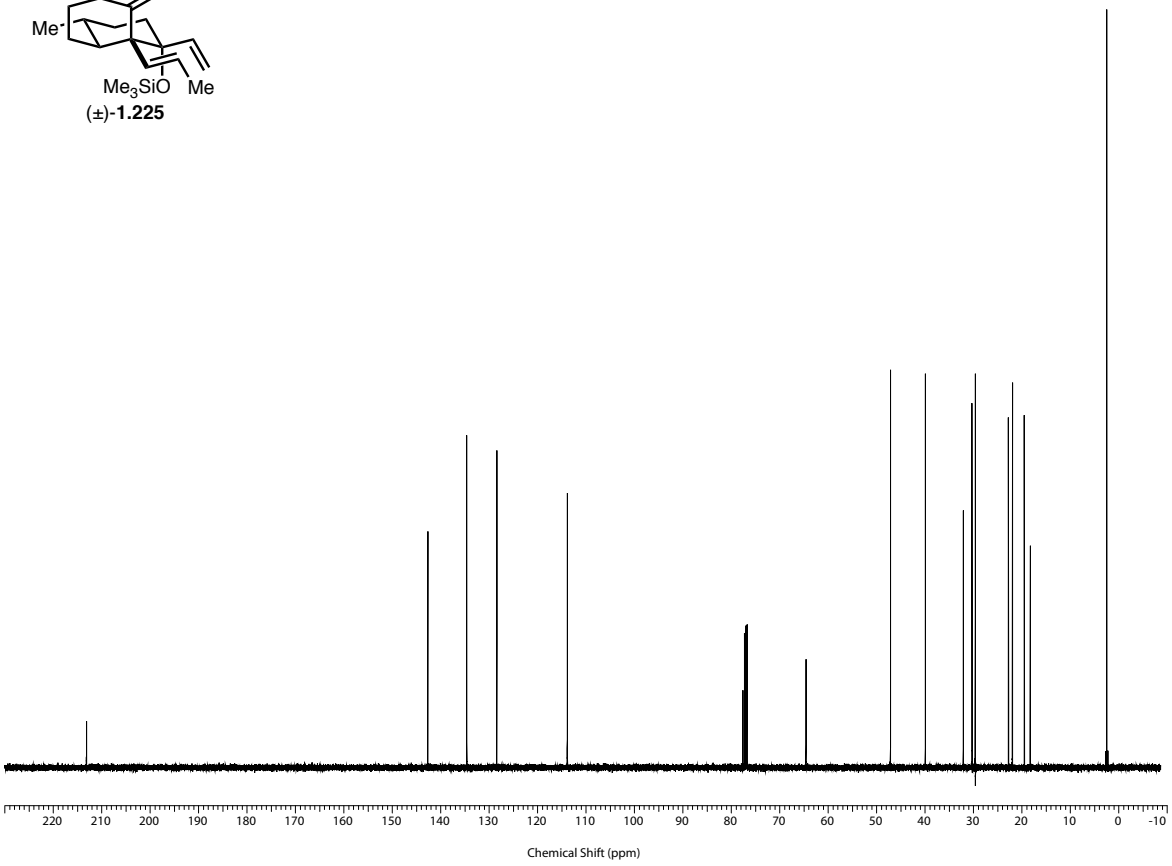

O
Me
Me3SiO
Me

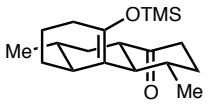
(±)-**1.225**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

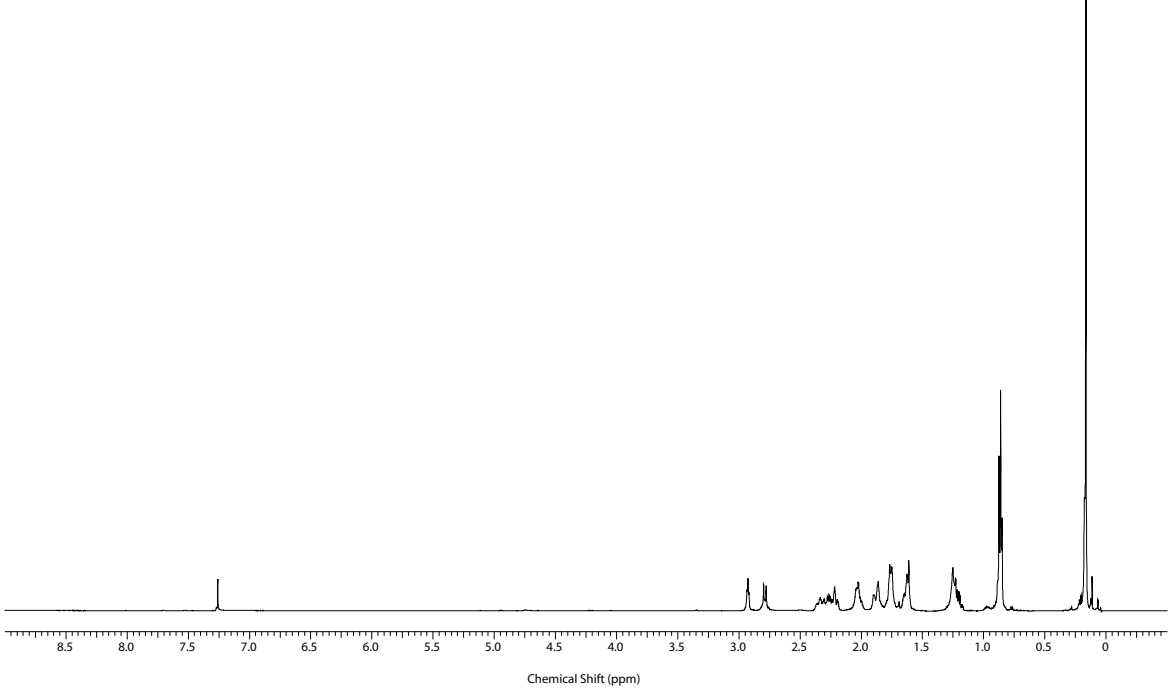

O
Me
Me3SiO
Me

(±)-**1.225**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

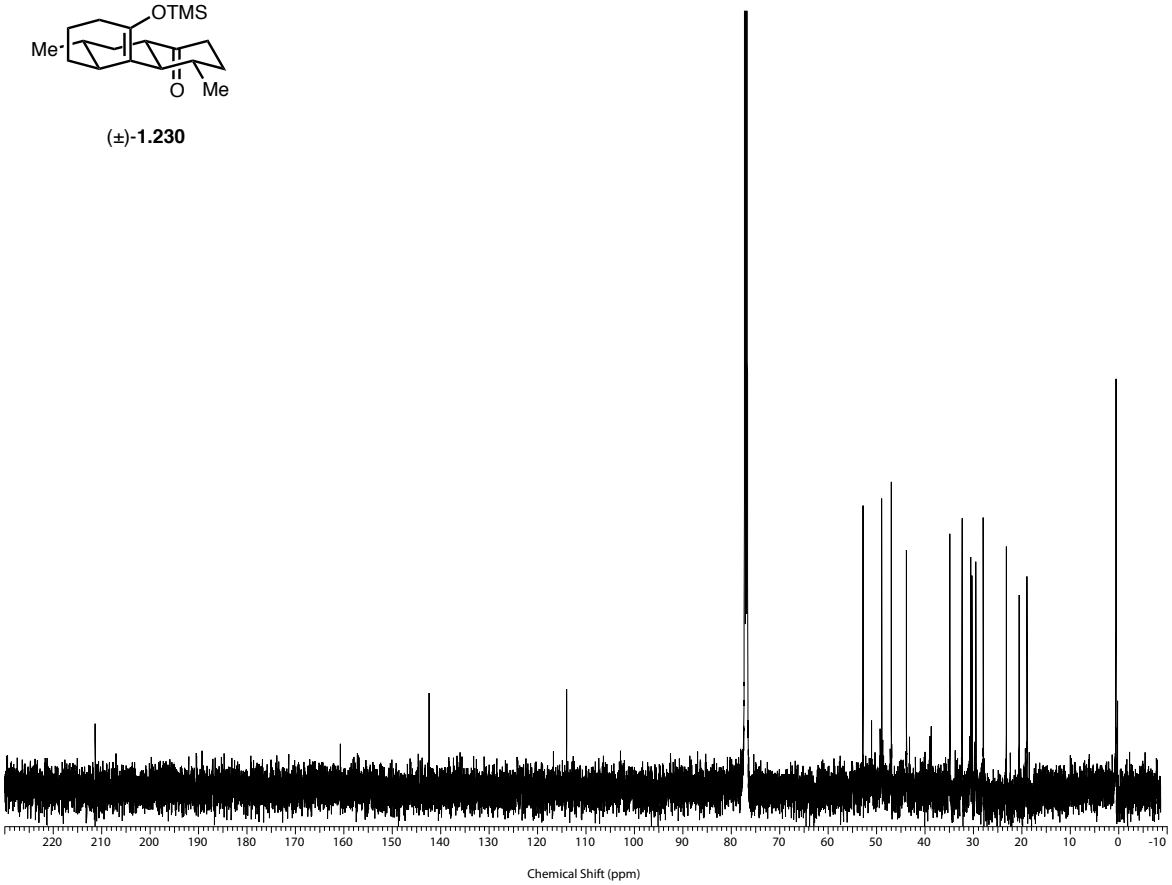

OTMS
Me
O
Me

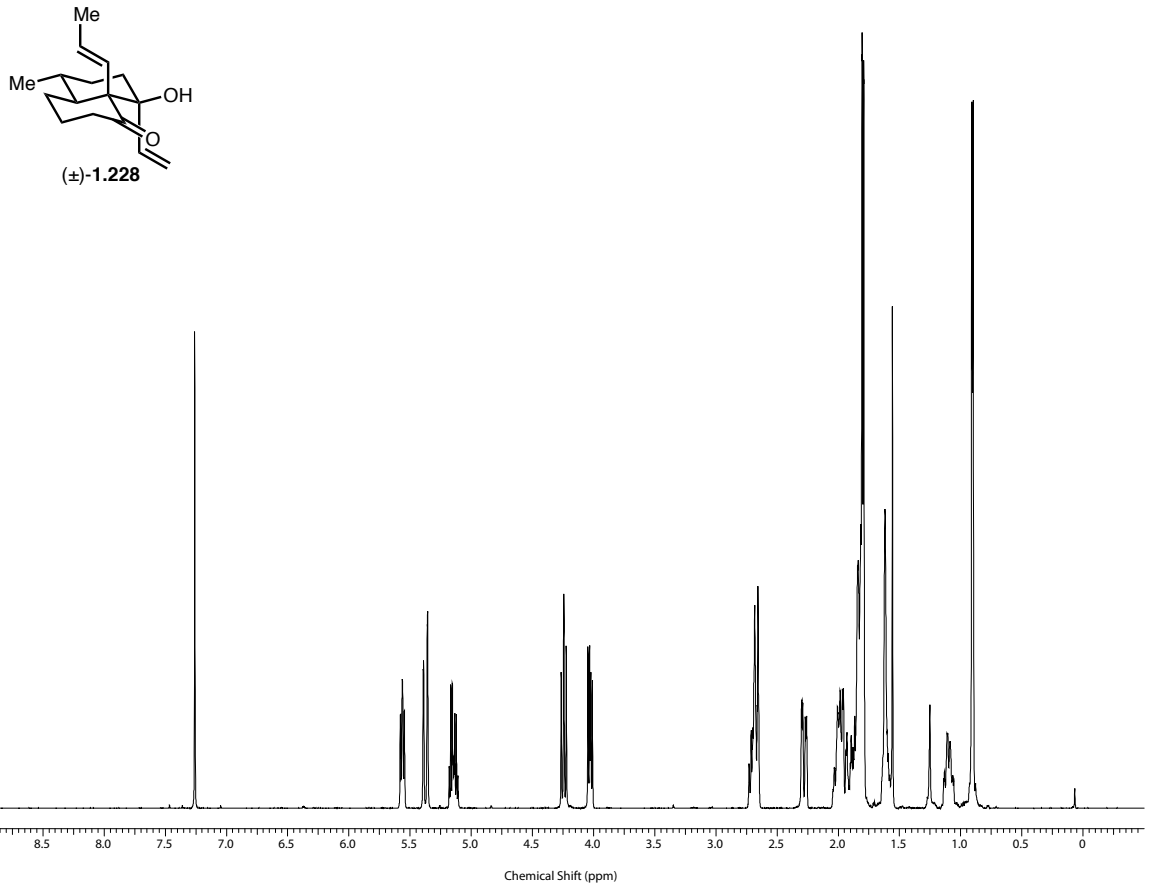
(±)-**1.230**

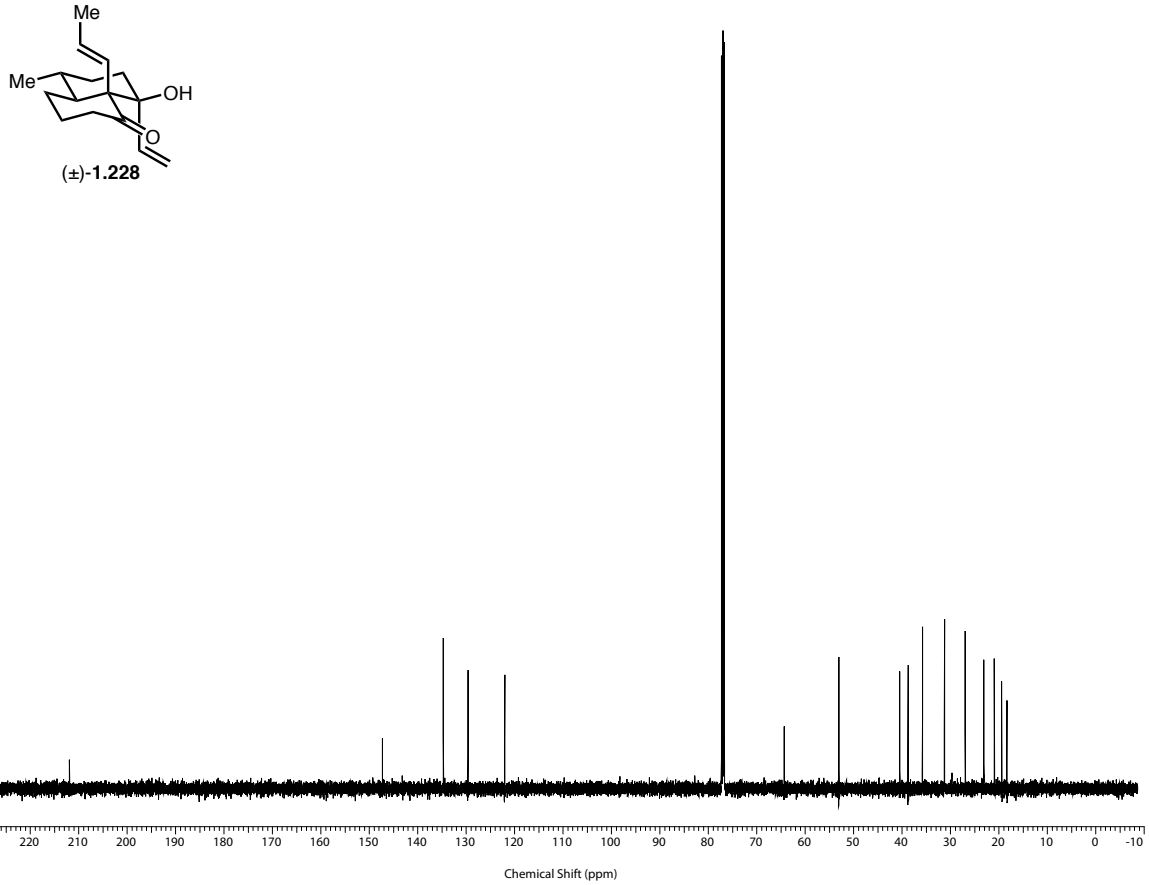

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

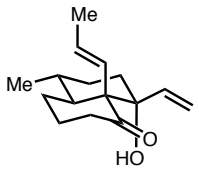
OTMS
Me
O
Me

(±)-**1.230**

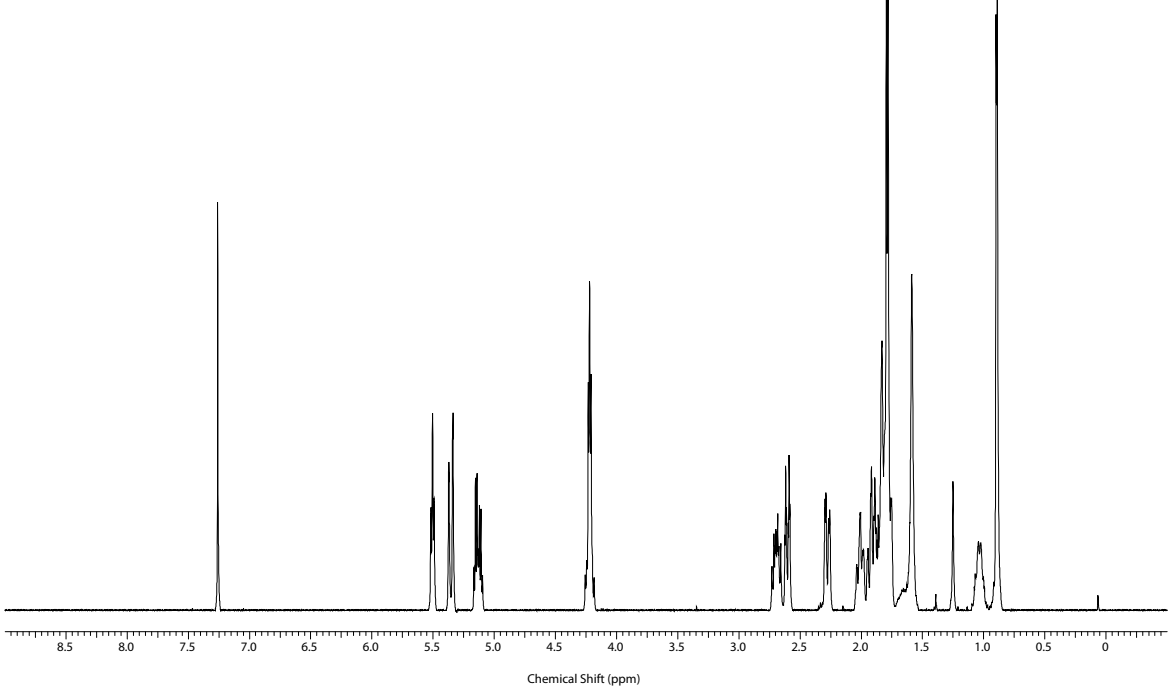

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

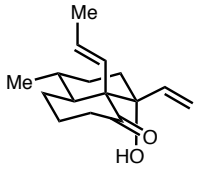

Me
Me
OH
O
(±)-1.228
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


Me
Me
OH
O
(±)-1.228
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

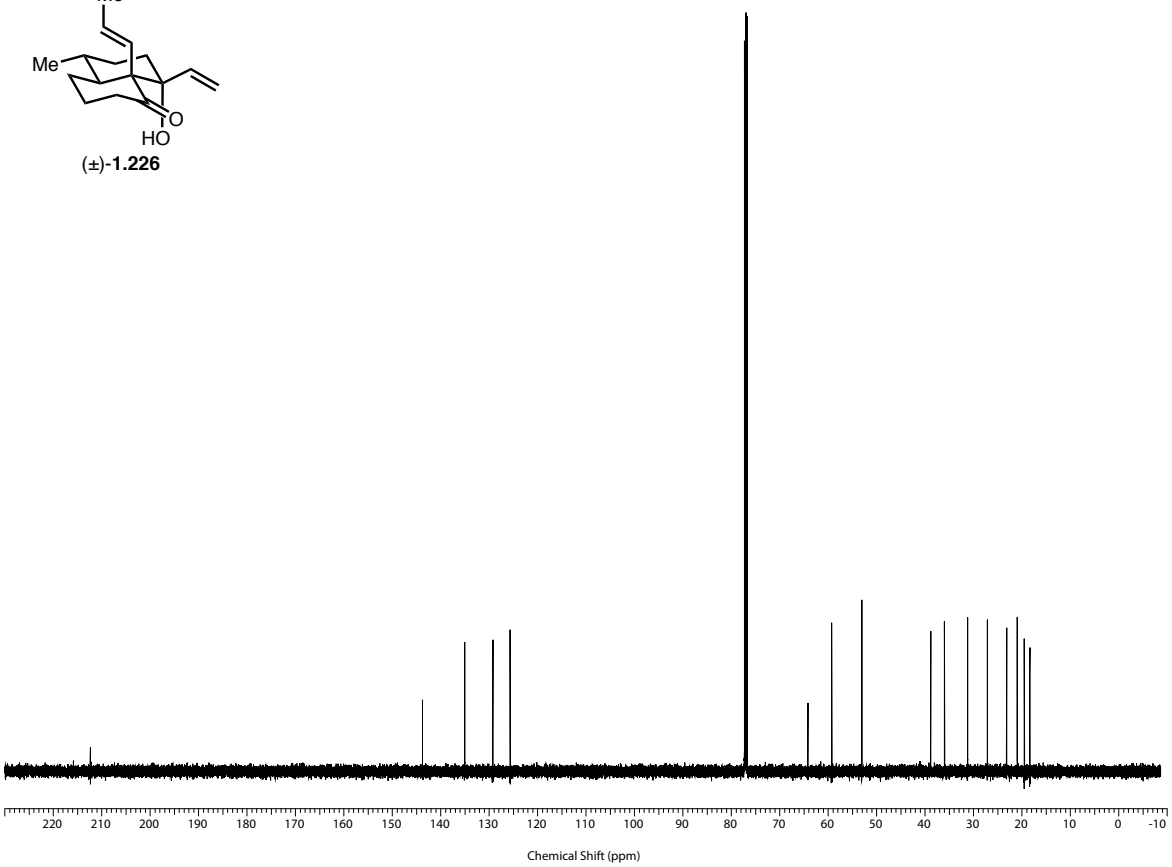

Me
Me
O
HO

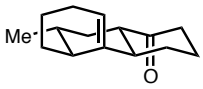
(±)-**1.226**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

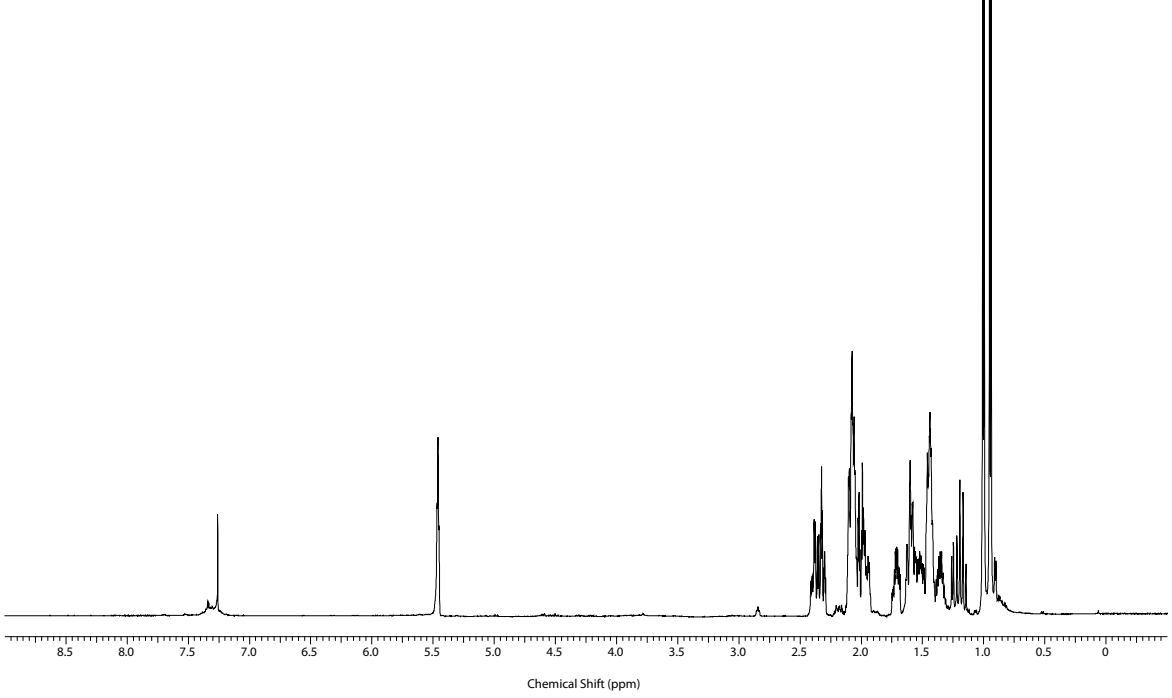

Me
Me
O
HO

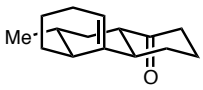
(±)-**1.226**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

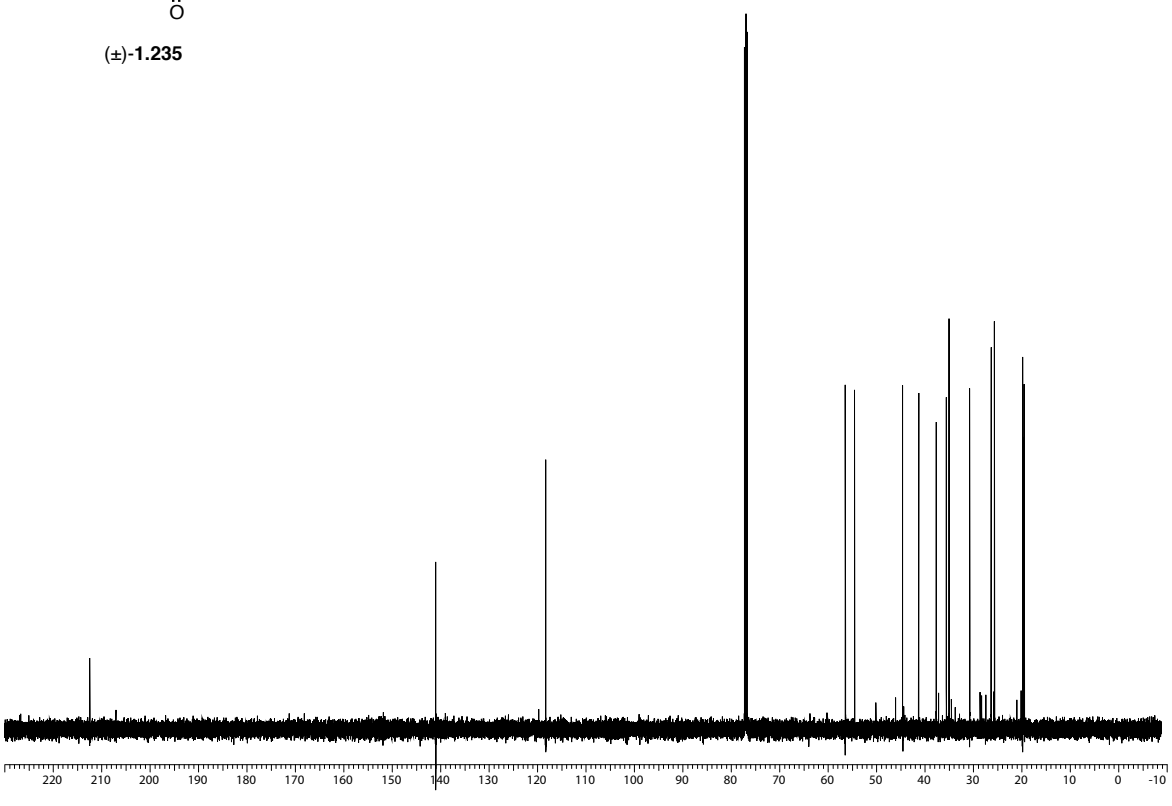

Me
O

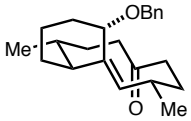
(±)-**1.235**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

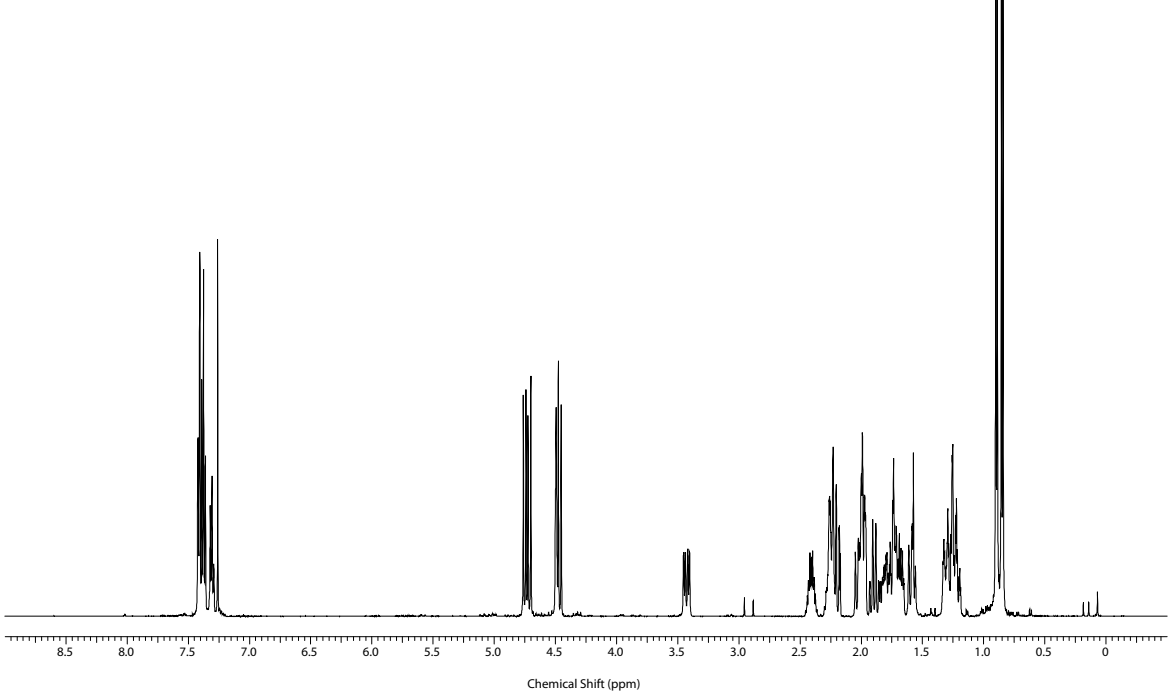

Me
O

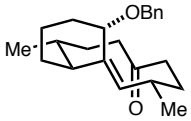
(±)-**1.235**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

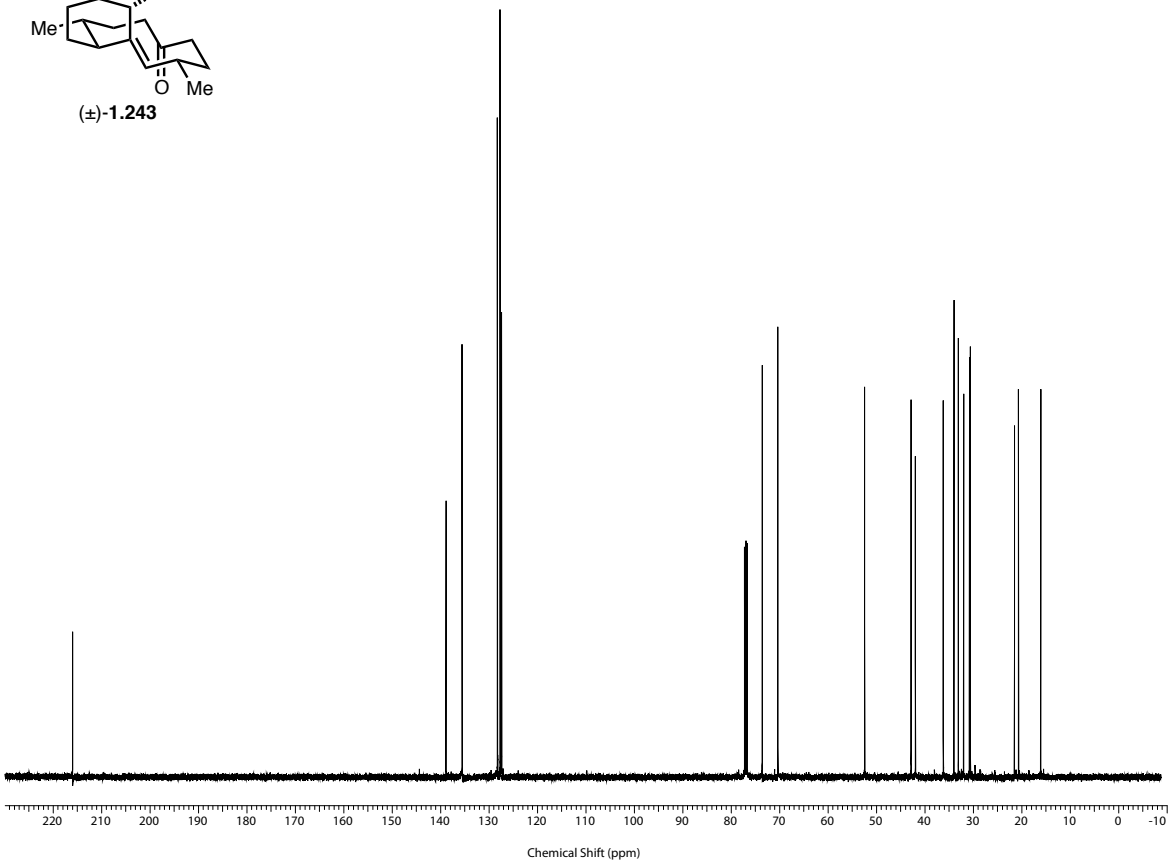

OBn
Me
O
Me

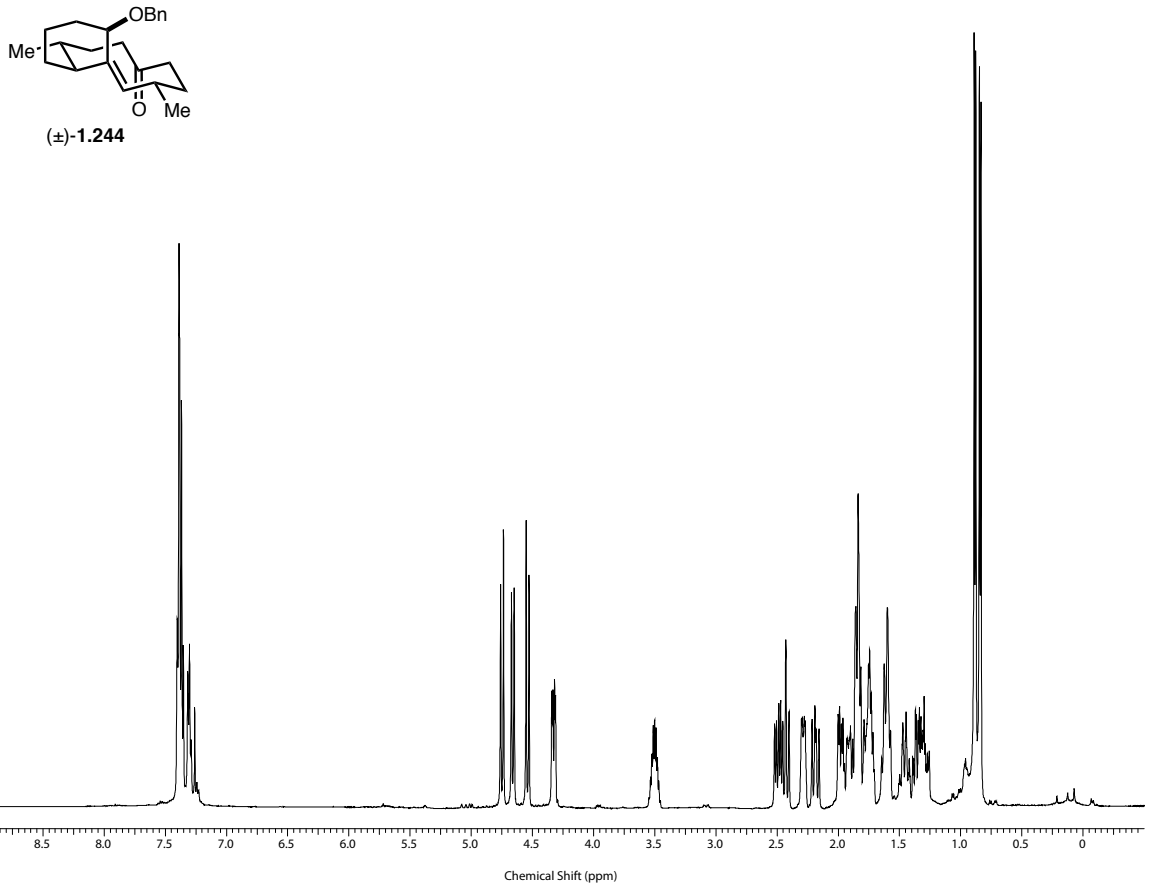
(±)-**1.243**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

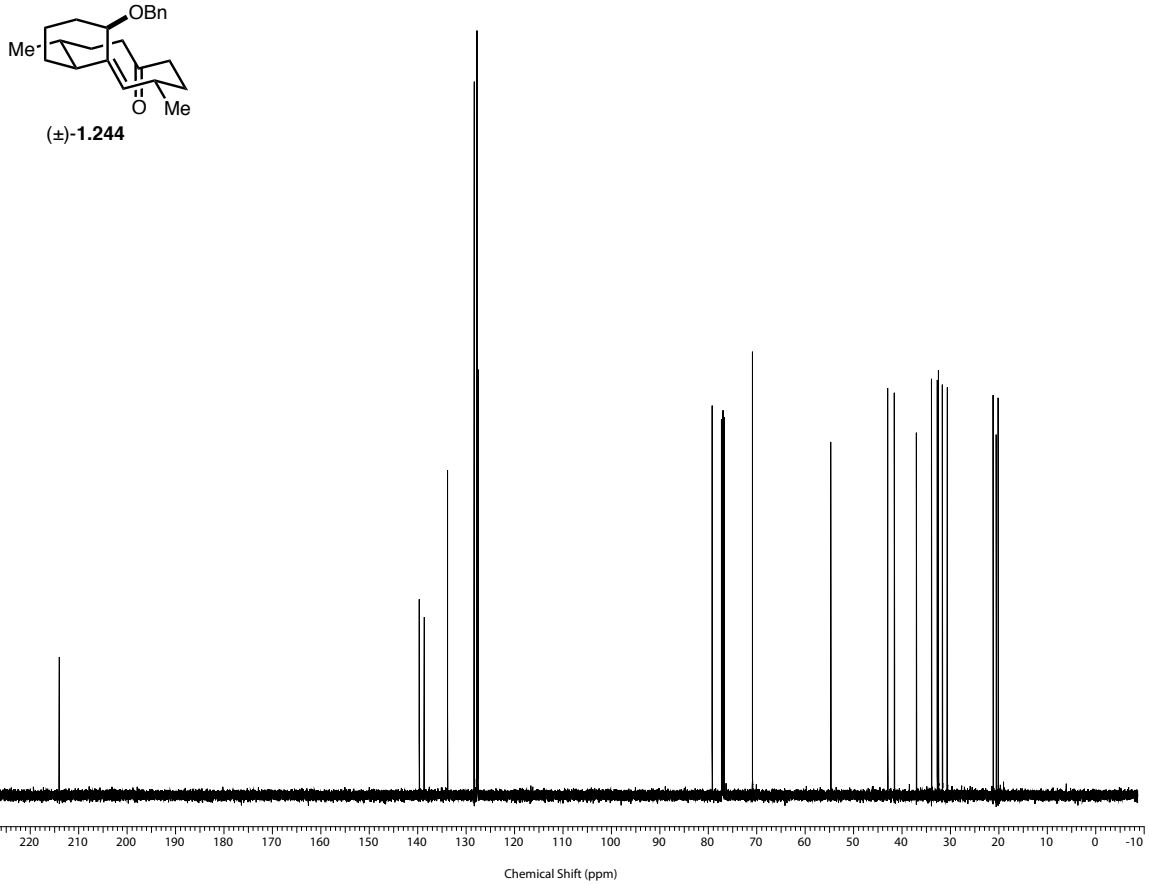

OBn
Me
O
Me

(±)-**1.243**

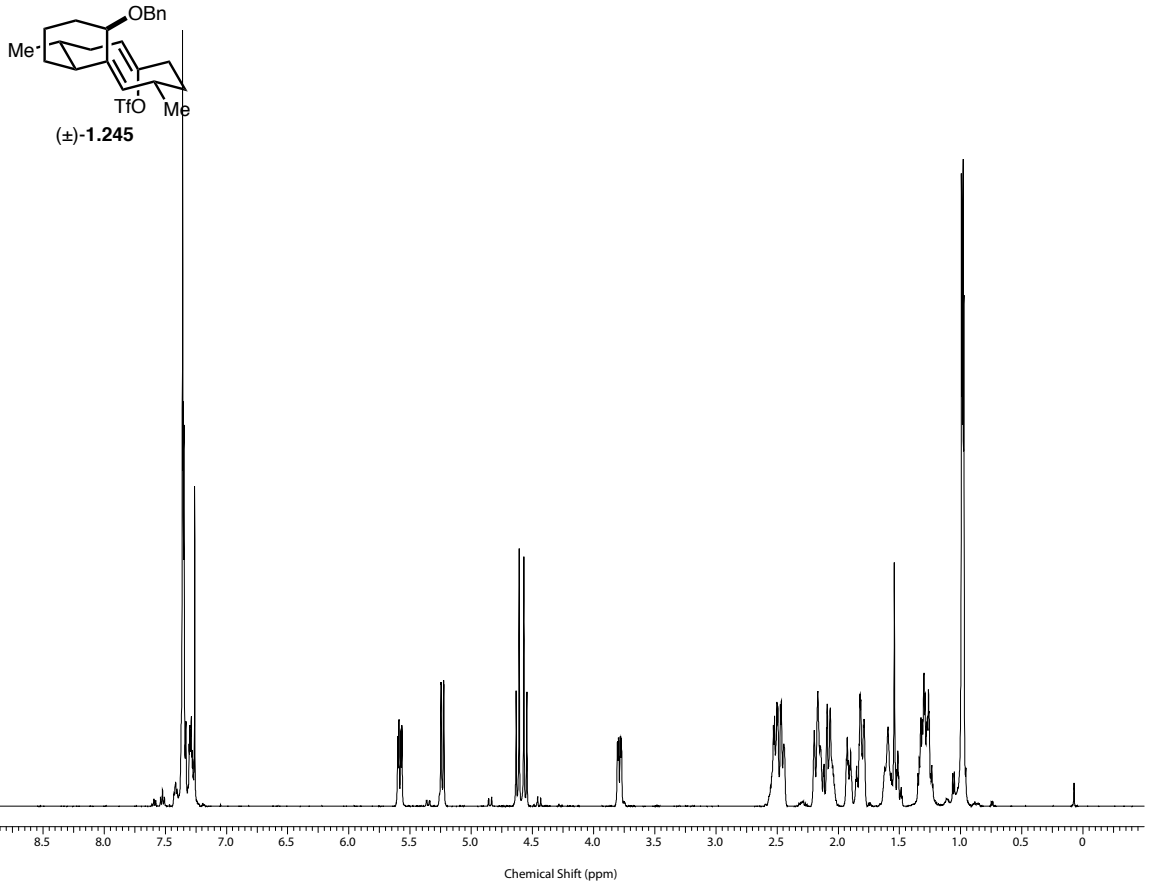

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

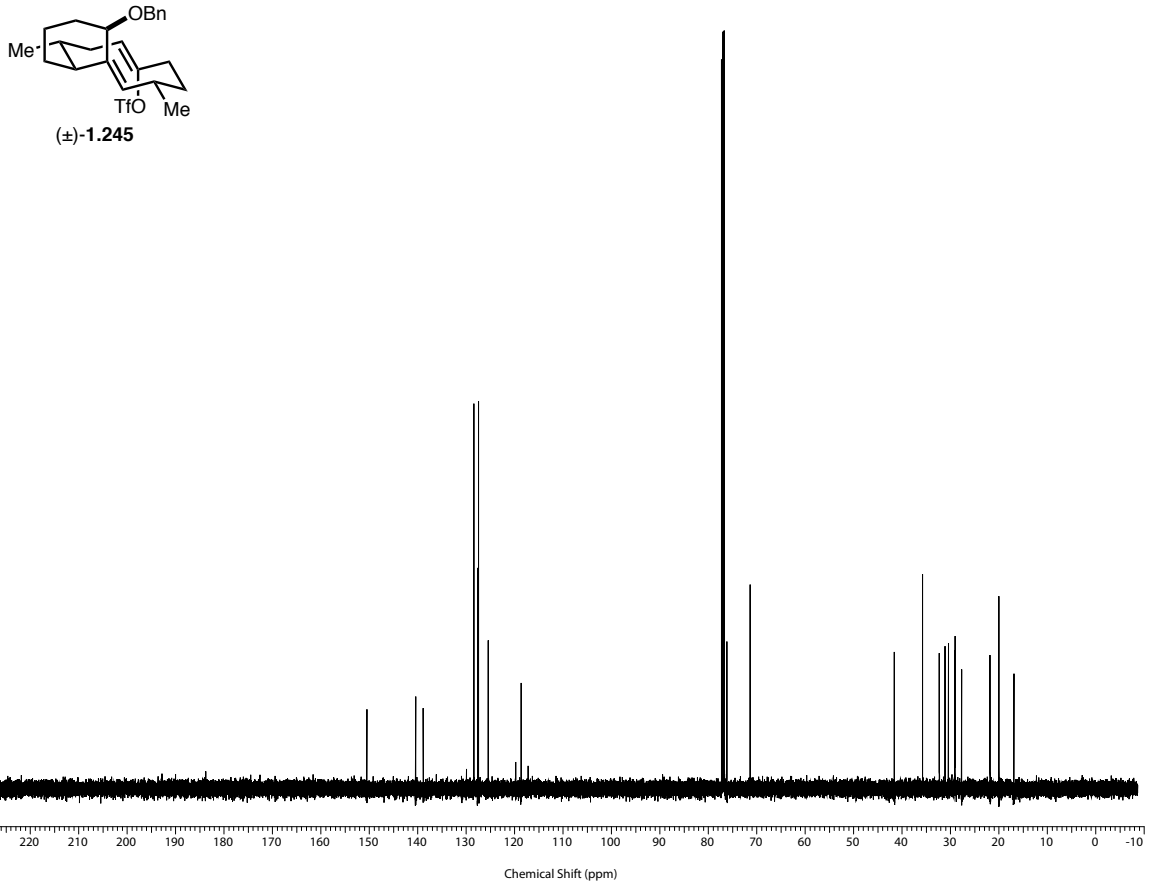

OBn
Me
O
Me
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

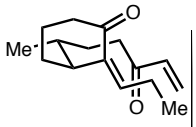
(±)-**1.244**


OBn
Me
O
Me
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

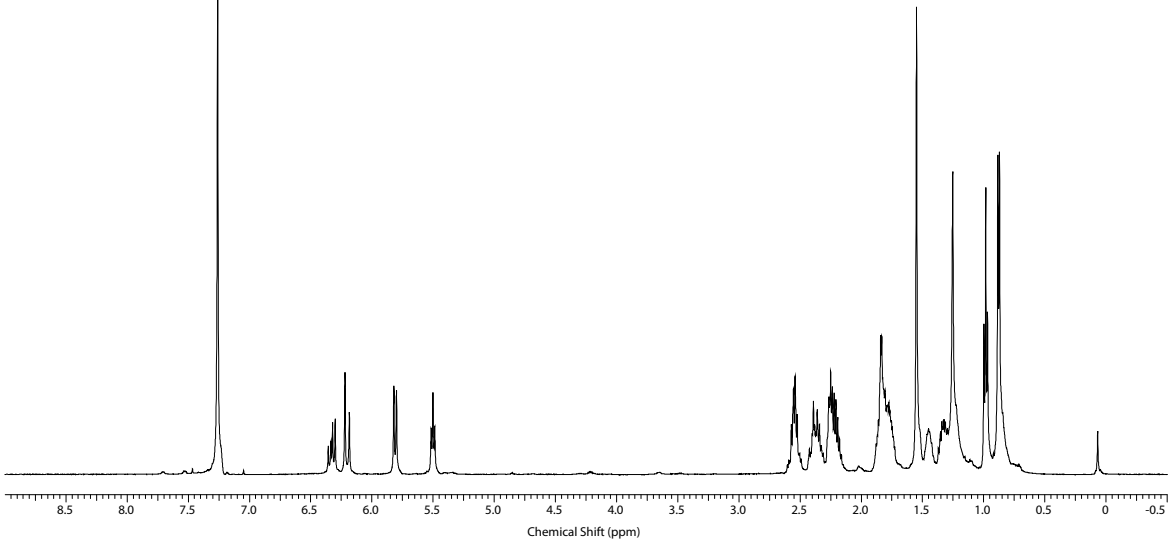
(±)-**1.244**

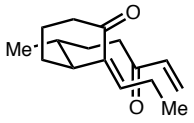

OBn
Me
TfO
Me
(±)-1.245
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
Me
TfO
Me
(±)-1.245
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

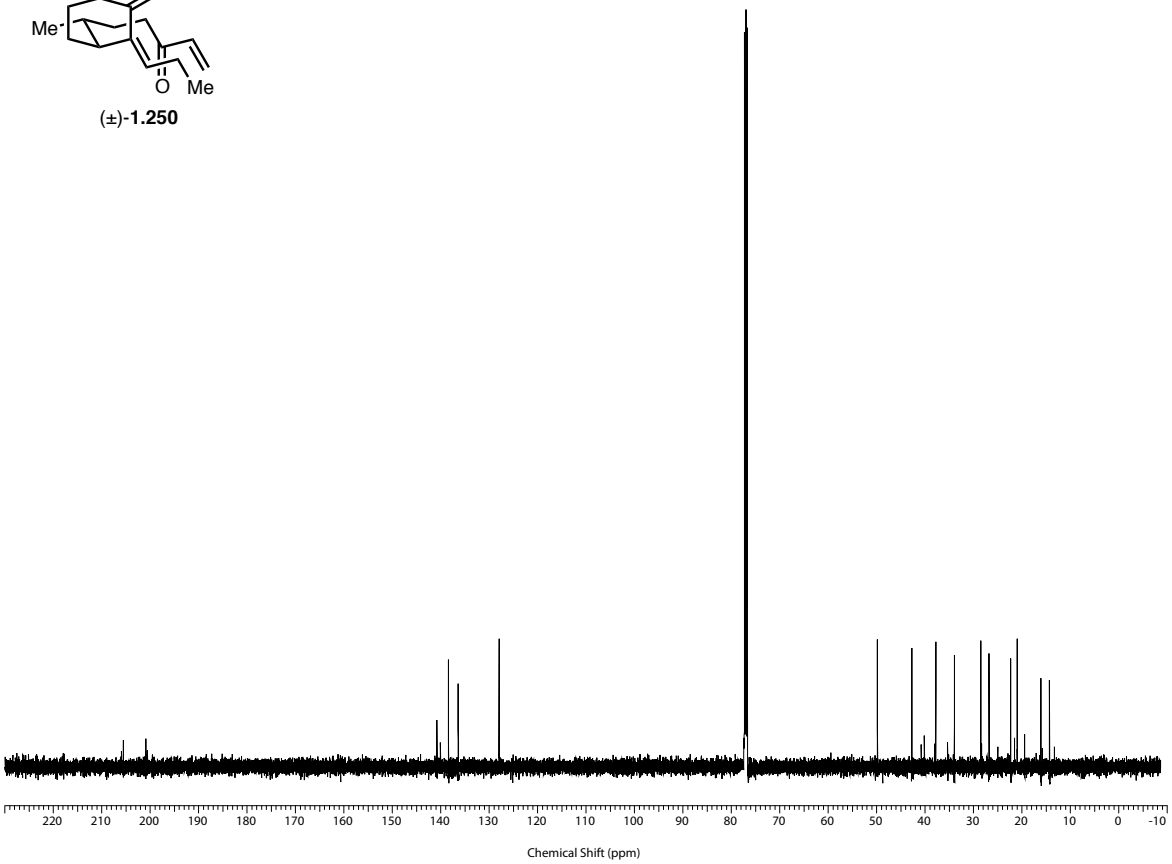

Me
O
O
Me

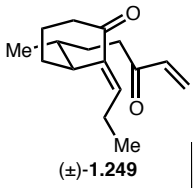
(±)-**1.250**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

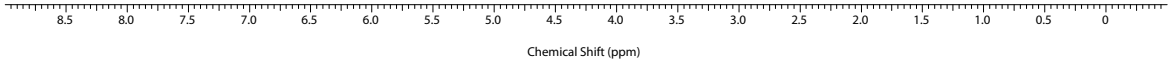

Me
O
O
Me

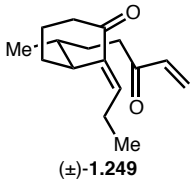
(±)-**1.250**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

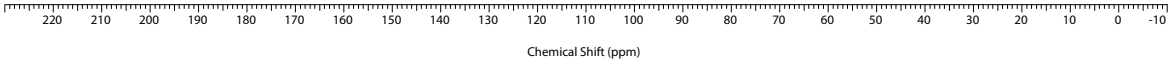

Me
O
O
Me

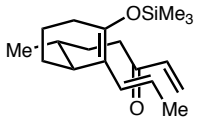
(±)-**1.249**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

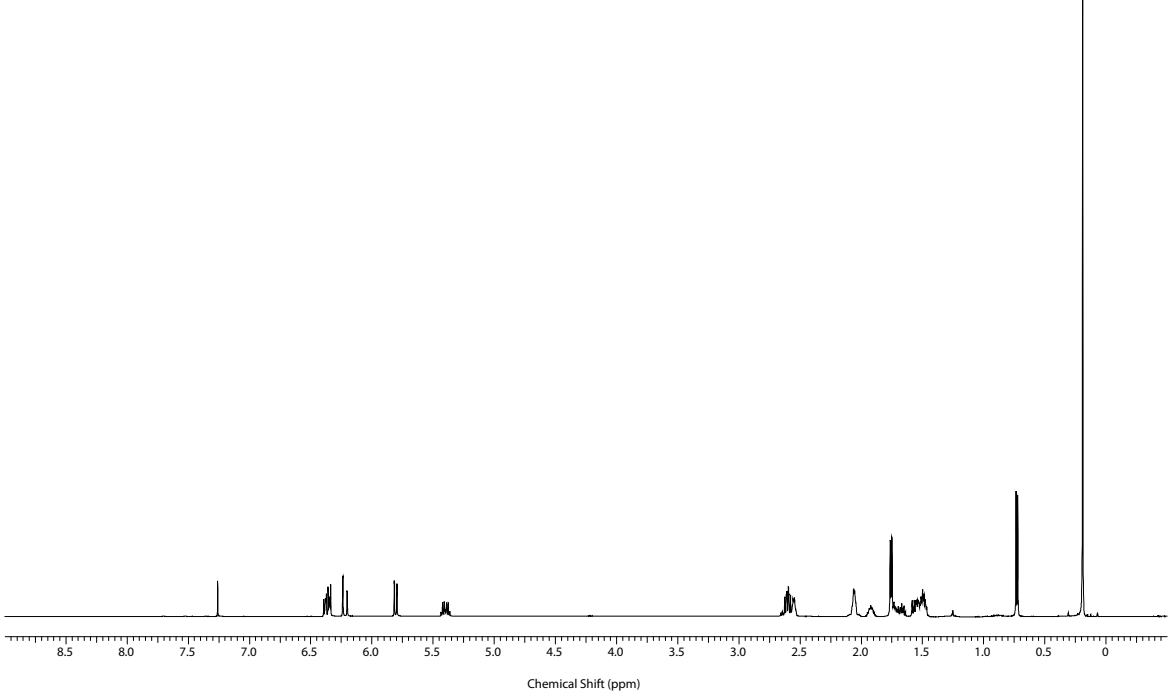

Me
O
O
Me

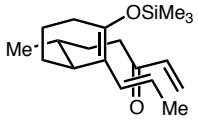
(±)-**1.249**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

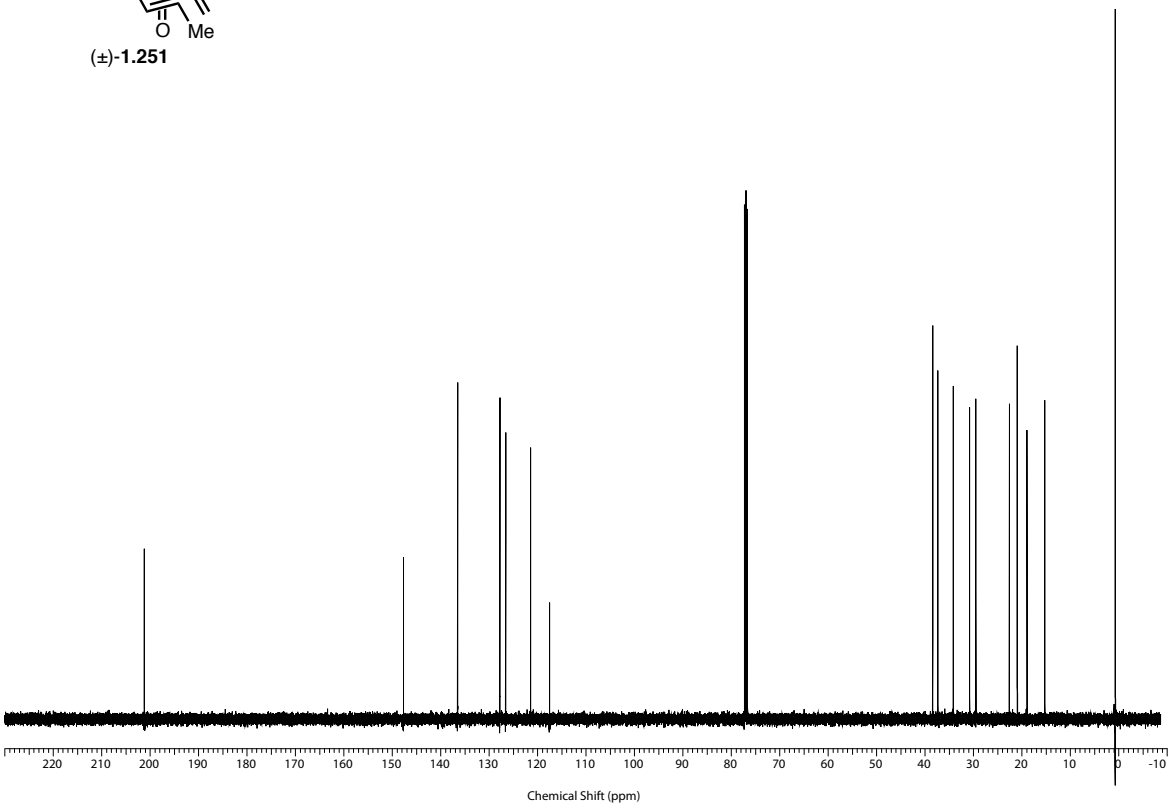

OSiMe3
Me
O
Me

(±)-**1.251**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OSiMe3
Me
O
Me

(±)-**1.251**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210
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190
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170
160
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140
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120
110
100
90
80
70
60
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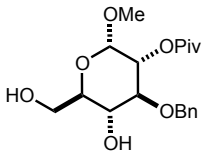
40
30
20
10
0
-10
Chemical Shift (ppm)

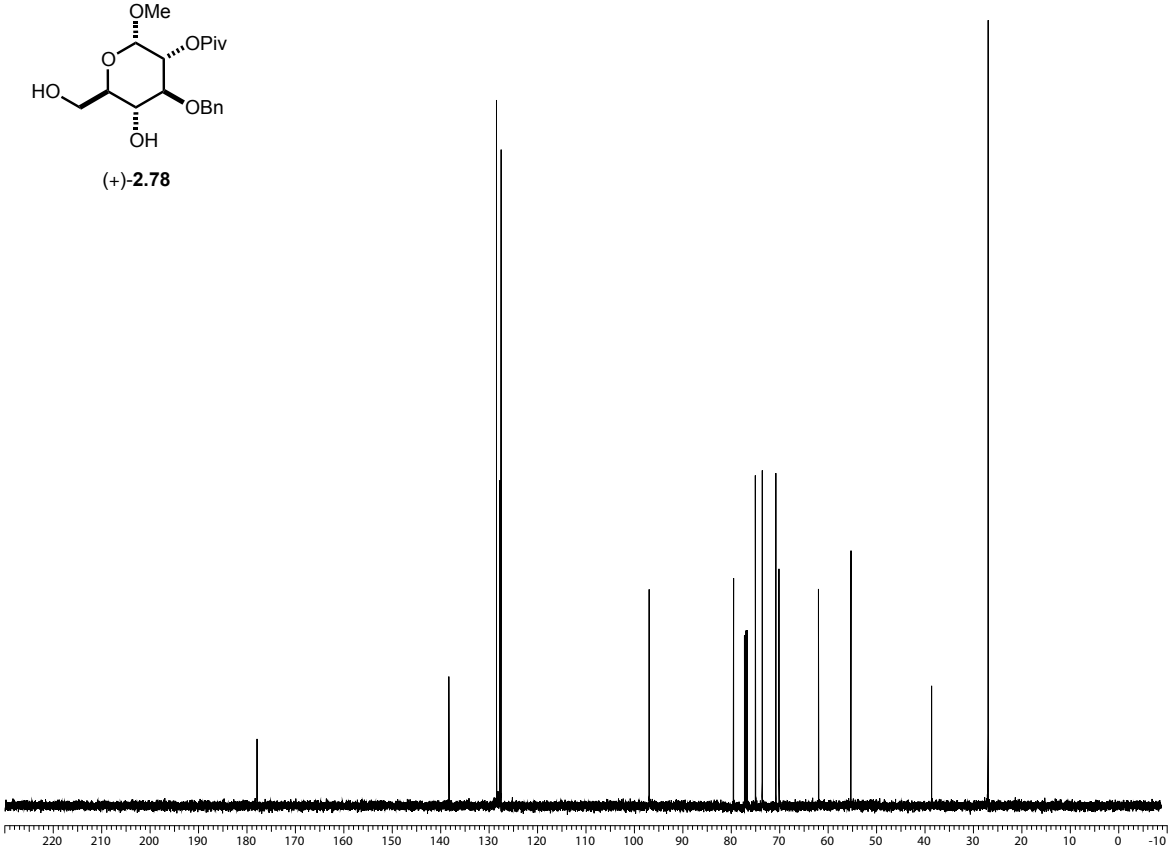

OMe
OPiv
O
HO
OBn
OH

(+)-**2.78**

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

OMe
OPiv
O
HO
OBn
OH

(+)-**2.78**


220
210
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190
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170
160
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140
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120
110
100
90
80
70
60
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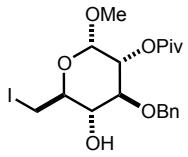
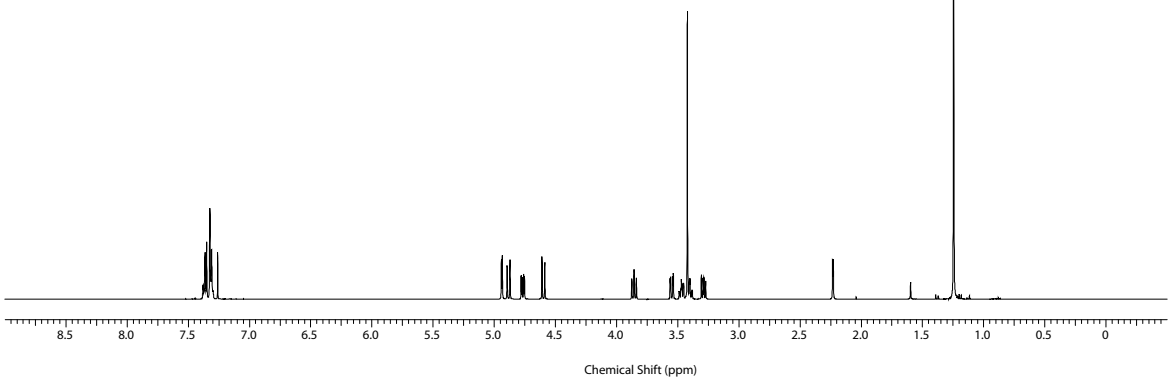
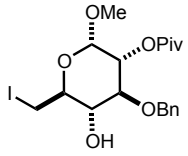
40
30
20
10
0
-10
Chemical Shift (ppm)

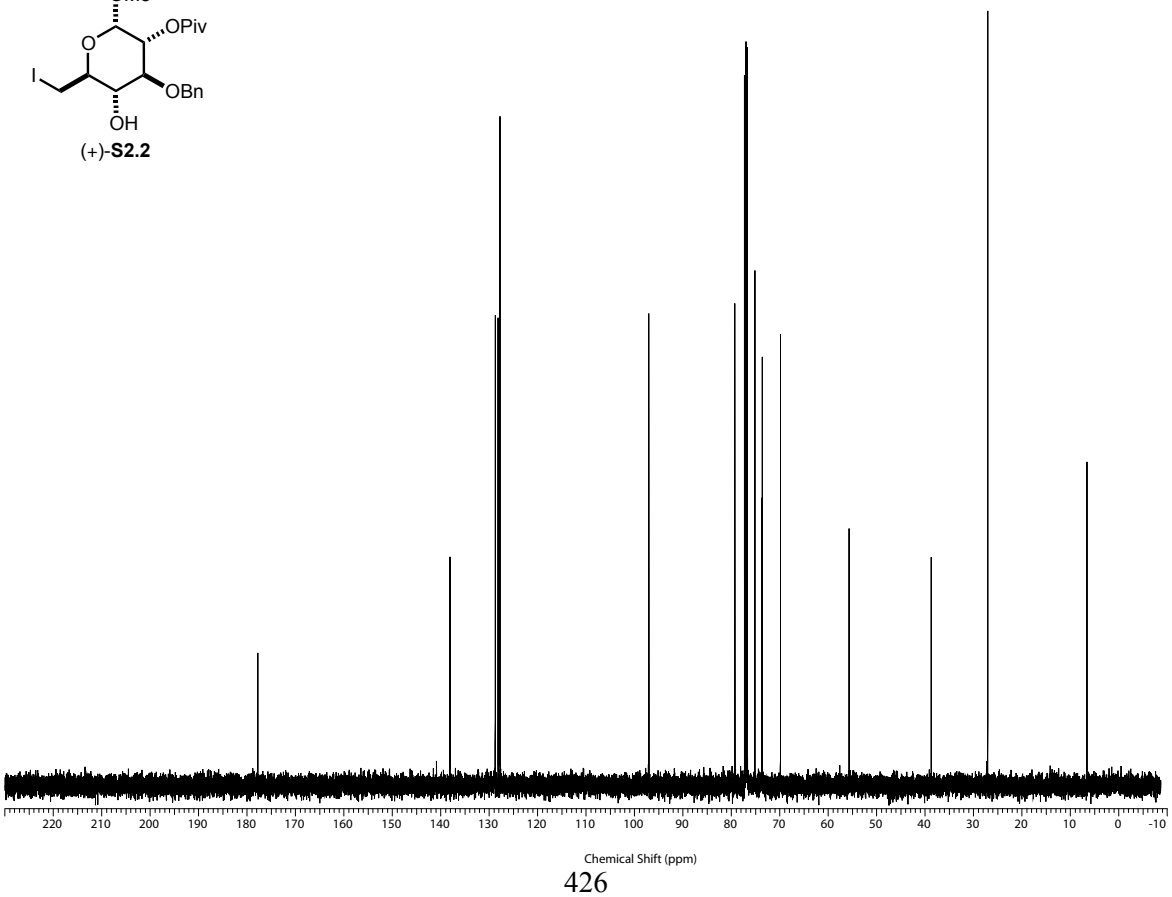

OMe
OPiv
O
I
OBn
OH

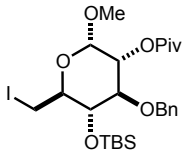
(+)-**S2.2**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

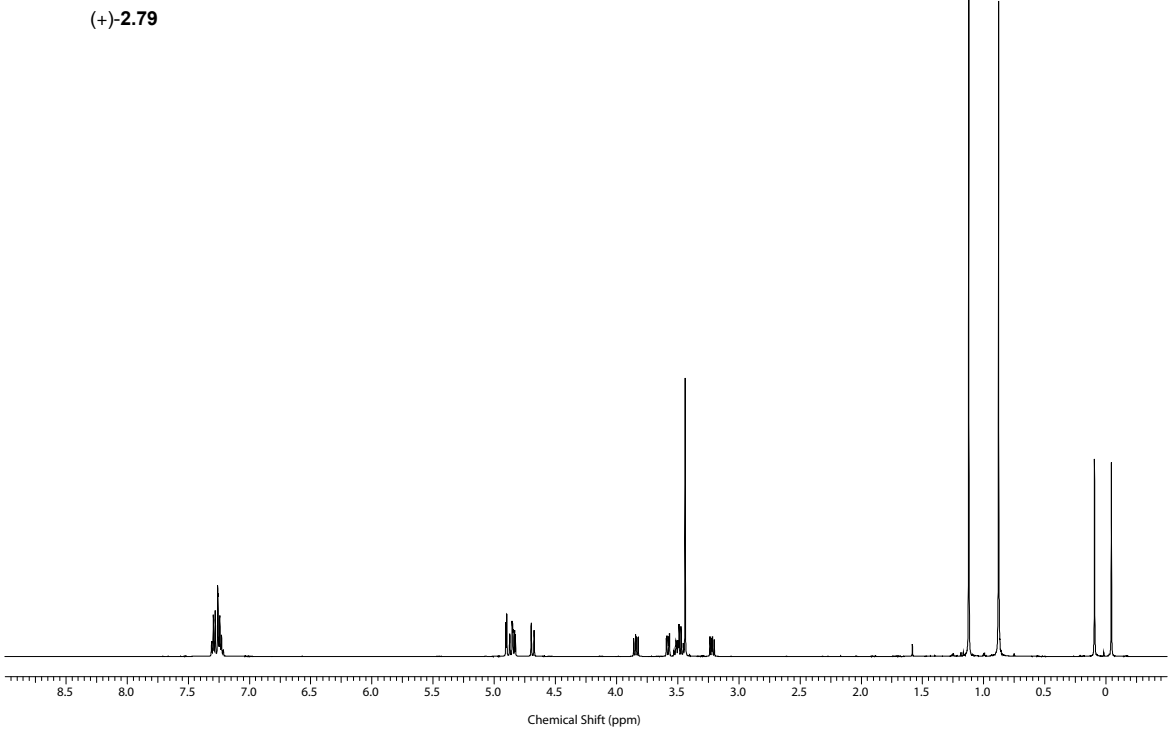

OMe
OPiv
O
I
OBn
OH

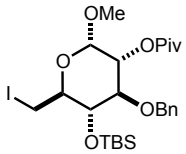
(+)-**S2.2**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

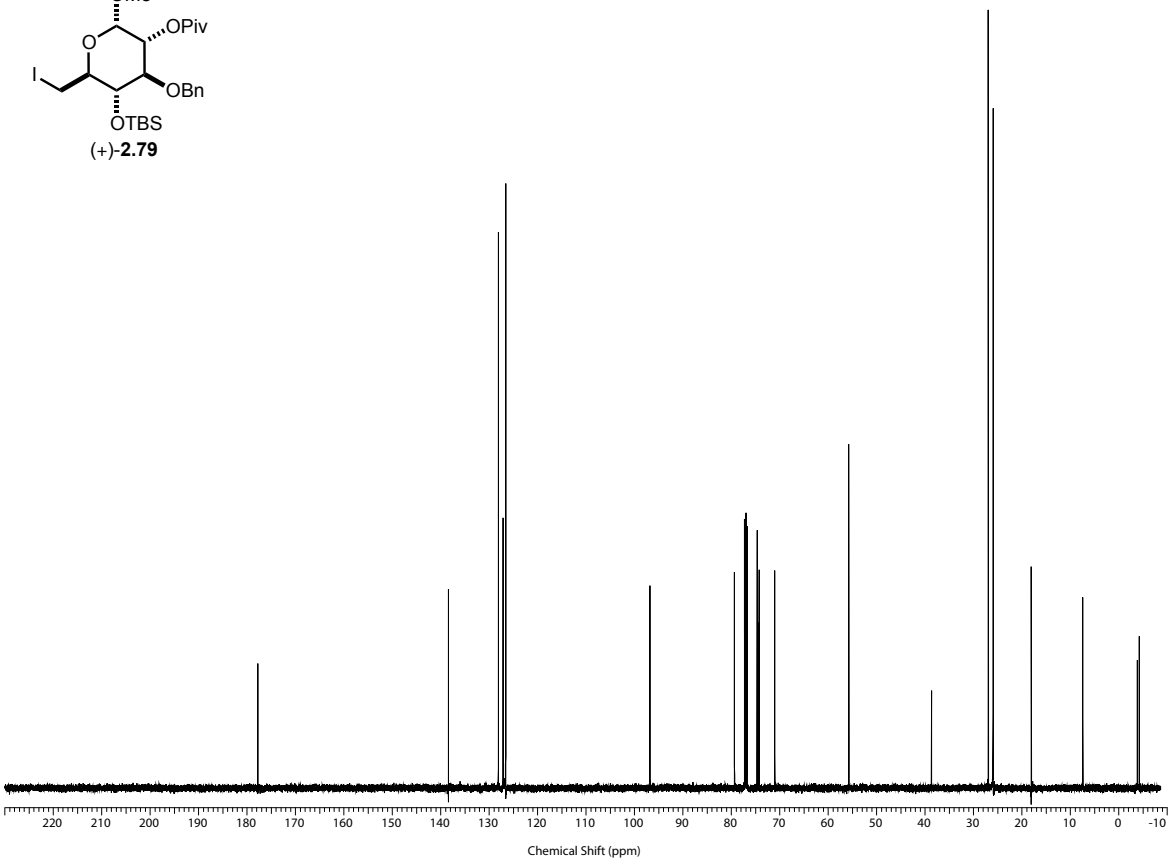

OMe
OPiv
O
I
OBn
OTBS

(+)-**2.79**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

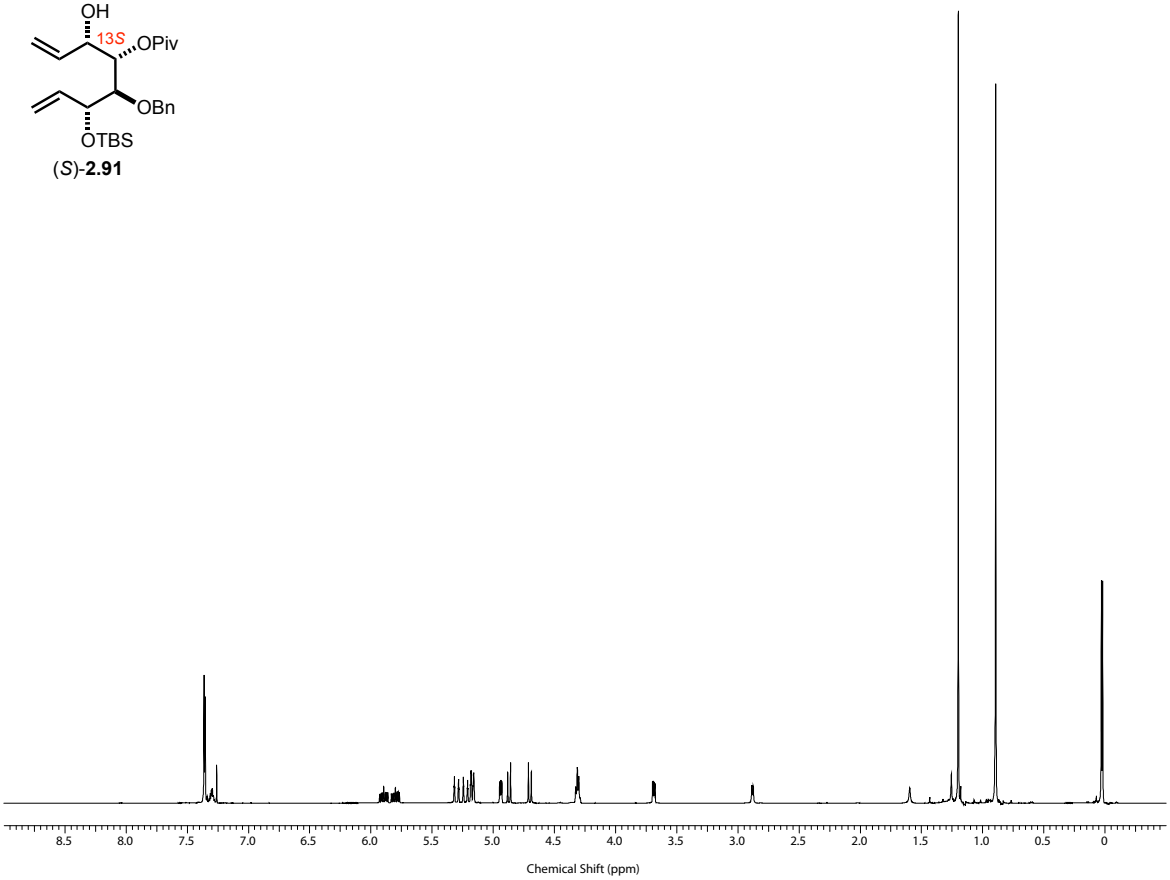

OMe
OPiv
O
I
OBn
OTBS

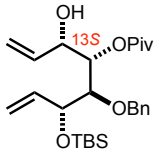
(+)-**2.79**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

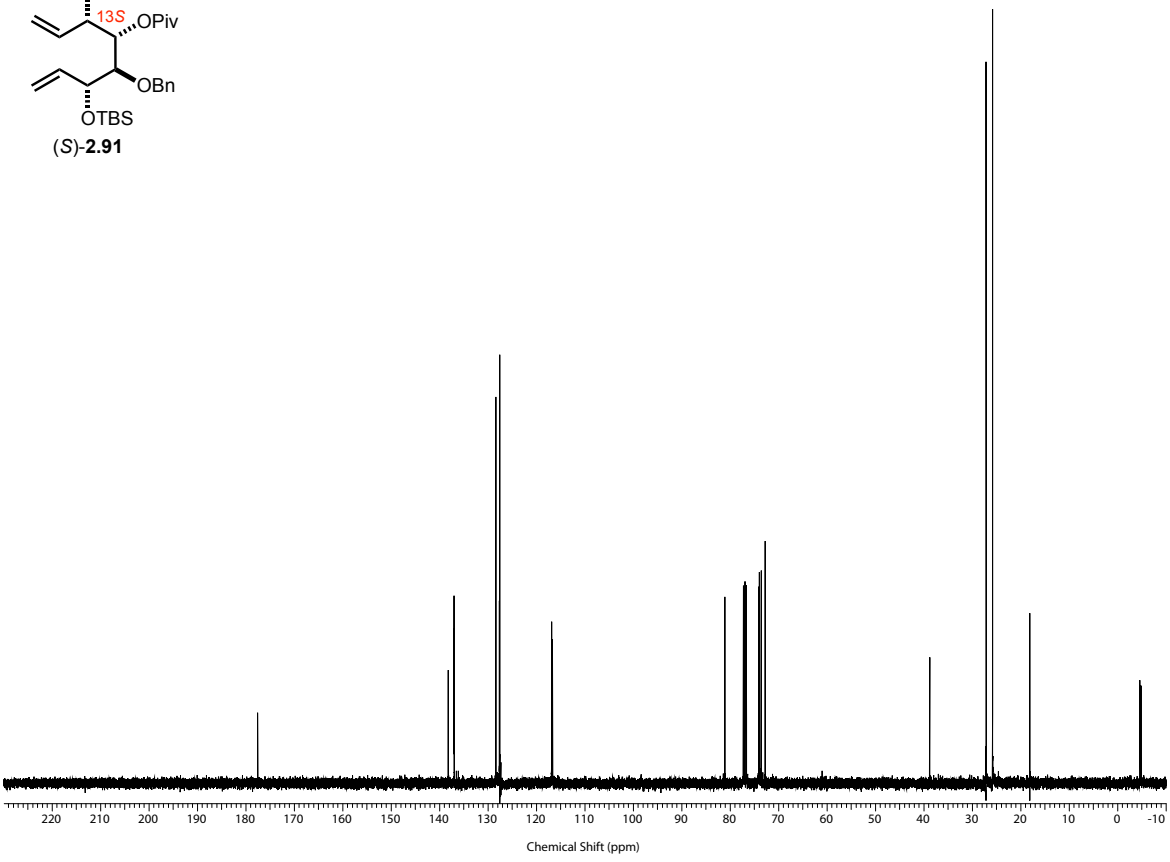
OH
13S
OPiv
OBn
OTBS

(*S*)-**2.91**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

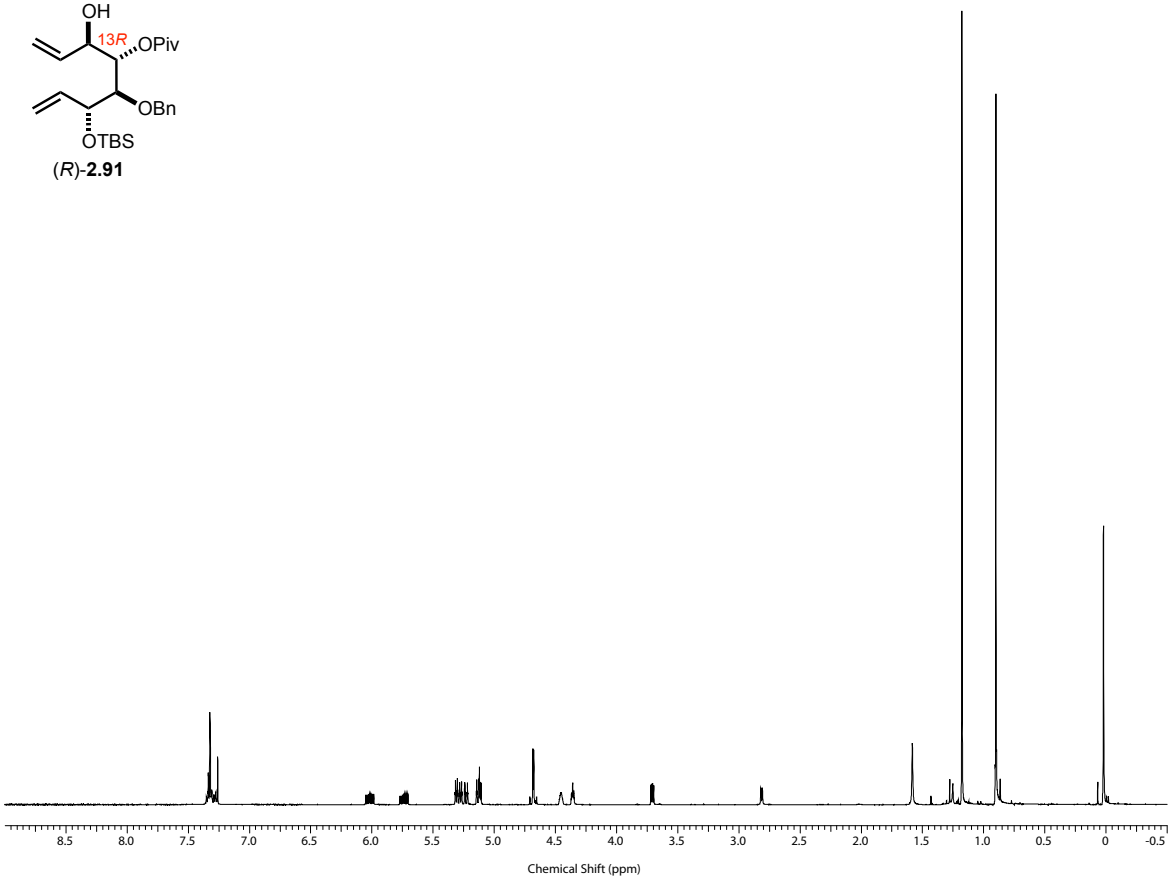

OH
13S
OPiv
OBn
OTBS

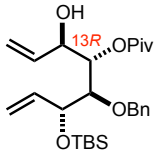
(*S*)-**2.91**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

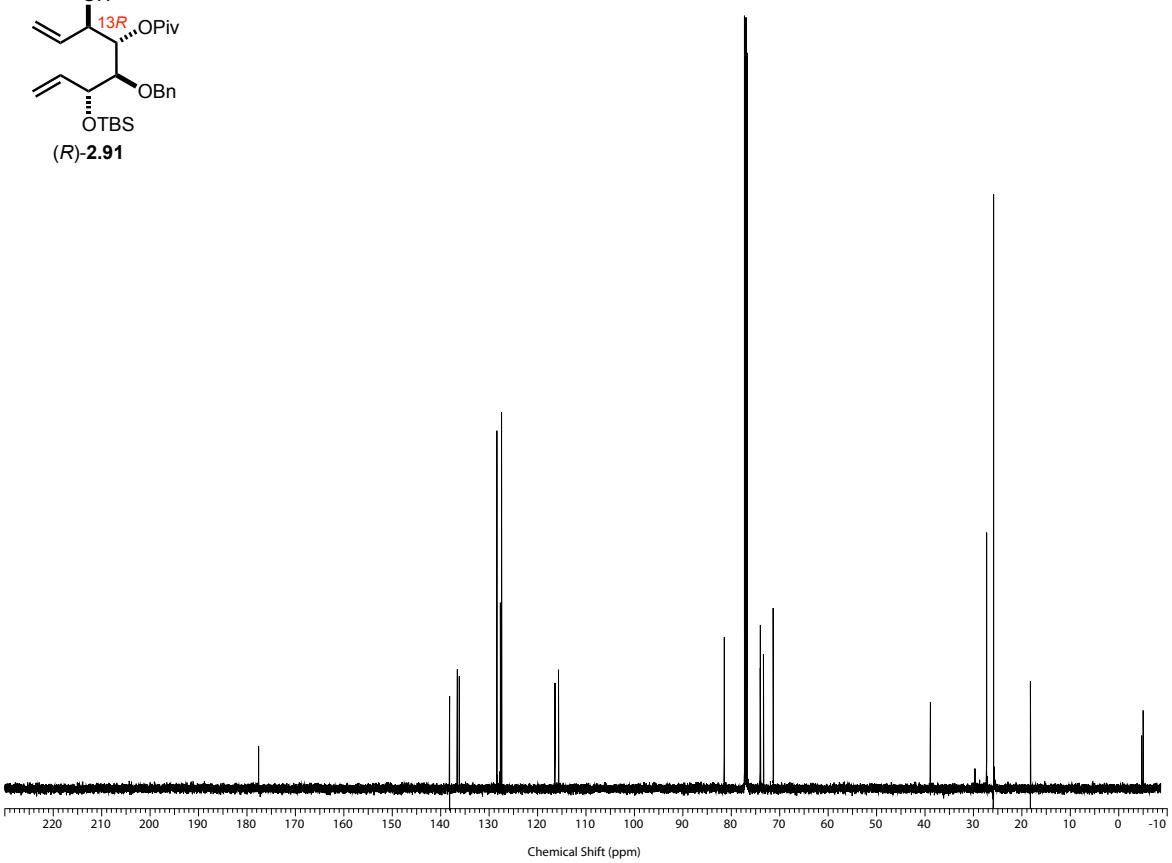
OH
13R
OPiv
OBn
OTBS

(*R*)-**2.91**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

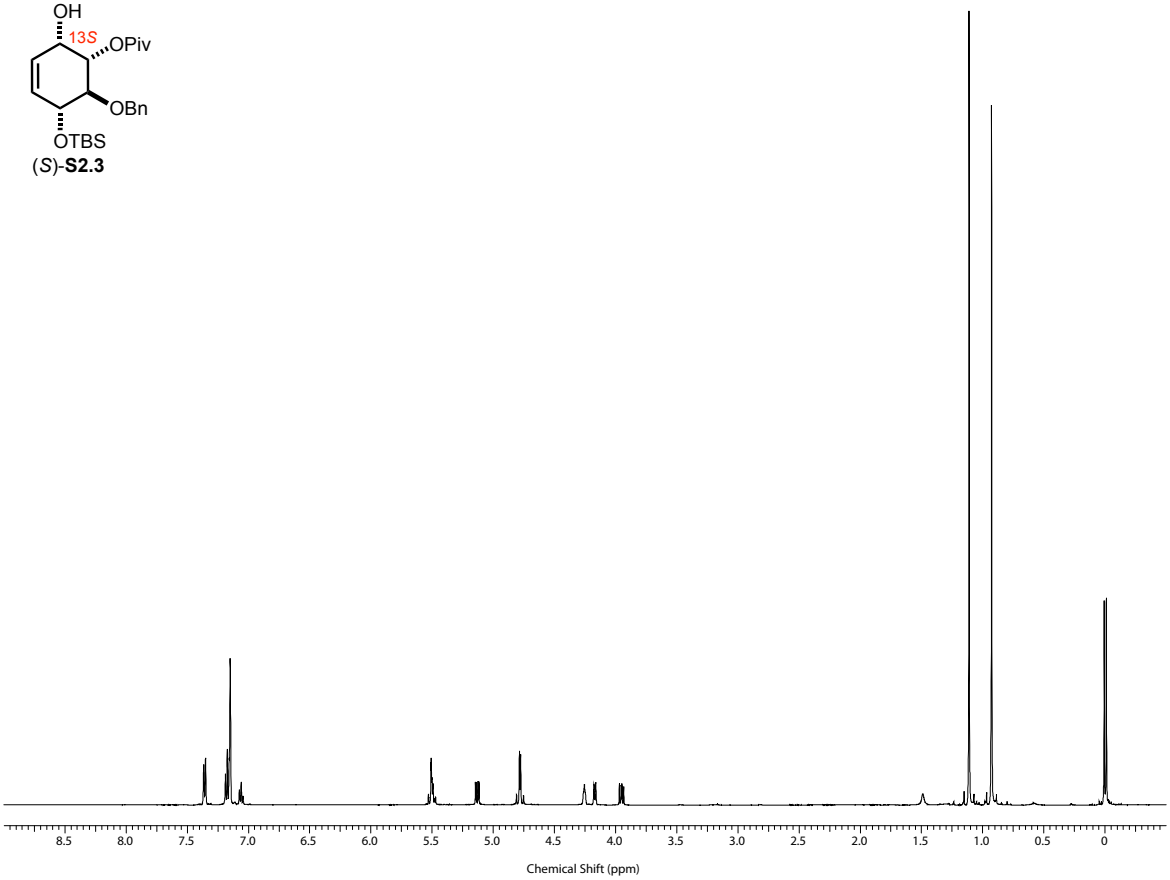

OH
13R
OPiv
OBn
OTBS

(*R*)-**2.91**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

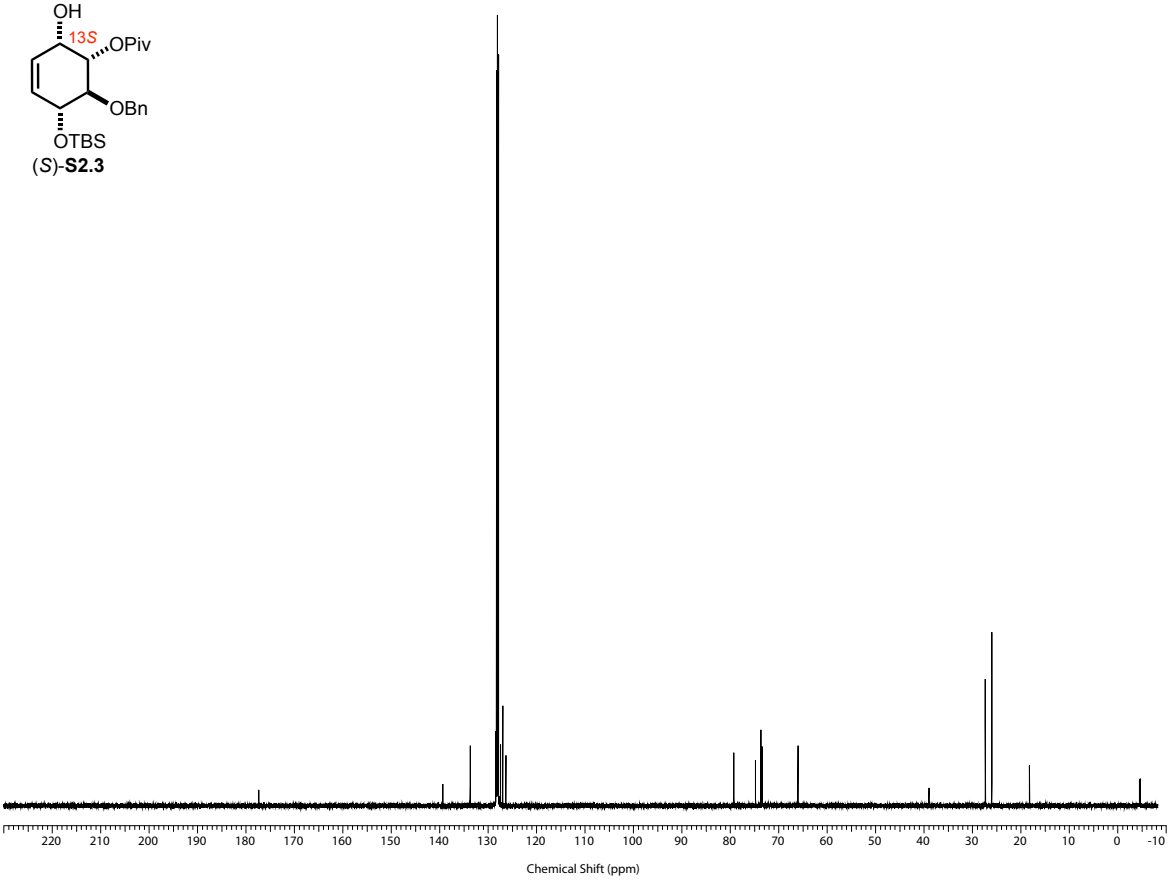
OH
13S
OPiv
OBn
OTBS

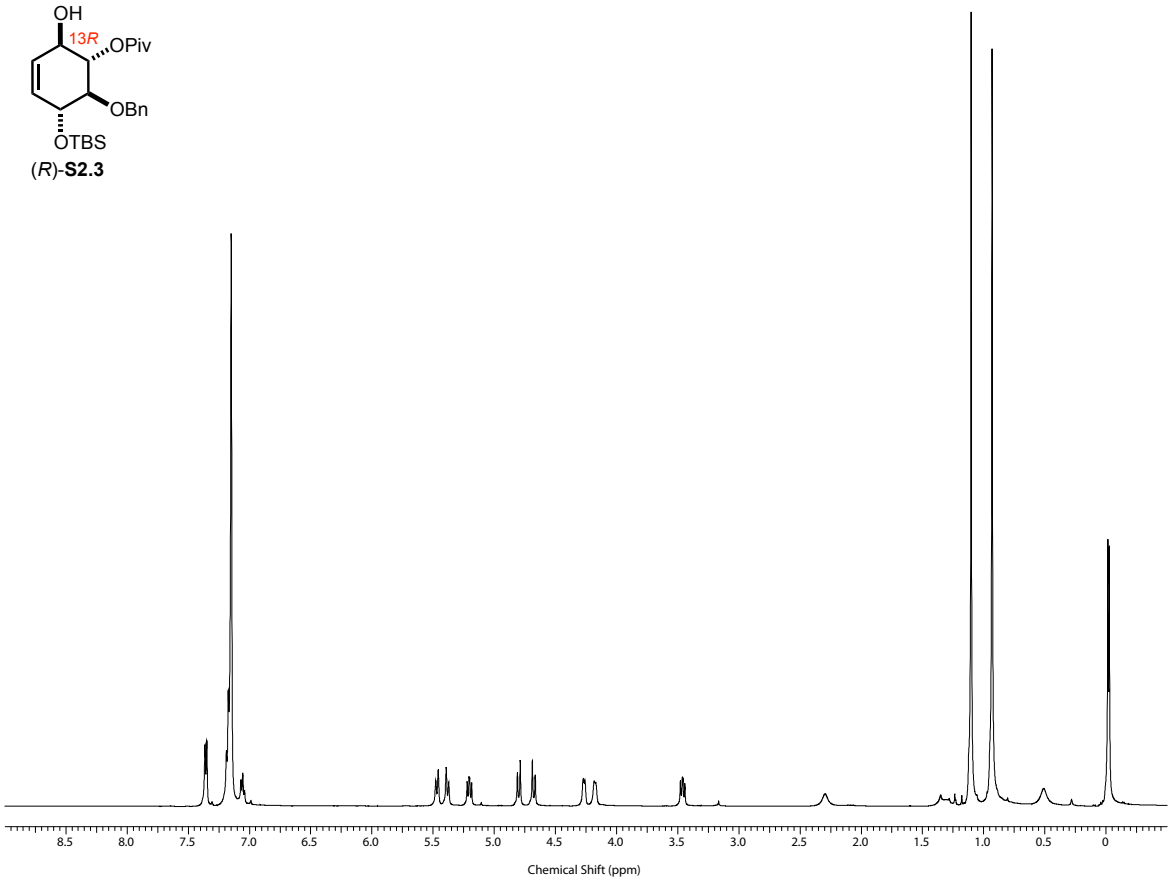
(*S*)-**S2.3**

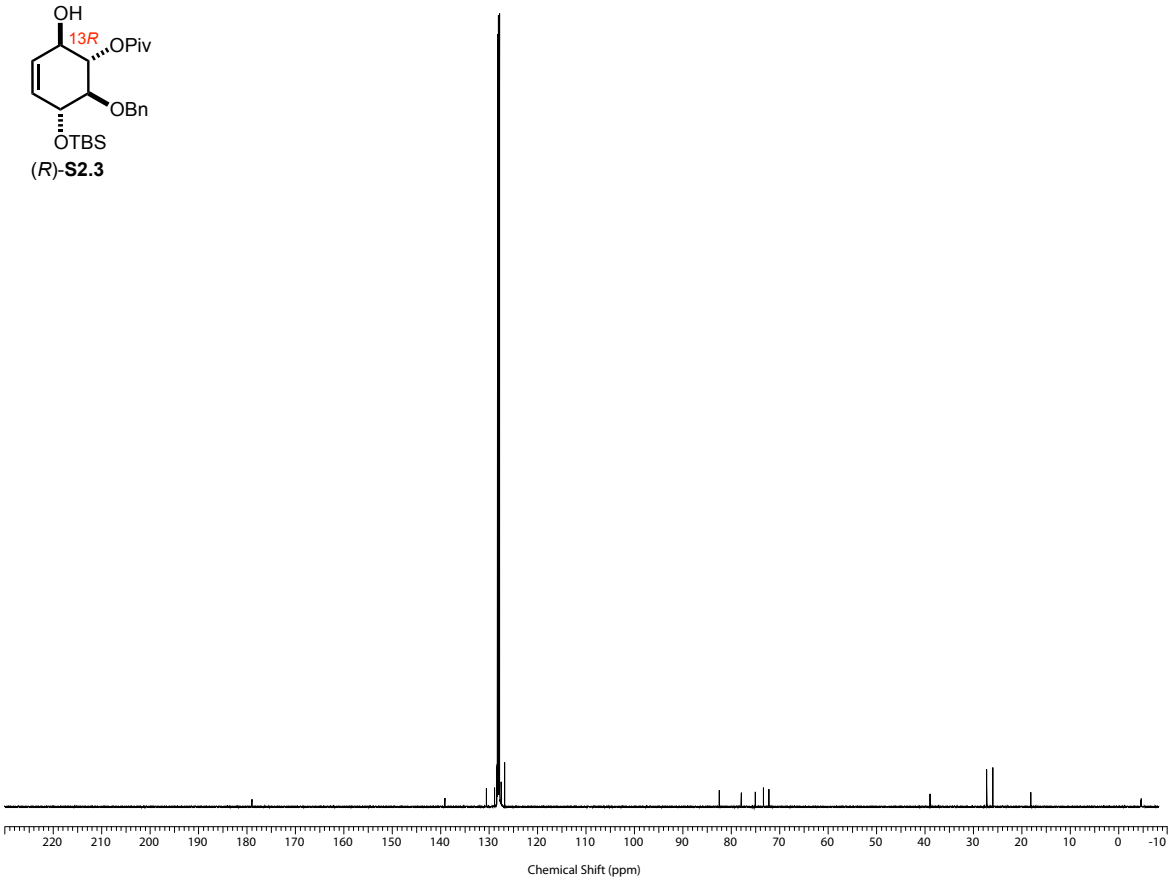

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

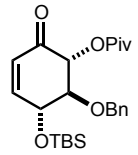
OH
13S
OPiv
OBn
OTBS

(*S*)-**S2.3**

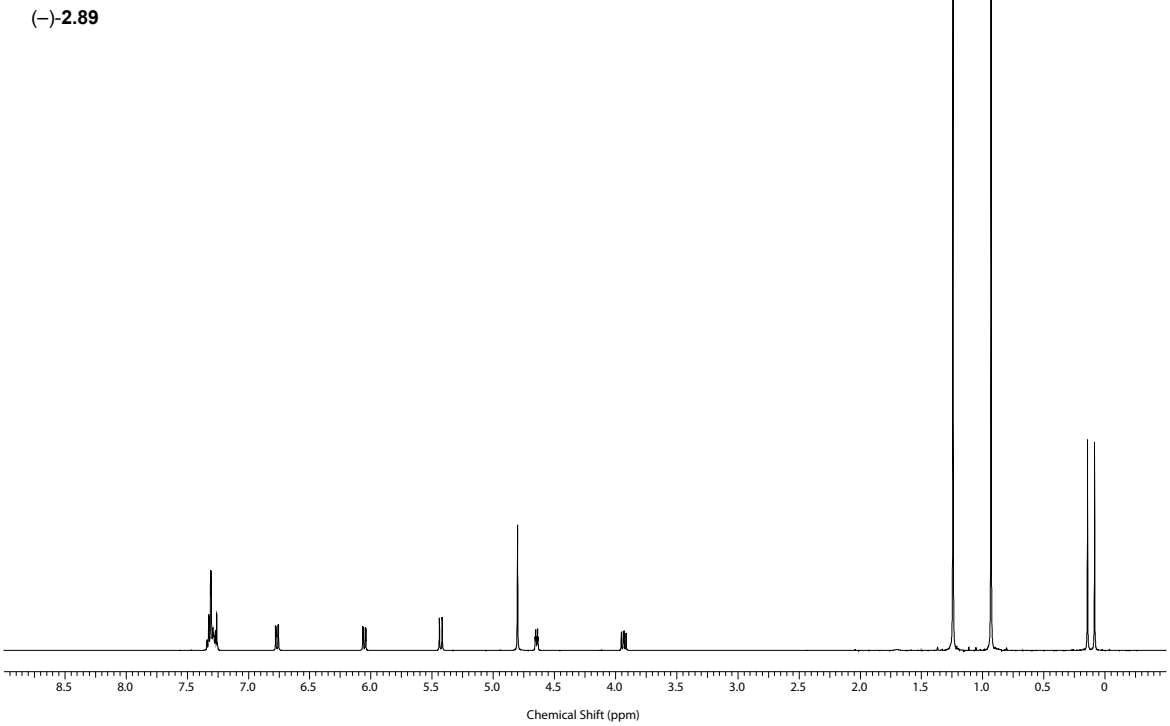

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

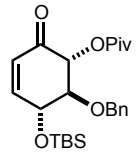

OH
13R
OPiv
OBn
OTBS
(R)-S2.3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OH
13R
OPiv
OBn
OTBS
(R)-S2.3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

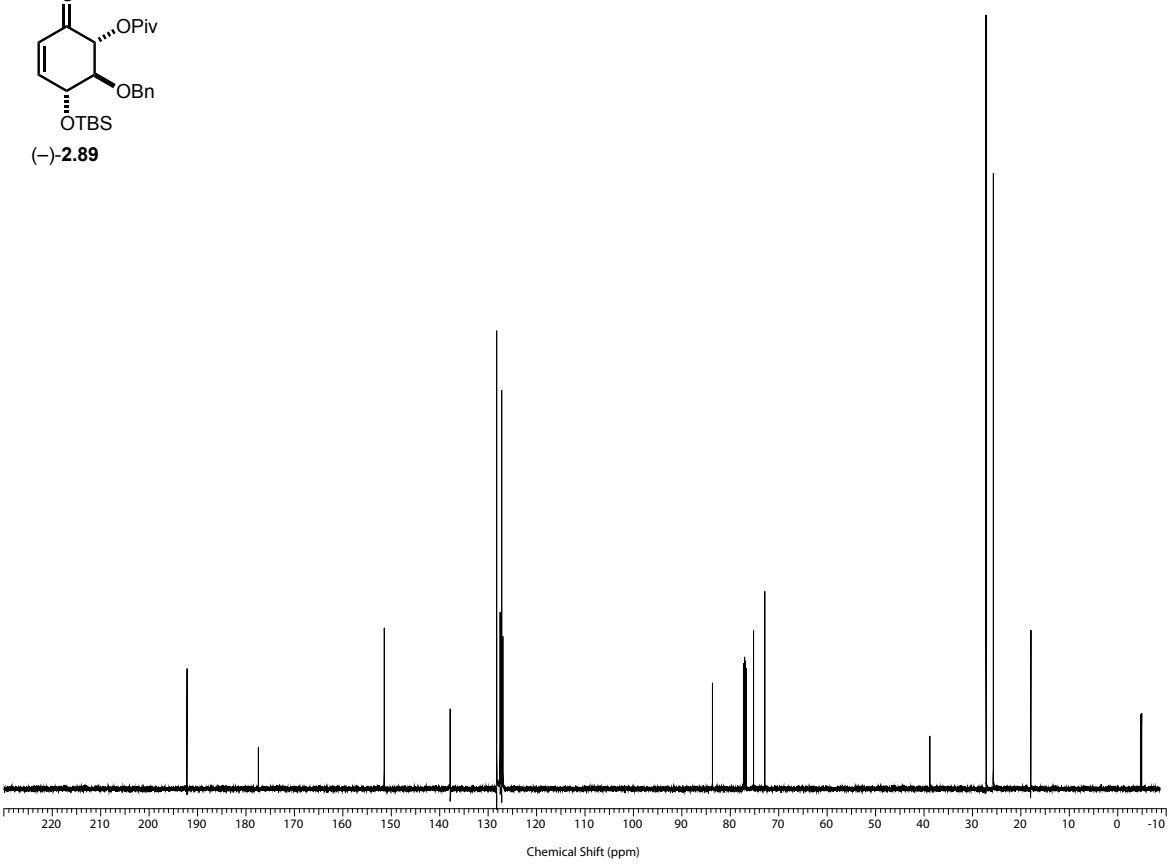

O
OPiv
OBn
OTBS

(–)-**2.89**

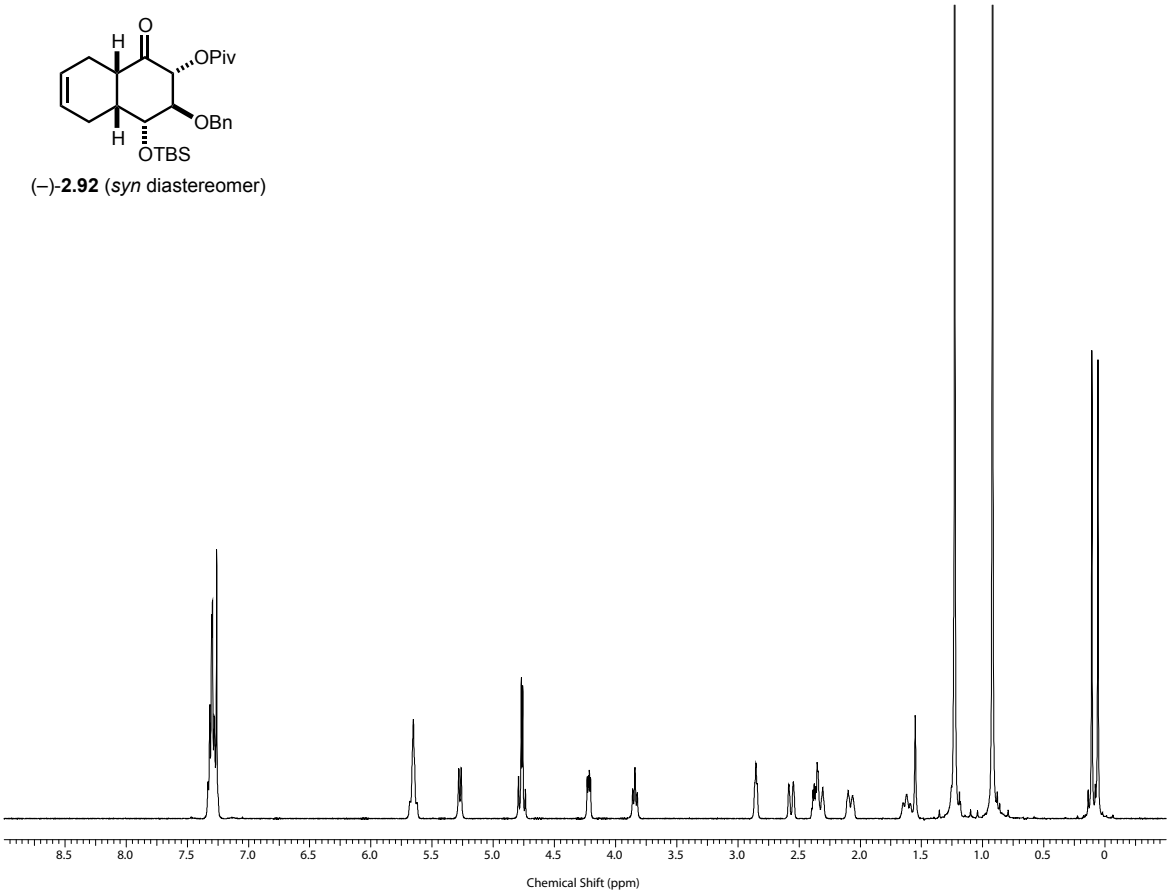

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
OPiv
OBn
OTBS

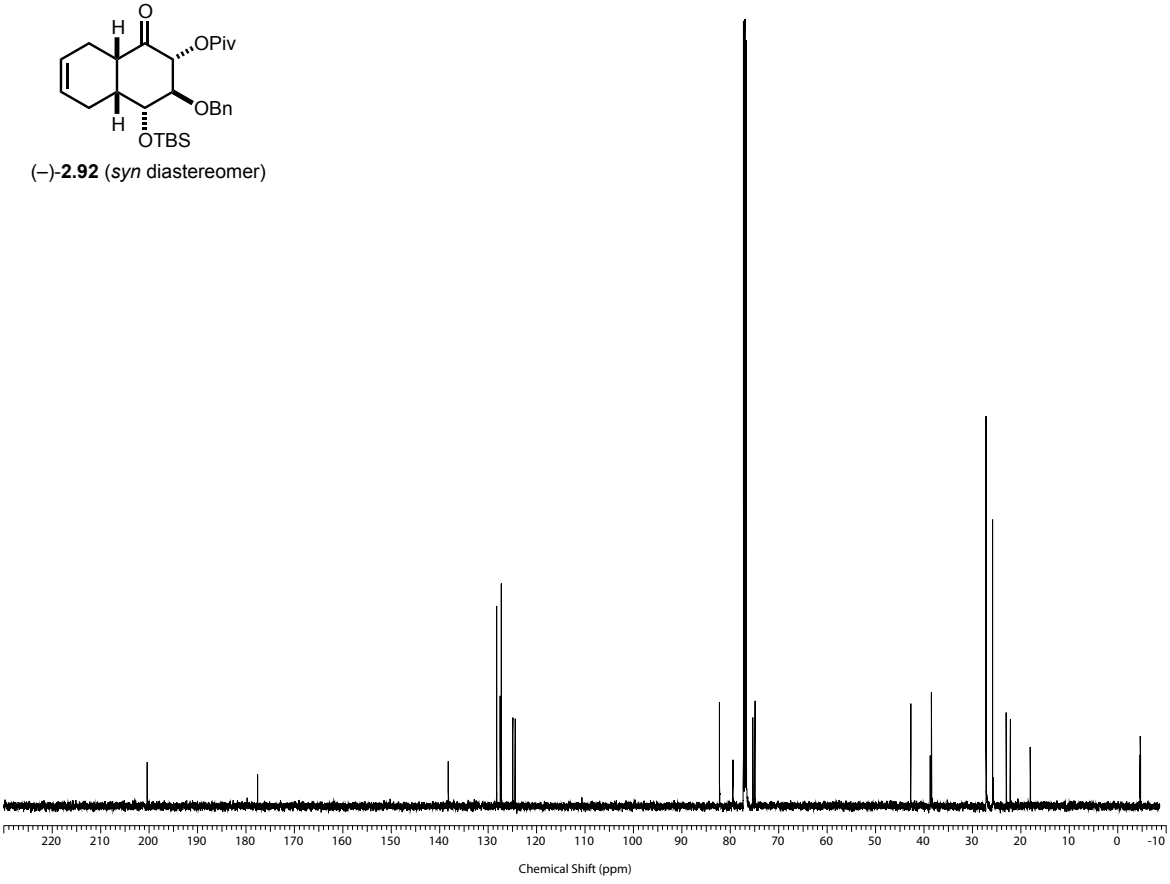
(–)-**2.89**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

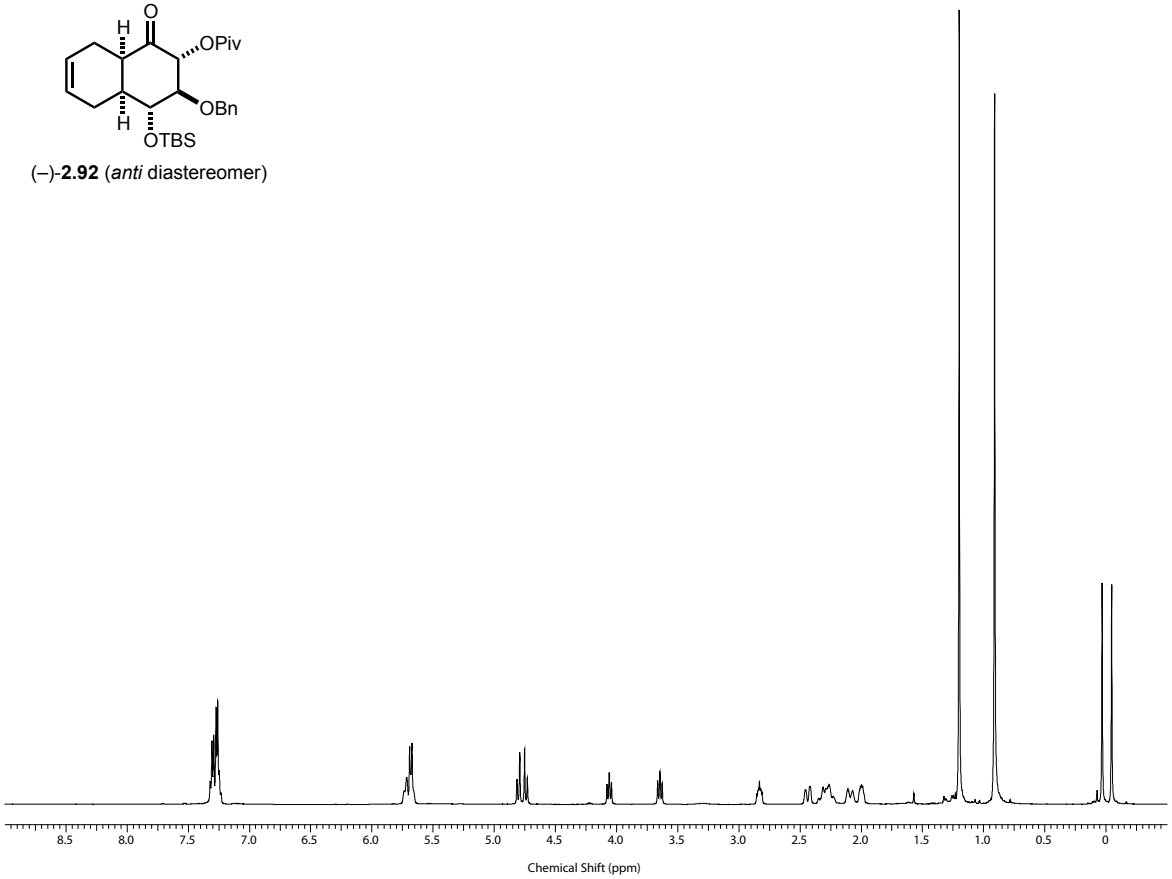
(–)-**2.92** (*syn* diastereomer)



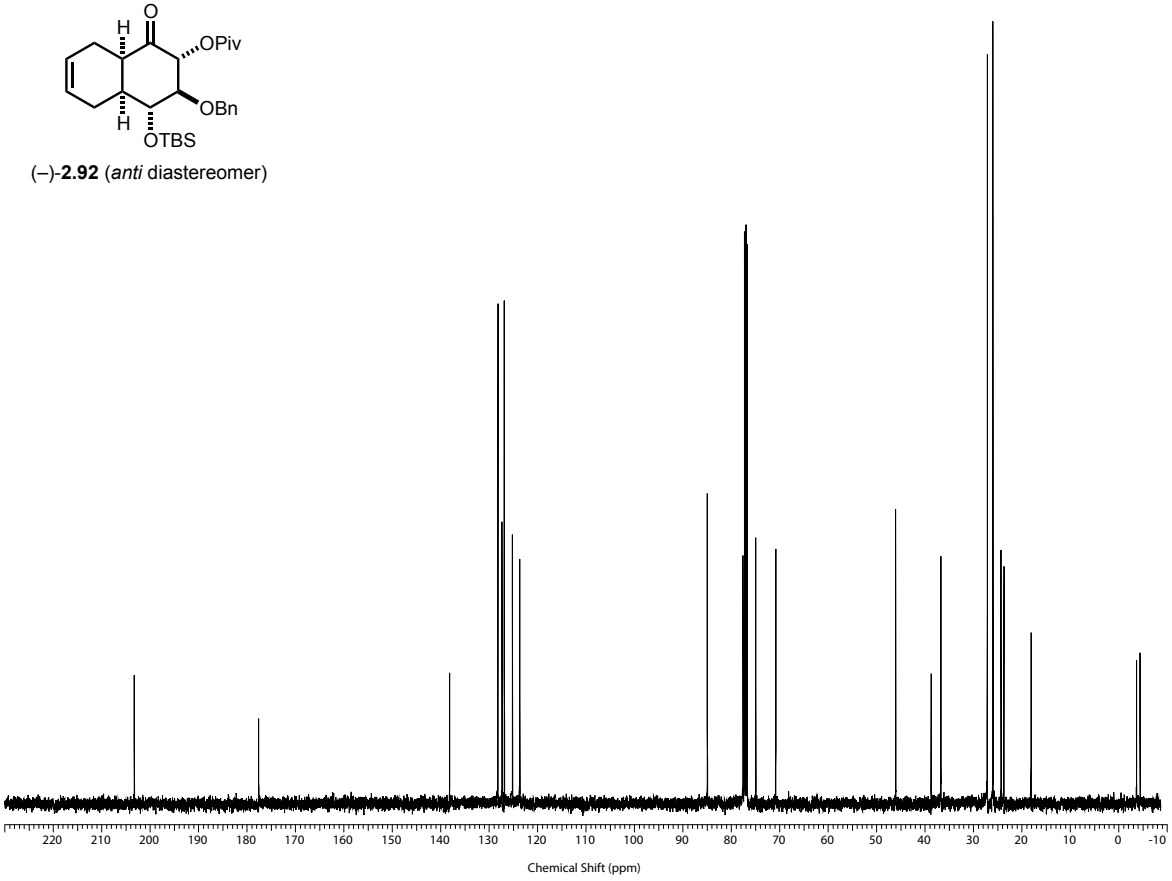
(–)-**2.92** (*syn* diastereomer)

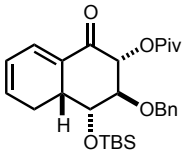


(–)-**2.92** (*anti* diastereomer)

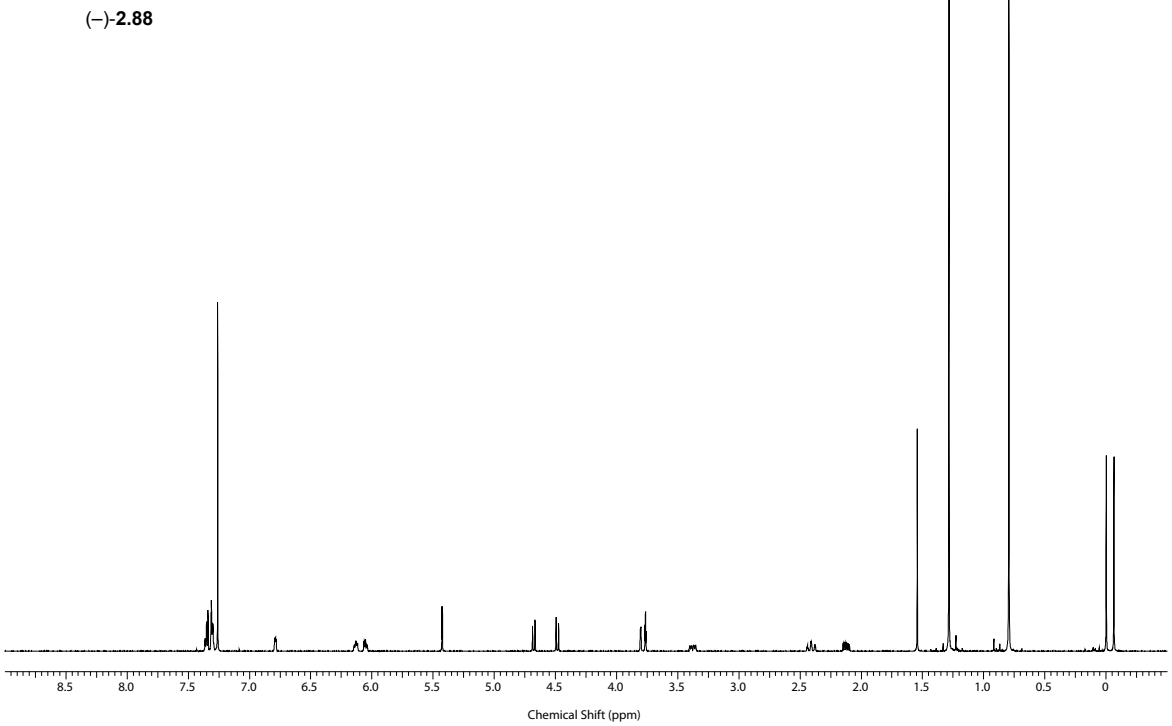


(–)-**2.92** (*anti* diastereomer)



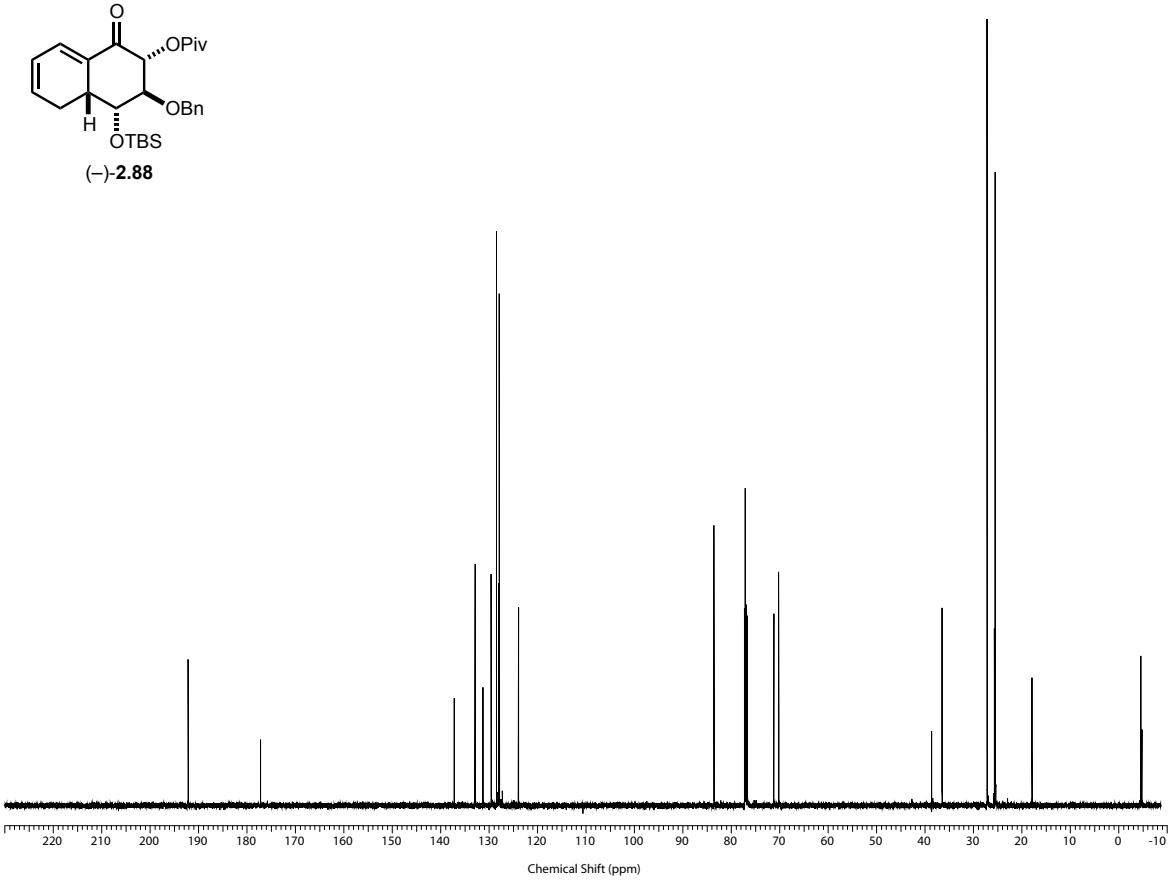

O
OPiv
OBn
H
OTBS

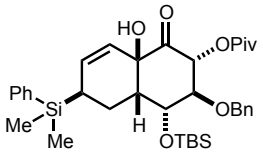
(–)-**2.88**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

O
OPiv
OBn
H
OTBS

(–)-**2.88**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

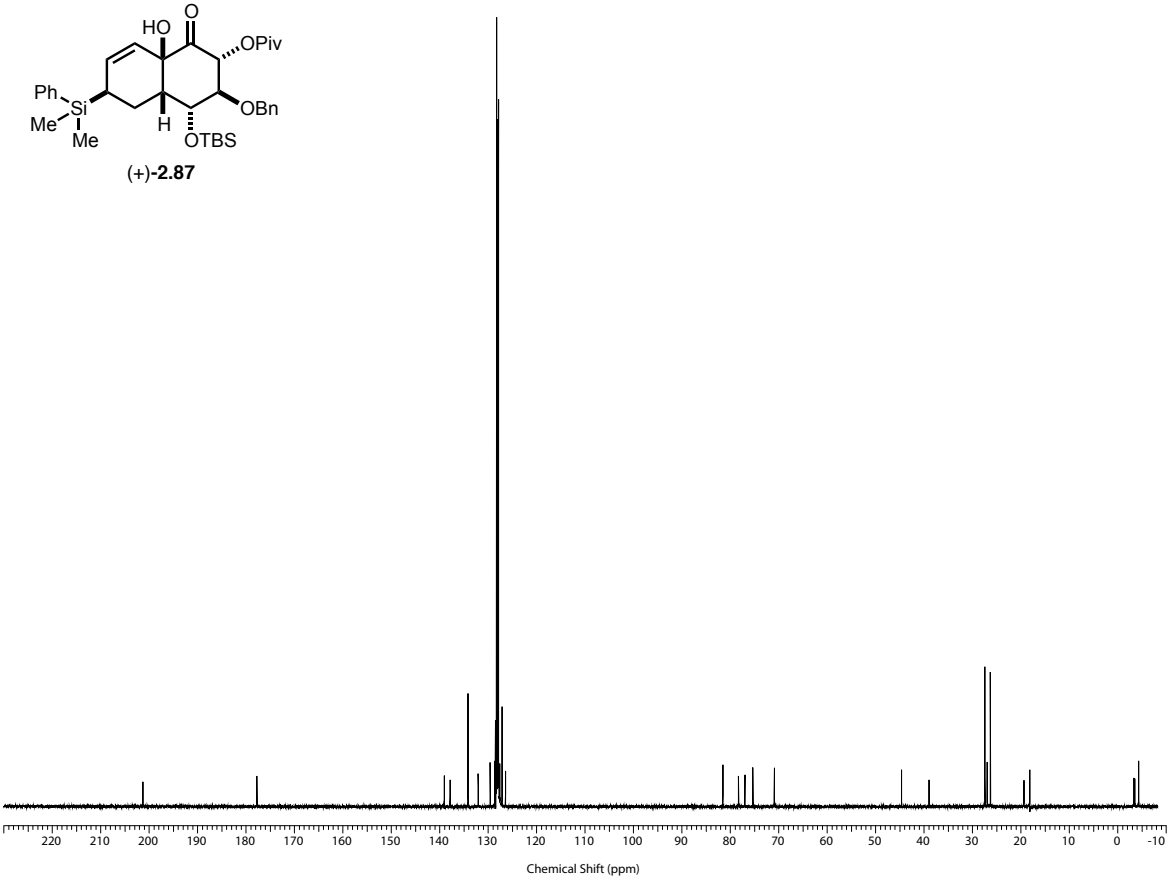

HO
O
OPiv
Ph
Si
Me
Me
H
OBn
OTBS

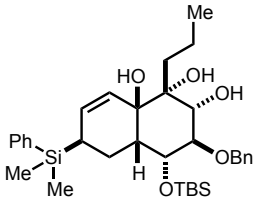
(+)-**2.87**

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

HO
O
OPiv
Ph
Si
Me
Me
H
OBn
OTBS

(+)-**2.87**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

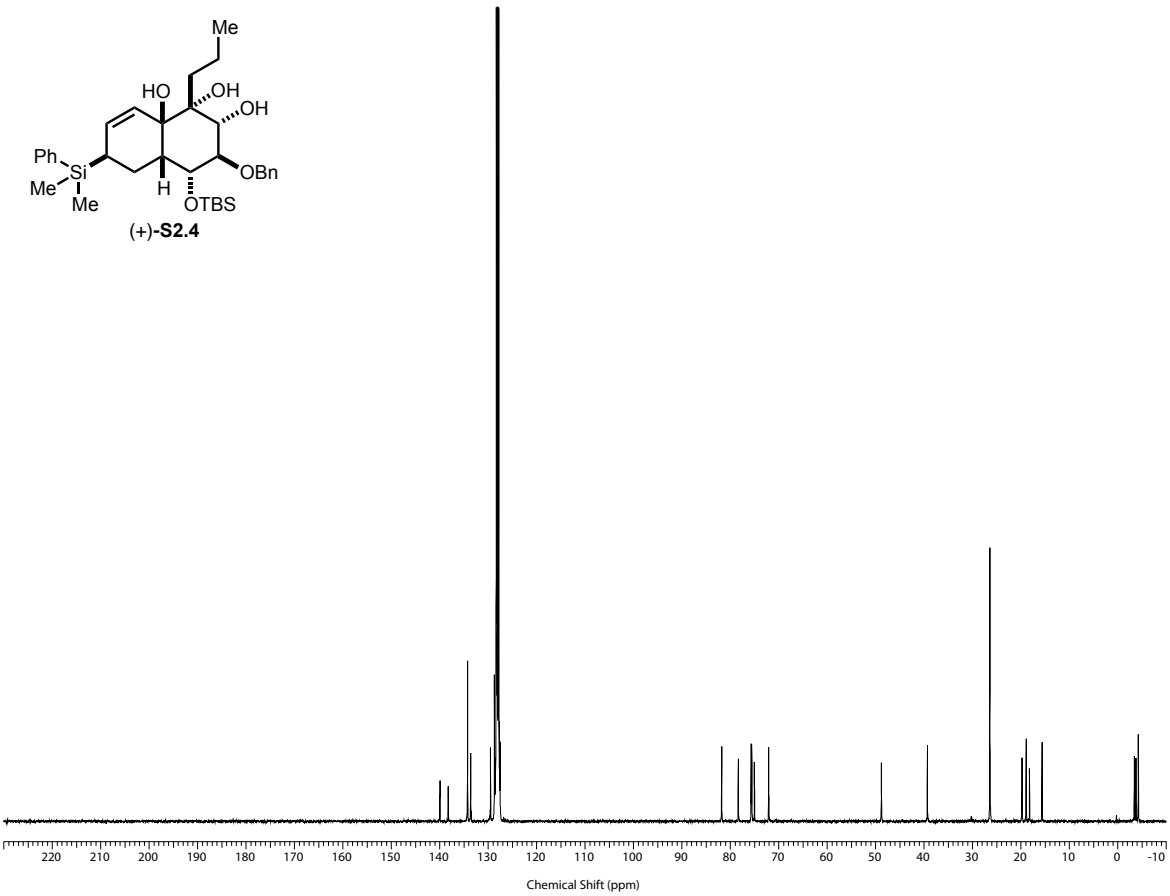

Me
HO
OH
OH
Ph
Si
Me
Me
H
OBn
OTBS

(+)-**S2.4**

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

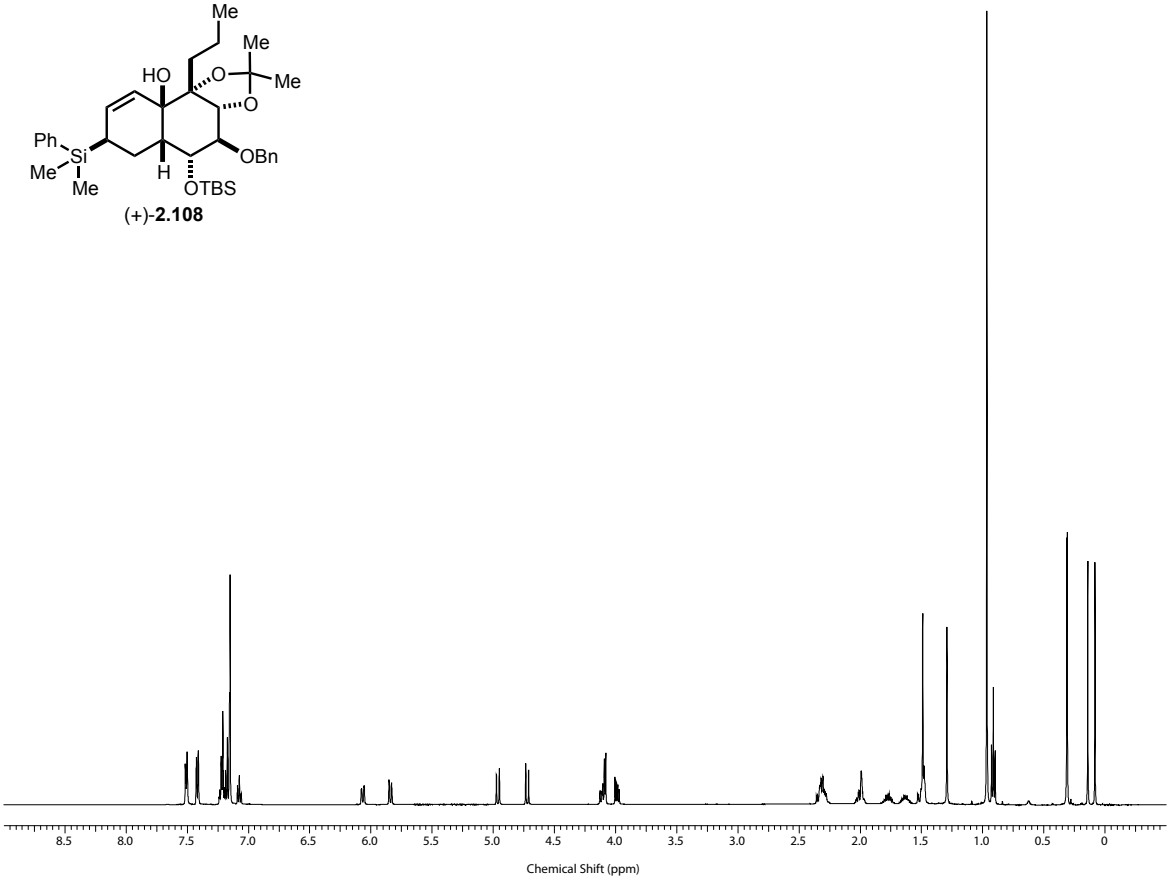
Me
HO
OH
OH
Ph
Si
Me
Me
H
OBn
OTBS

(+)-**S2.4**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

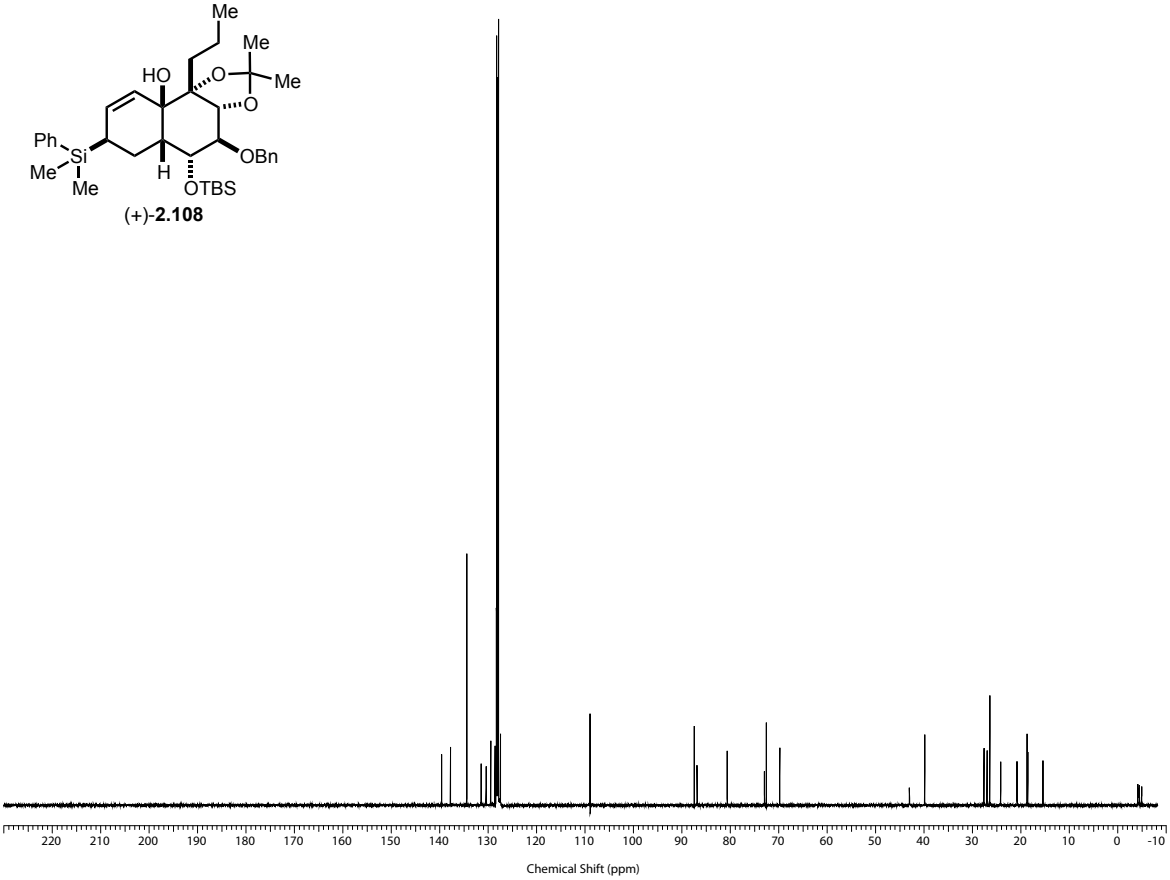
Me
Me
HO
O
Me
O
Ph
Si
Me
Me
H
OBn
OTBS

(+)-**2.108**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

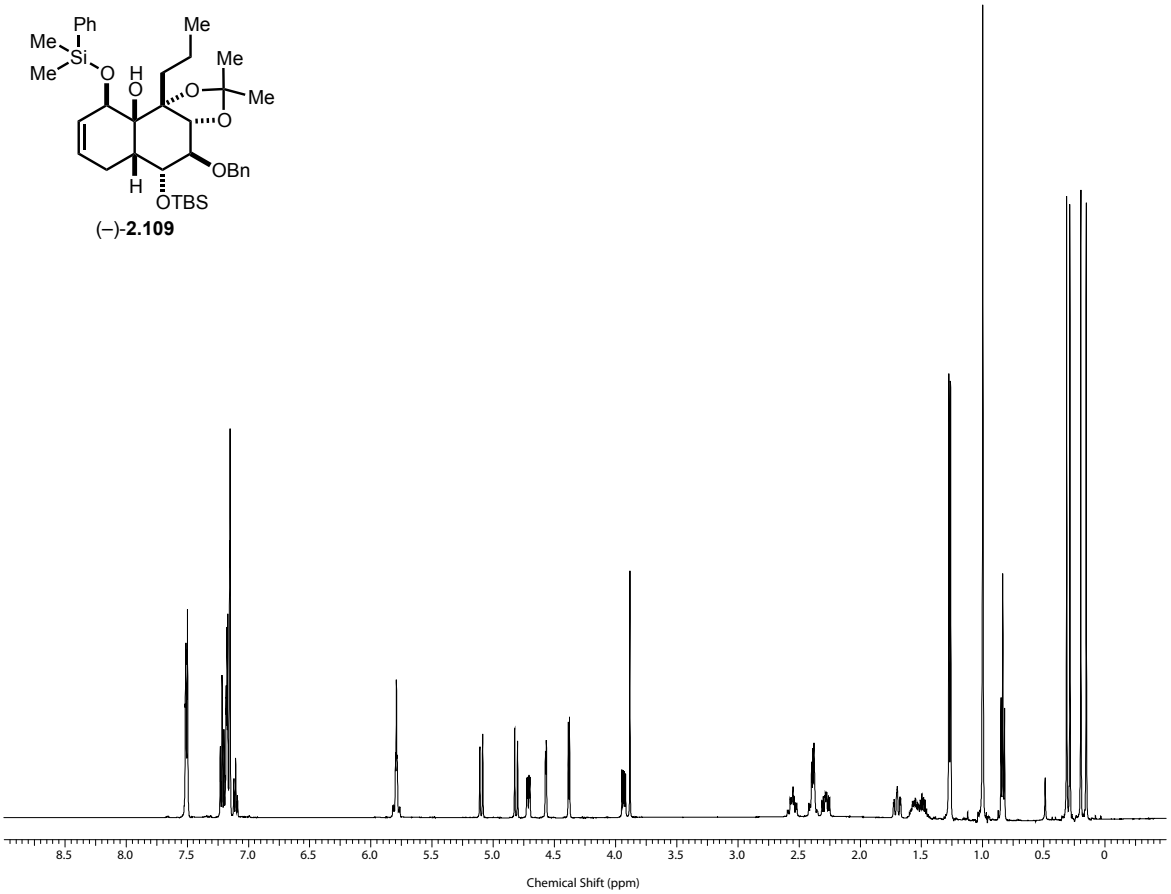
Me
Me
HO
O
Me
O
Ph
Si
Me
Me
H
OBn
OTBS

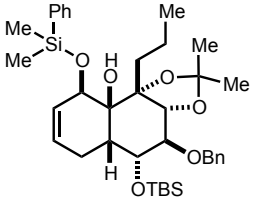
(+)-**2.108**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

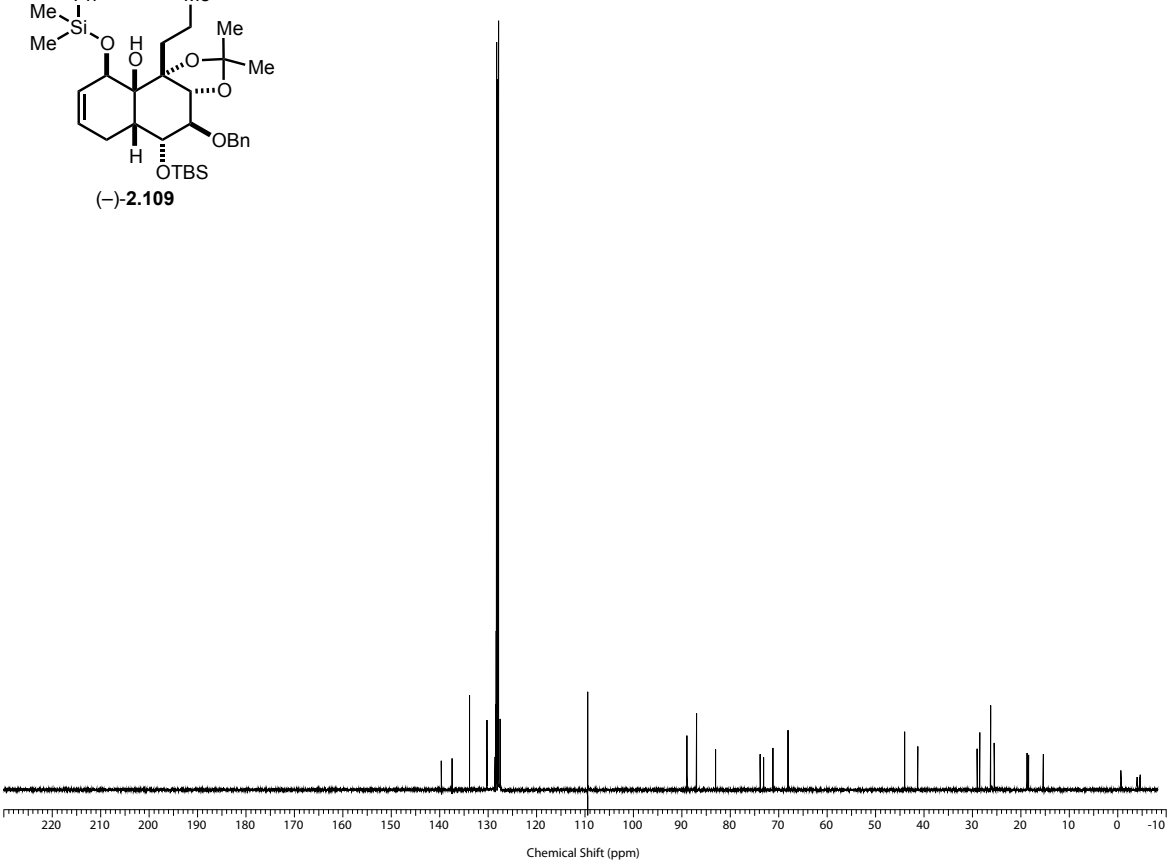
Ph
Me
Si
Me
O
H
O
Me
O
Me
O
OBn
H
OTBS

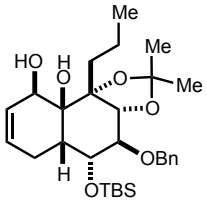
(–)-**2.109**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


Ph
Me
Si
Me
O
H
O
Me
O
Me
O
OBn
H
OTBS

(–)-**2.109**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

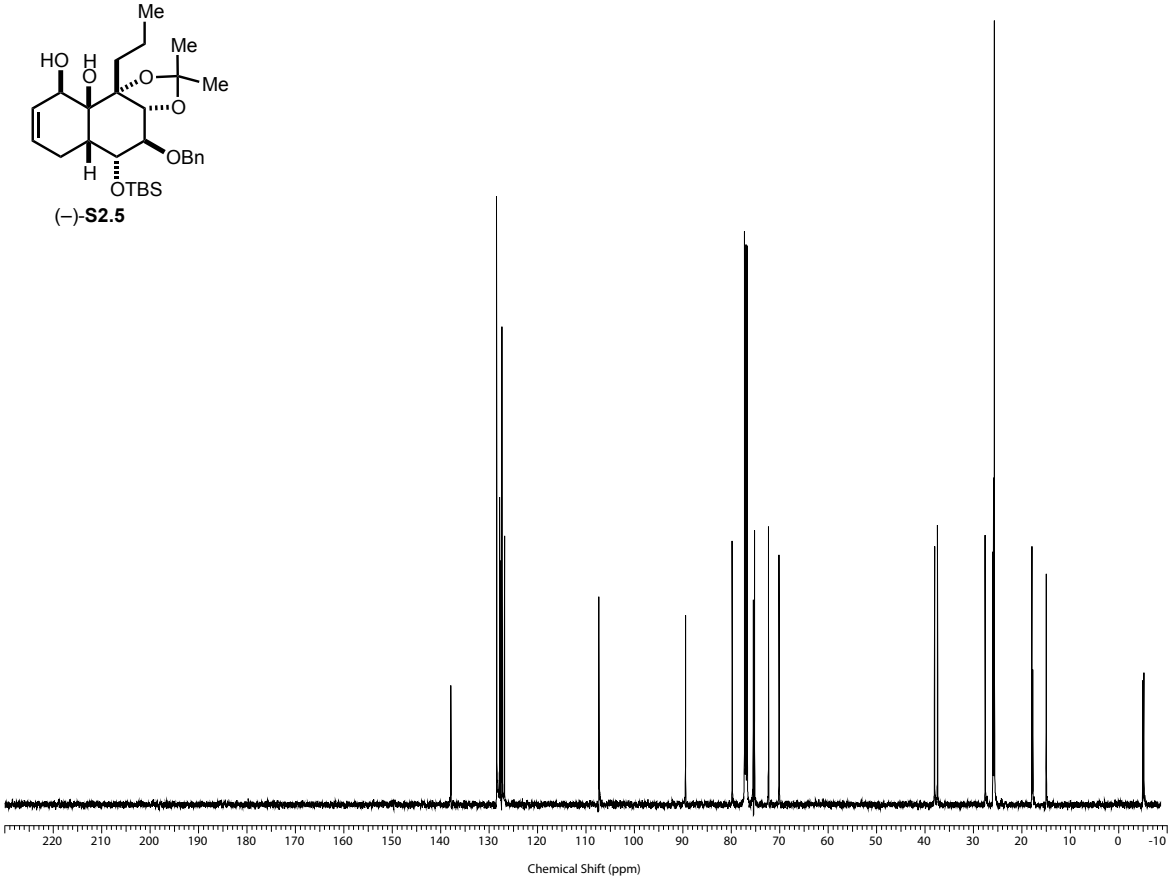

Me
HO
H
O
Me
O
Me
O
OBn
H
OTBS

(–)-**S2.5**

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

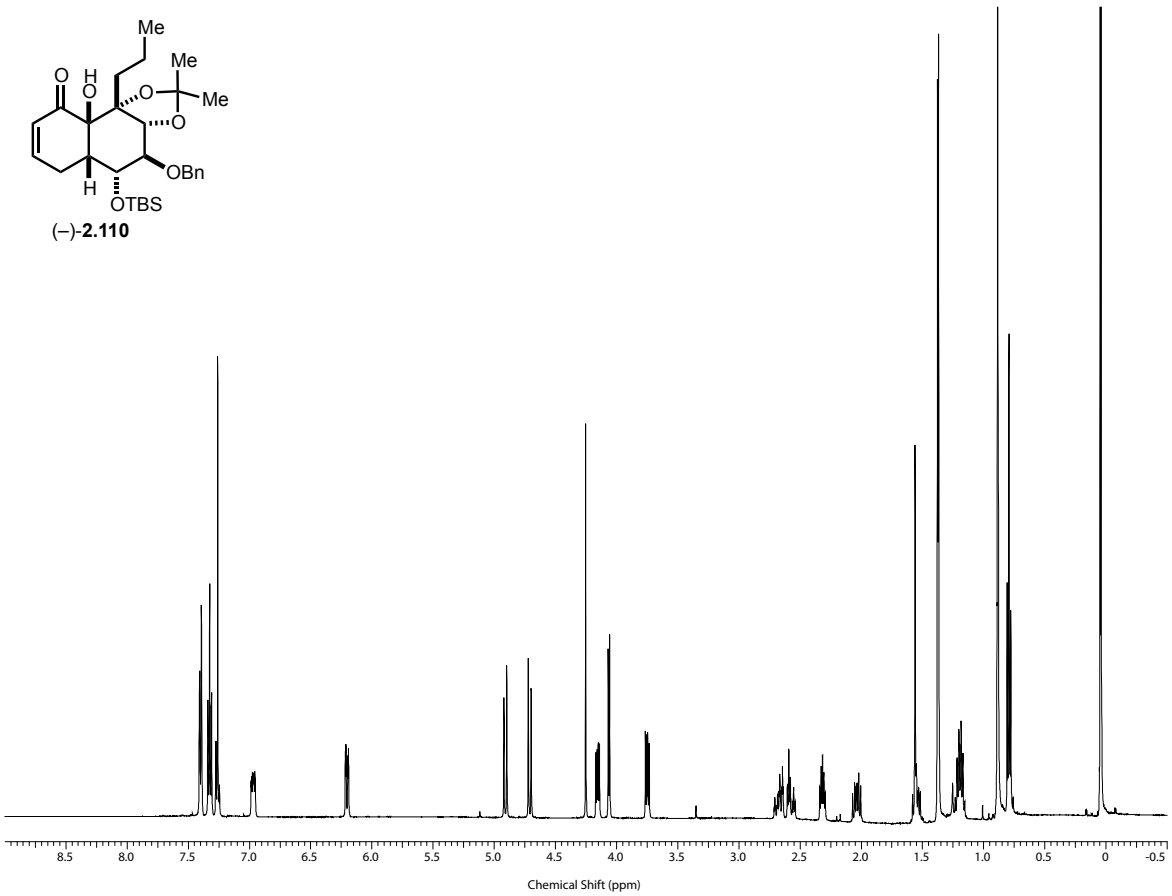
Me
HO
H
O
Me
O
Me
O
OBn
H
OTBS

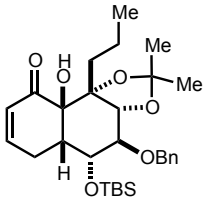
(–)-**S2.5**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

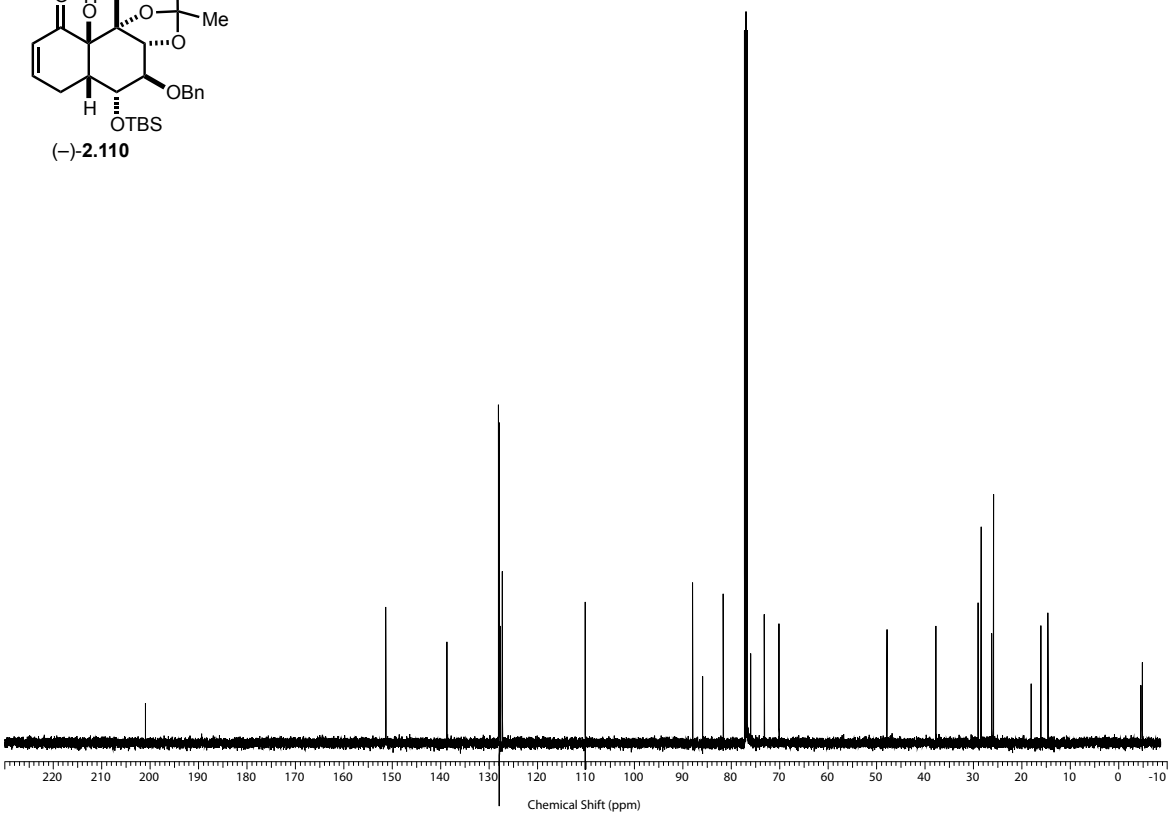
Me
Me
O
H
O
O
Me
O
OBn
H
OTBS

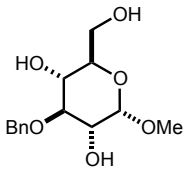
(–)-**2.110**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

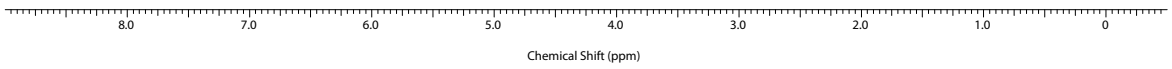

Me
Me
O
H
O
O
Me
O
OBn
H
OTBS

(–)-**2.110**

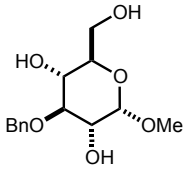

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



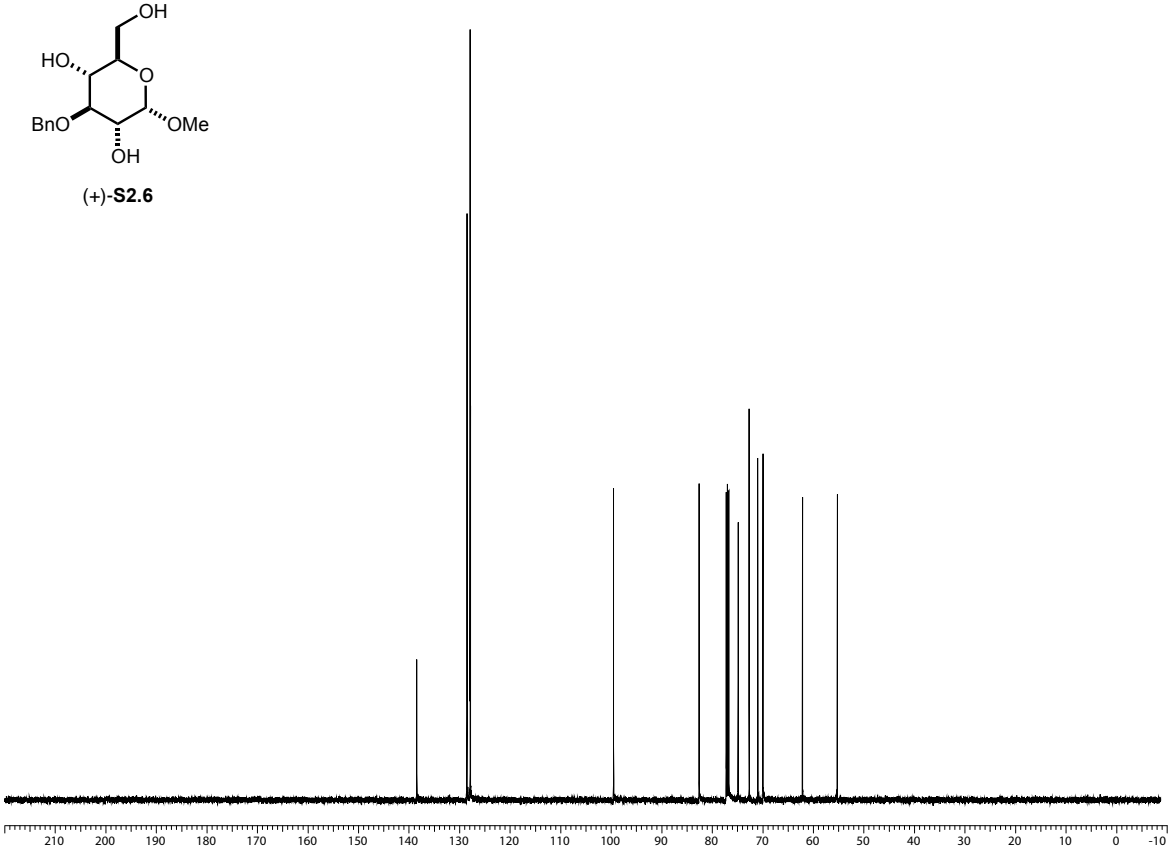
(+)-**S2.6**



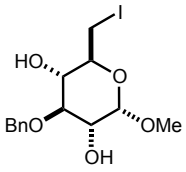
Chemical Shift (ppm)



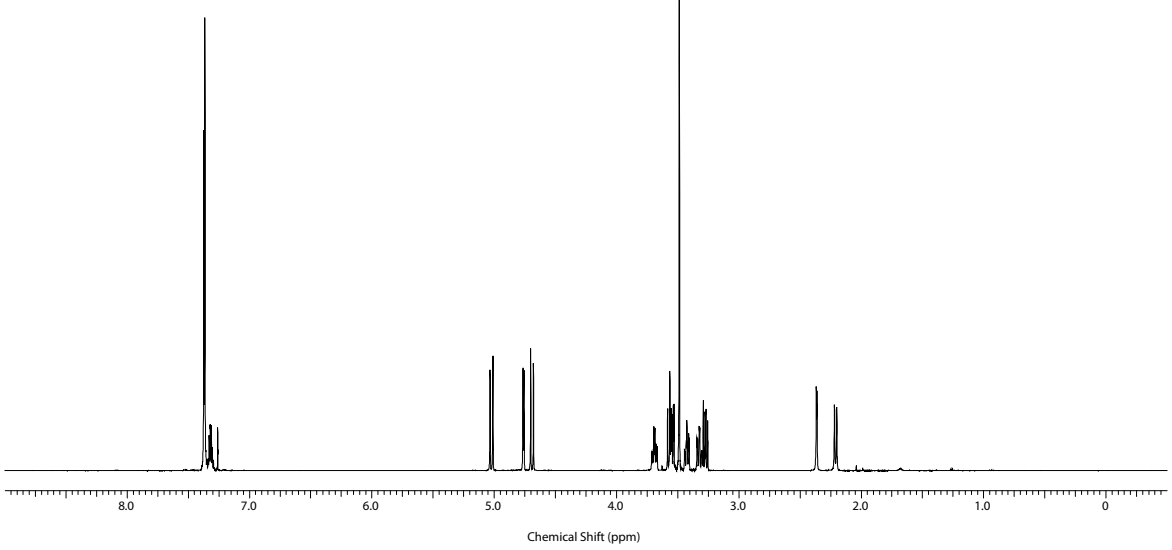
(+)-**S2.6**

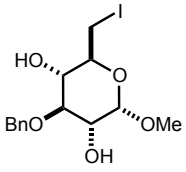


Chemical Shift (ppm)

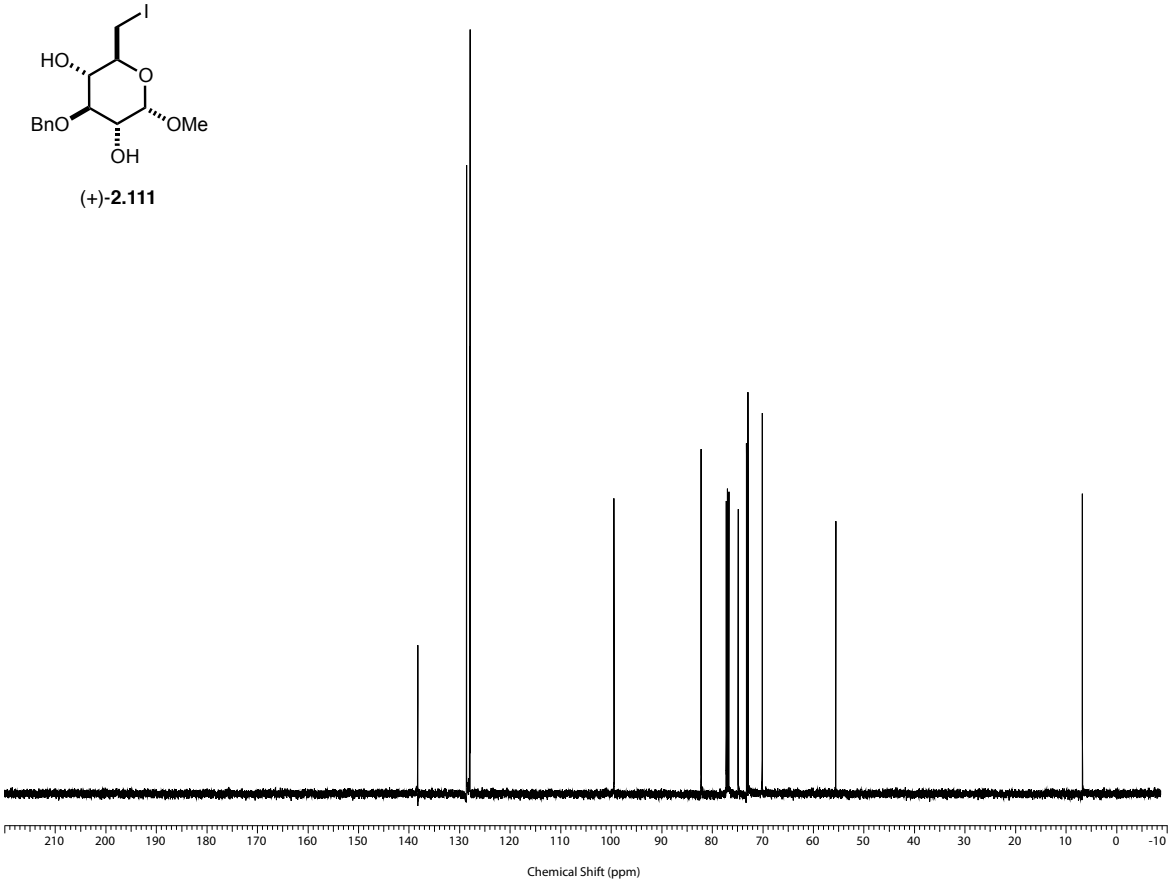

I
HO
O
BnO
OMe
OH

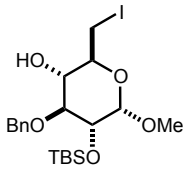
(+)-**2.111**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

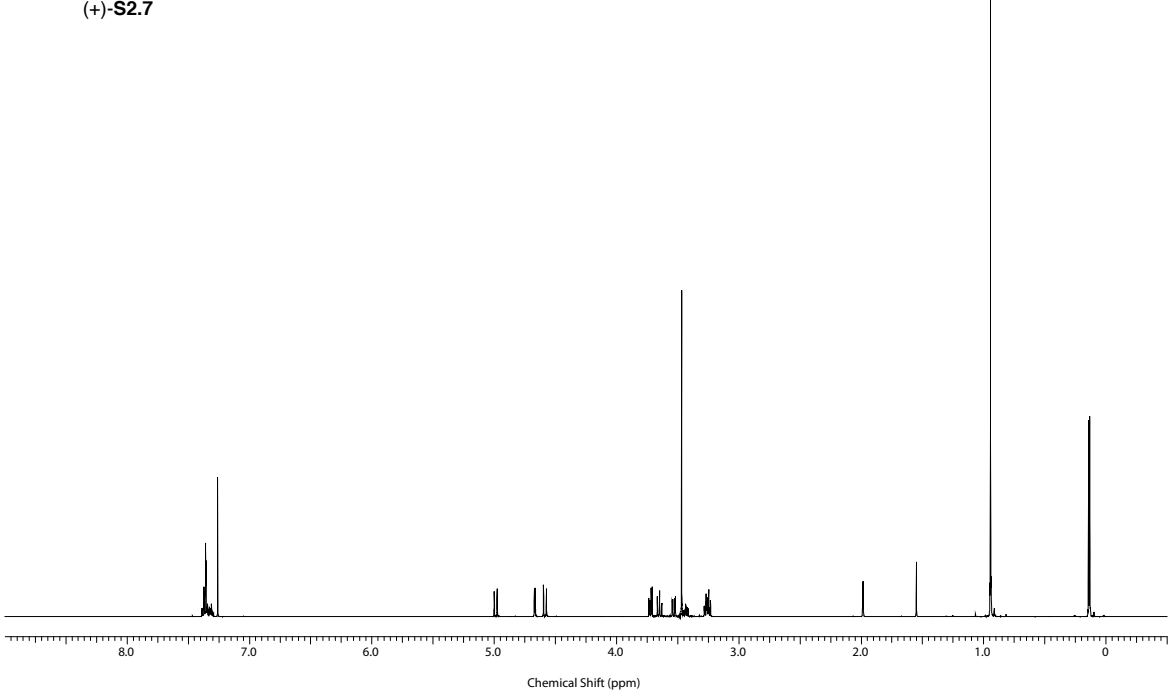

I
HO
O
BnO
OMe
OH

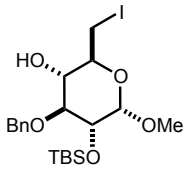
(+)-**2.111**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

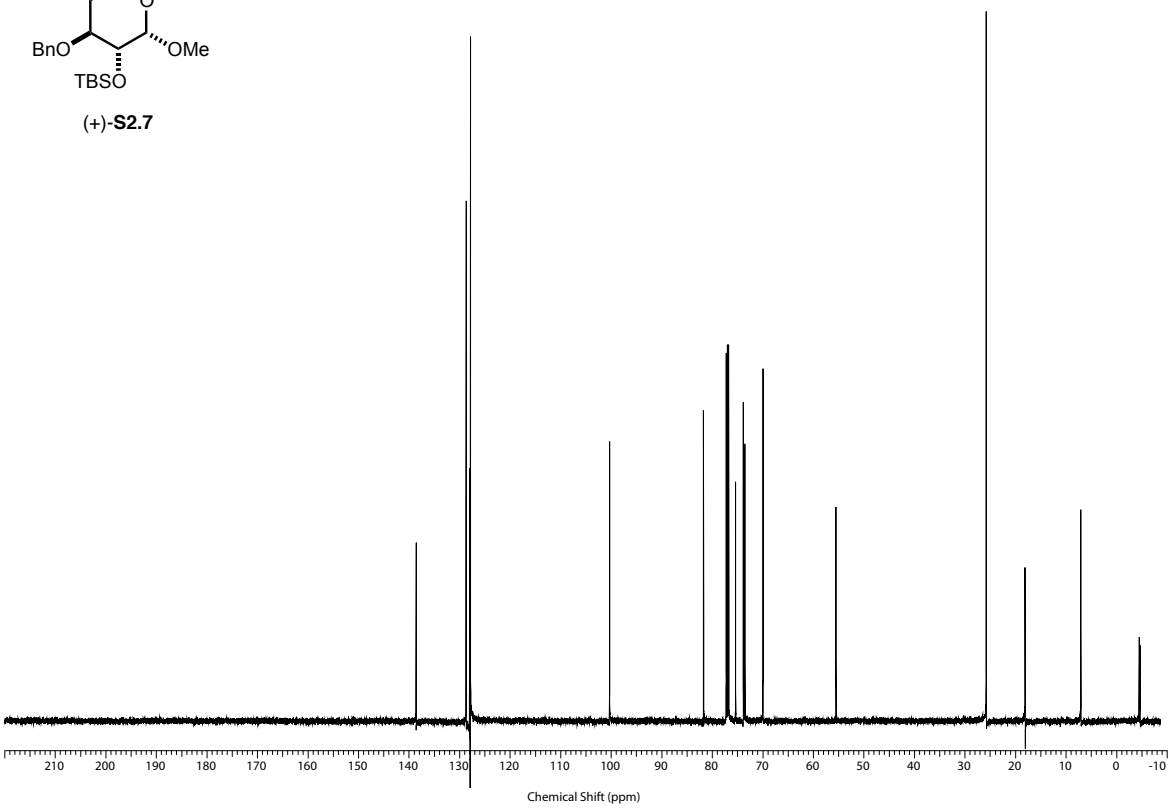

I
HO
O
BnO
OMe
TBSO

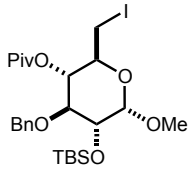
(+)-**S2.7**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

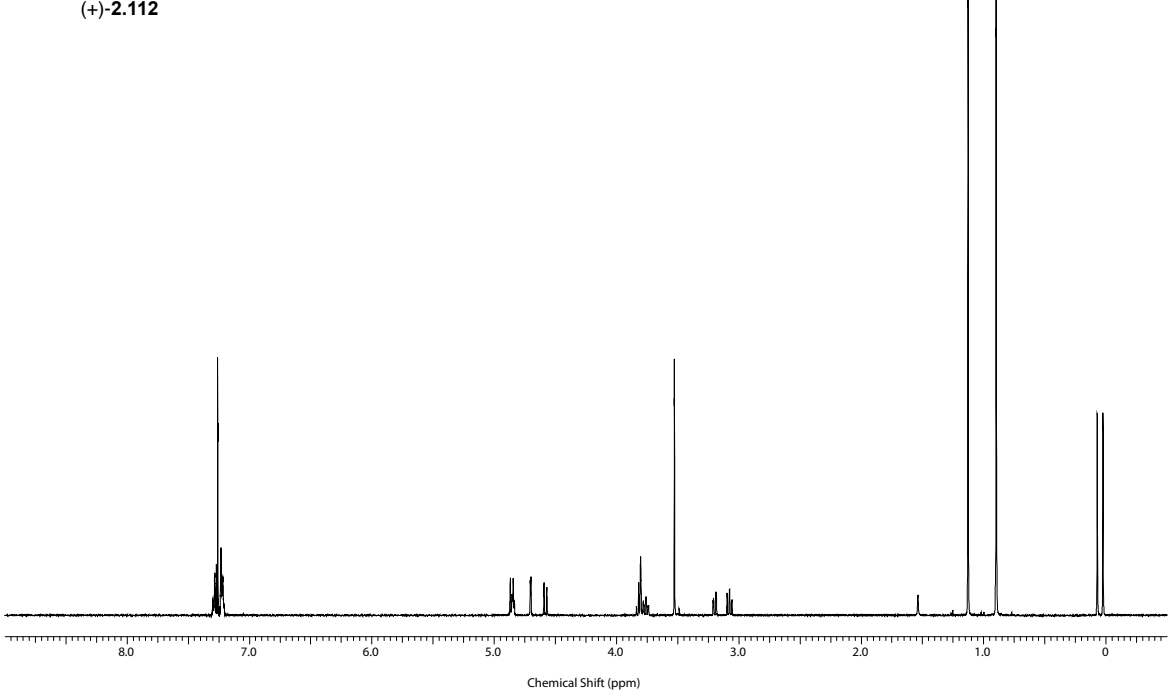

I
HO
O
BnO
OMe
TBSO

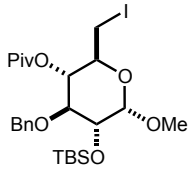
(+)-**S2.7**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

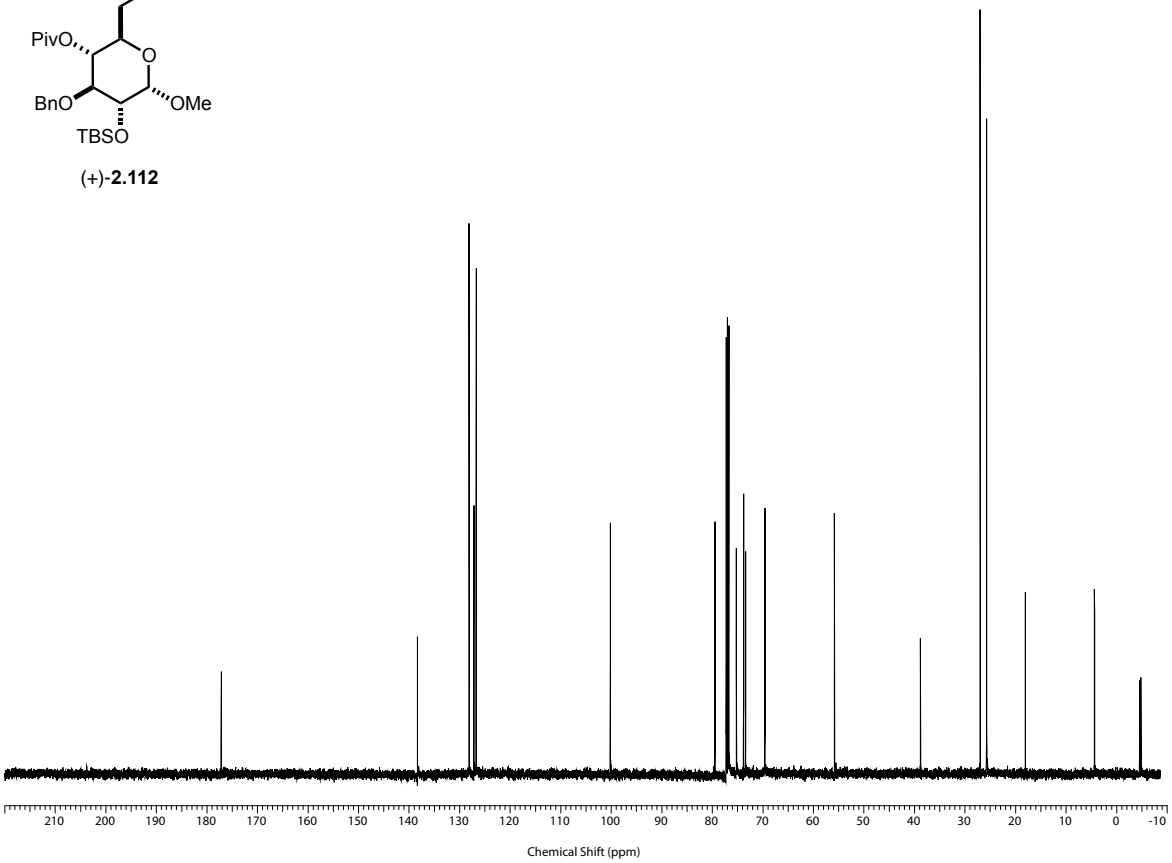

I
PivO
O
BnO
OMe
TBSO

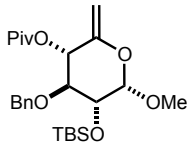
(+)-**2.112**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

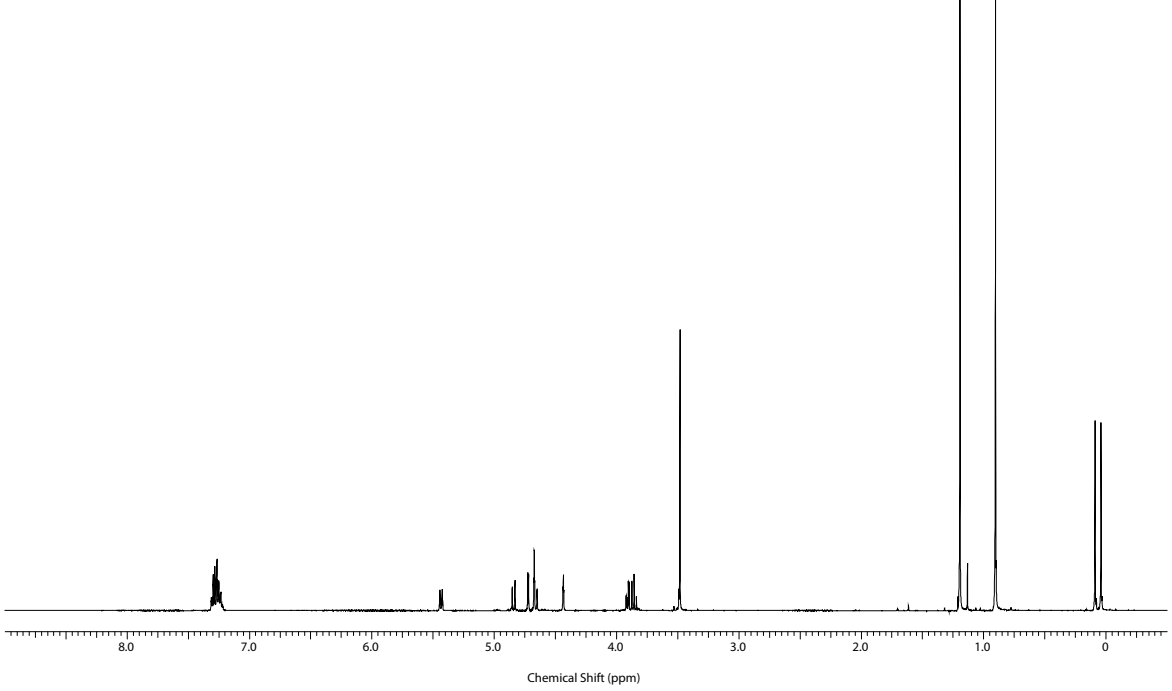

I
PivO
O
BnO
OMe
TBSO

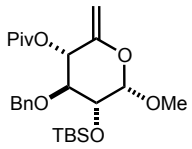
(+)-**2.112**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

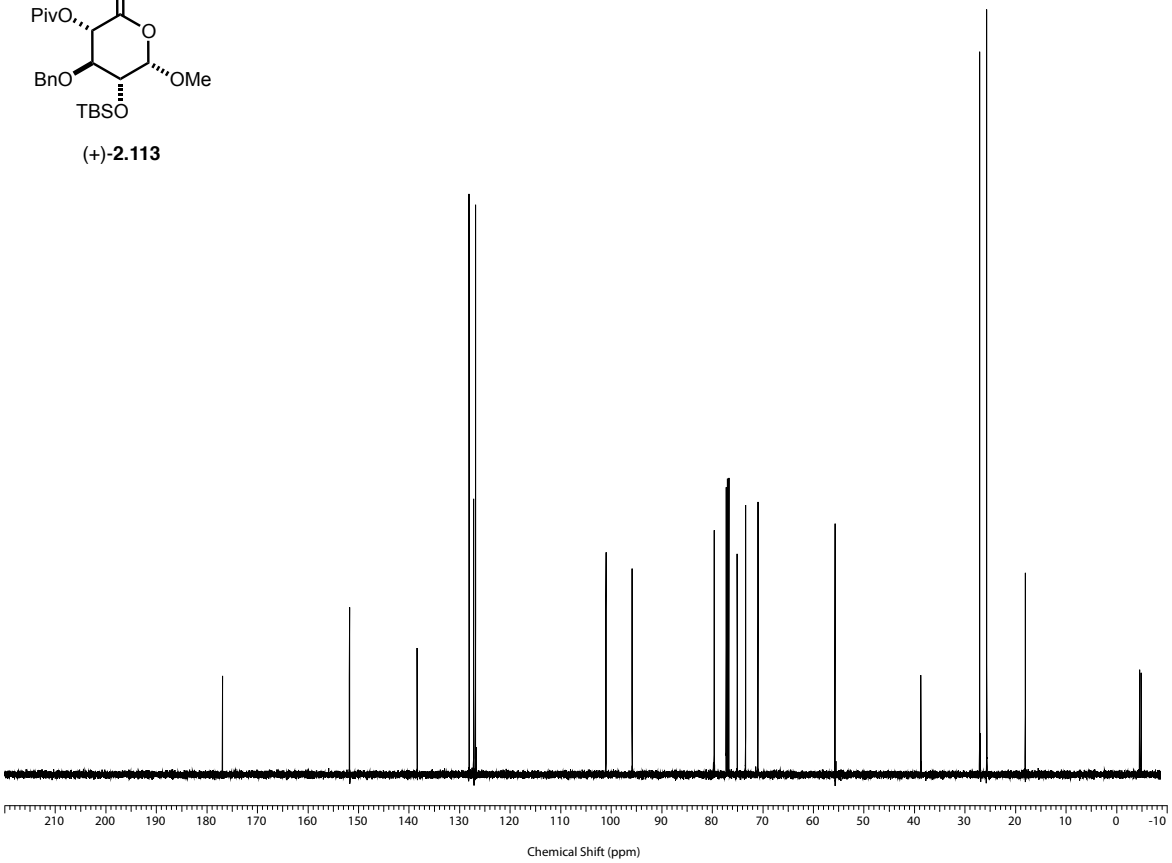

PivO
O
BnO
OMe
TBSO

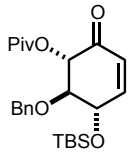
(+)-**2.113**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

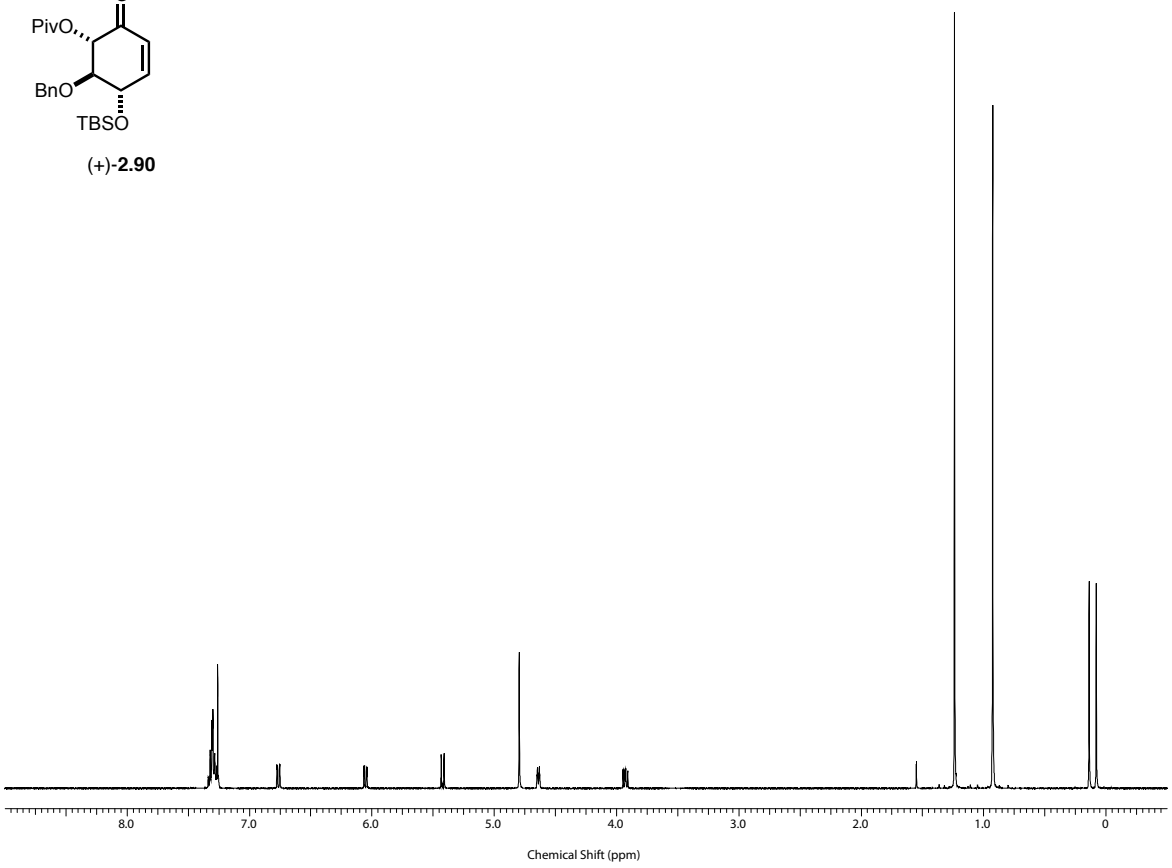

PivO
O
BnO
OMe
TBSO

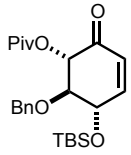
(+)-**2.113**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

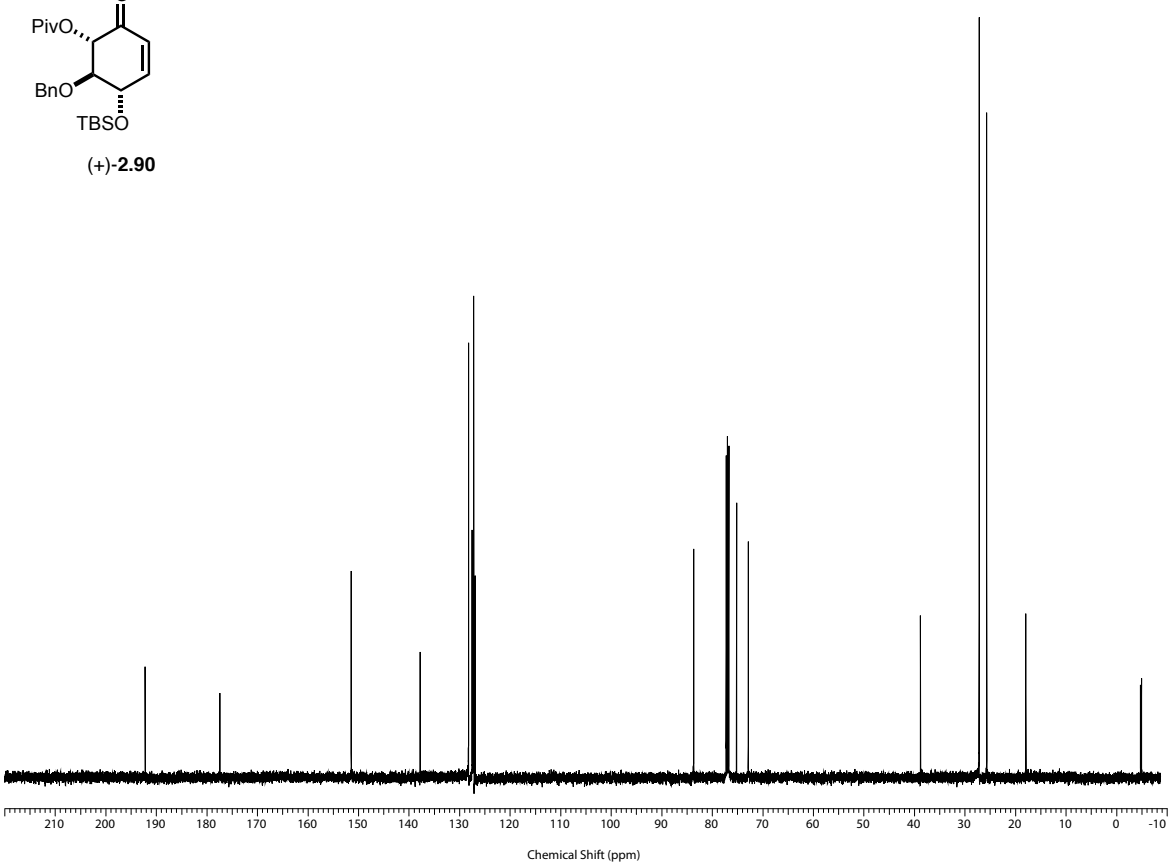

O
PivO
BnO
TBSO

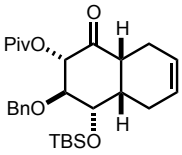
(+)-**2.90**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

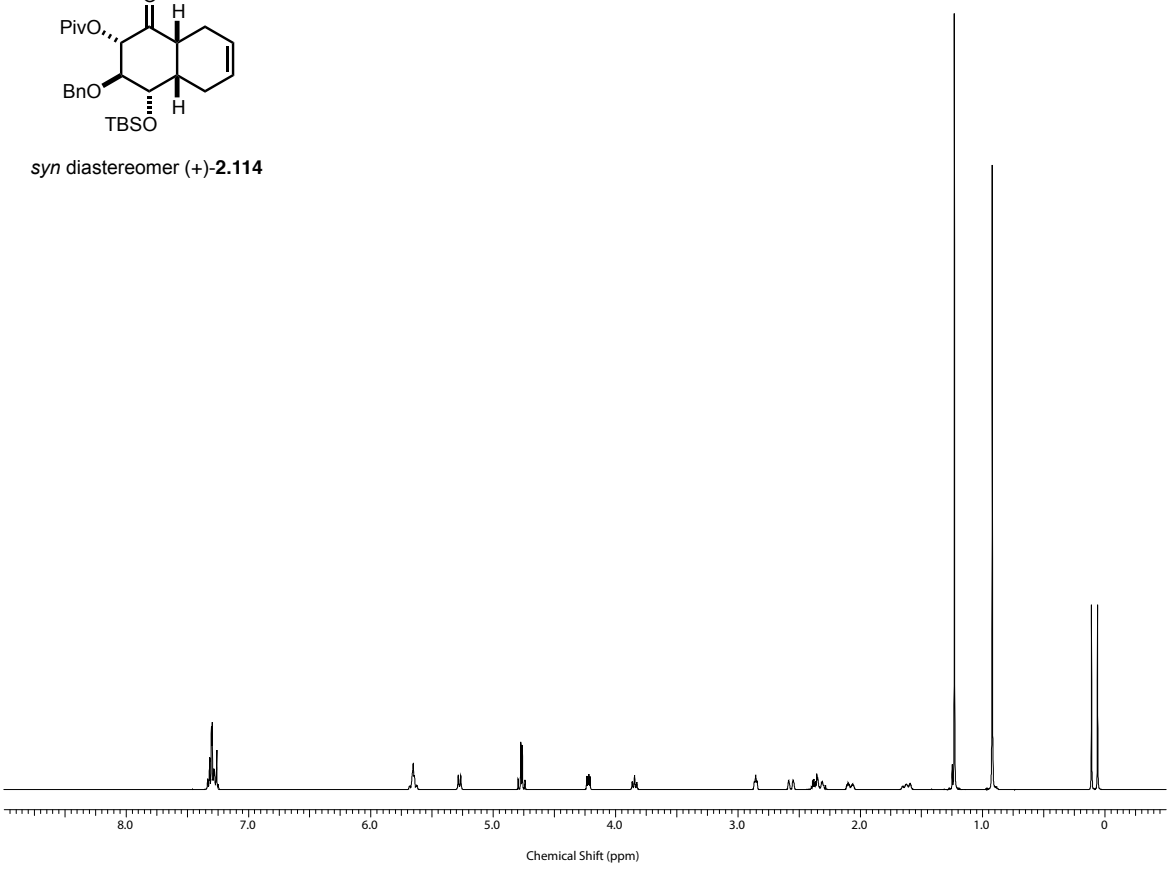

O
PivO
BnO
TBSO

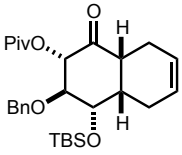
(+)-**2.90**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

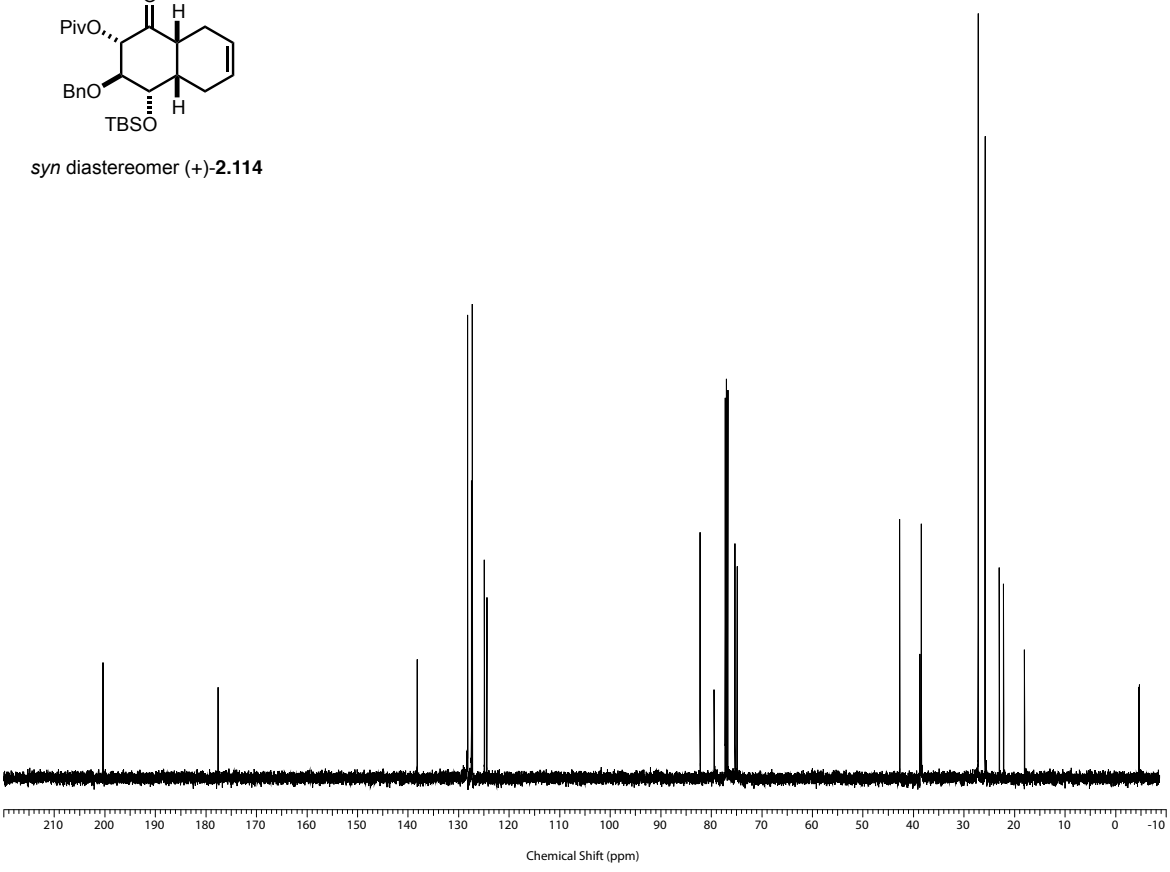


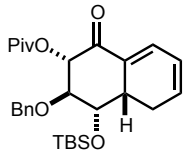
syn diastereomer (+)-**2.114**



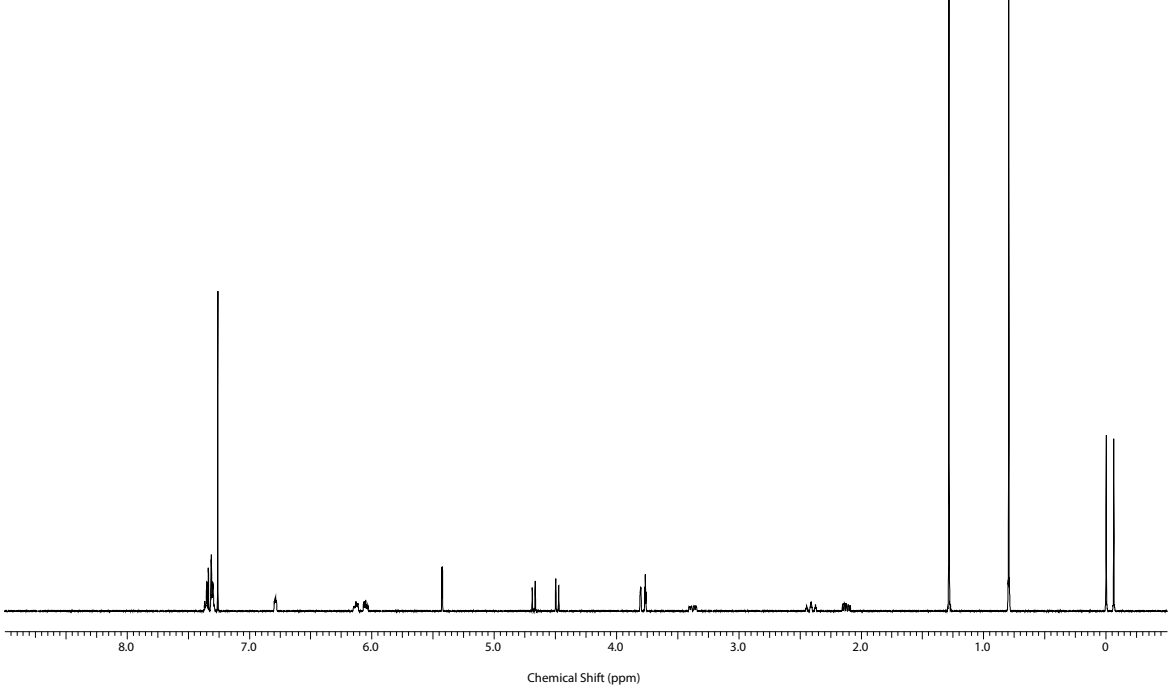


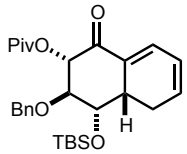
syn diastereomer (+)-**2.114**



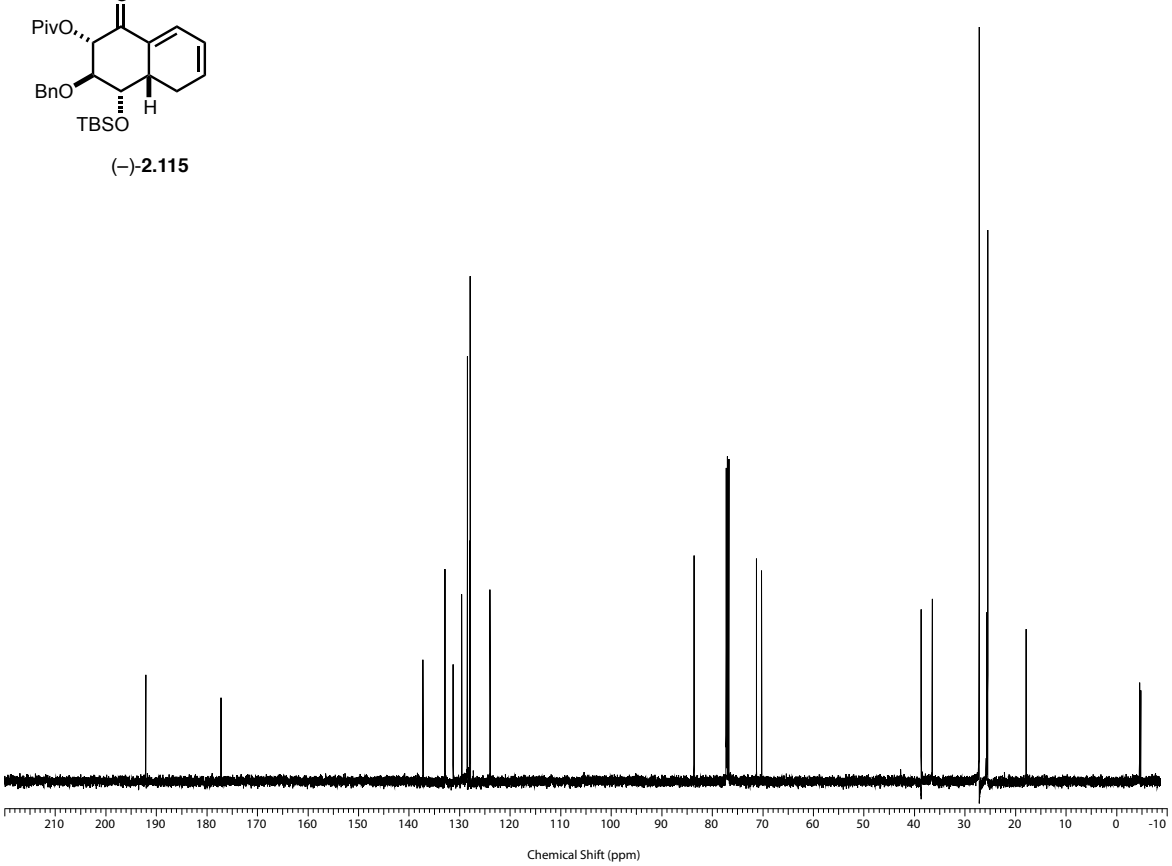

O
PivO
BnO
H
TBSO

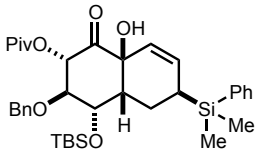
(–)-**2.115**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

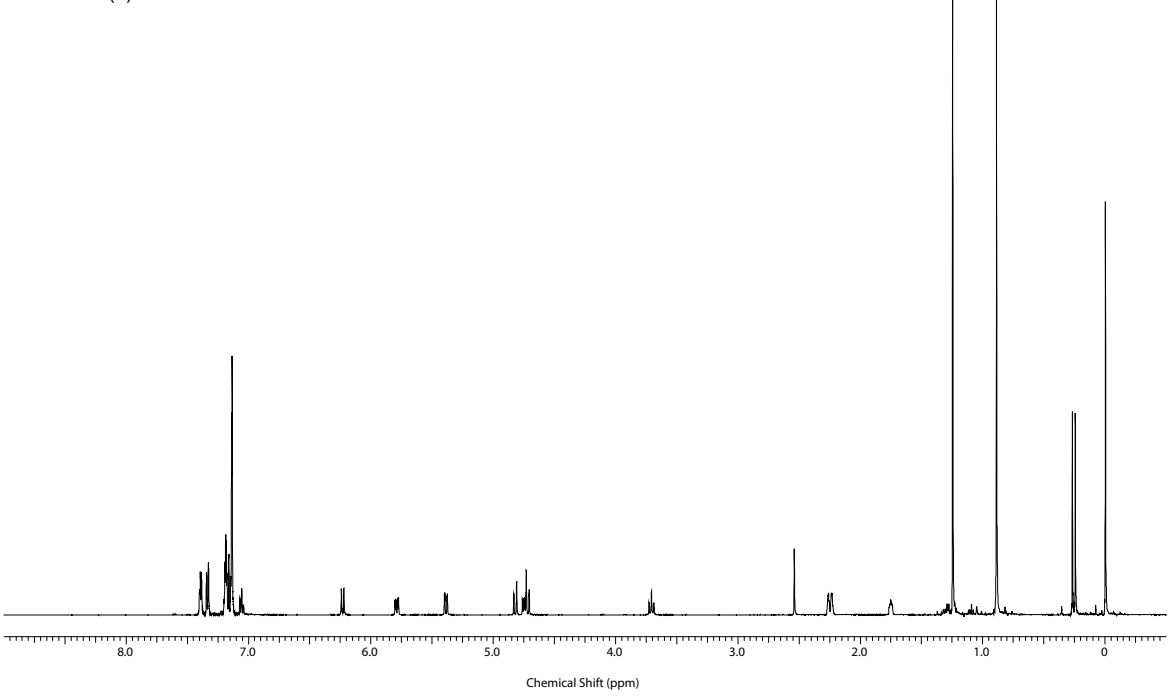

O
PivO
BnO
H
TBSO

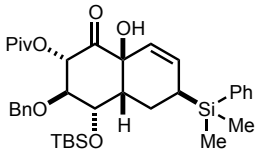
(–)-**2.115**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

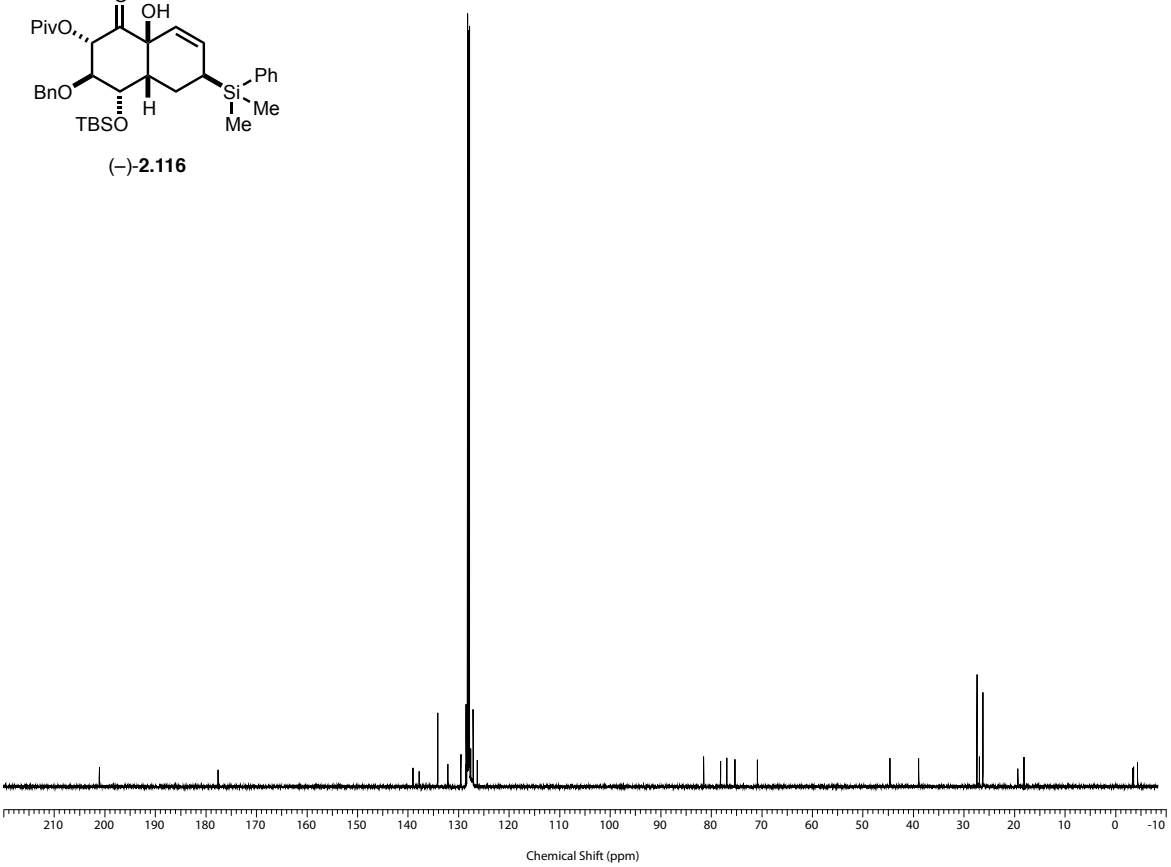

O
OH
PivO
Ph
BnO
Si
Me
H
TBSO
Me

(–)-**2.116**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

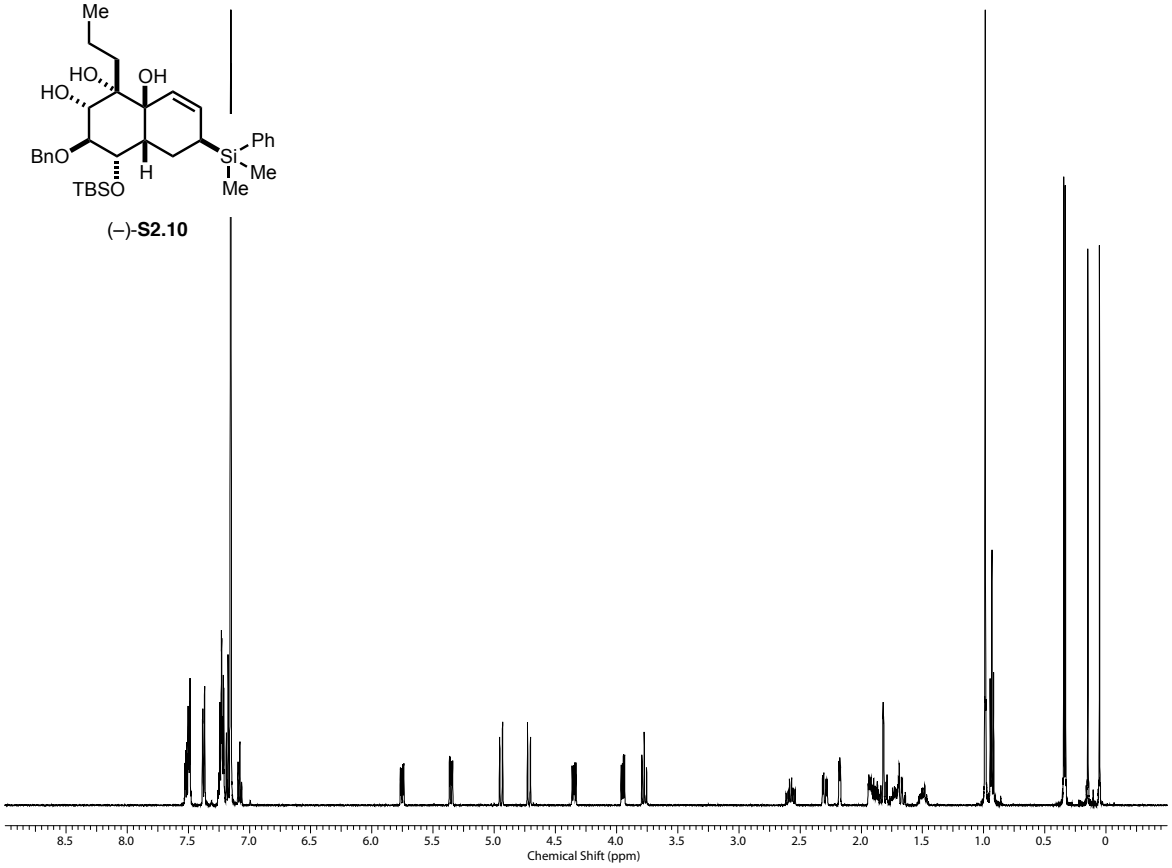

O
OH
PivO
Ph
BnO
Si
Me
H
TBSO
Me

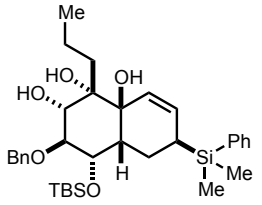
(–)-**2.116**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

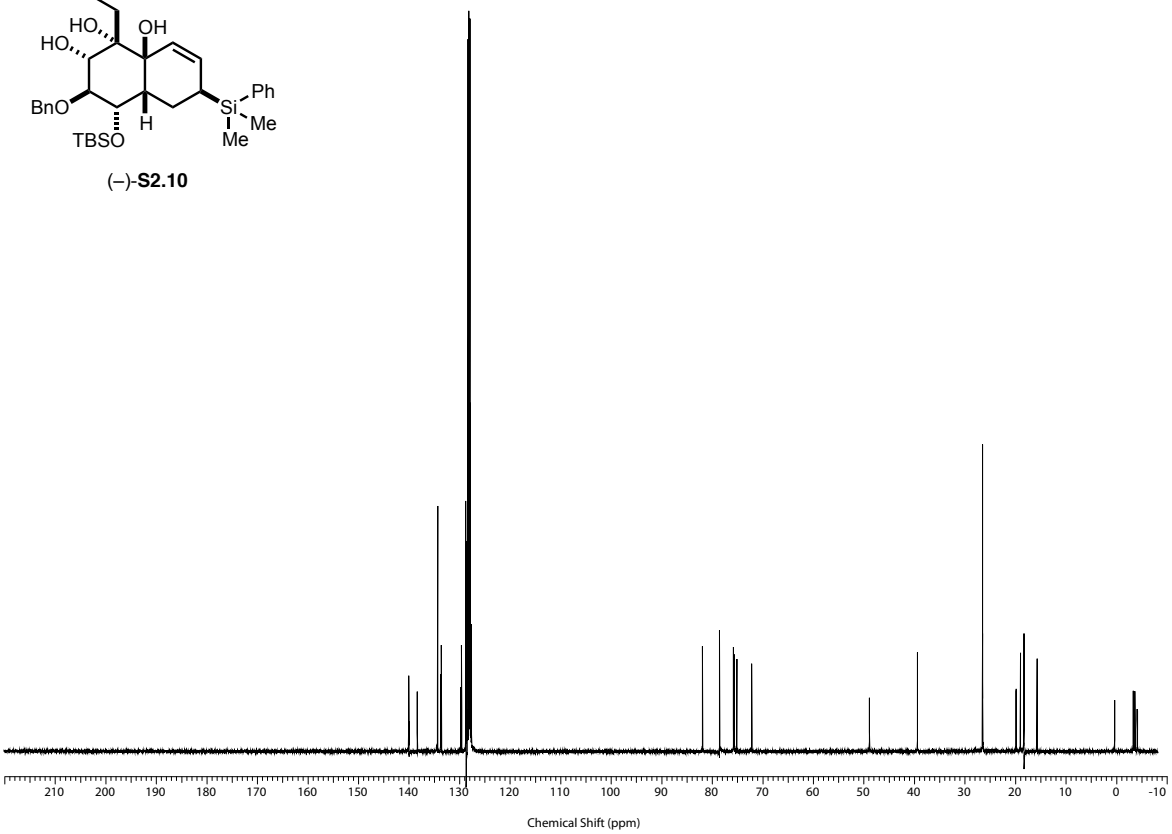
Me
HO
HO
OH
BnO
H
Si
Ph
Me
Me
TBSO

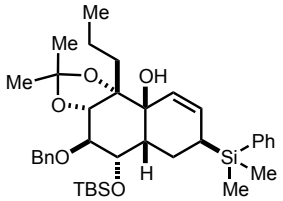
(–)-**S2.10**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

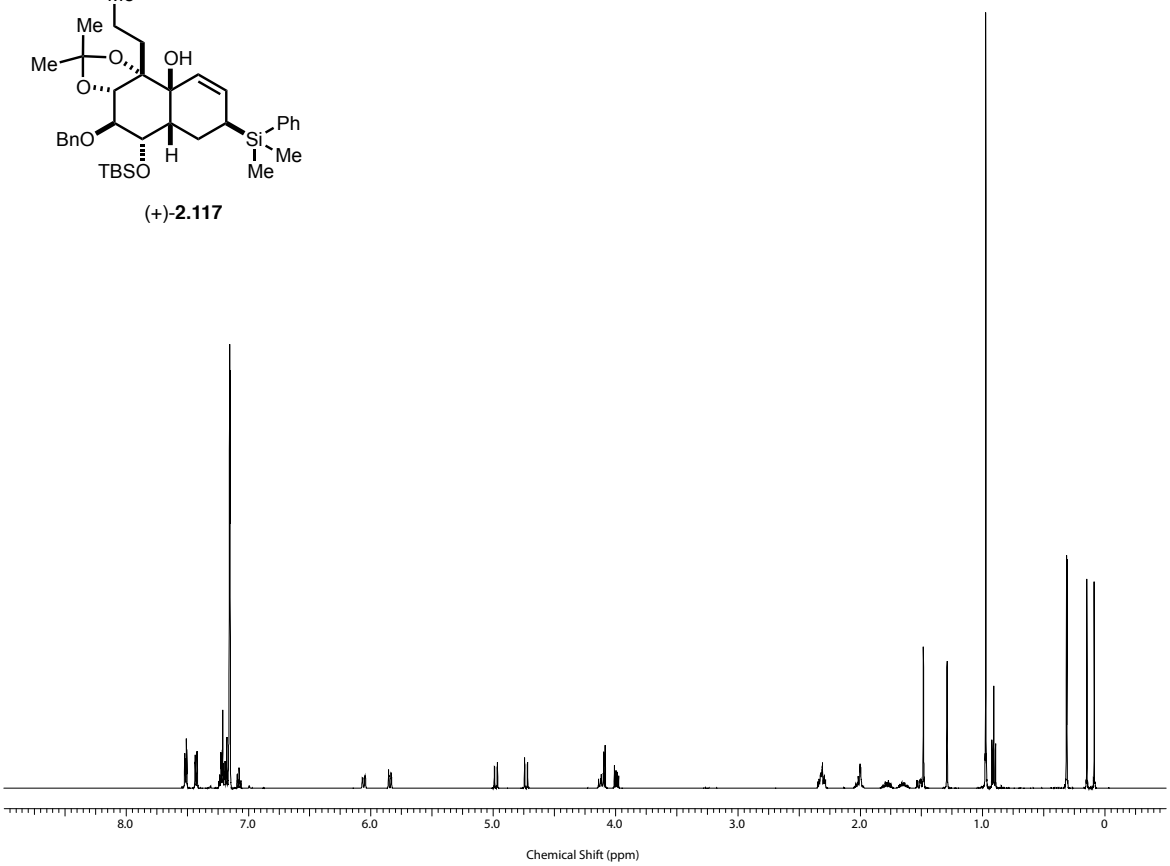

Me
HO
HO
OH
BnO
H
Si
Ph
Me
Me
TBSO

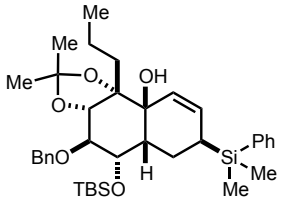
(–)-**S2.10**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

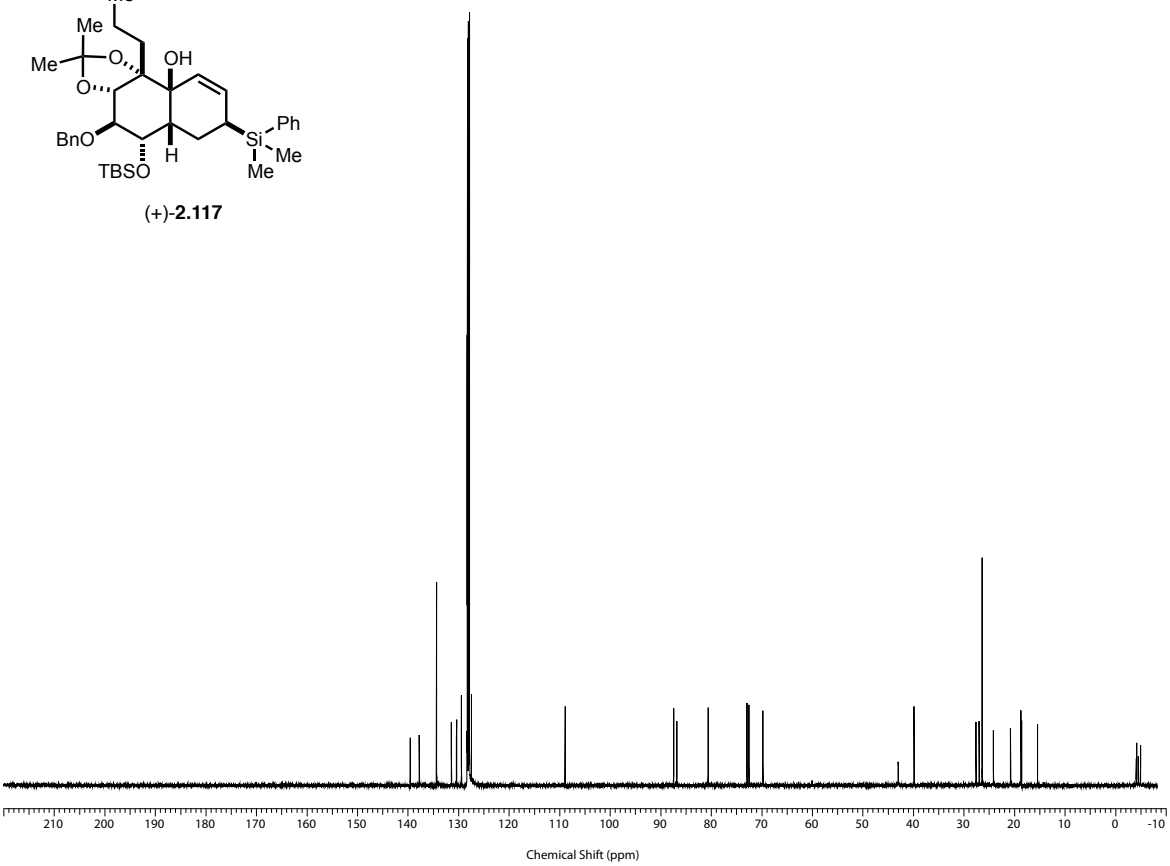

Me
Me
Me
O
O
OH
BnO
H
TBSO
Si
Ph
Me
Me

(+)-**2.117**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

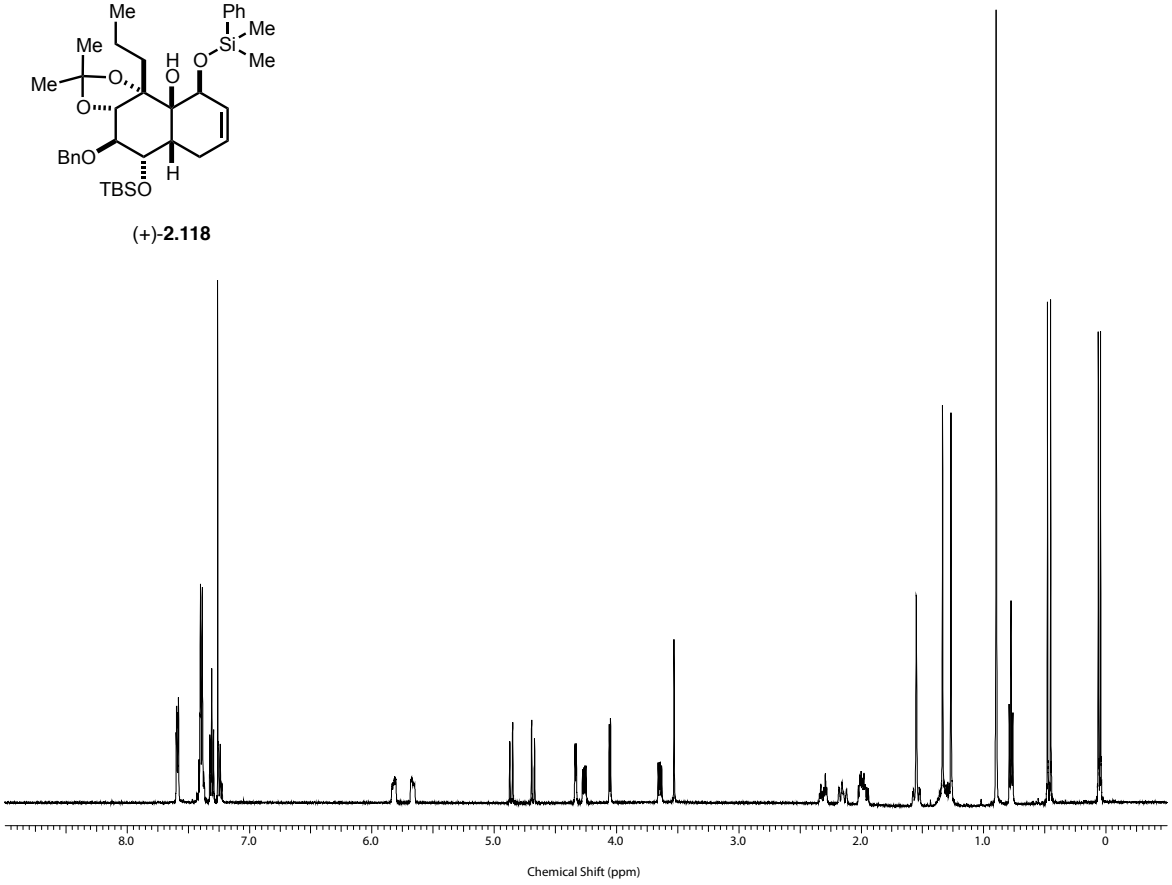

Me
Me
Me
O
O
OH
BnO
H
TBSO
Si
Ph
Me
Me

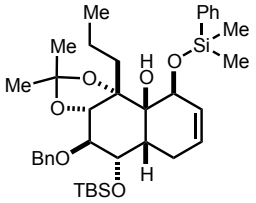
(+)-**2.117**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

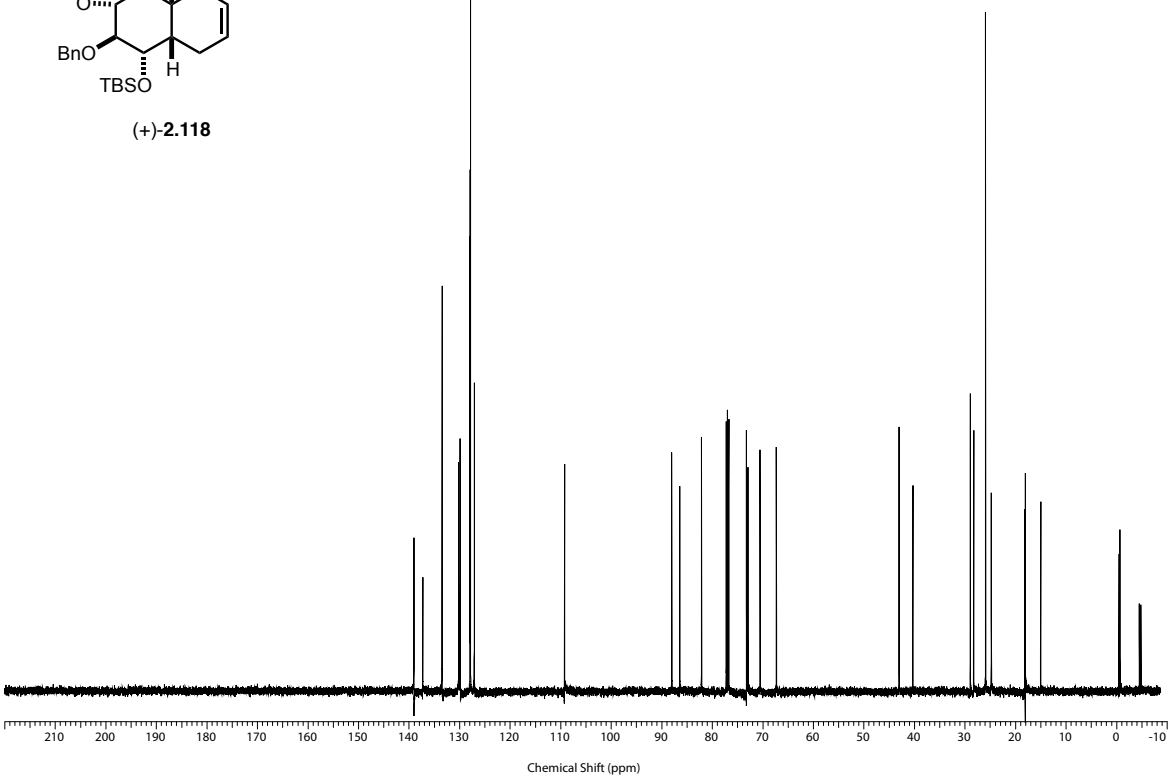
Me
Ph
Me
Si
Me
Me
H
O
Me
O
O
O
BnO
H
TBSO

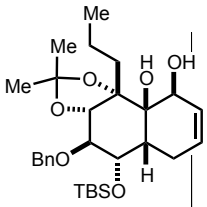
(+)-**2.118**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

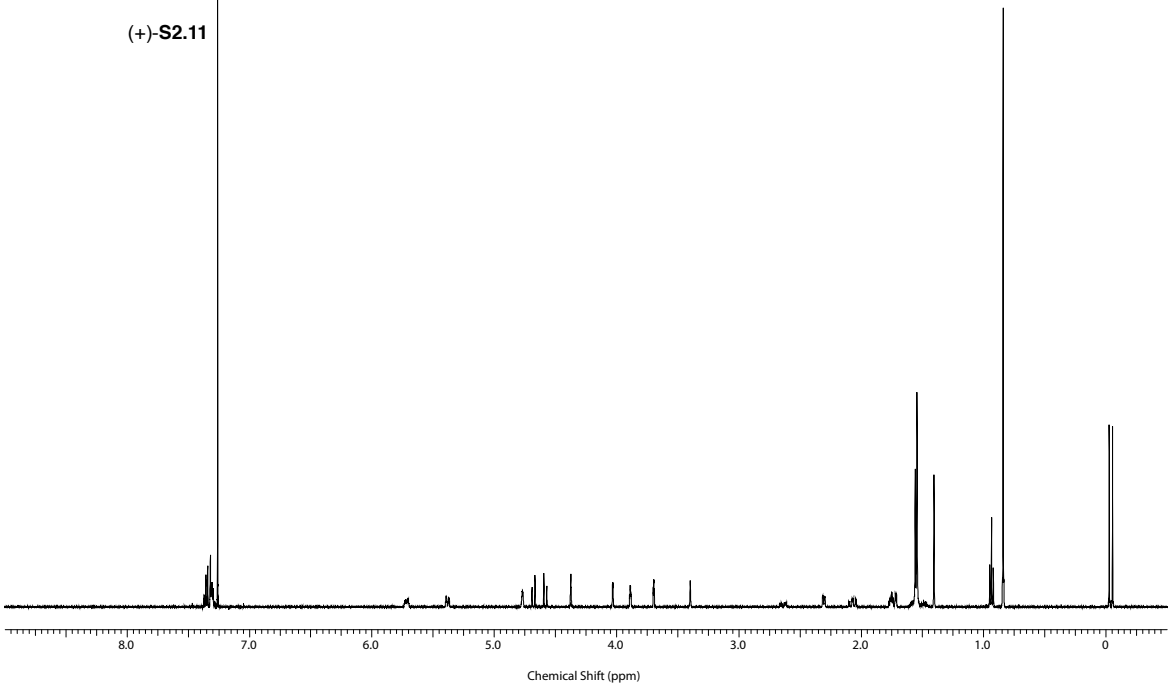

Me
Ph
Me
Si
Me
Me
H
O
Me
O
O
O
BnO
H
TBSO

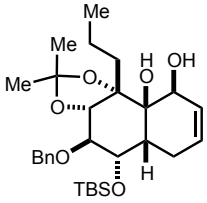
(+)-**2.118**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

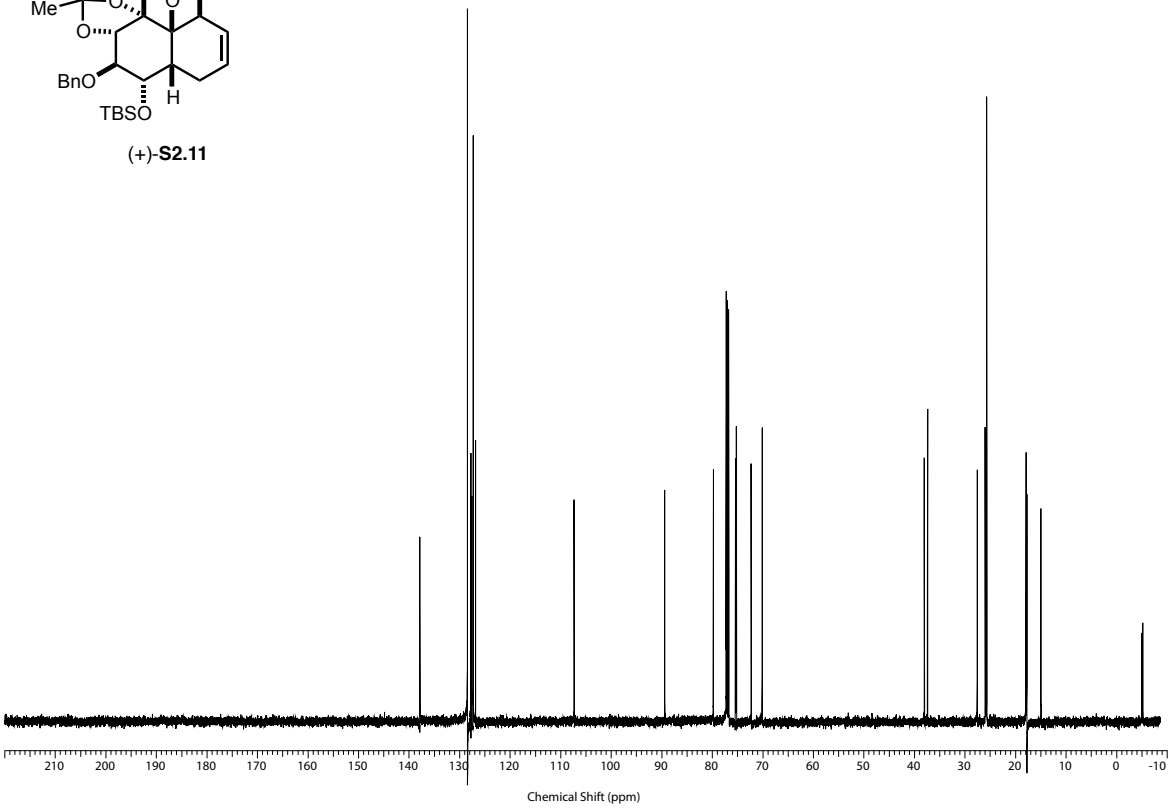

Me
Me
Me
O
O
H
O
OH
BnO
H
TBSO

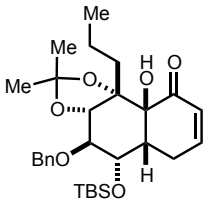
(+)-**S2.11**


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)


Me
Me
Me
O
O
H
O
OH
BnO
H
TBSO

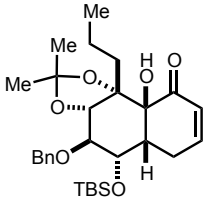
(+)-**S2.11**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

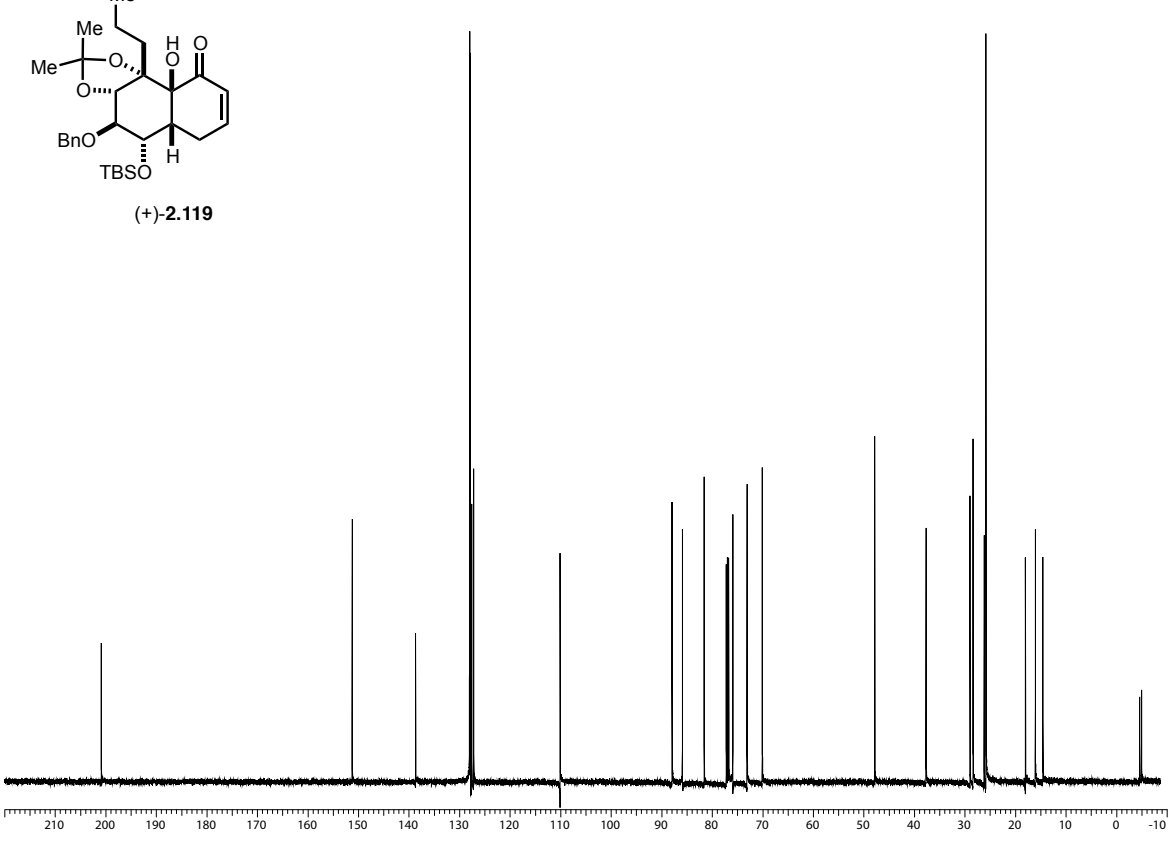

Me
Me
Me
O
O
H
O
O
BnO
H
TBSO

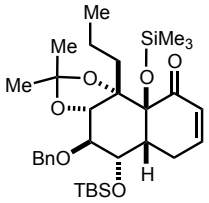
(+)-**2.119**

8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Chemical Shift (ppm)

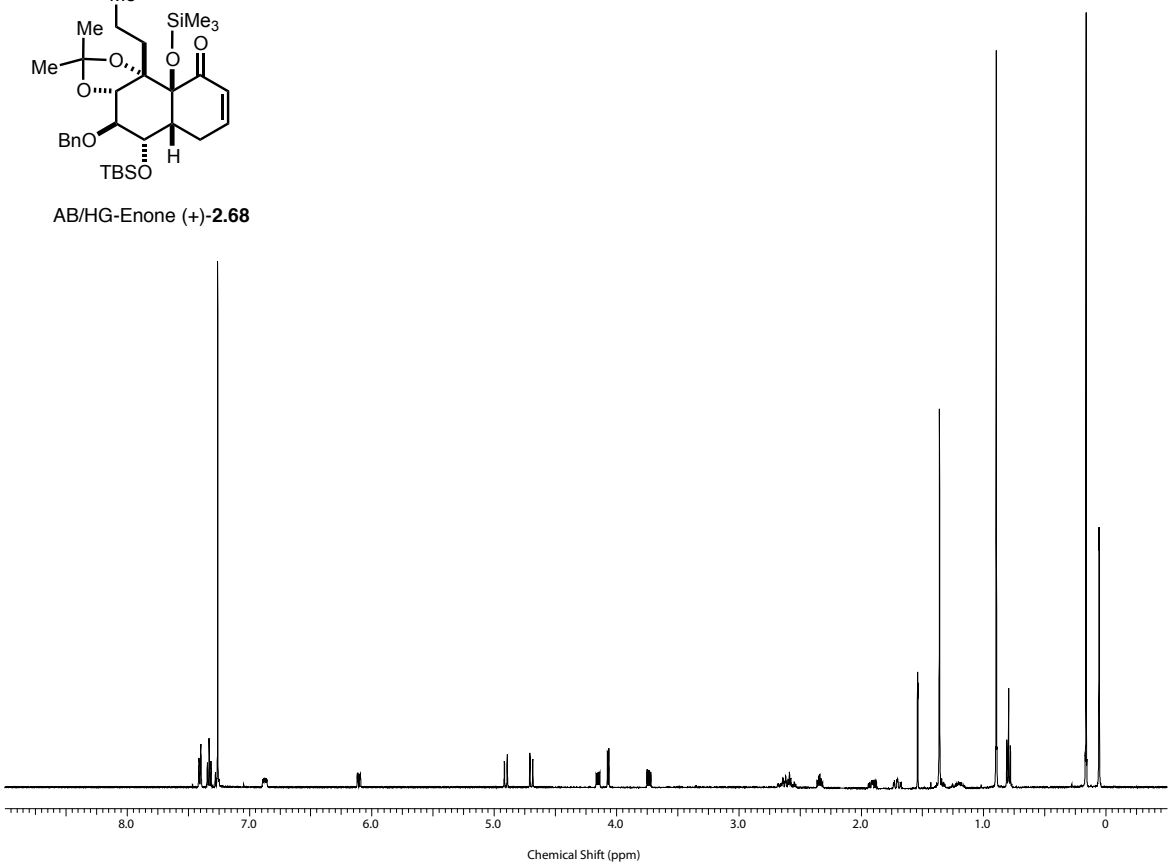

Me
Me
Me
O
O
H
O
O
BnO
H
TBSO

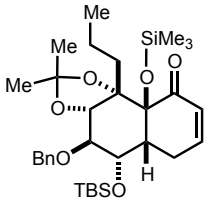
(+)-**2.119**


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

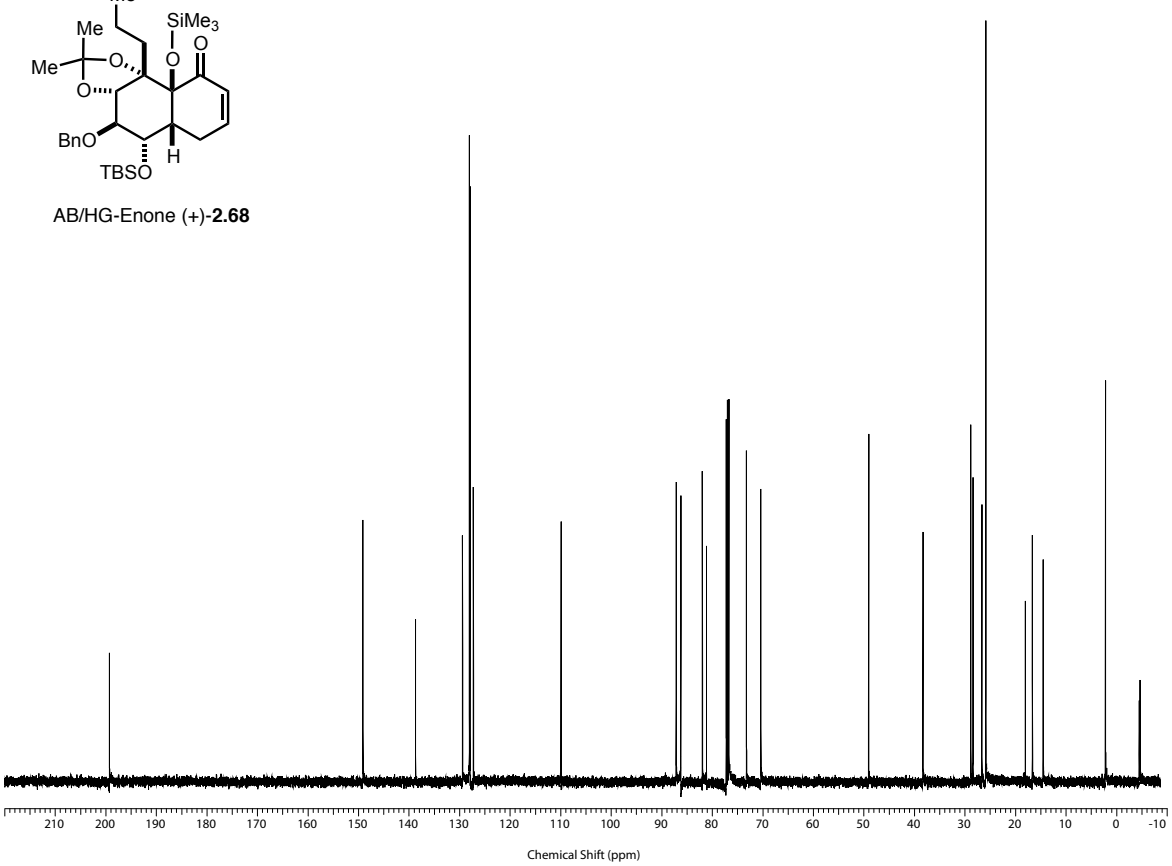


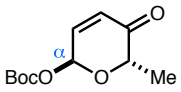
AB/HG-Enone (+)-**2.68**



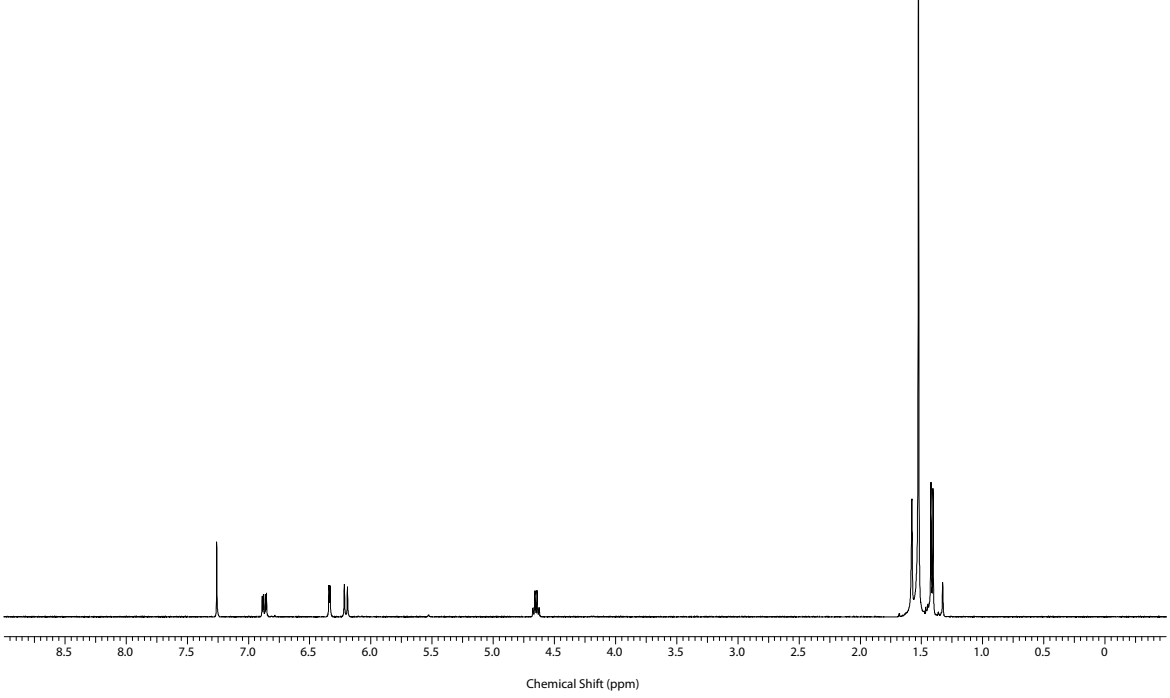


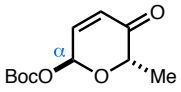
AB/HG-Enone (+)-**2.68**



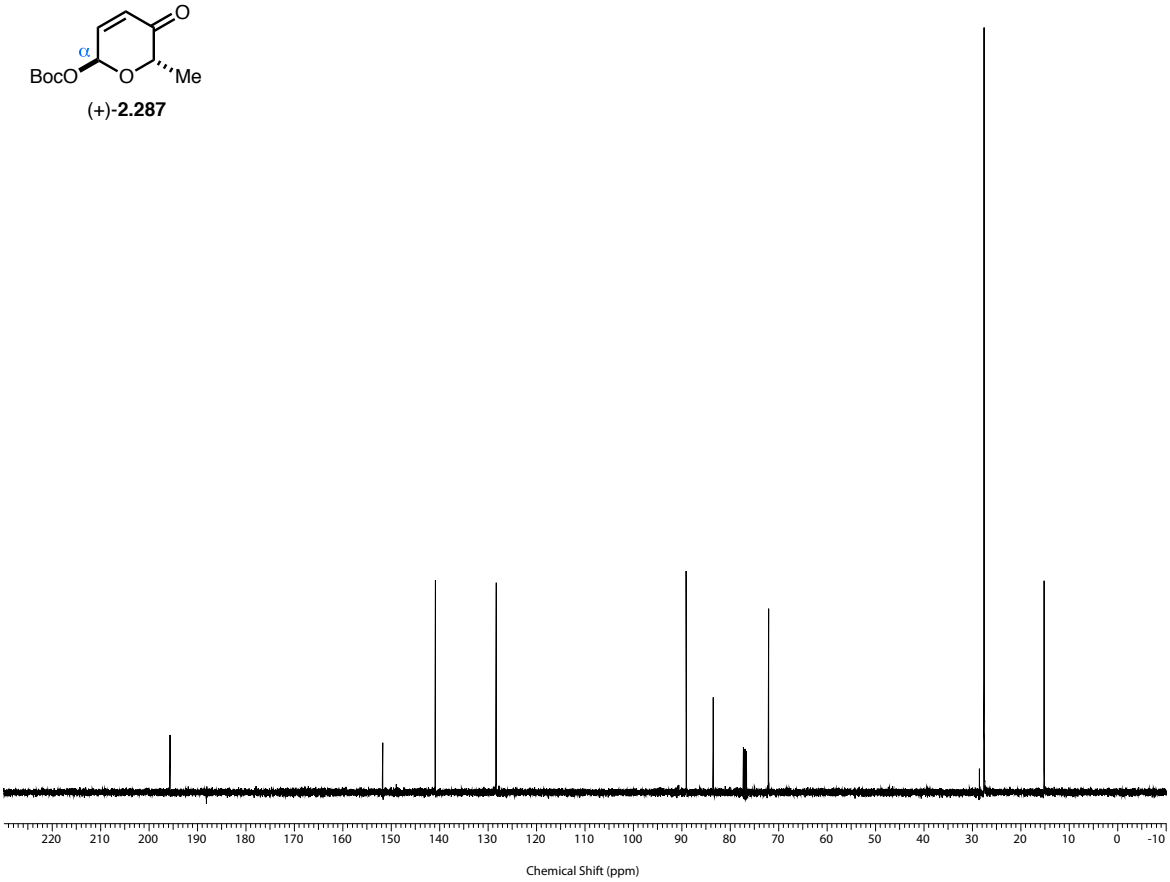

α
BocO
O
Me
O

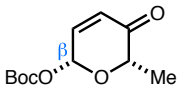
(+)-**2.287**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

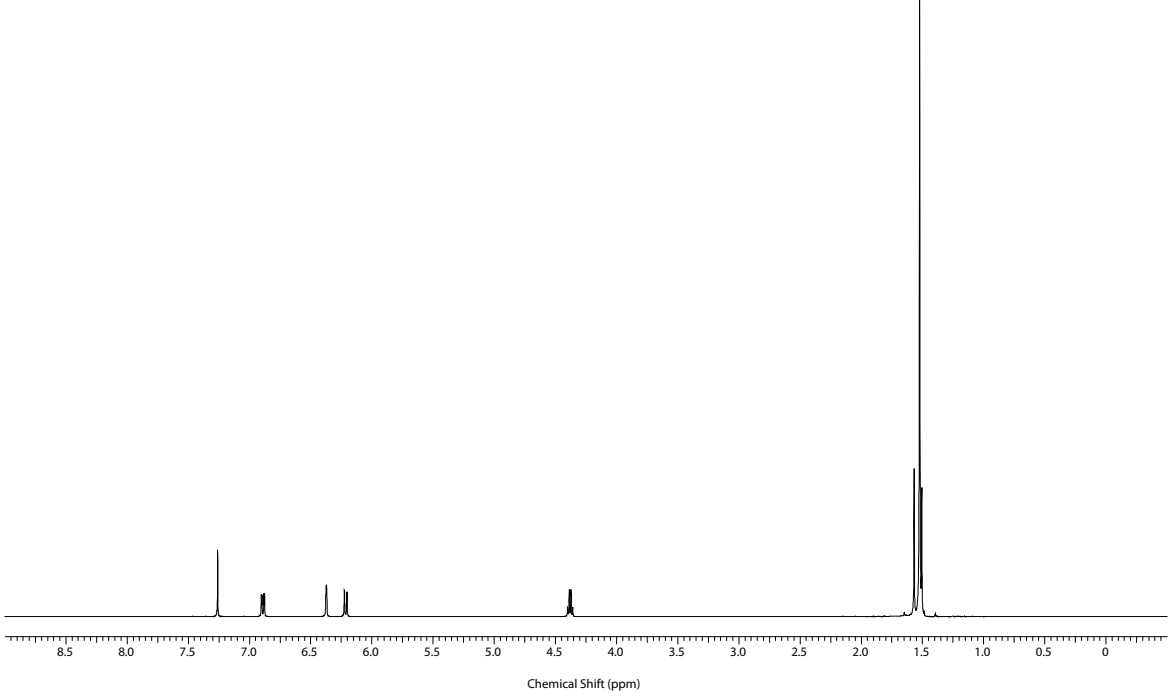

α
BocO
O
Me
O

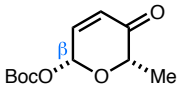
(+)-**2.287**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

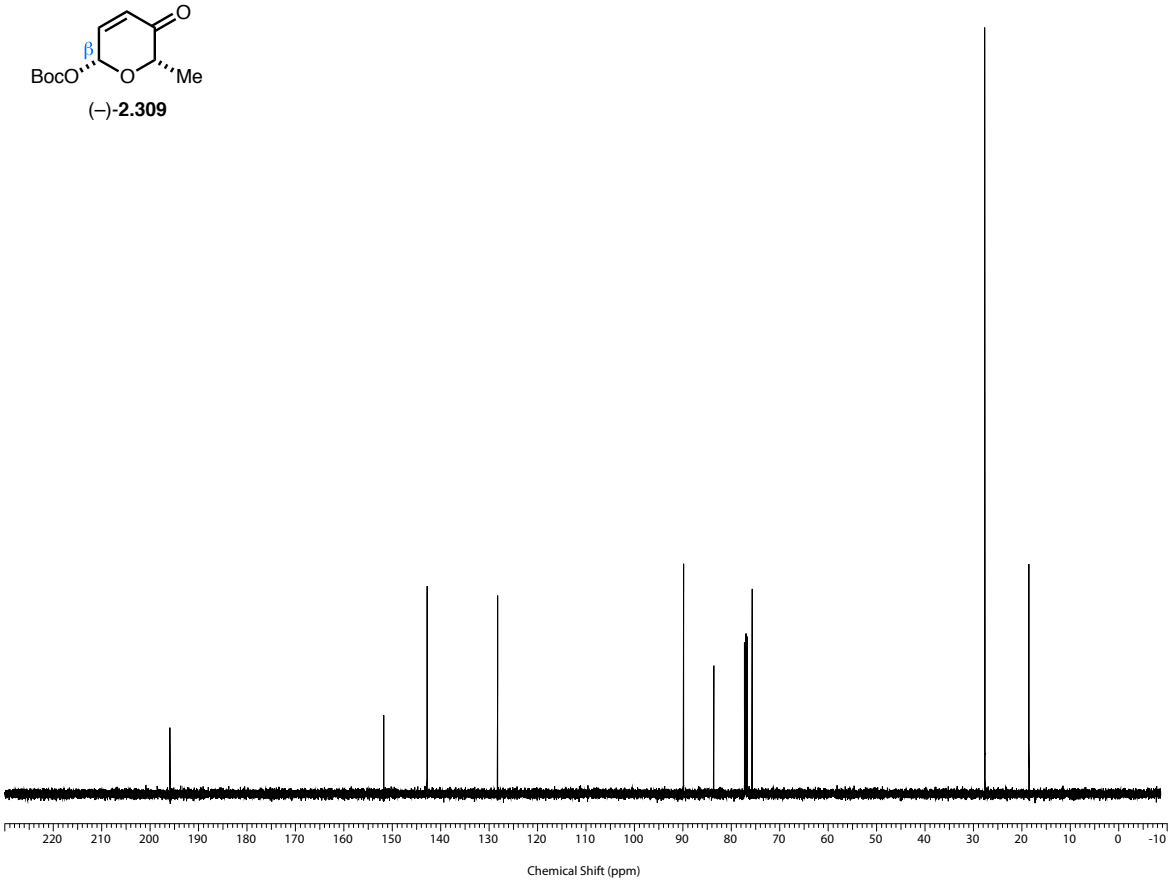

O
β
BocO
O
Me

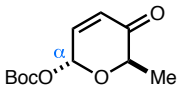
(–)-**2.309**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

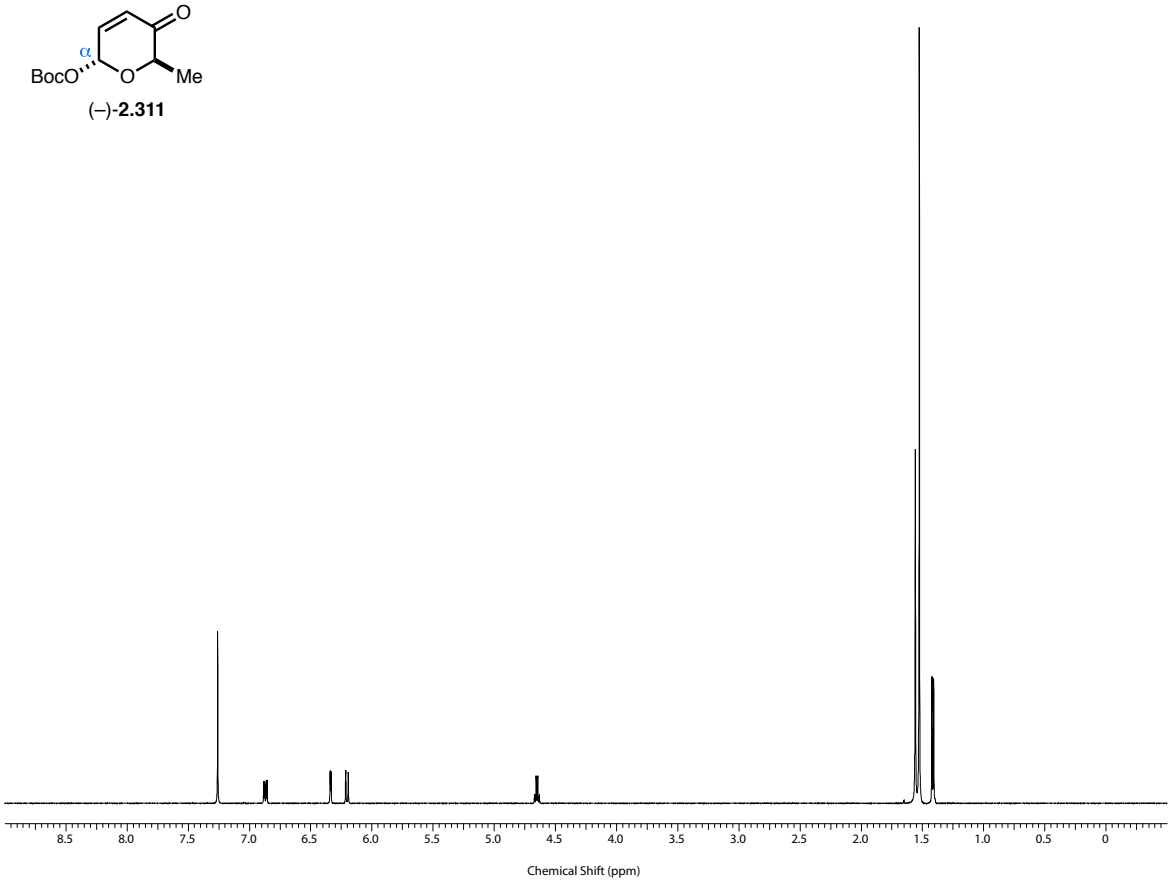

O
β
BocO
O
Me

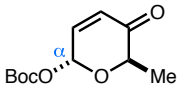
(–)-**2.309**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

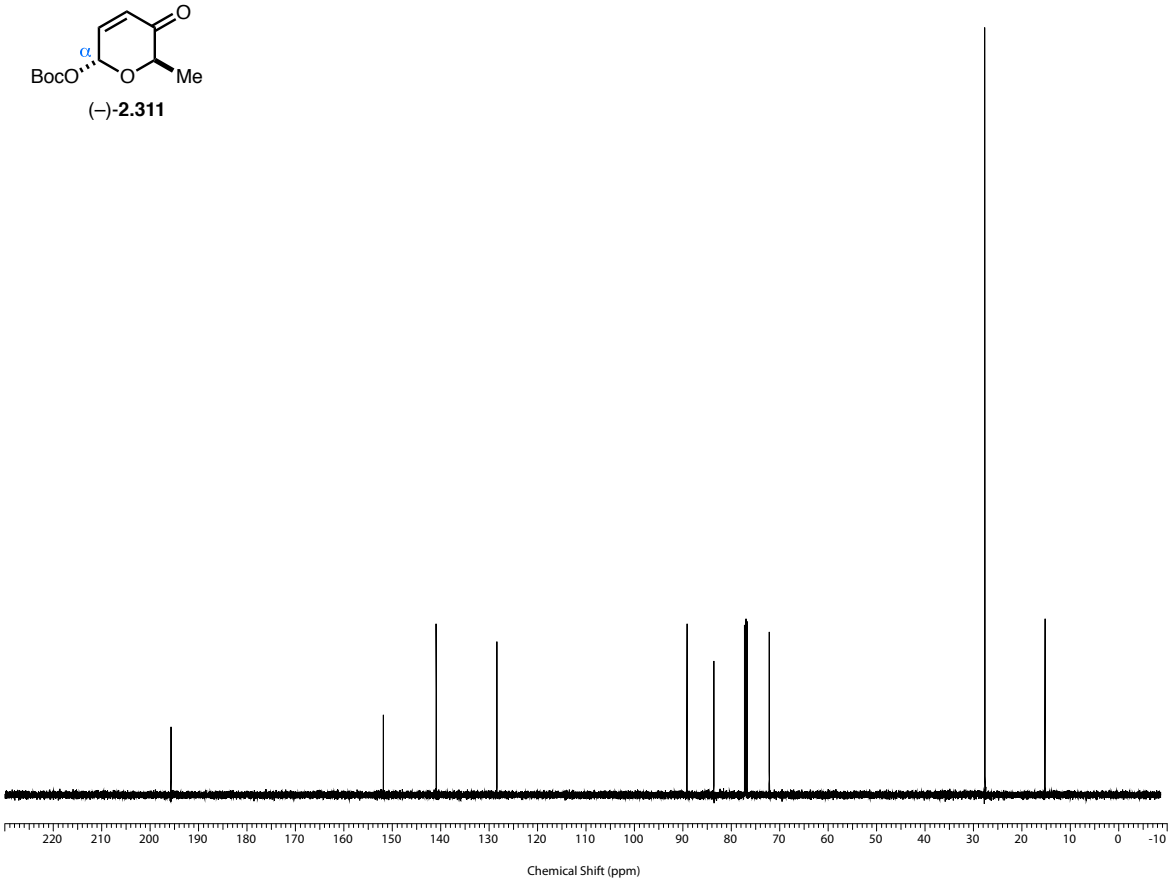

α
BocO
O
Me
O

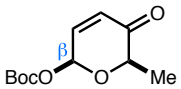
(–)-**2.311**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

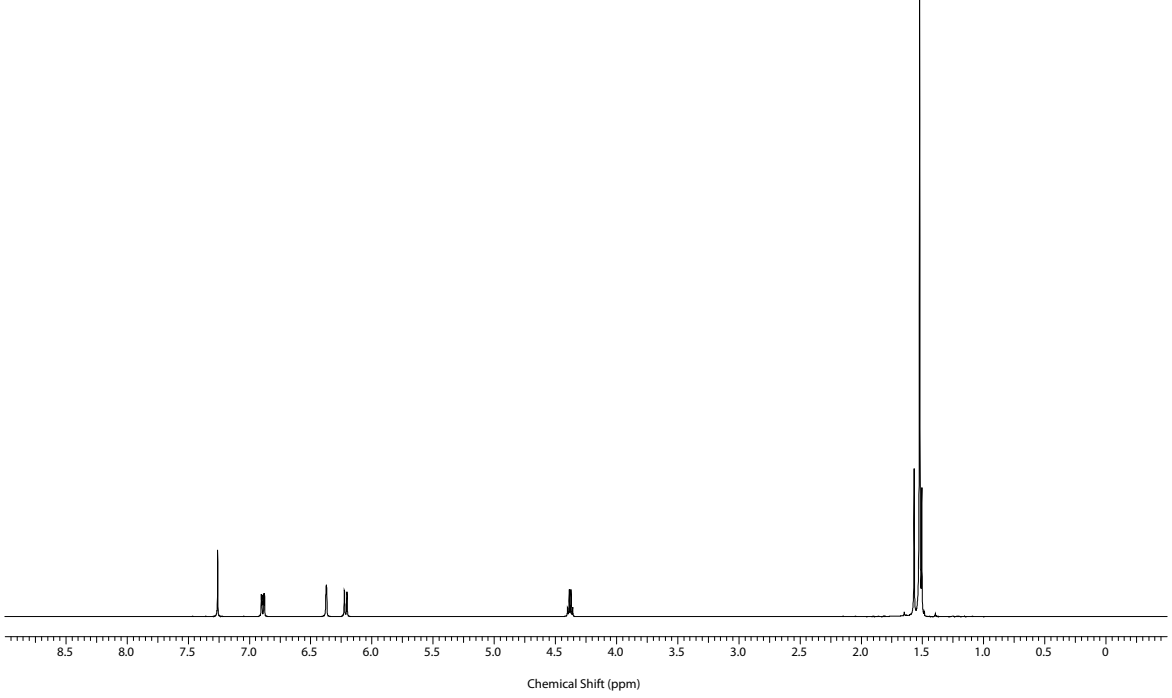

α
BocO
O
Me
O

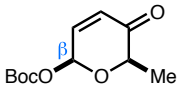
(–)-**2.311**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

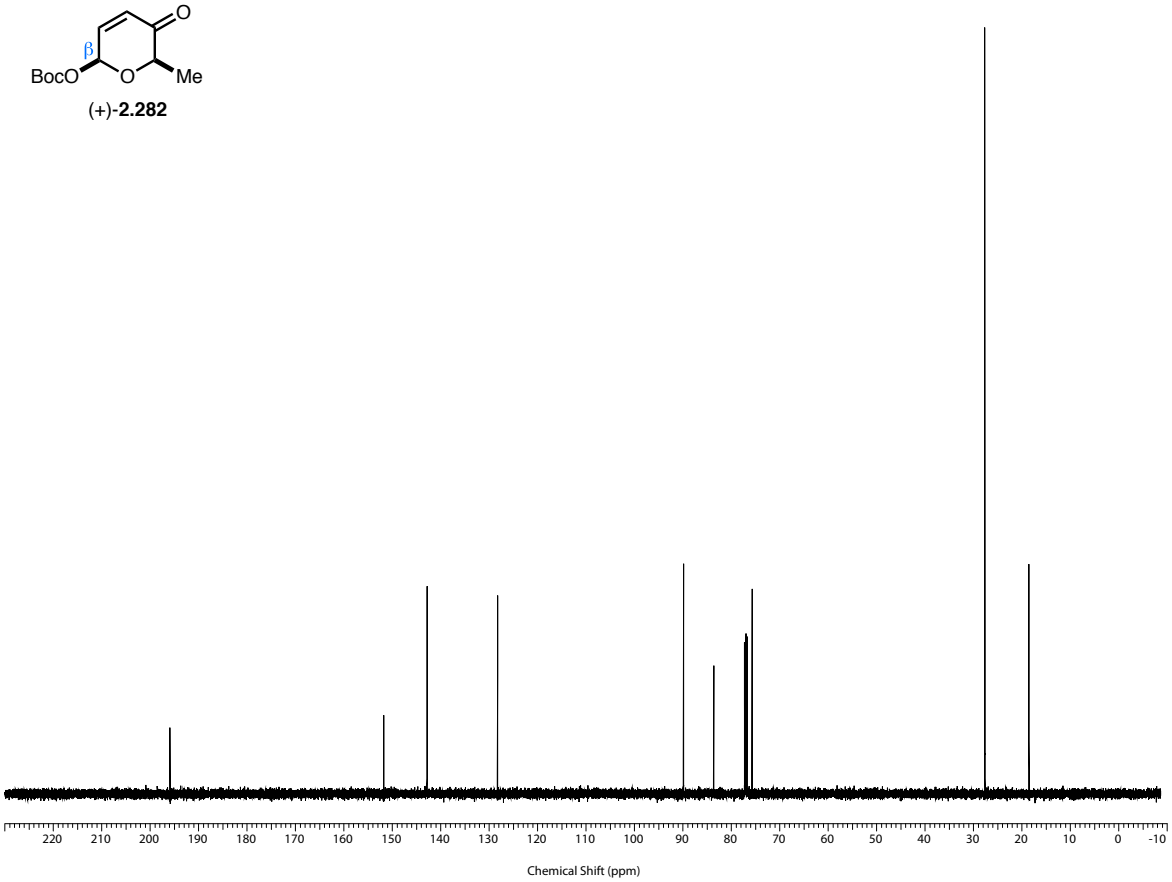

O
β
BocO
O
Me

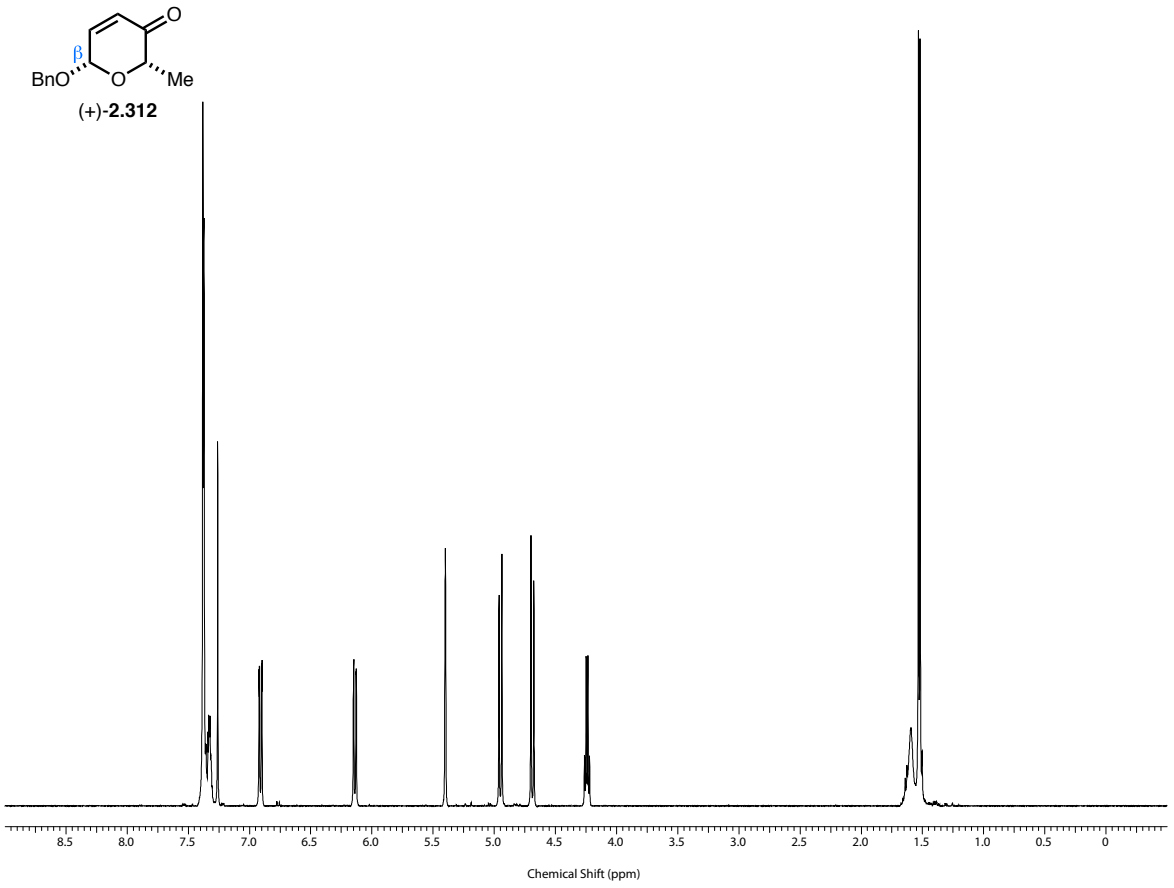
(+)-**2.282**

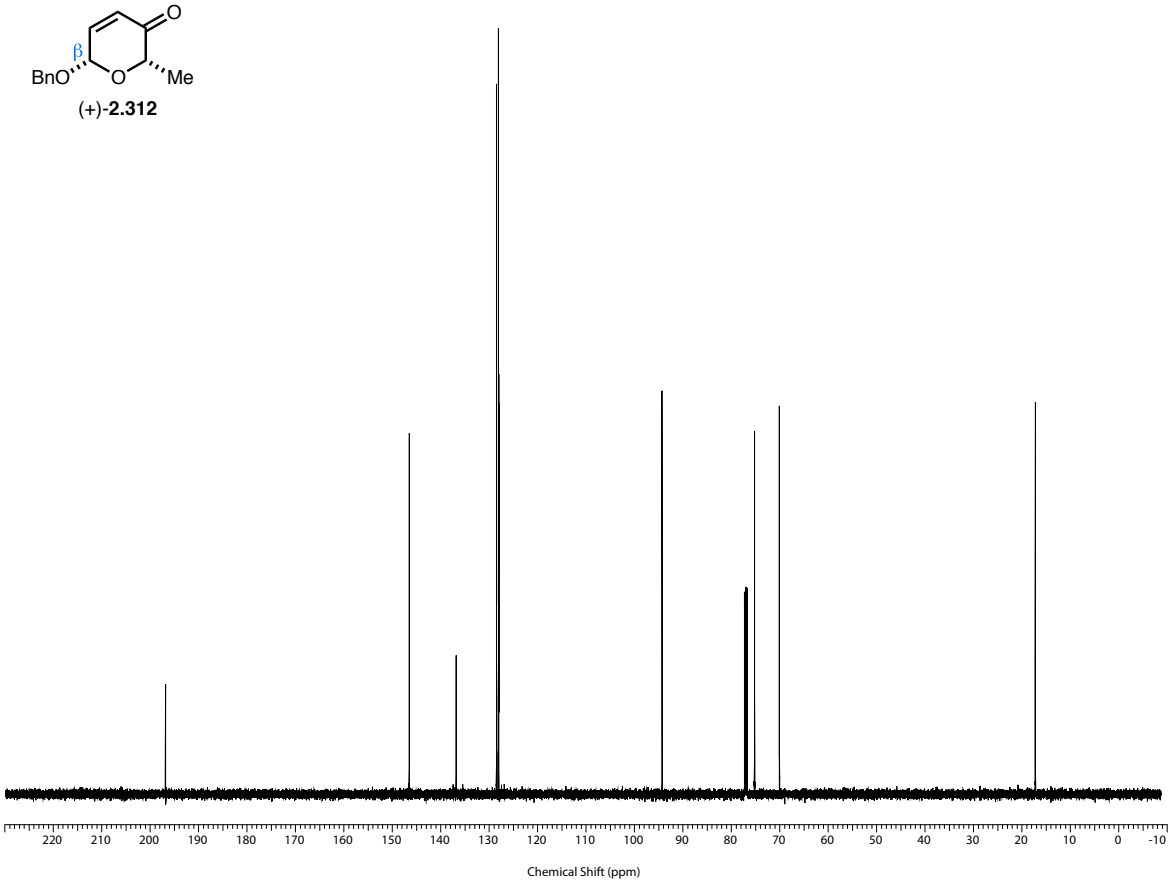

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

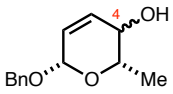

O
β
BocO
O
Me

(+)-**2.282**

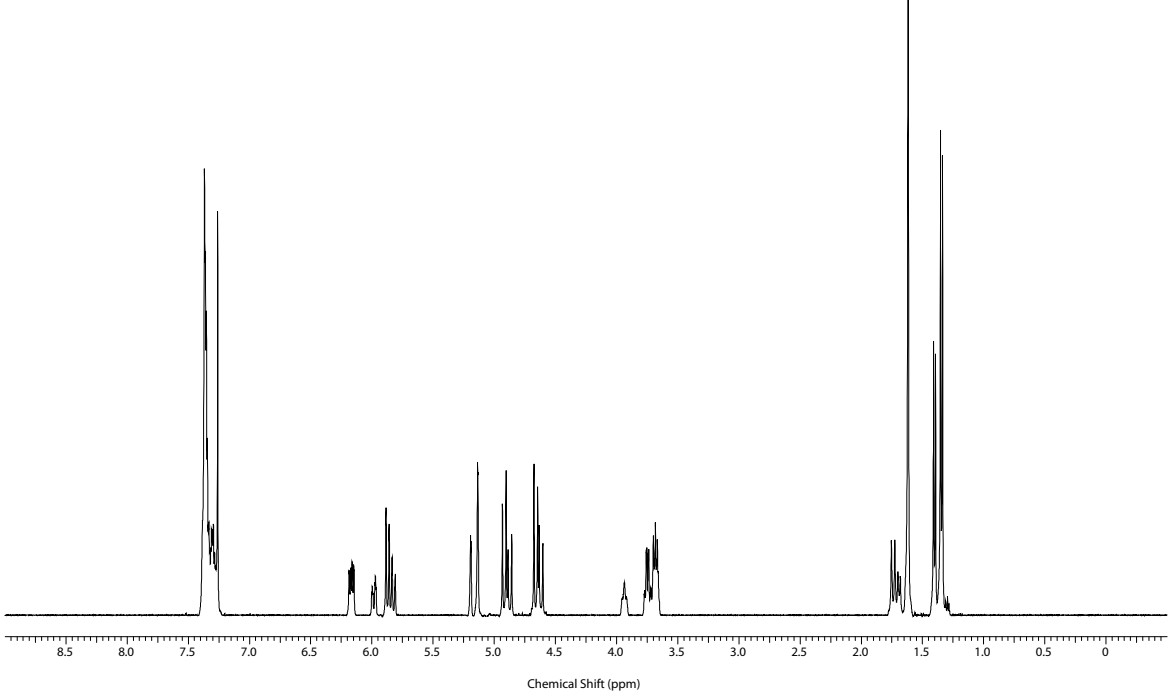

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

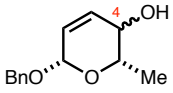

O
β
BnO
O
Me
(+)-2.312
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
β
BnO
O
Me
(+)-2.312
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

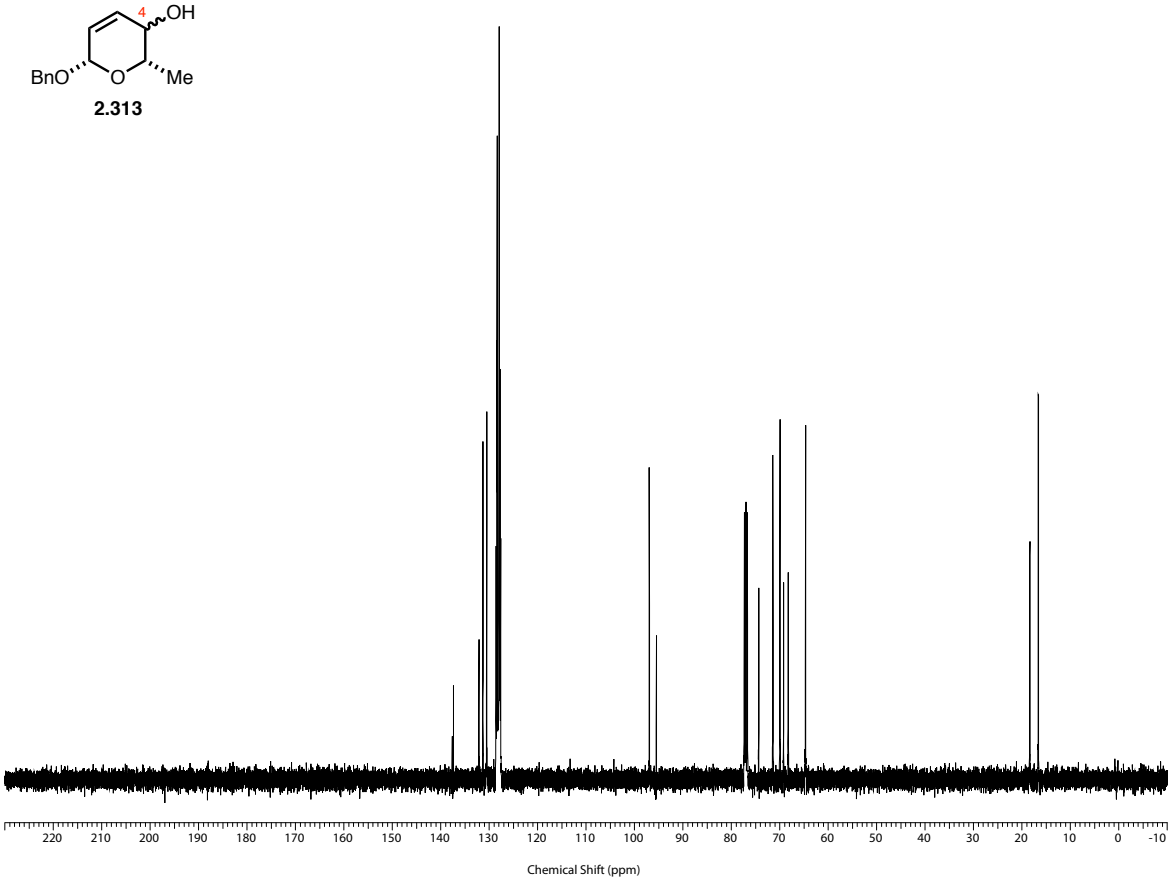

4
OH
BnO
O
Me

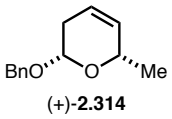
2.313


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

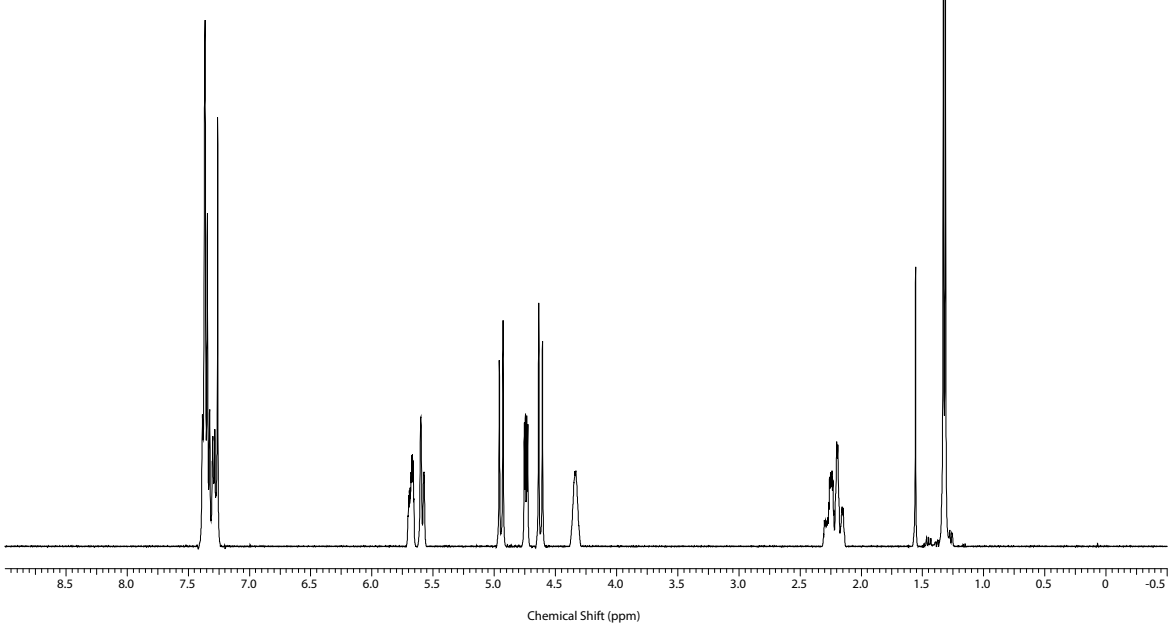

4
OH
BnO
O
Me

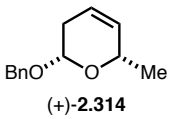
2.313


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

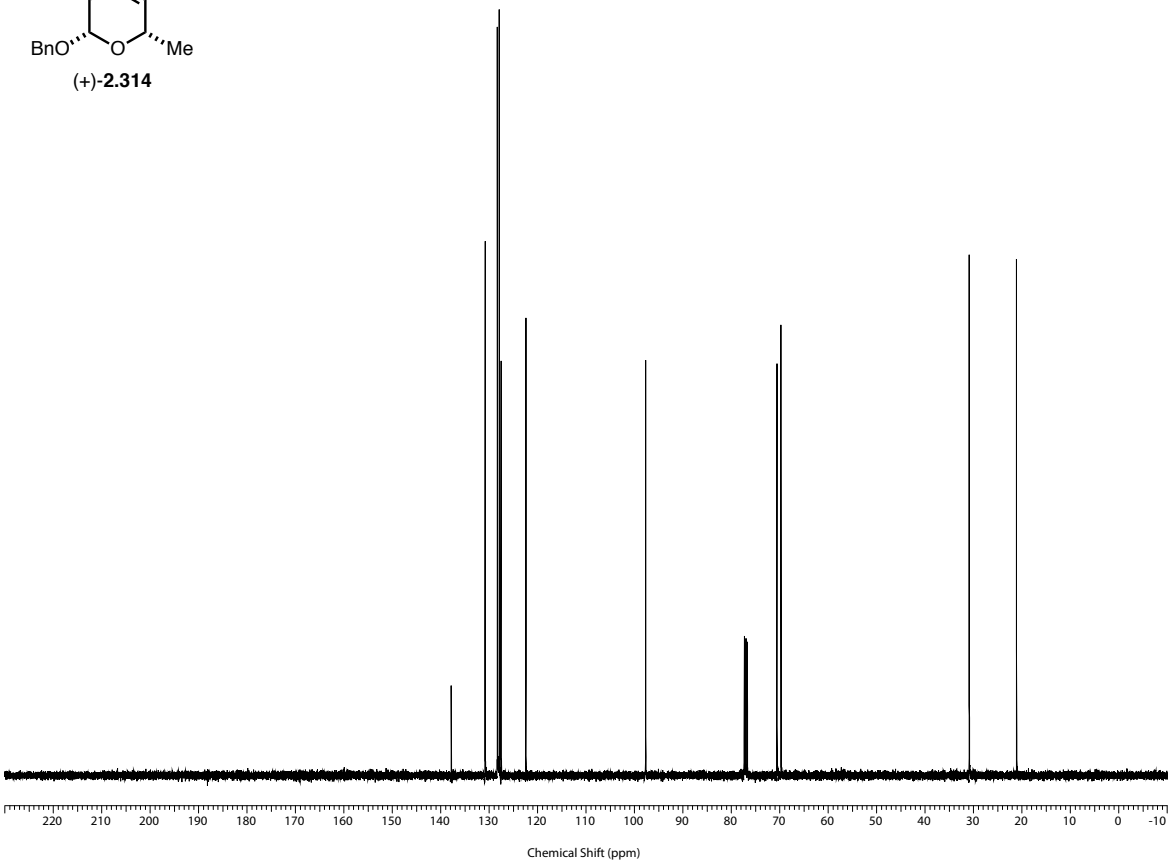

BnO
O
Me

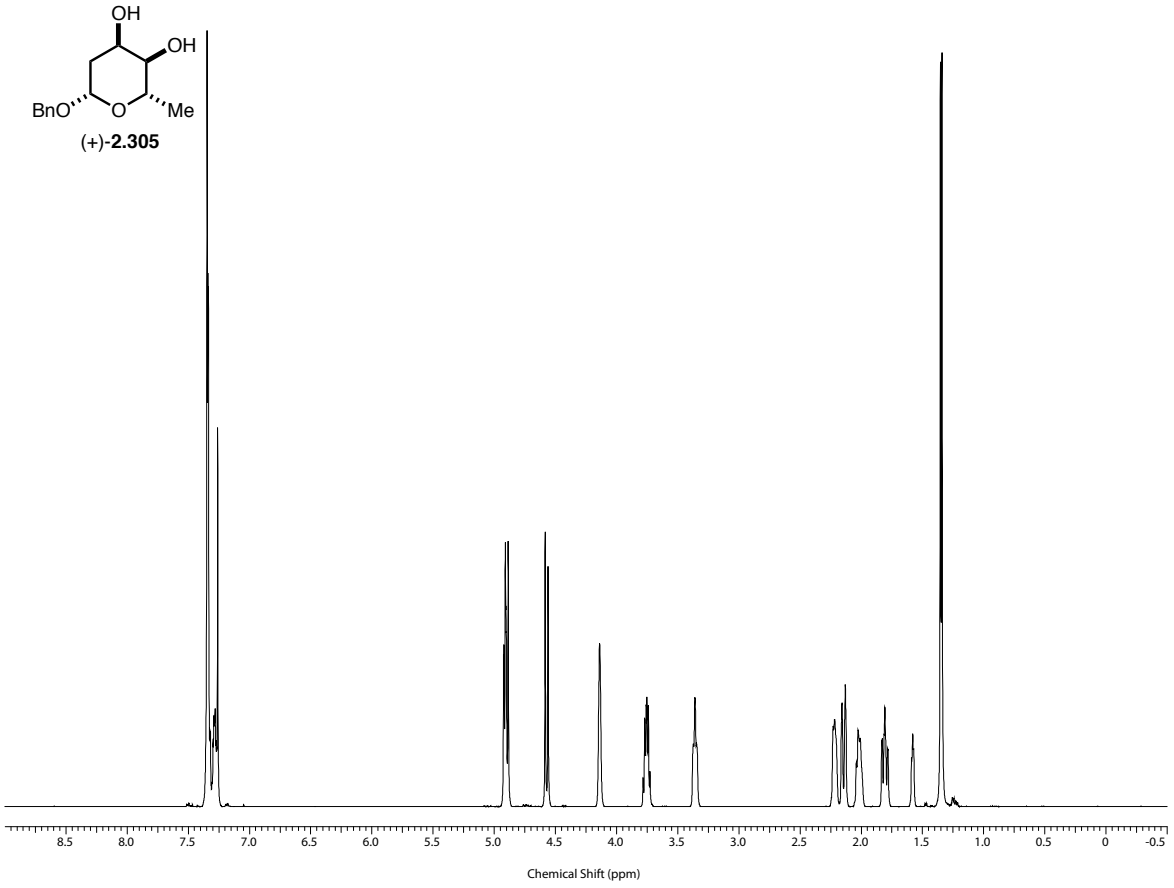
(+)-**2.314**

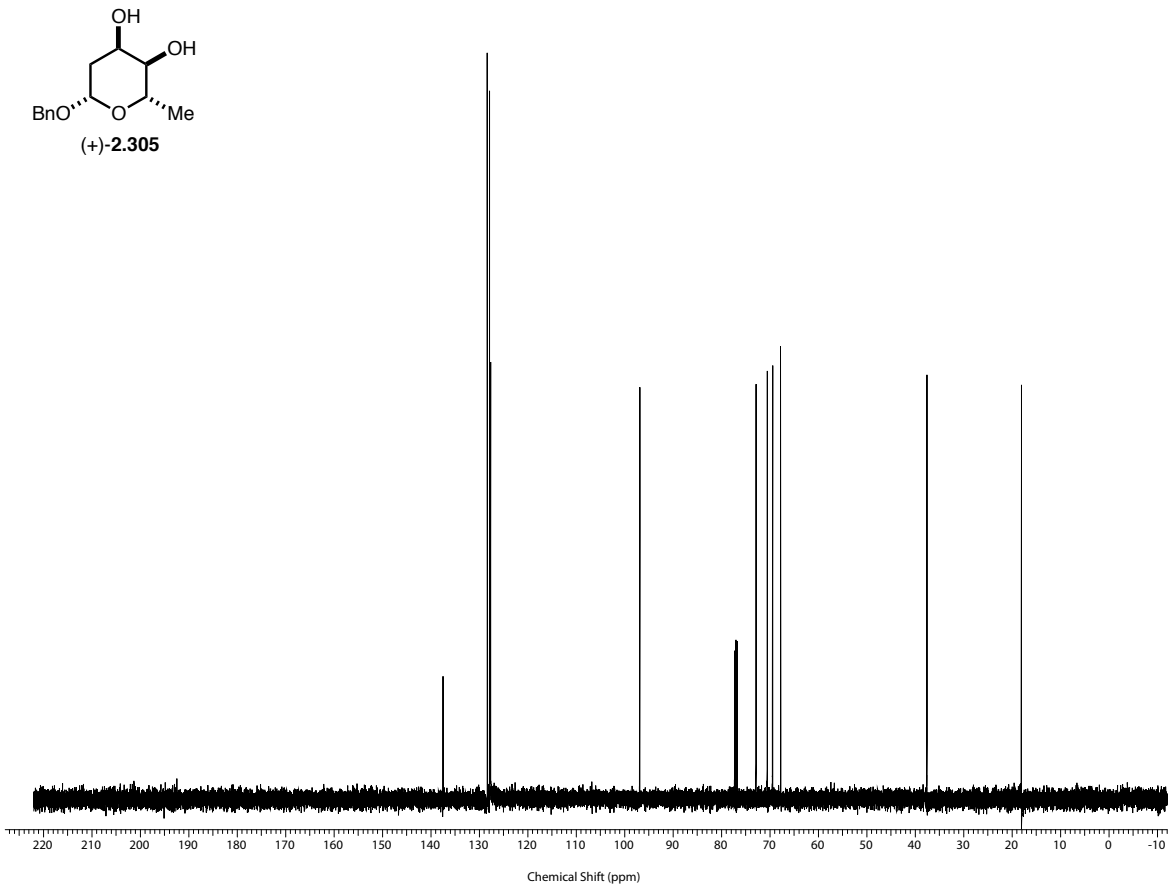

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

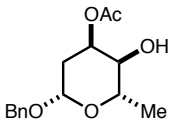

BnO
O
Me

(+)-**2.314**

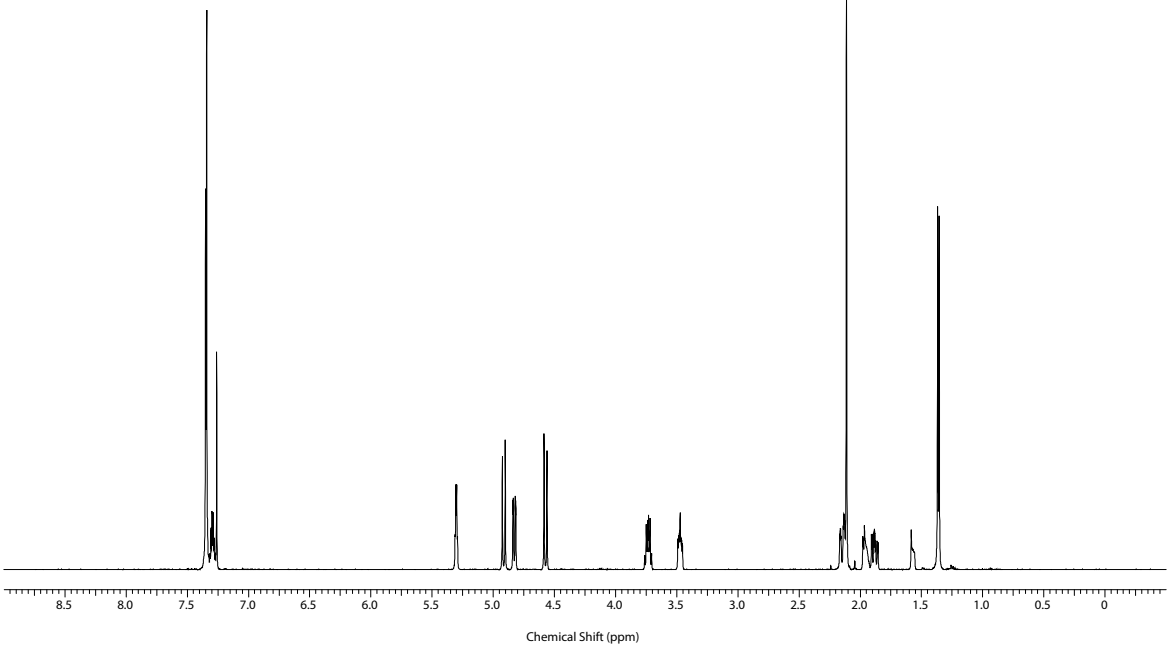

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

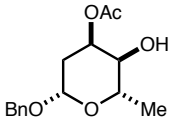

OH
OH
BnO
O
Me
(+)-2.305
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


OH
OH
BnO
O
Me
(+)-2.305
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

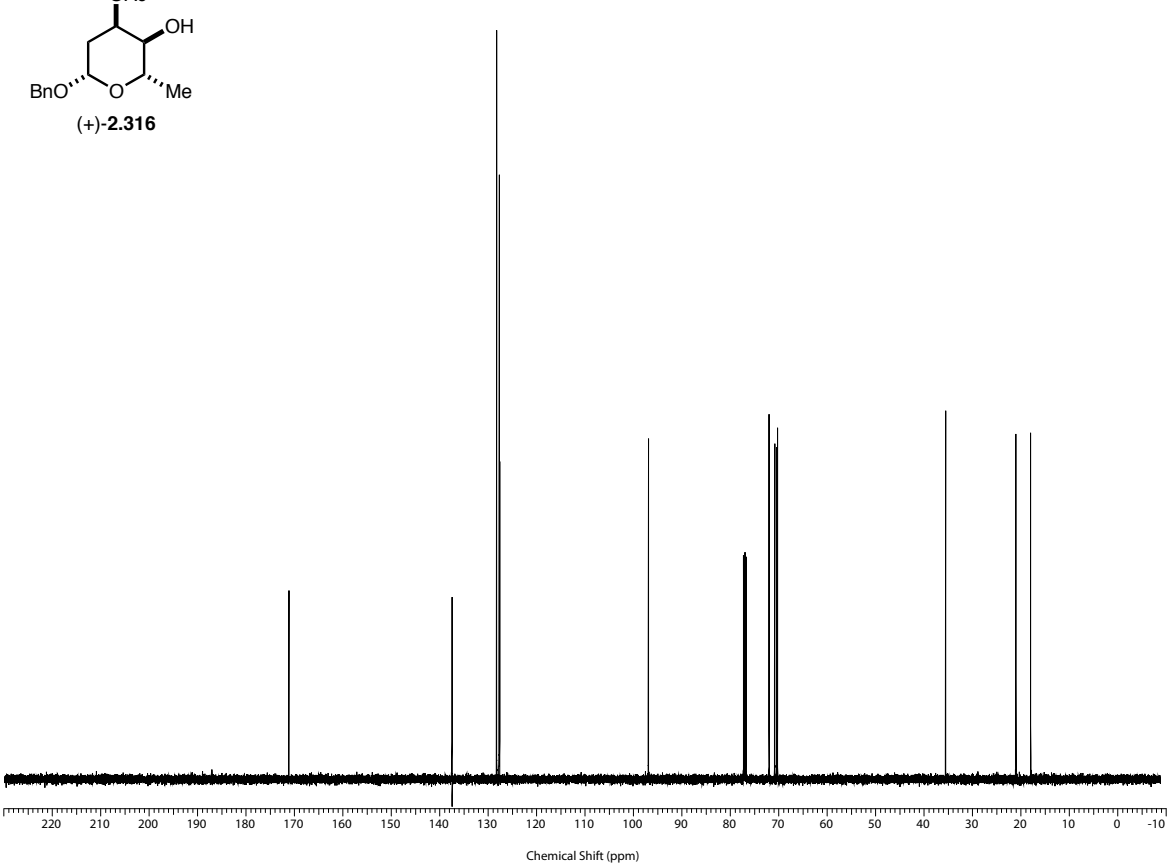

OAc
OH
BnO
O
Me

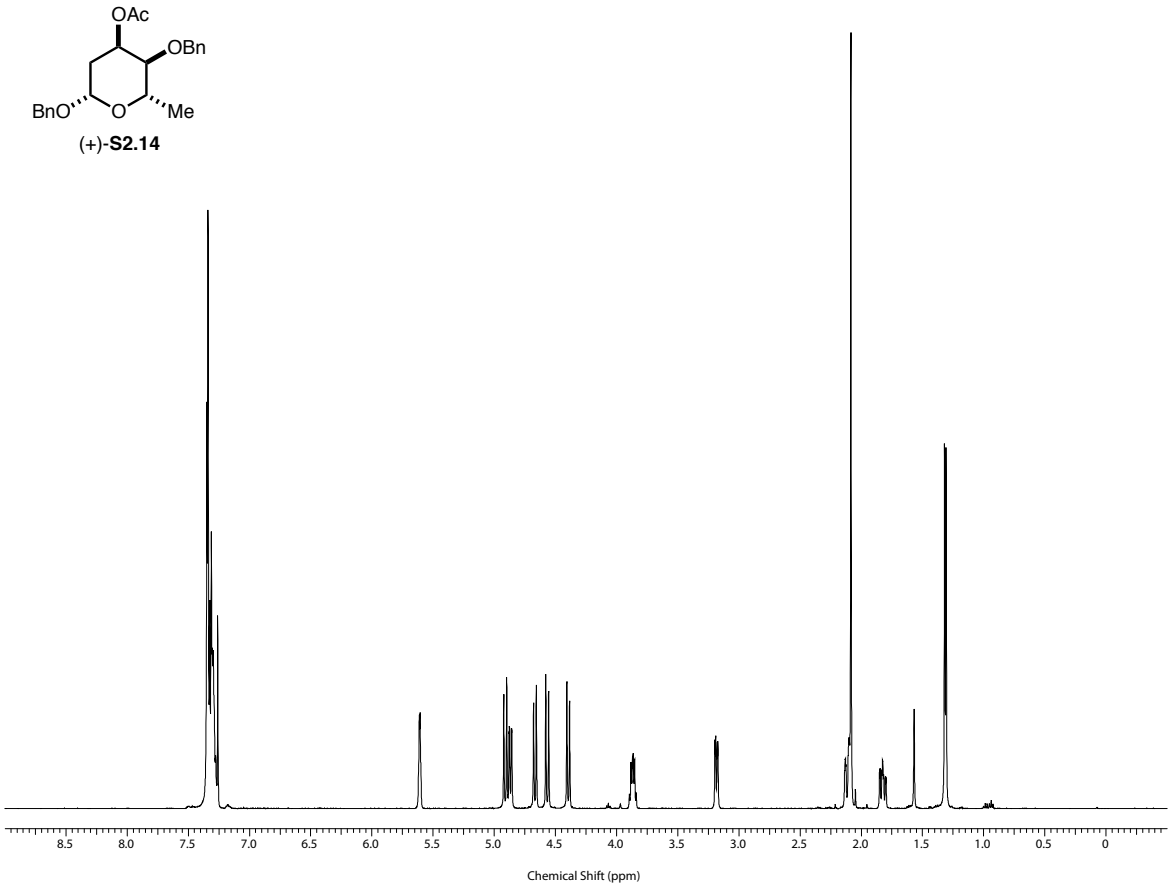
(+)-**2.316**

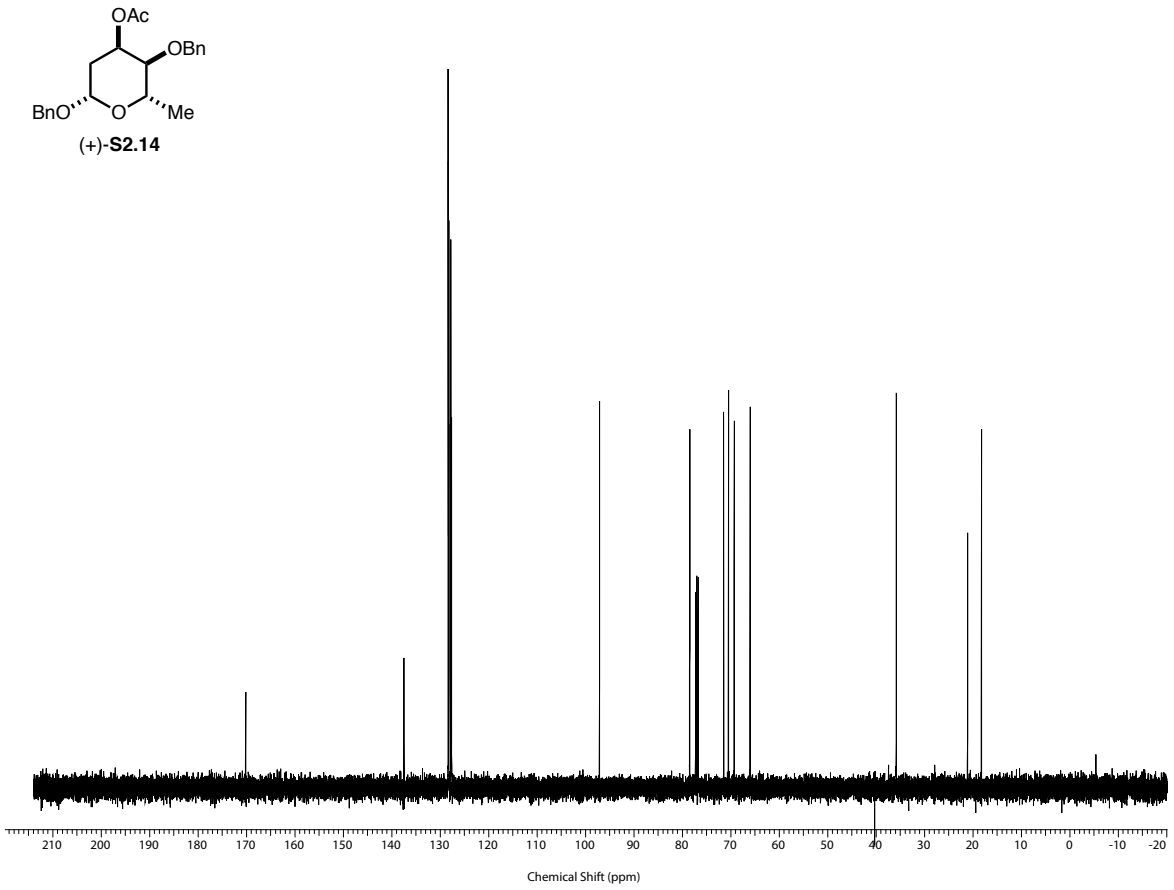

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

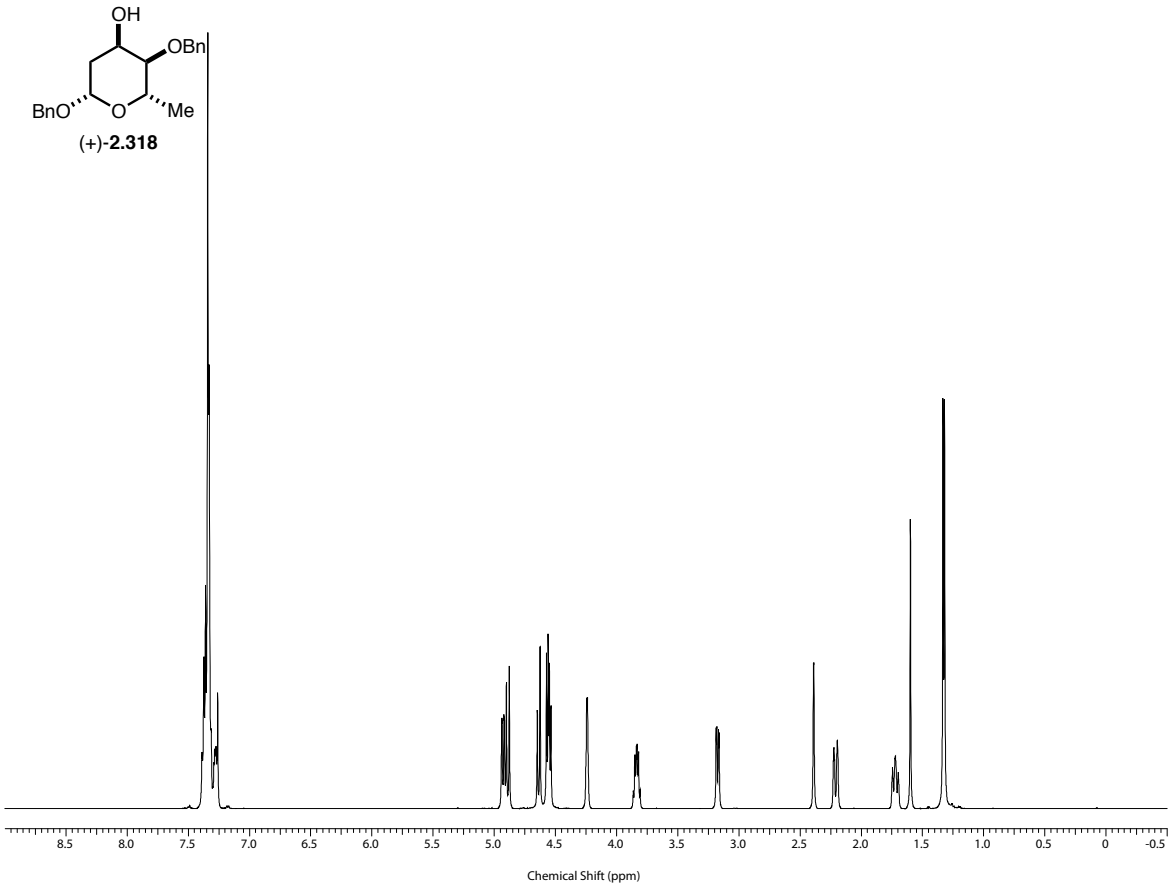

OAc
OH
BnO
O
Me

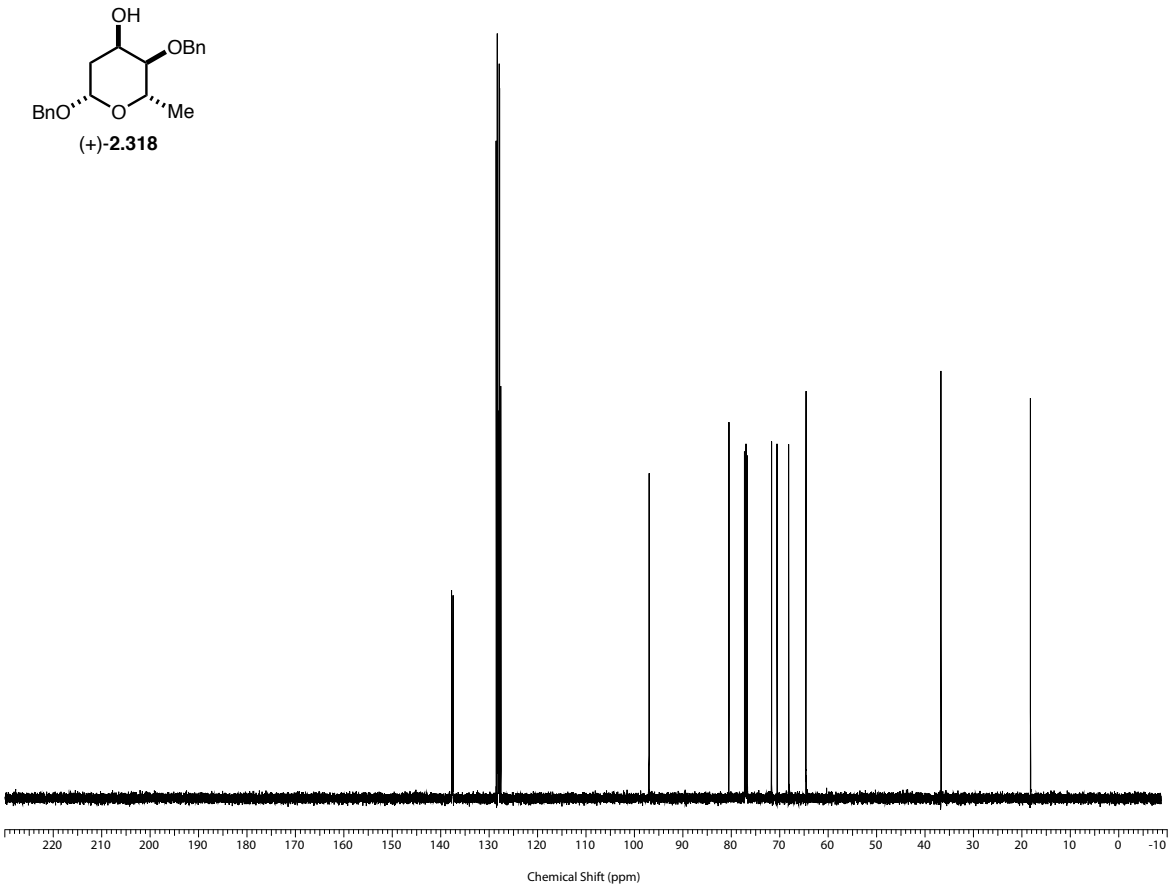
(+)-**2.316**

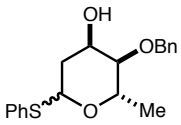

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OAc
OBn
BnO
O
Me
(+)-S2.14
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

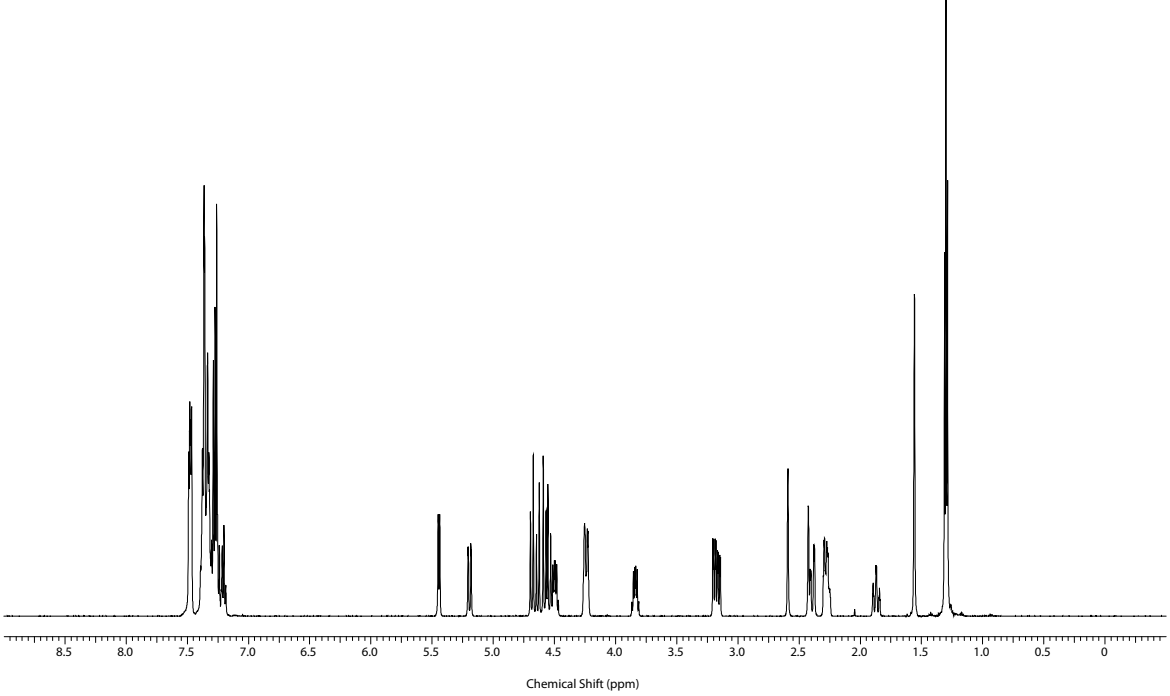

OAc
OBn
BnO
O
Me
(+)-S2.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

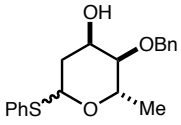

OH
OBn
BnO
O
Me
(+)-2.318
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


OH
OBn
BnO
O
Me
(+)-2.318
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

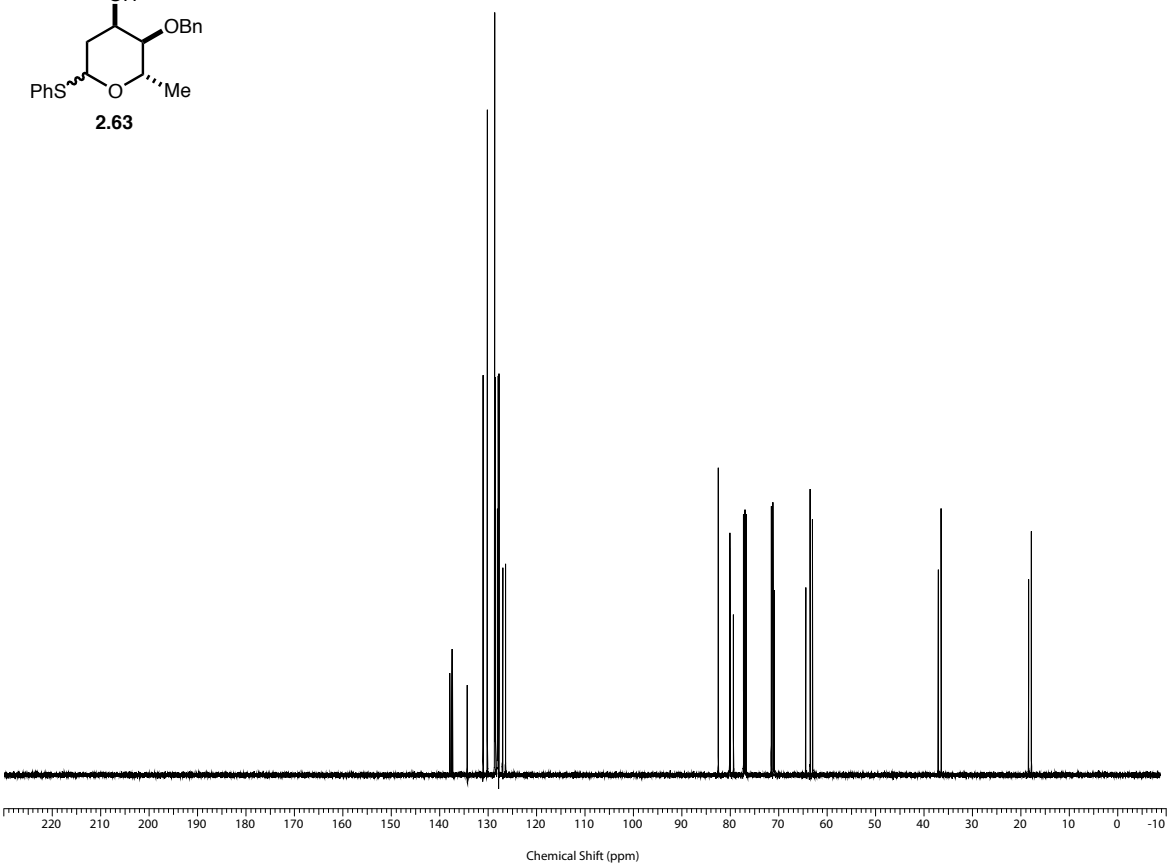

OH
OBn
PhS
O
Me

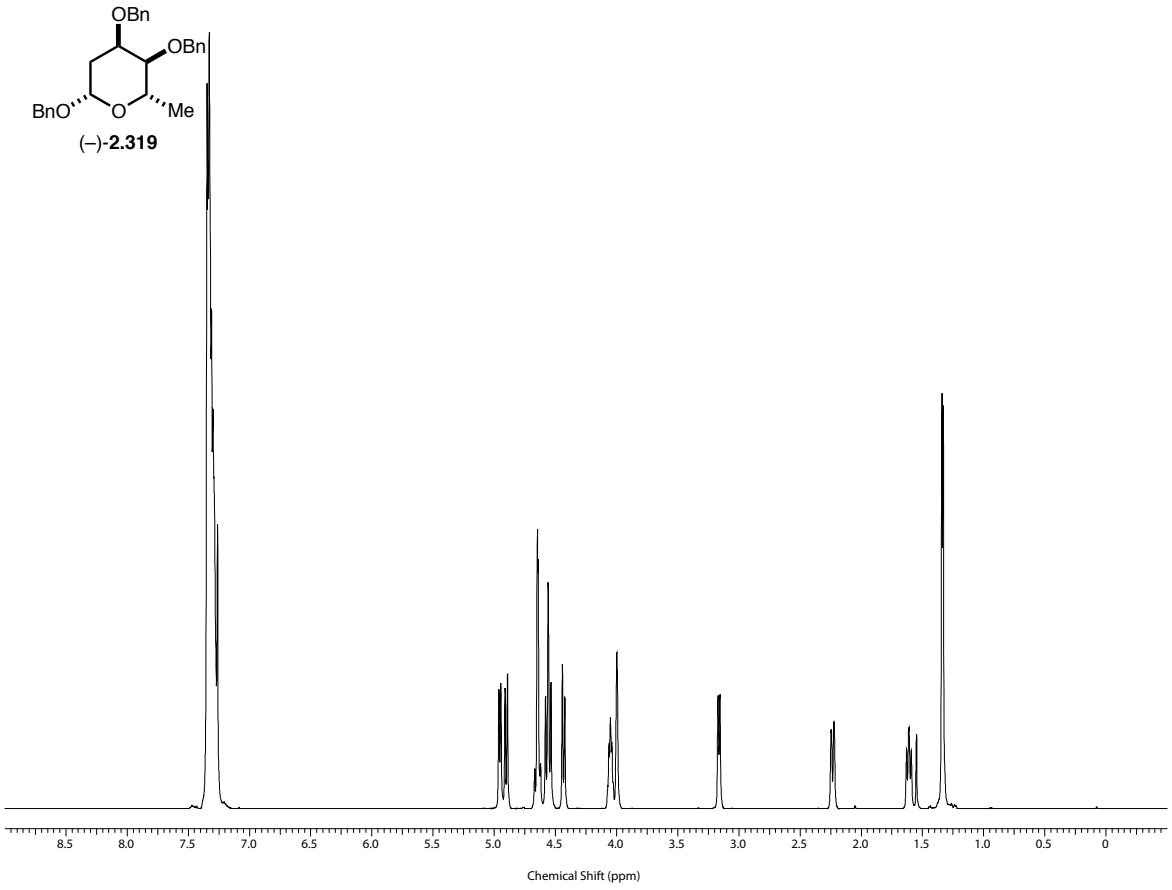
2.63

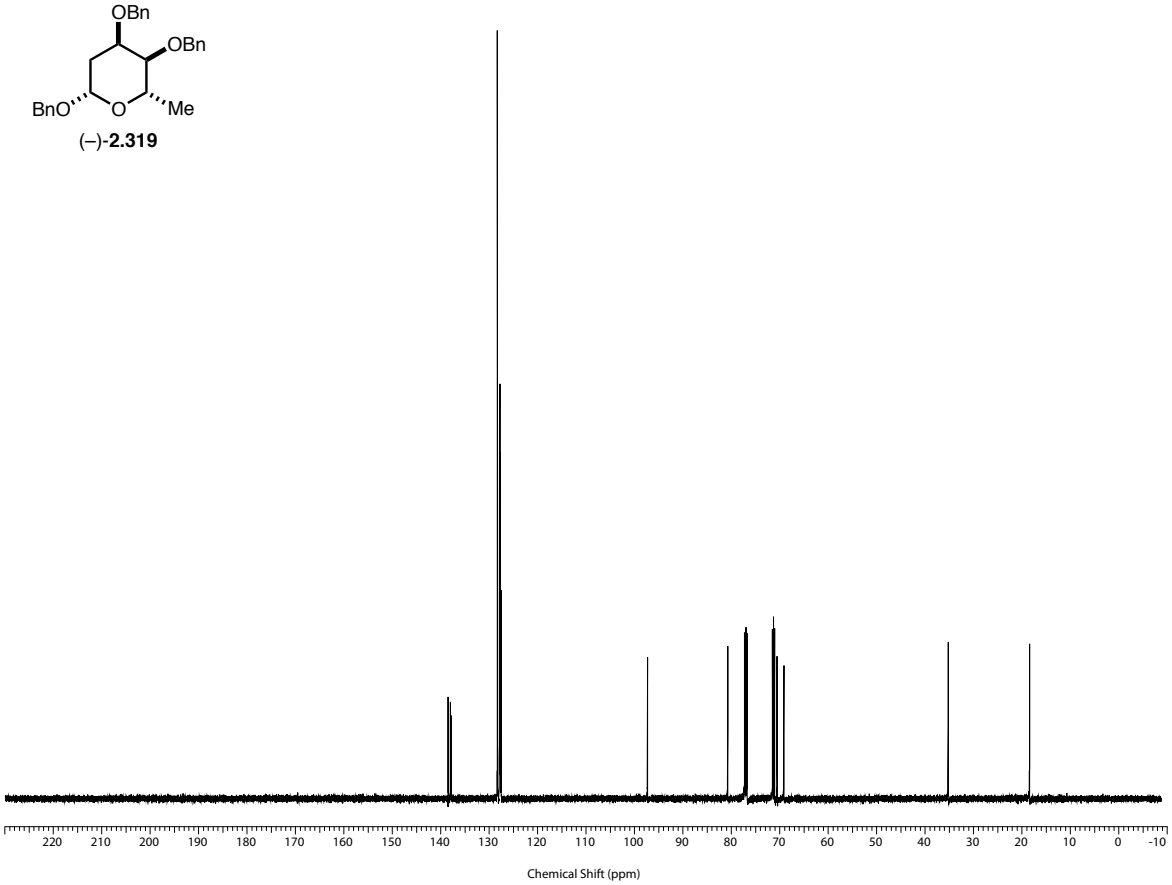

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

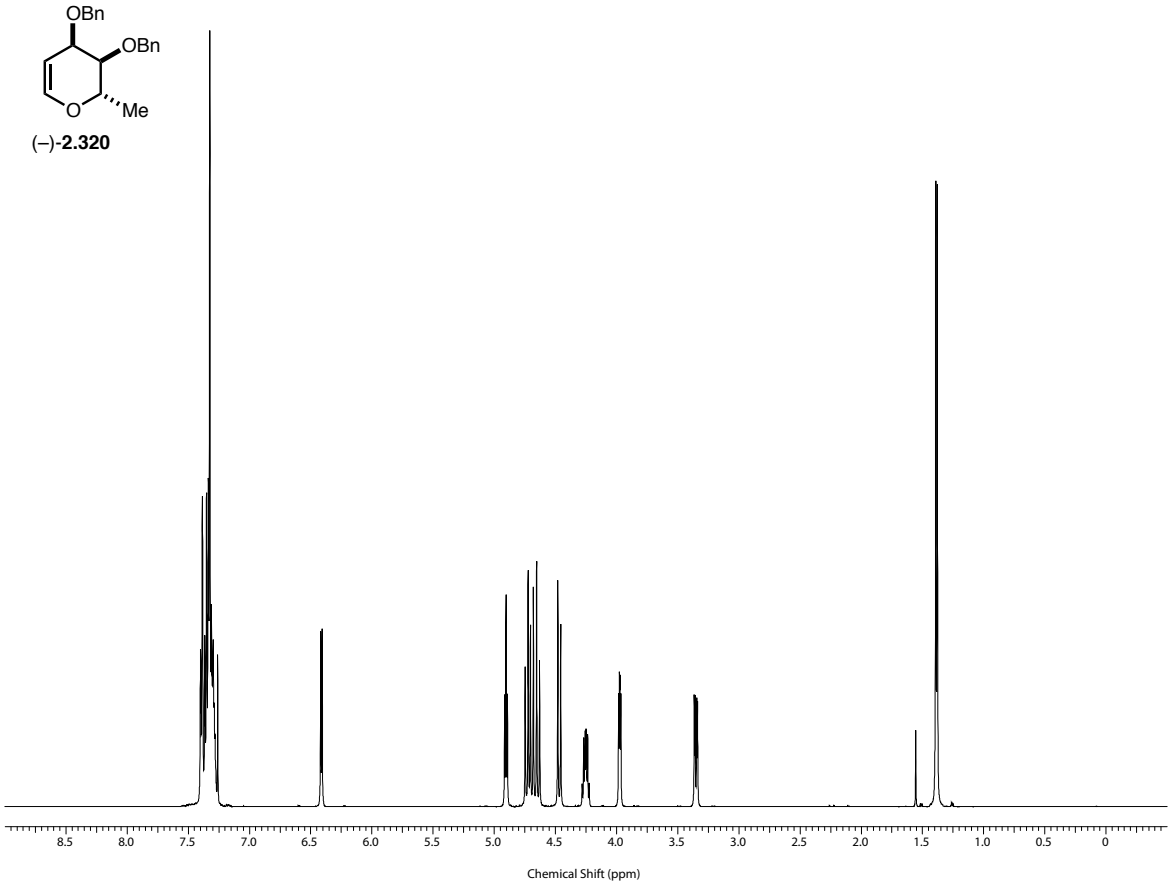

OH
OBn
PhS
O
Me

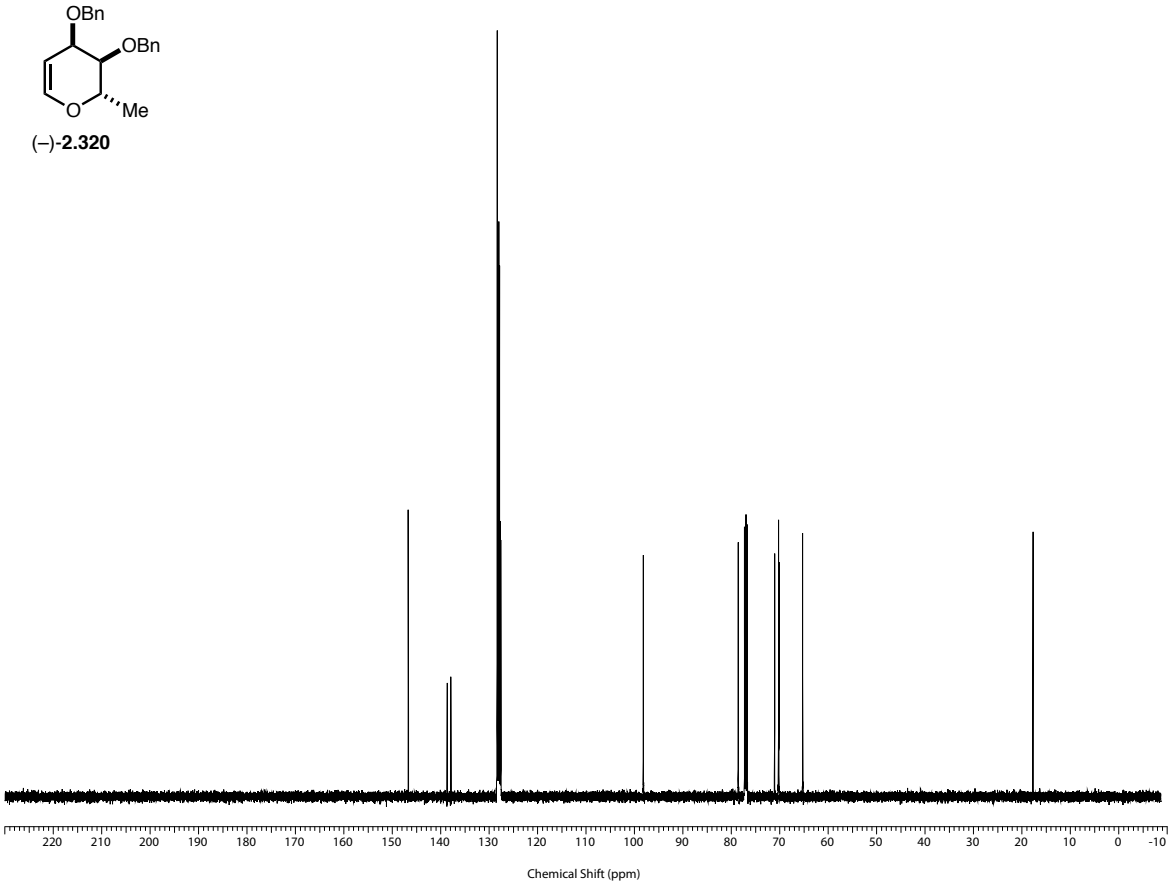
2.63

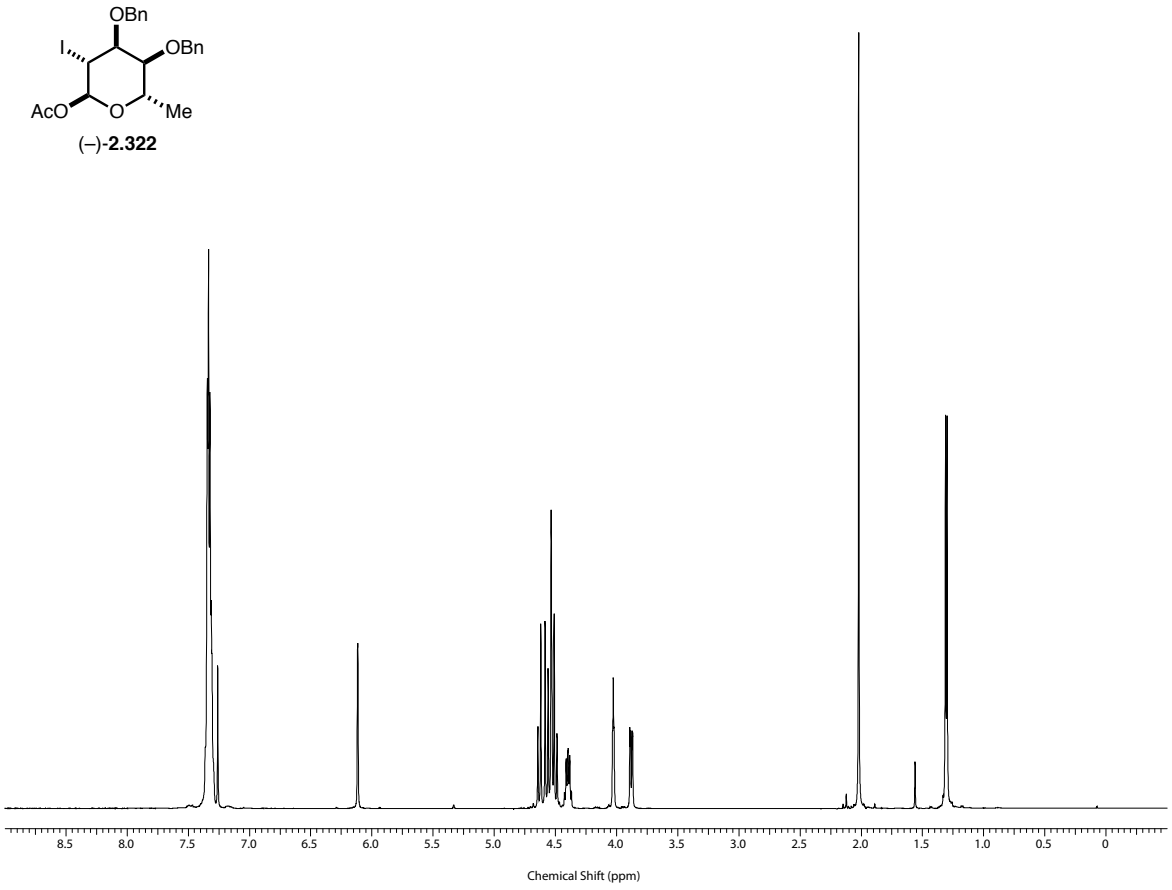

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

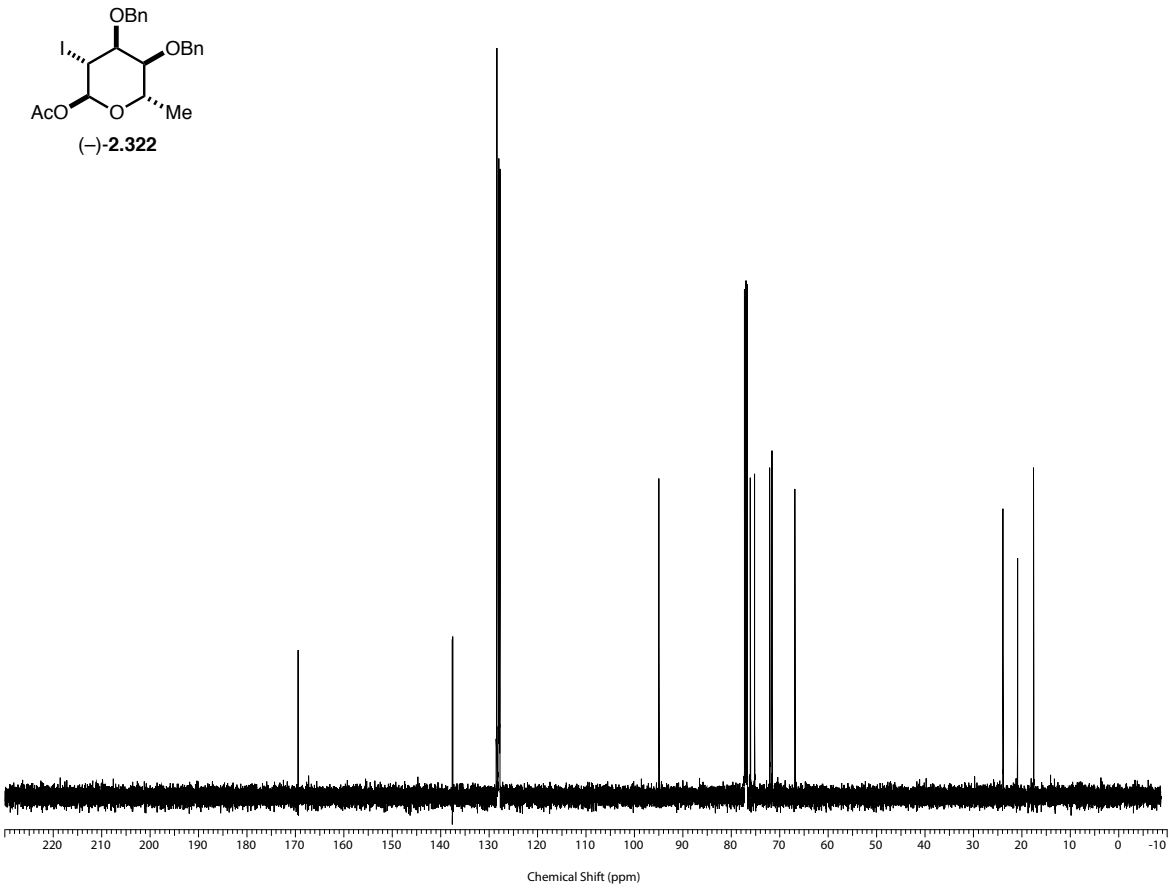

OBn
OBn
BnO
O
Me
(–)-2.319
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

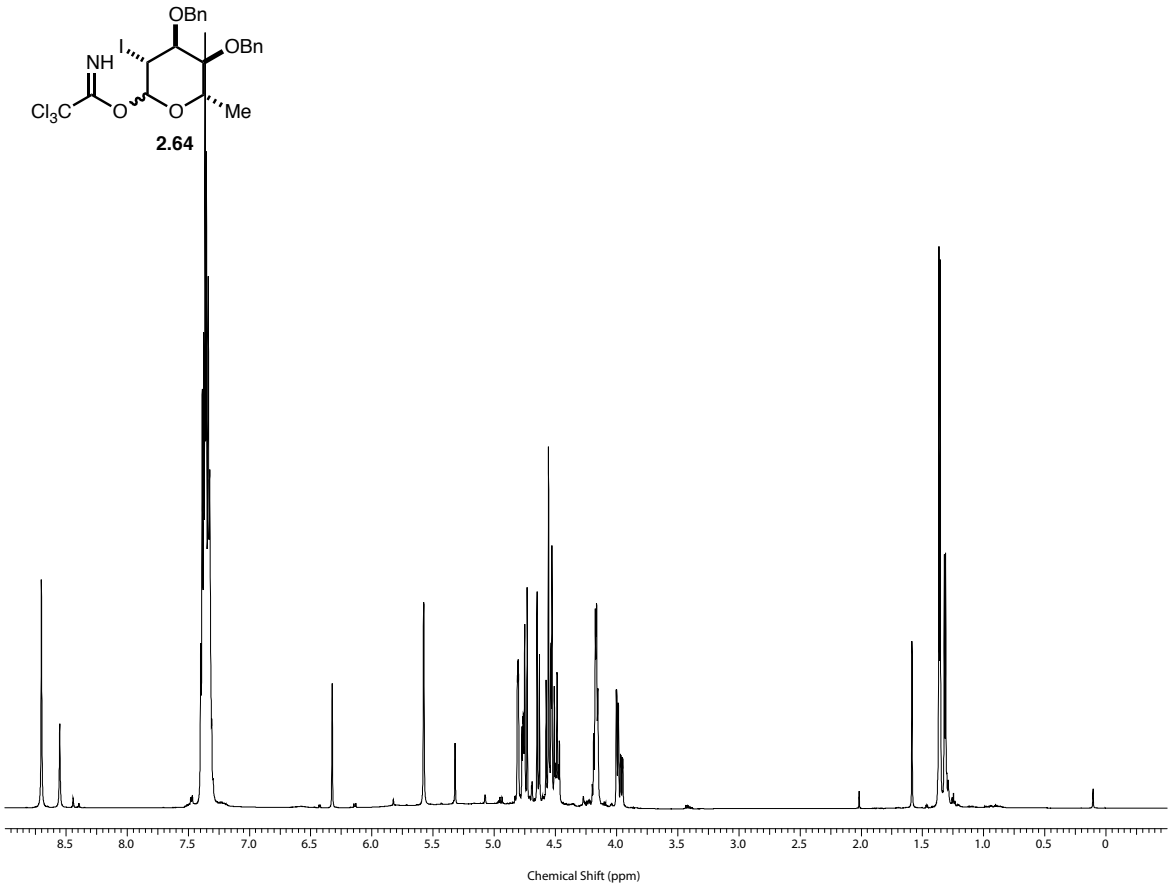

OBn
OBn
BnO
O
Me
(–)-2.319
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

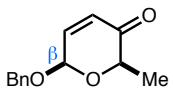

OBn
OBn
O
Me
(–)-2.320
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OBn
OBn
O
Me
(–)-2.320
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

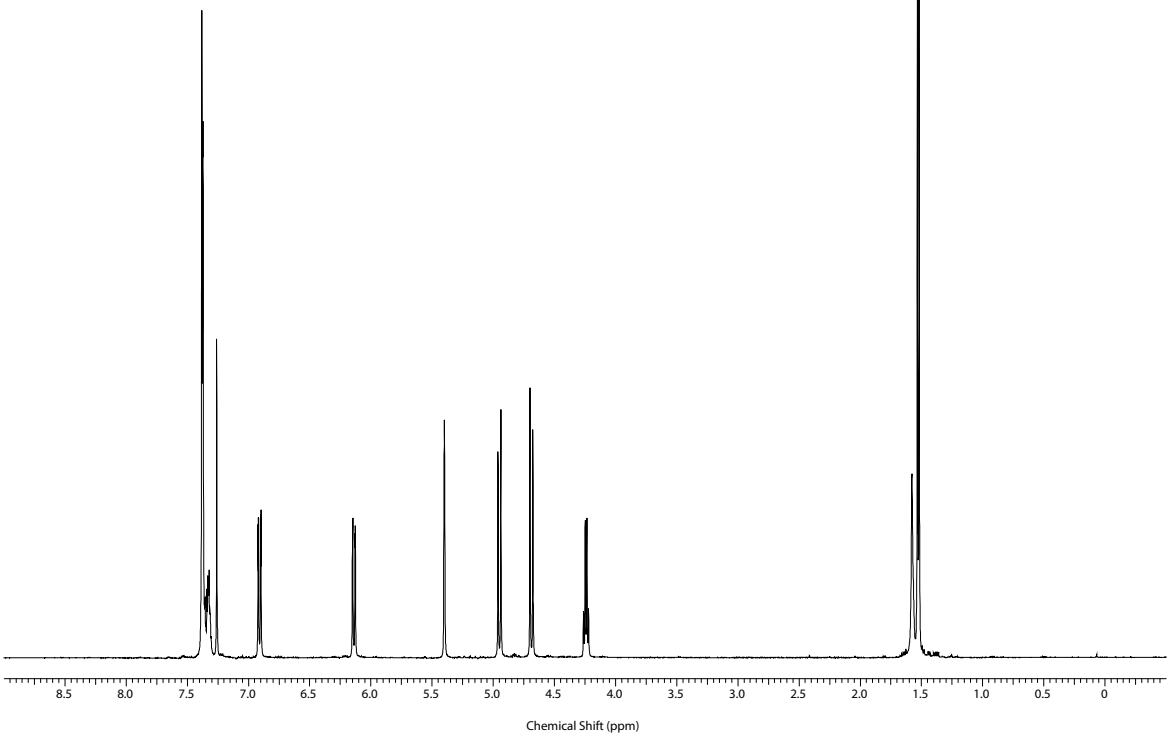

OBn
I
OBn
AcO
O
Me
(–)-2.322
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

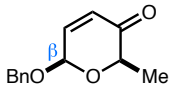

OBn
I
OBn
AcO
O
Me
(–)-2.322
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OBn
I
NH
OBn
Cl3C
O
O
Me
2.64
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

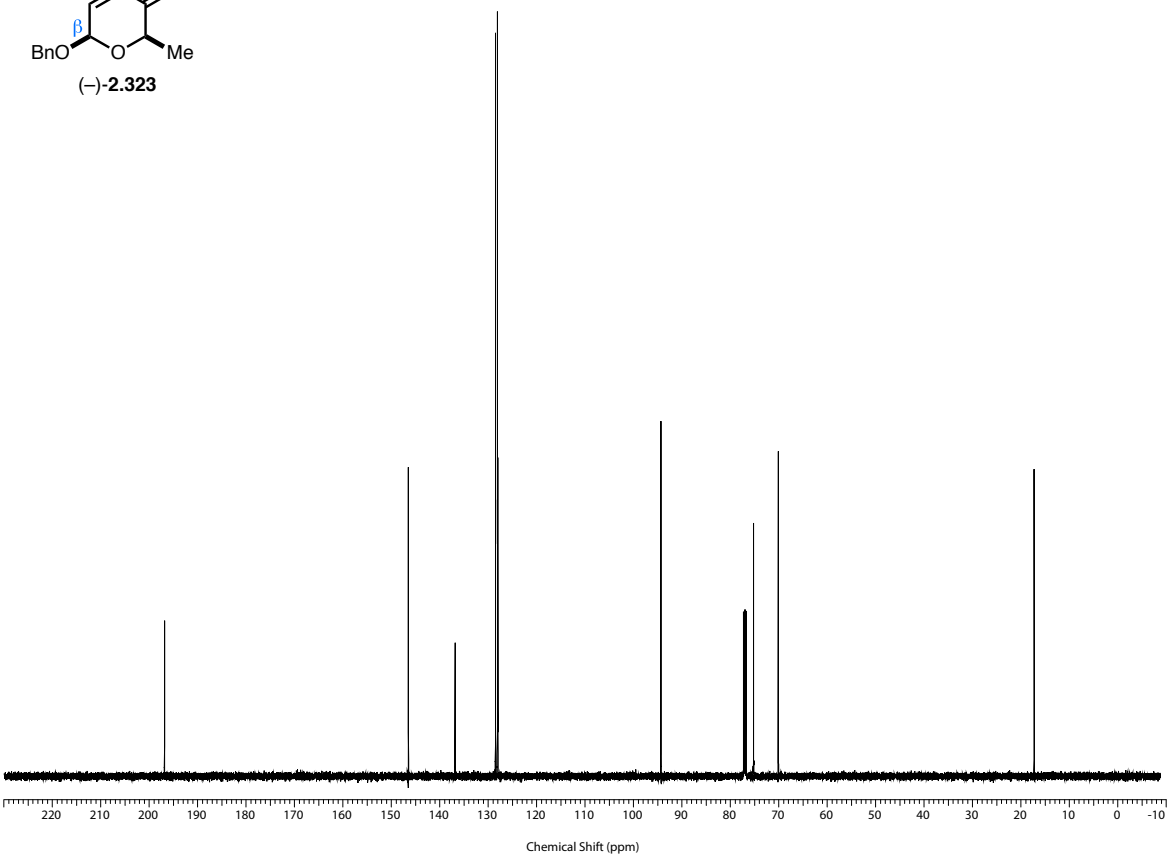

β
BnO
O
Me
O

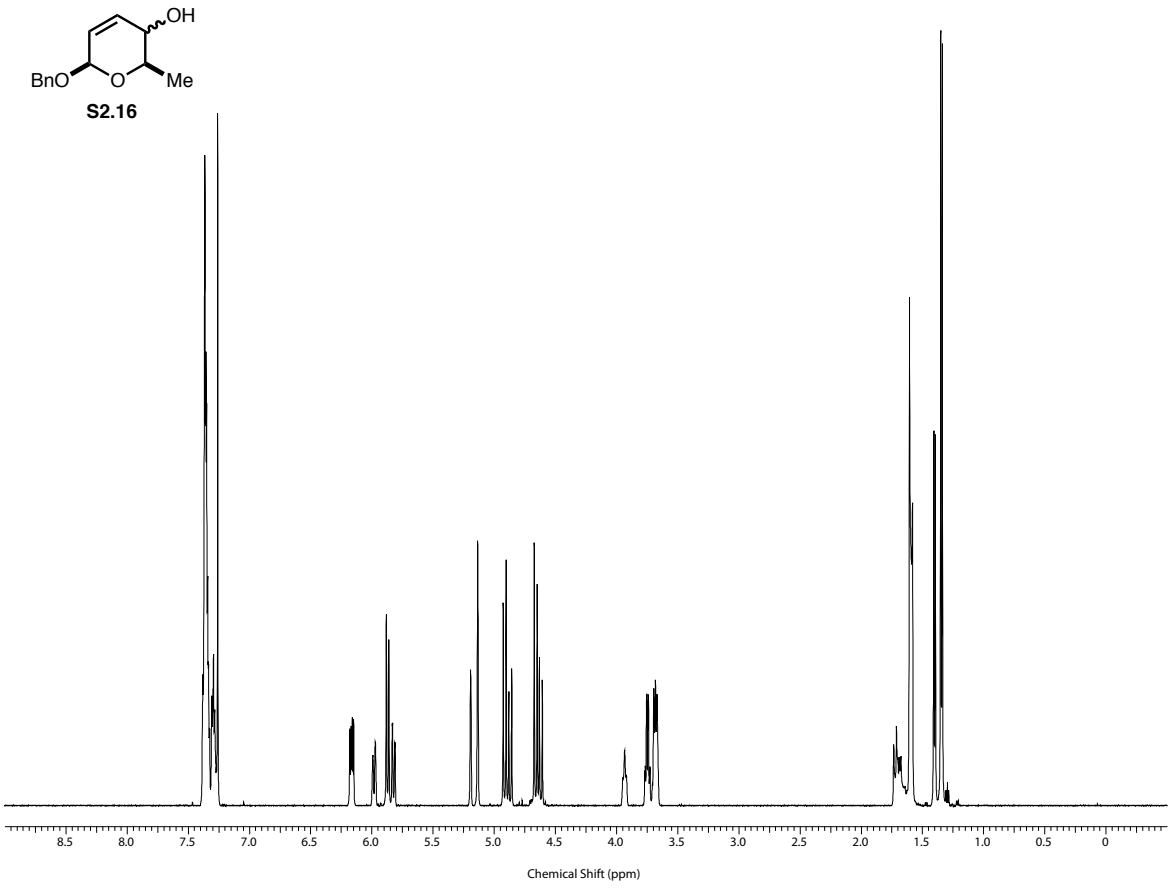
(–)-**2.323**

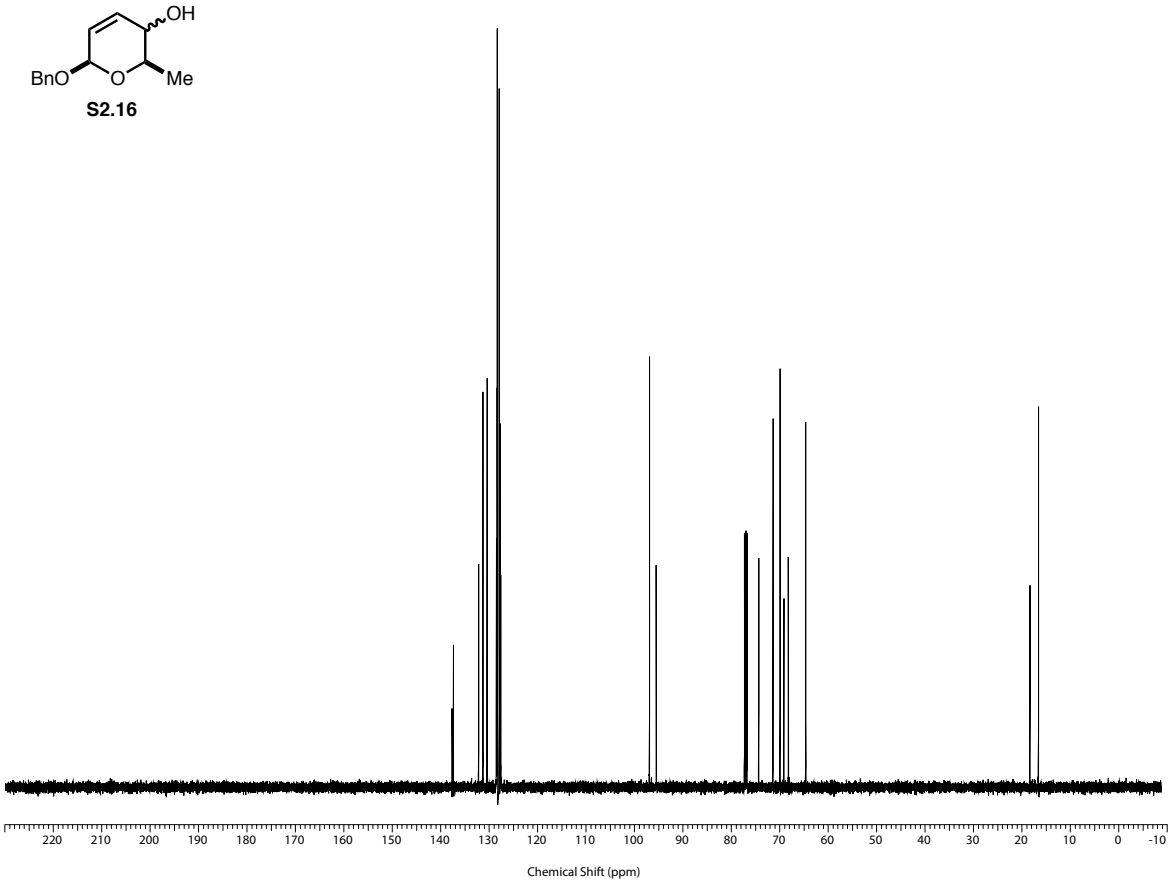

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

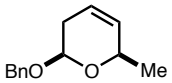

β
BnO
O
Me
O

(–)-**2.323**

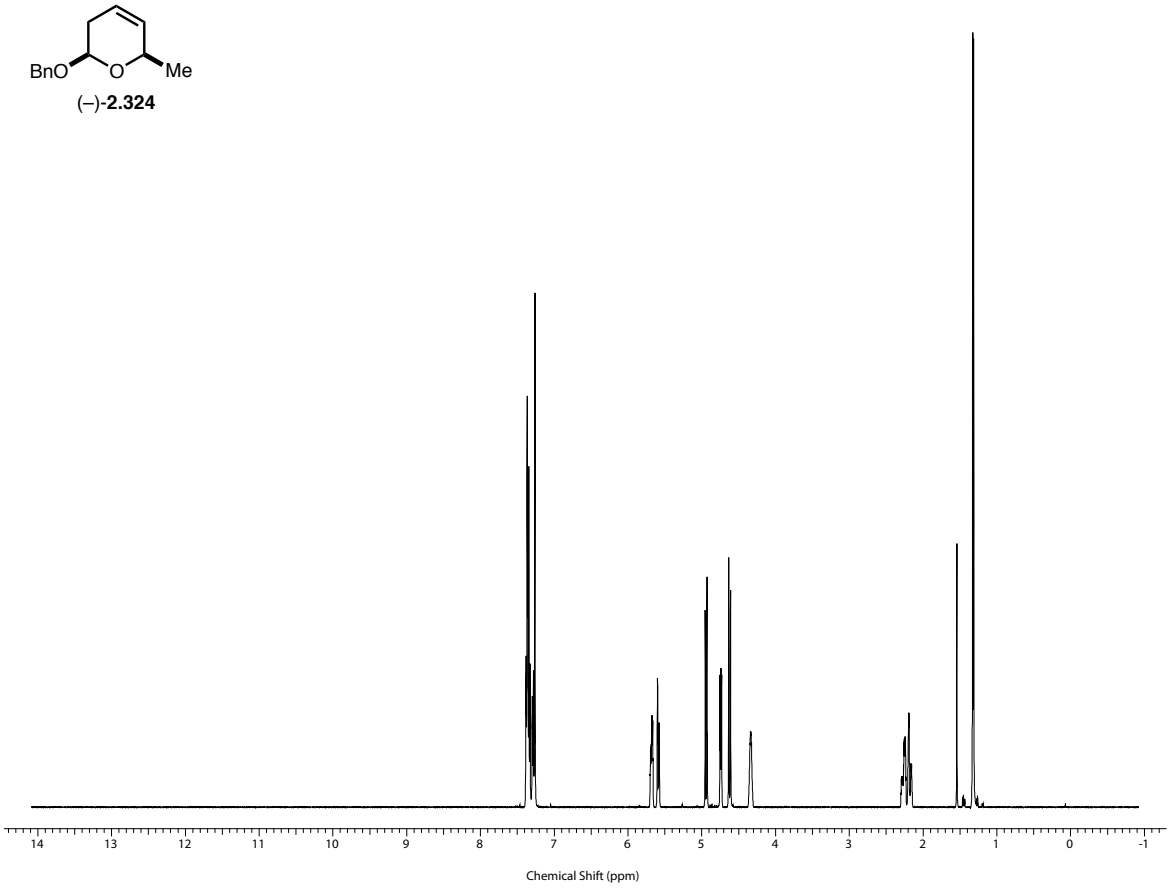

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

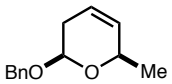

OH
BnO
O
Me
S2.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OH
BnO
O
Me
S2.16
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

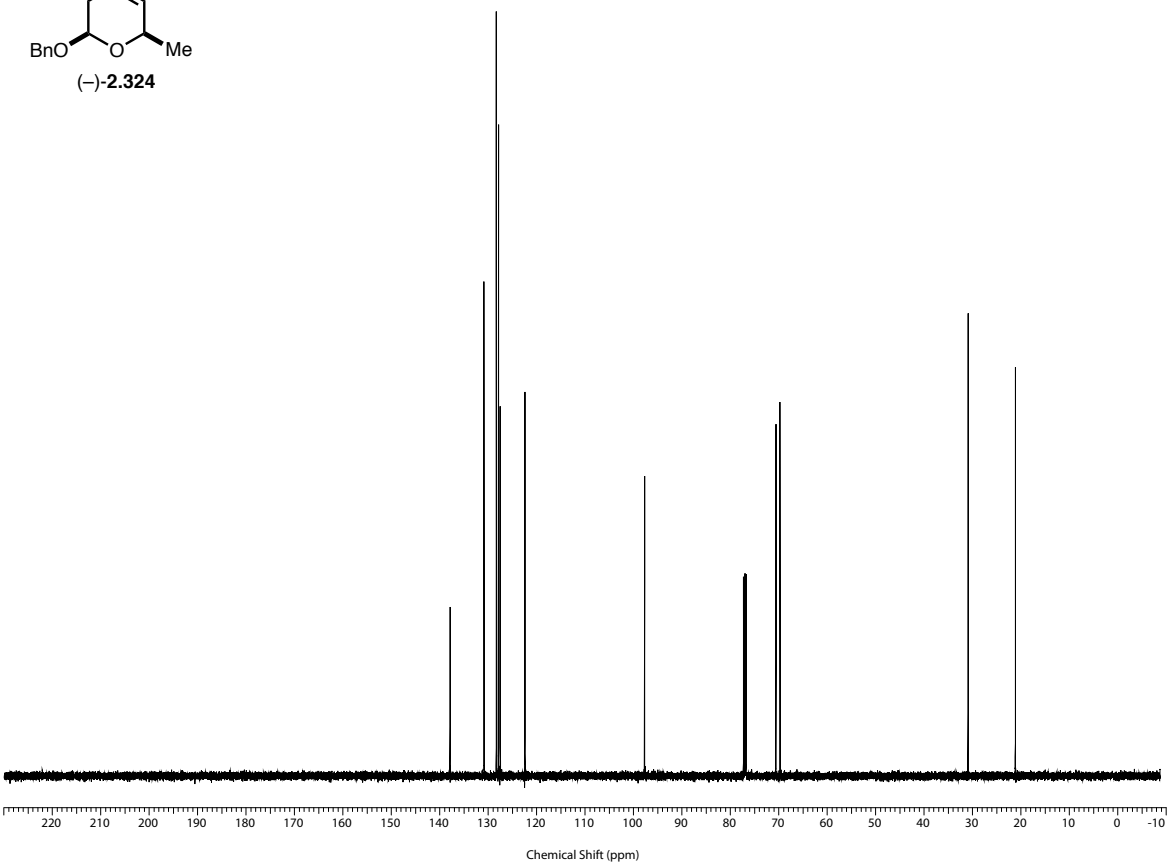

BnO
O
Me

(–)-**2.324**


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)

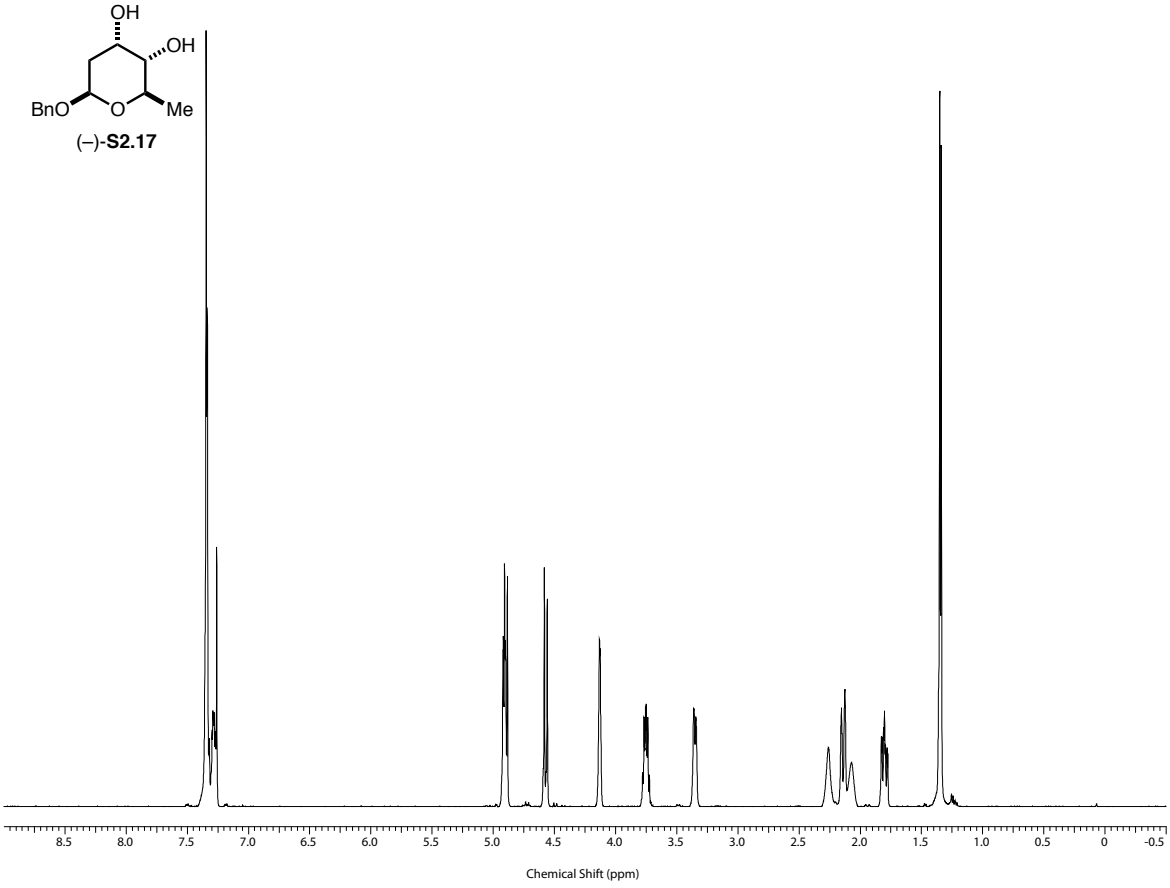

BnO
O
Me

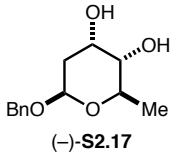
(–)-**2.324**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

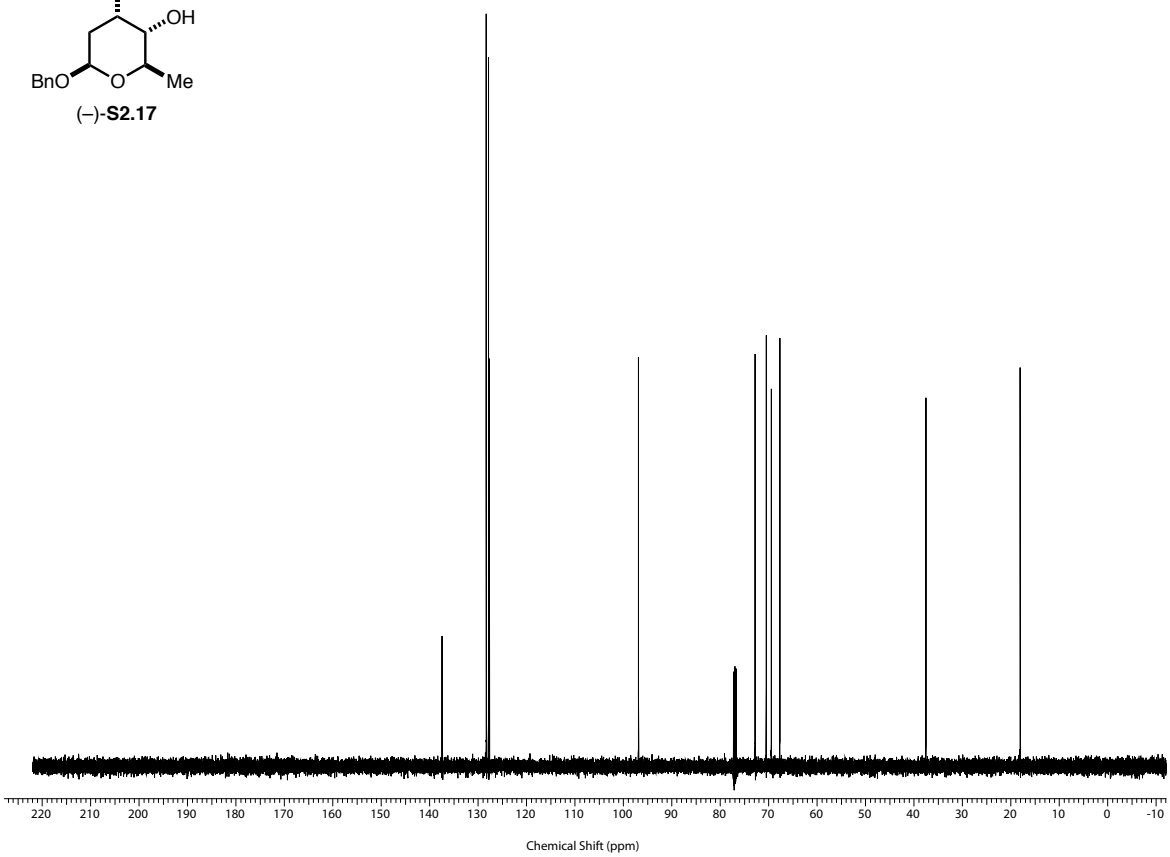
OH
OH
BnO
O
Me

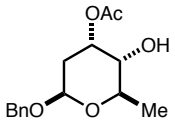
(–)-**S2.17**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

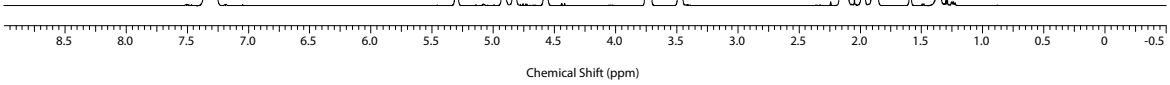

OH
OH
BnO
O
Me

(–)-**S2.17**

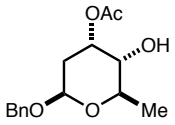

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



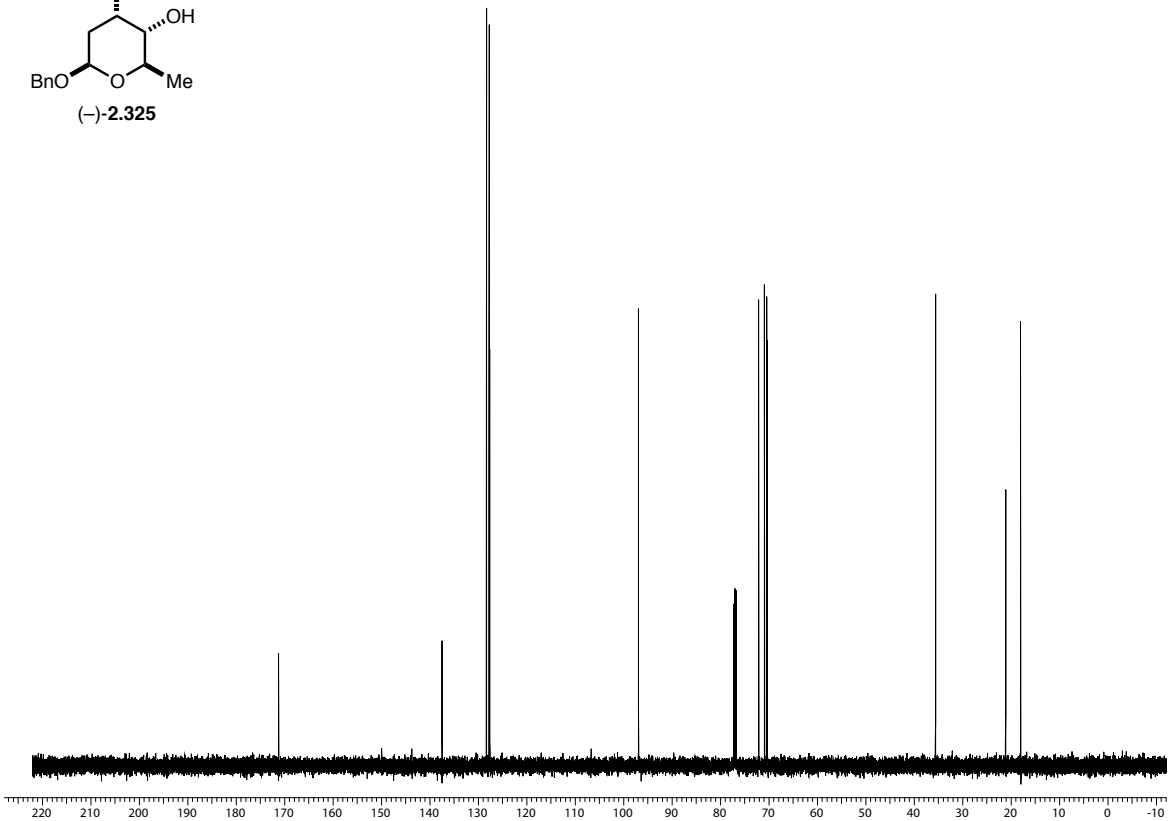
(–)-**2.325**



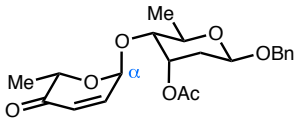
Chemical Shift (ppm)



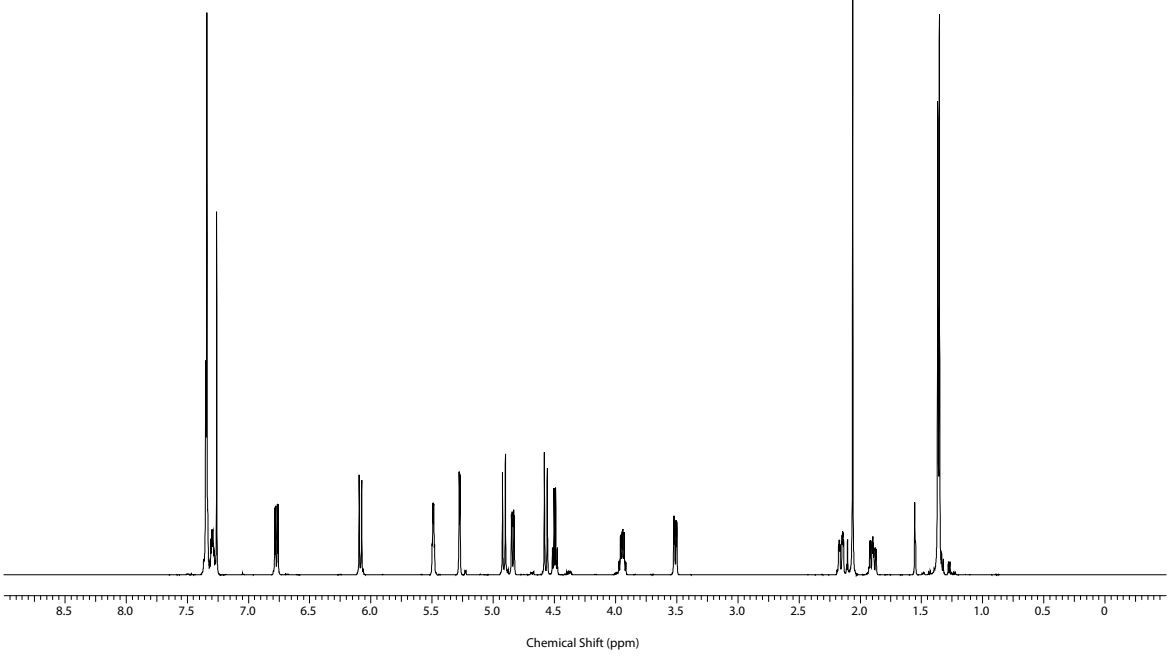
(–)-**2.325**

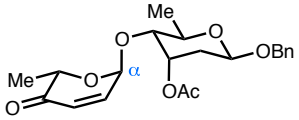


Chemical Shift (ppm)

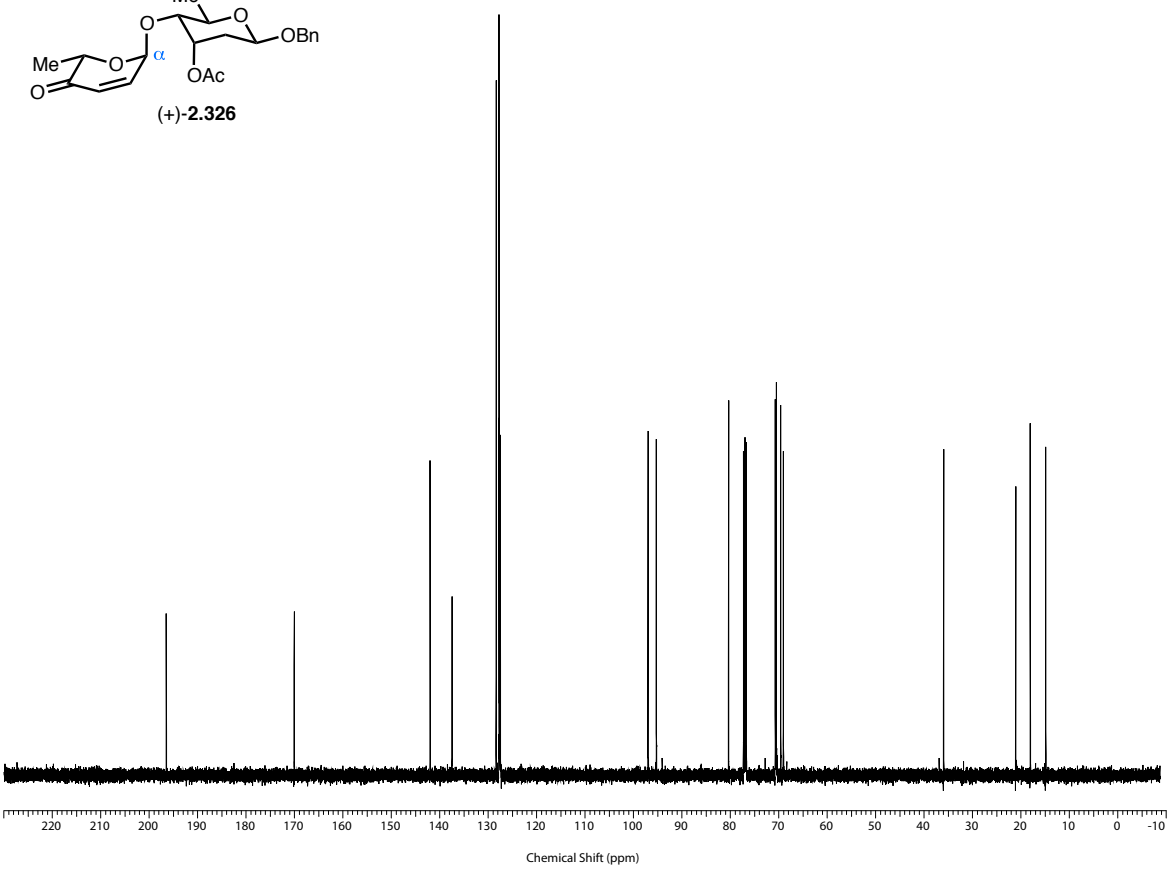

Me
O
O
OBn
Me
O
α
OAc
O

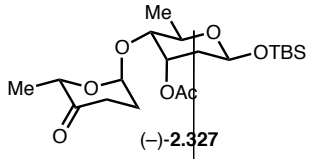
(+)-**2.326**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

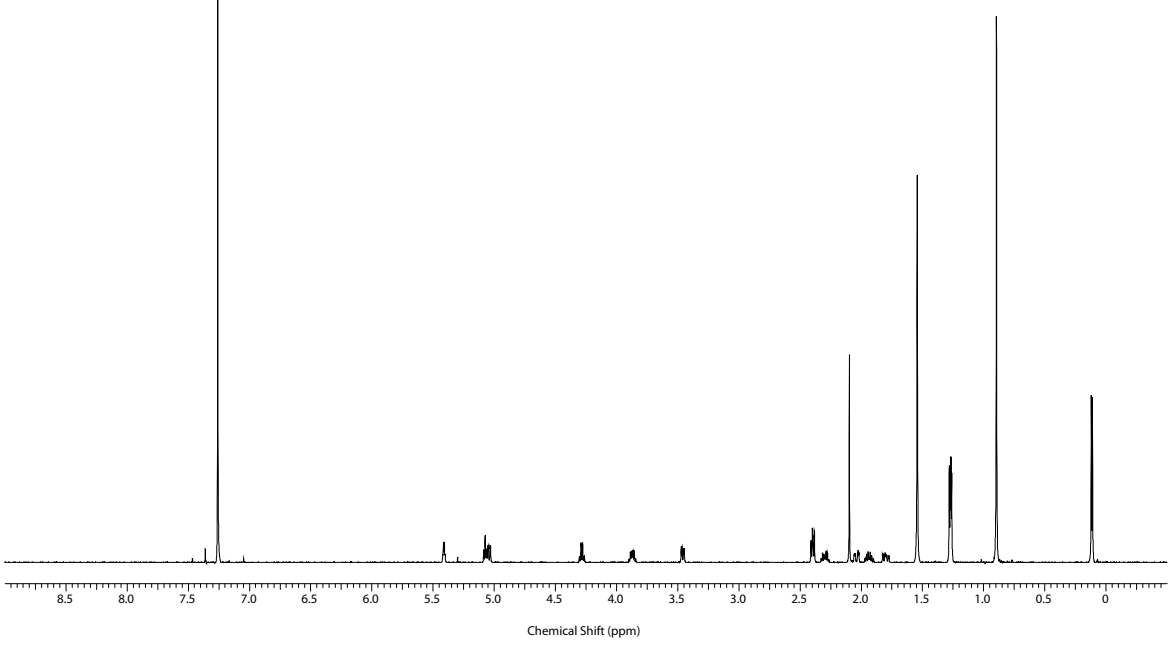

Me
O
O
OBn
Me
O
α
OAc
O

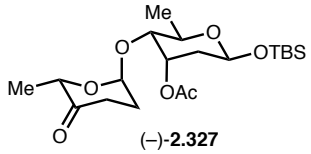
(+)-**2.326**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

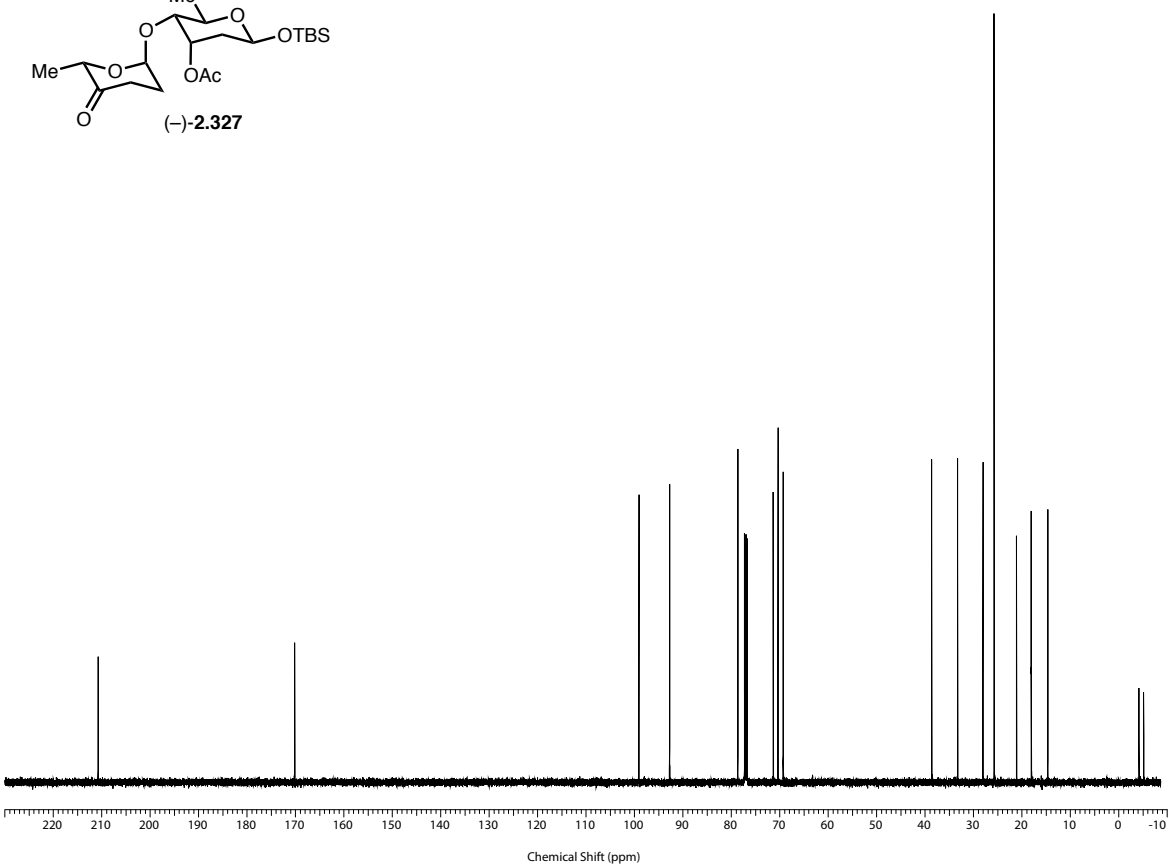

Me
O
OTBS
Me
O
OAc
O

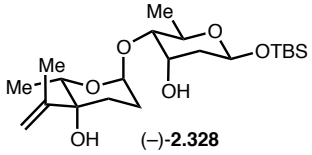
(–)-**2.327**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

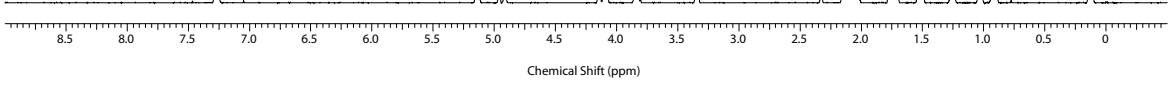

Me
O
OTBS
Me
O
OAc
O

(–)-**2.327**

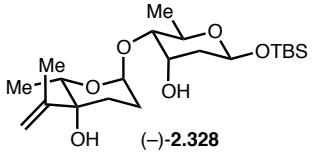

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



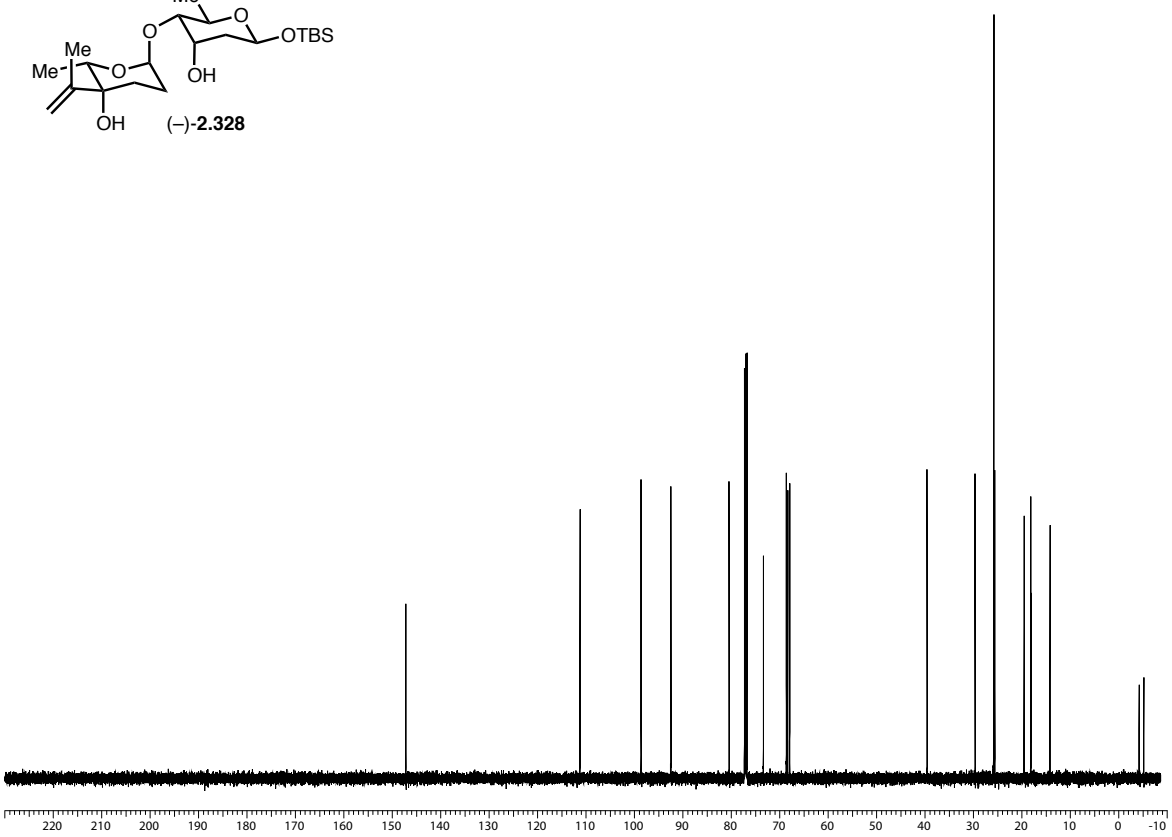
(–)-**2.328**



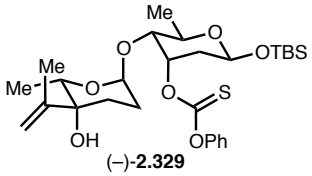
Chemical Shift (ppm)



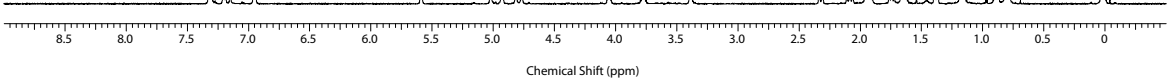
(–)-**2.328**

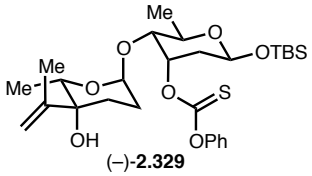


Chemical Shift (ppm)

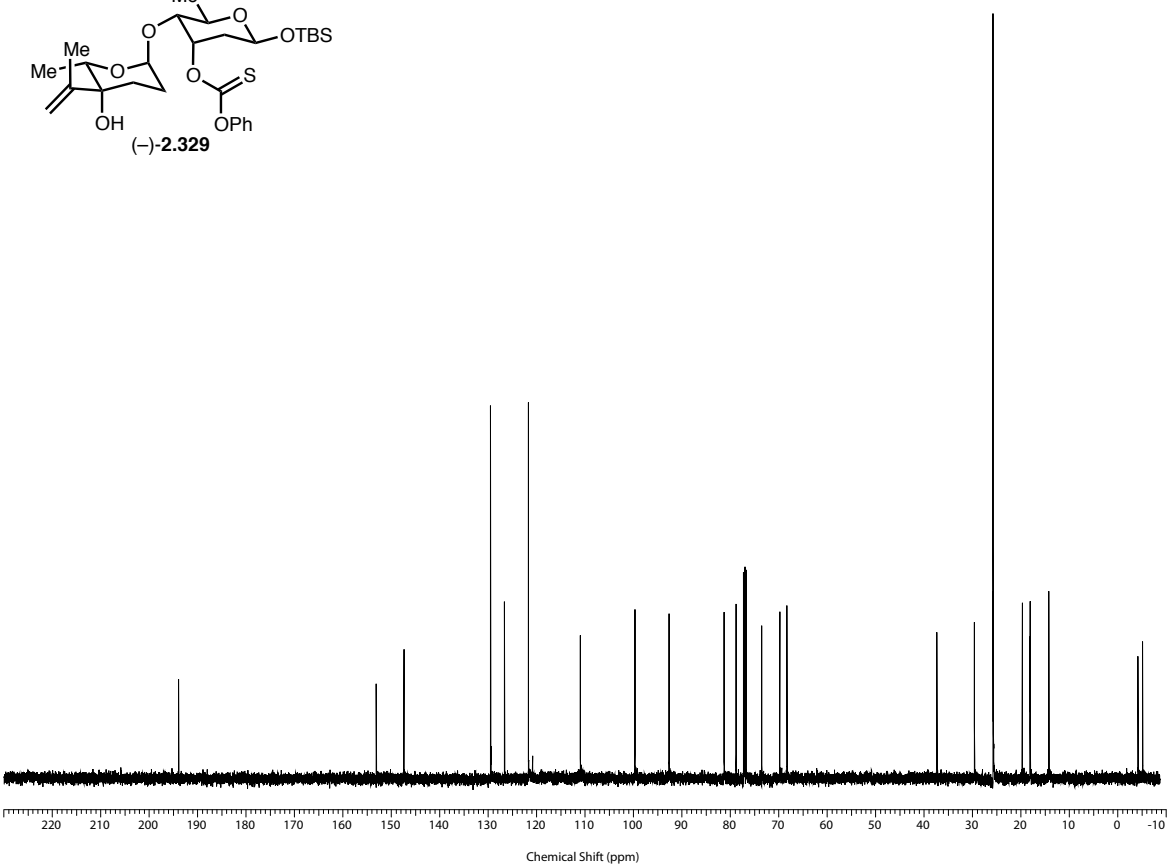

Me
O
OTBS
Me
Me
O
O
S
OH
OPh

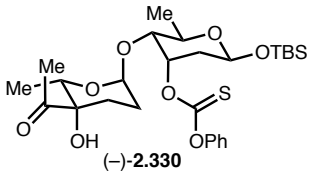
(–)-**2.329**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

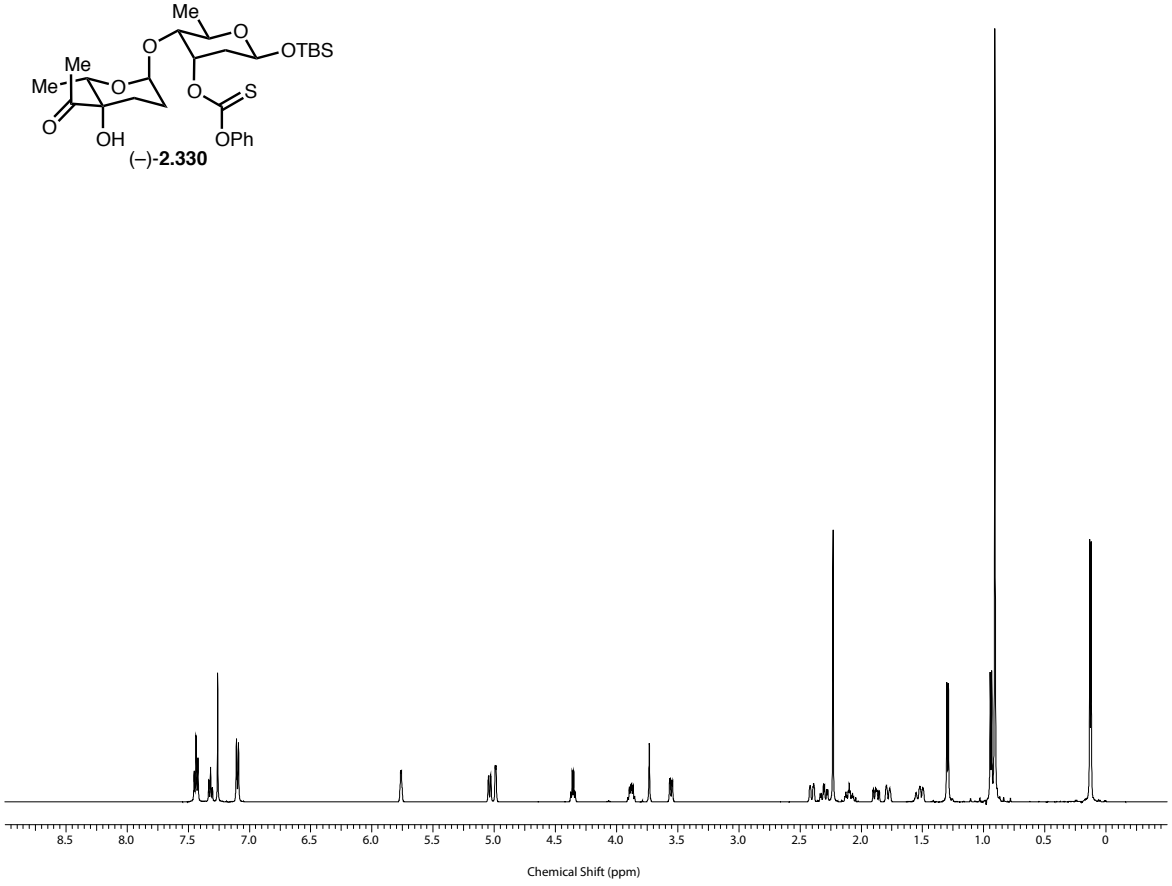

Me
O
OTBS
Me
Me
O
O
S
OH
OPh

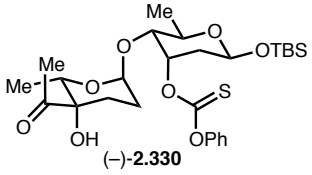
(–)-**2.329**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

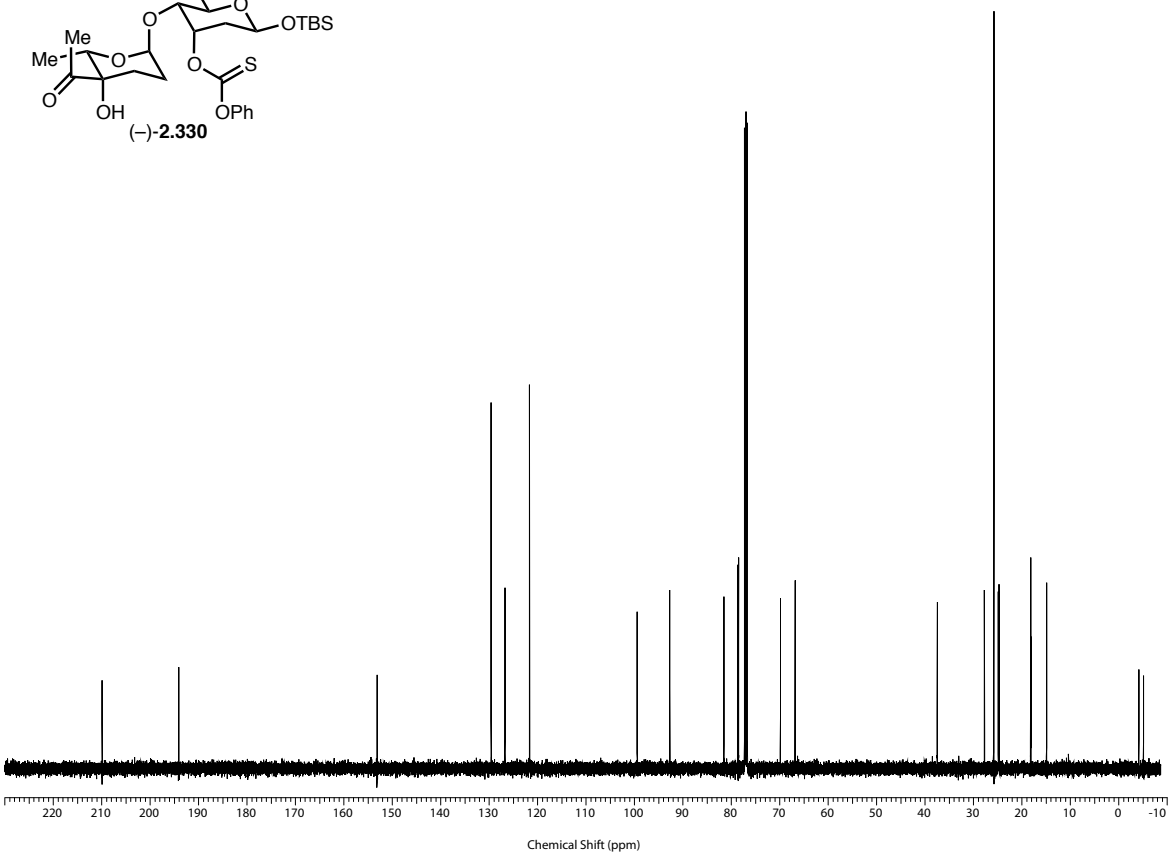

Me
O
OTBS
Me
Me
O
O
S
O
OH
OPh

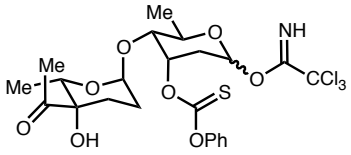
(–)-**2.330**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

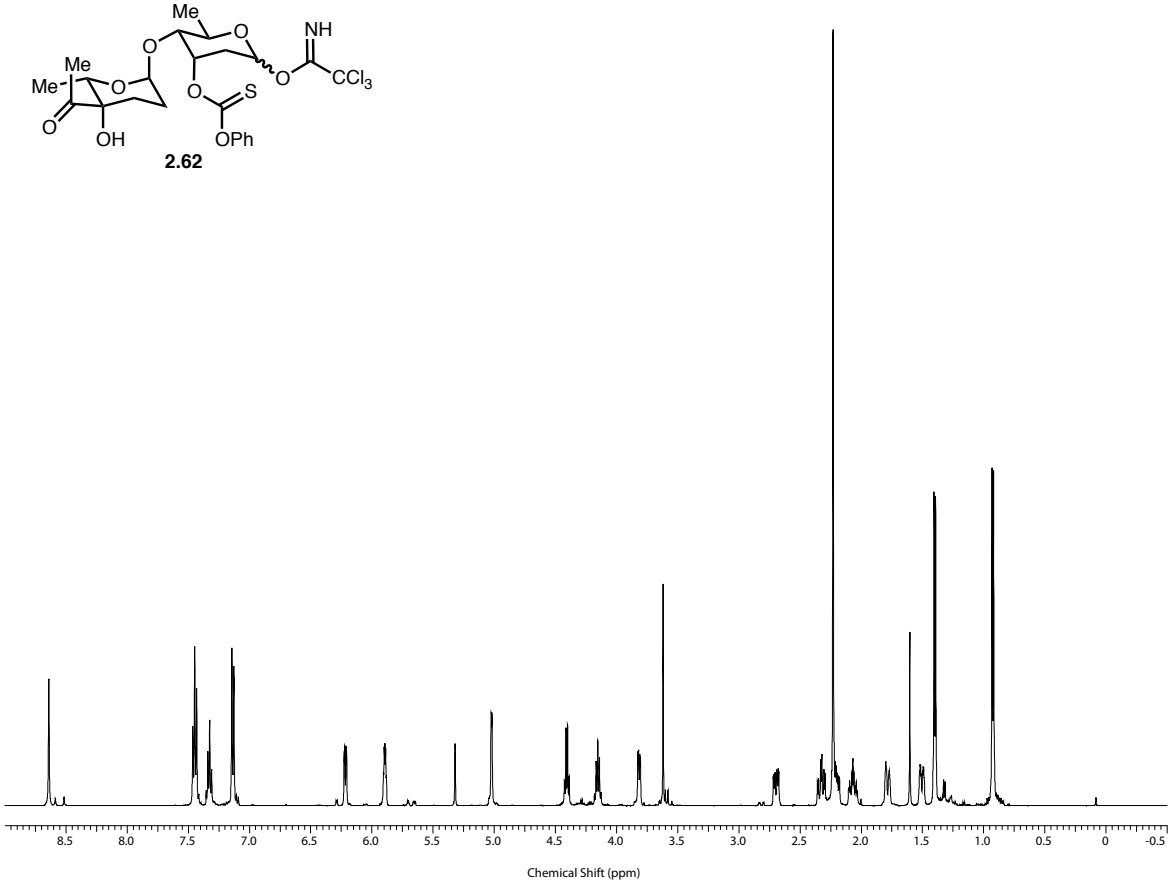

Me
O
OTBS
Me
Me
O
O
S
O
OH
OPh

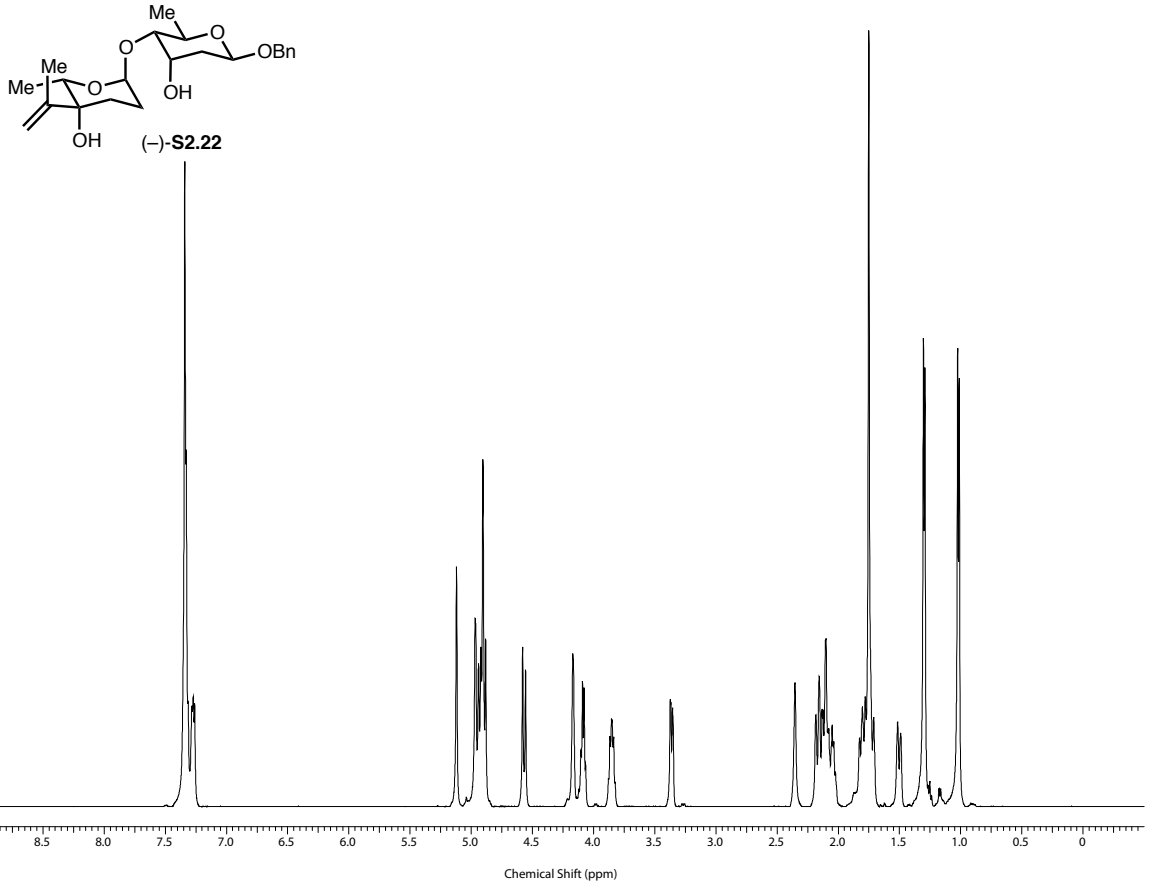
(–)-**2.330**

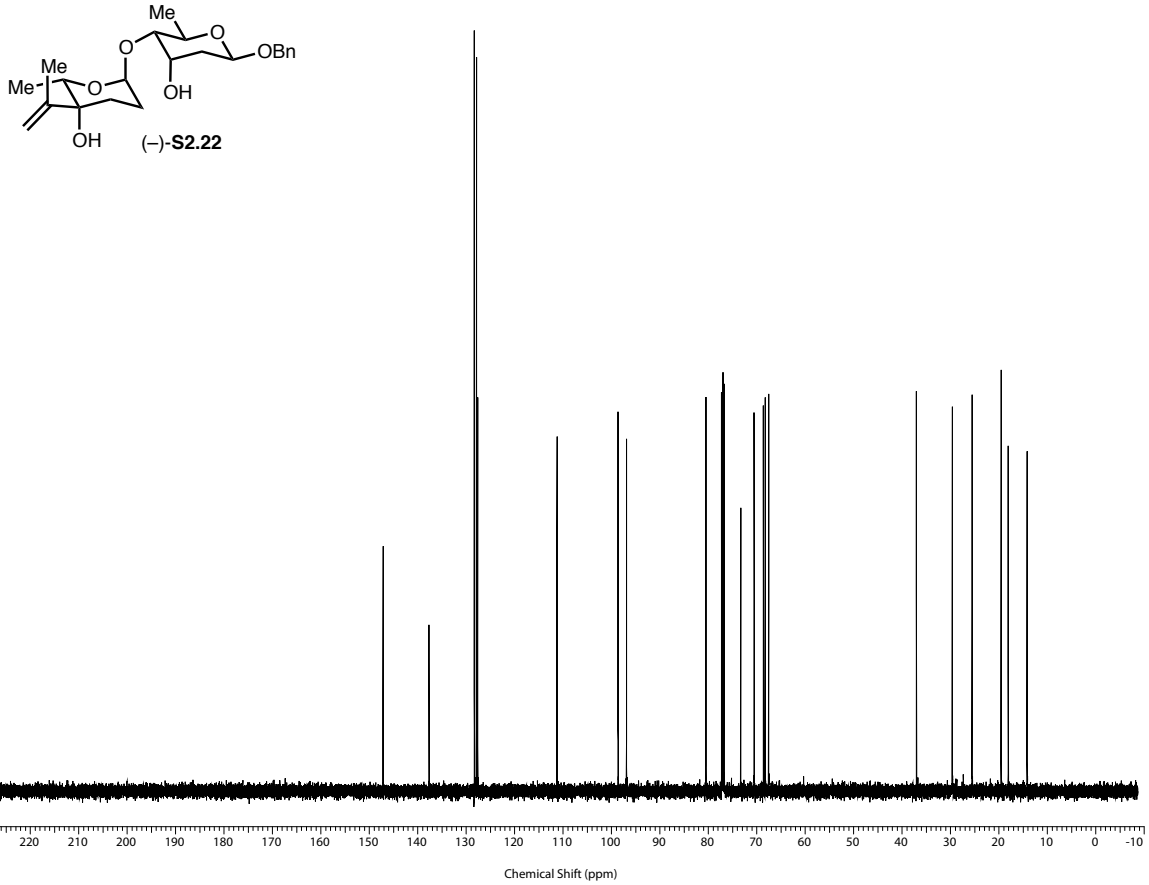

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

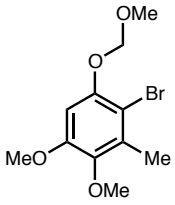

Me
O
NH
Me
Me
O
O
S
O
CCl3
O
OH
OPh

2.62

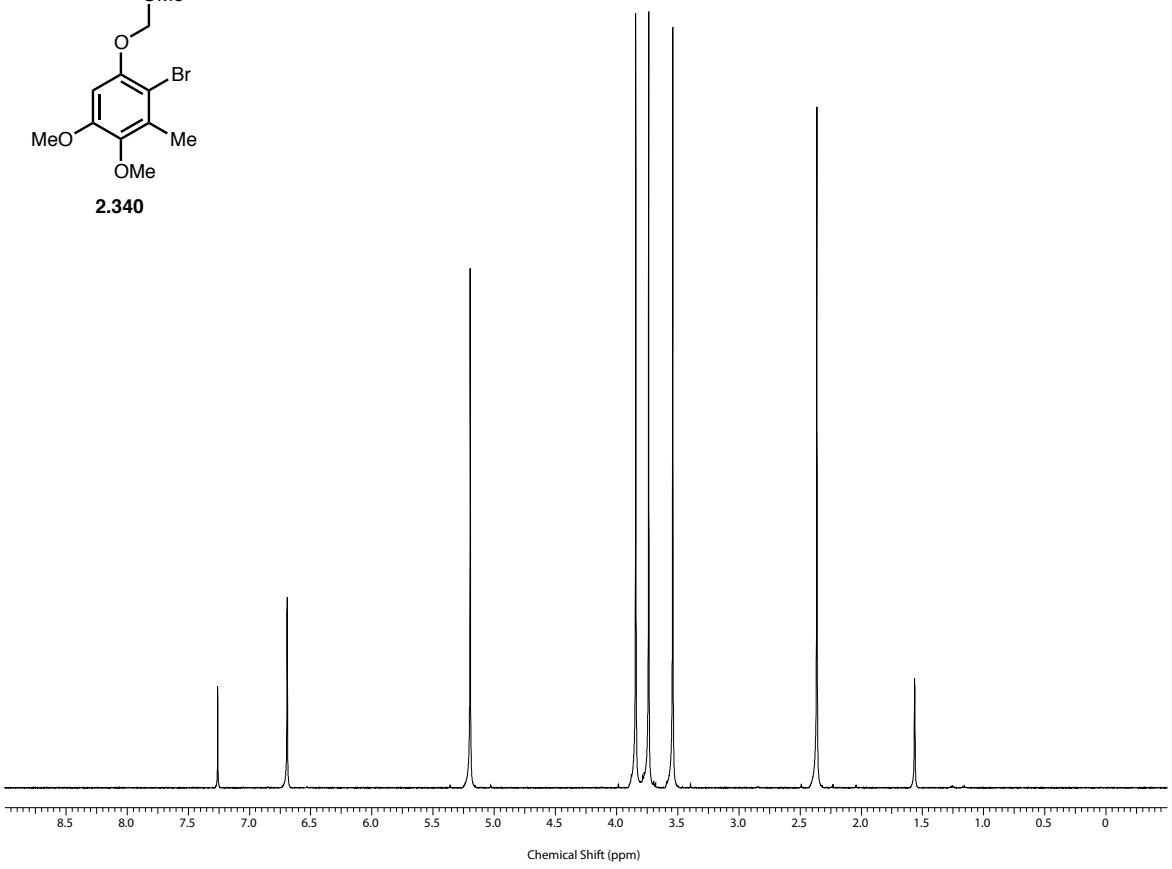

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)

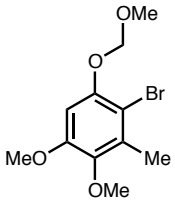

Me
O
OBn
Me
Me
O
OH
OH
(–)-S2.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


Me
O
OBn
Me
Me
O
OH
OH
(–)-S2.22
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

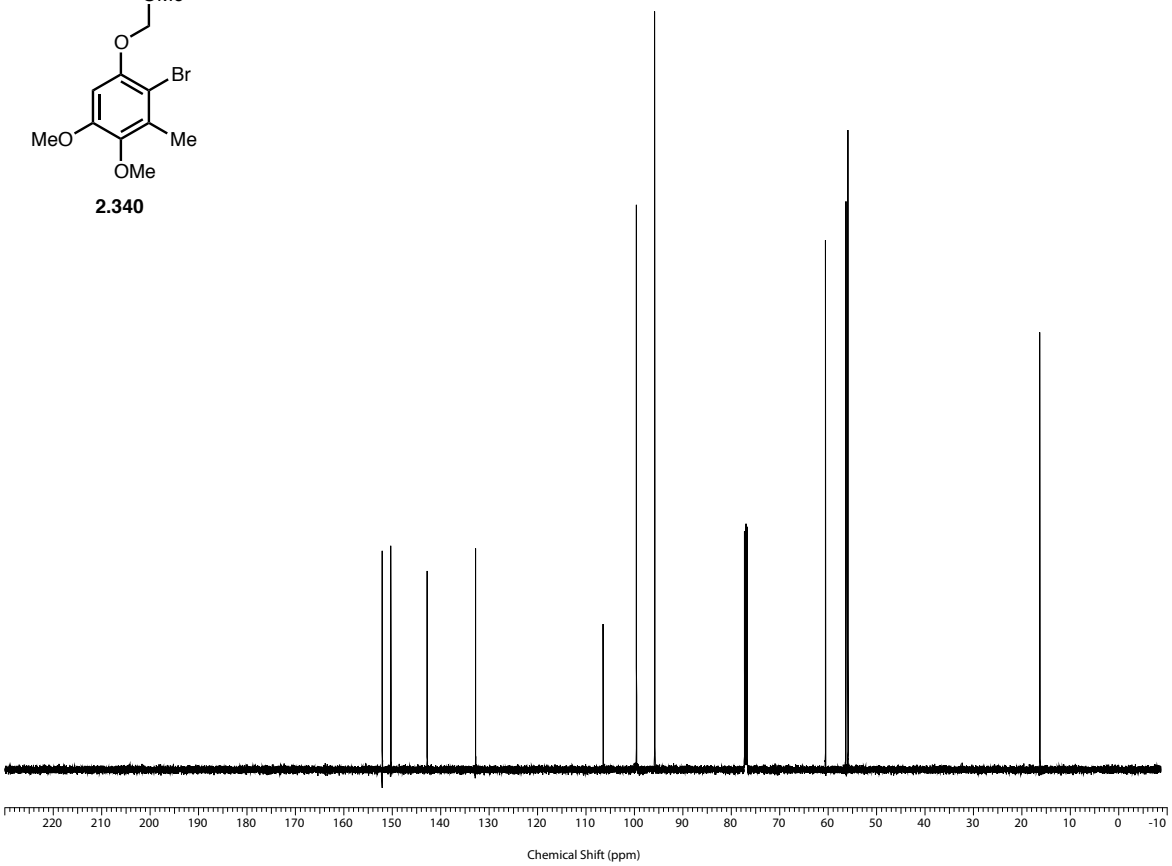

OMe
O
Br
MeO
Me
OMe

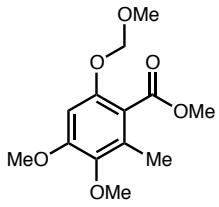
2.340


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

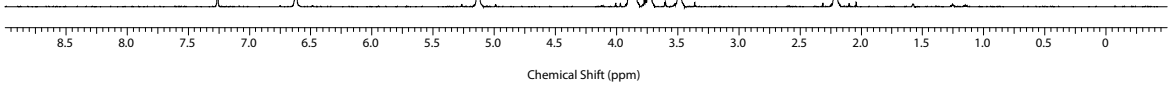

OMe
O
Br
MeO
Me
OMe

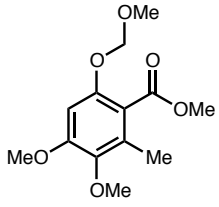
2.340


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

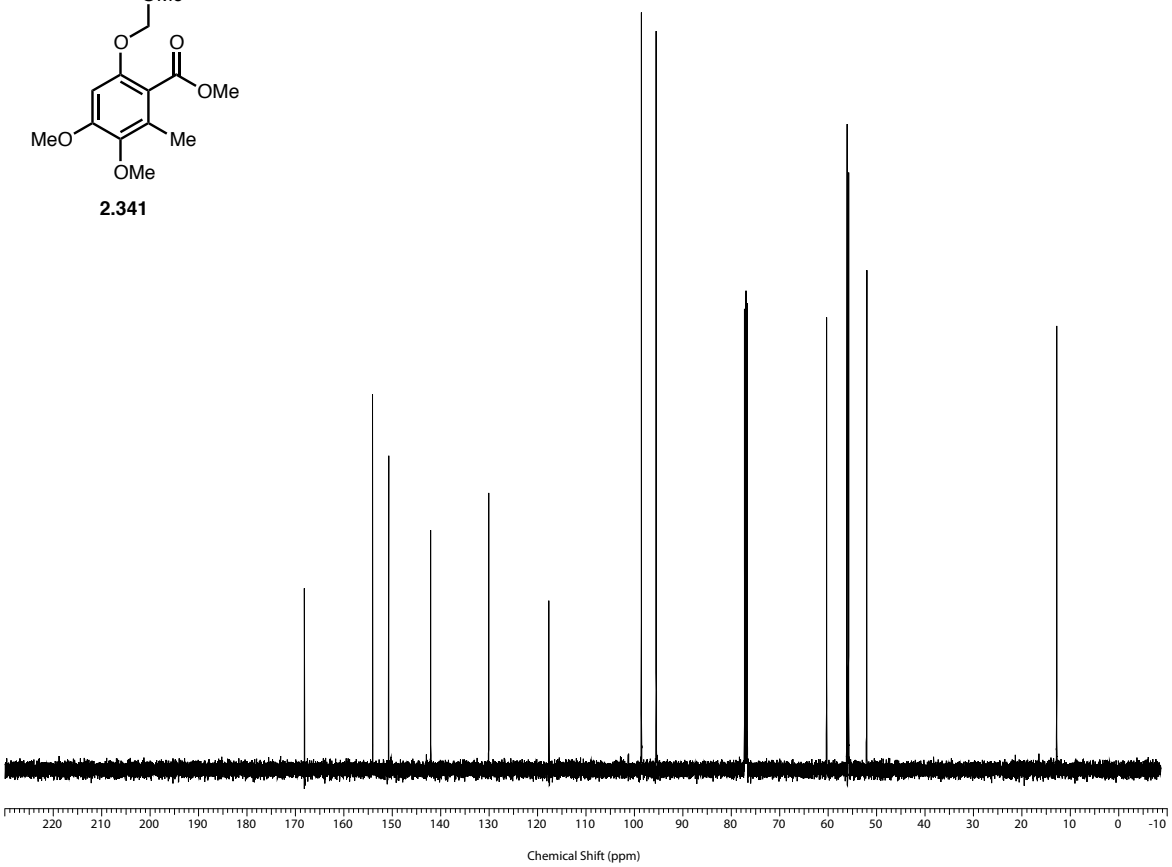

OMe
O
O
OMe
MeO
Me
OMe

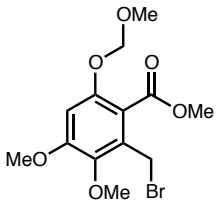
2.341


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


OMe
O
O
OMe
MeO
Me
OMe

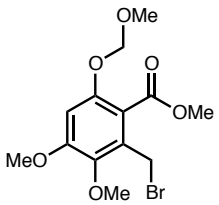
2.341


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

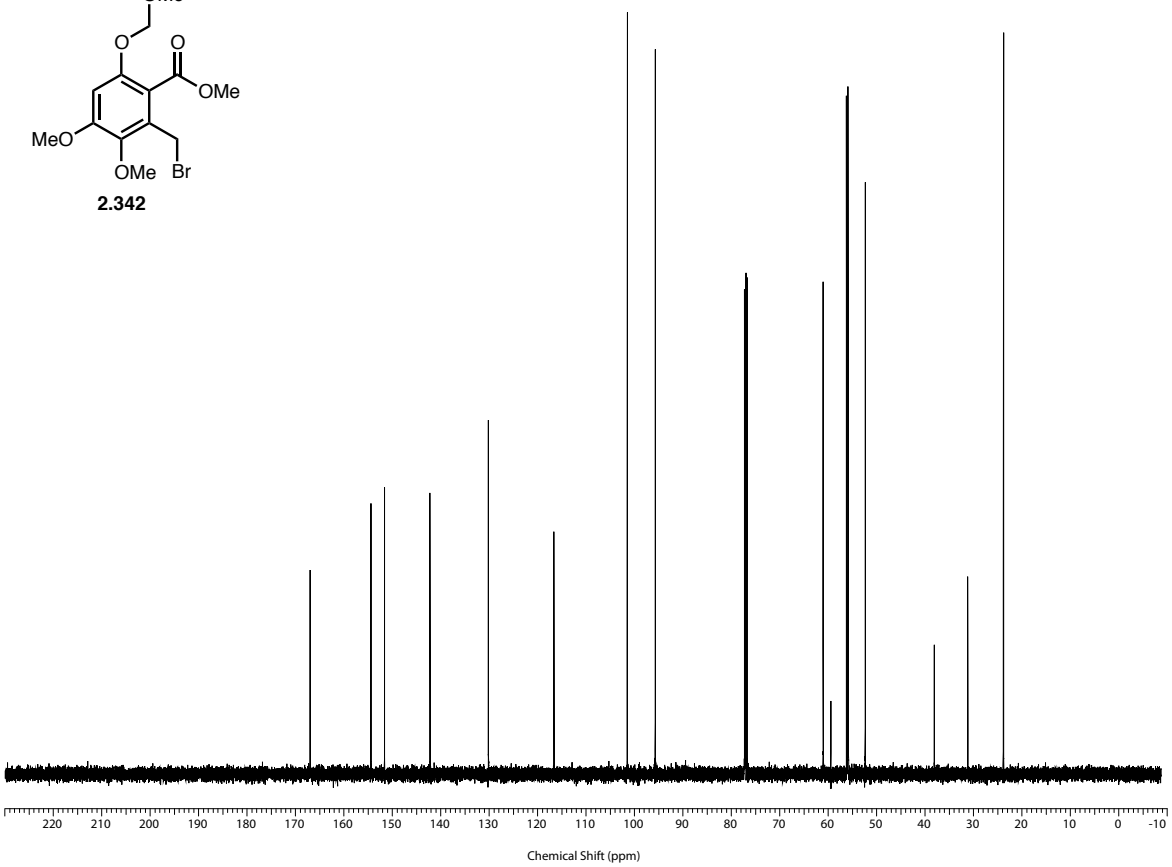

OMe
O
O
OMe
MeO
OMe
Br

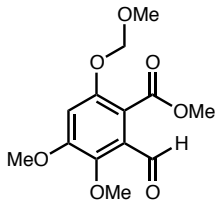
2.342

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

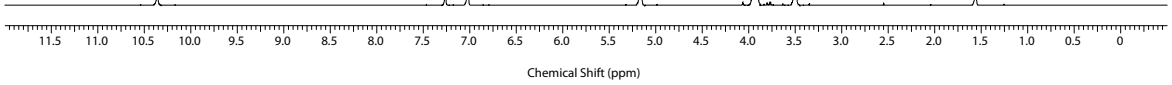

OMe
O
O
OMe
MeO
OMe
Br

2.342

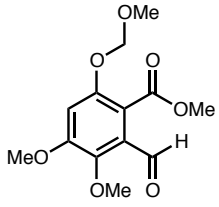

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



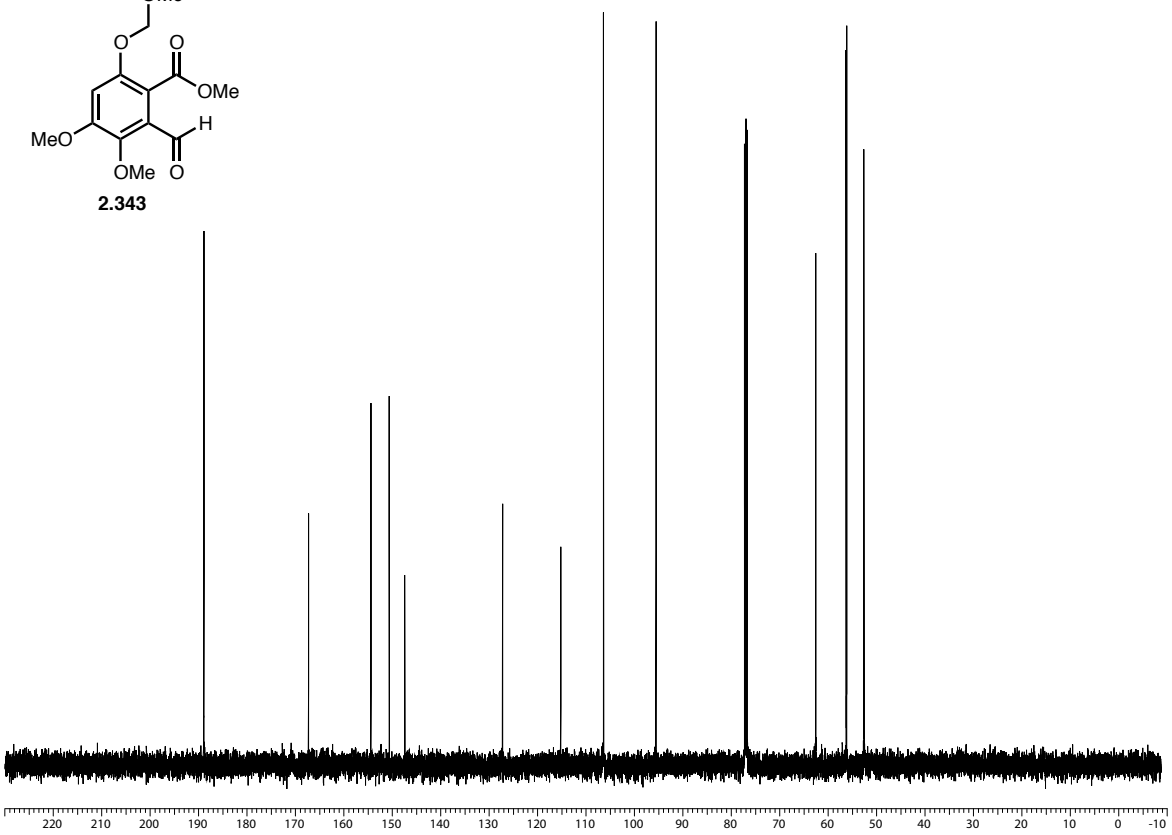
2.343



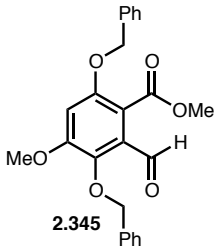
Chemical Shift (ppm)



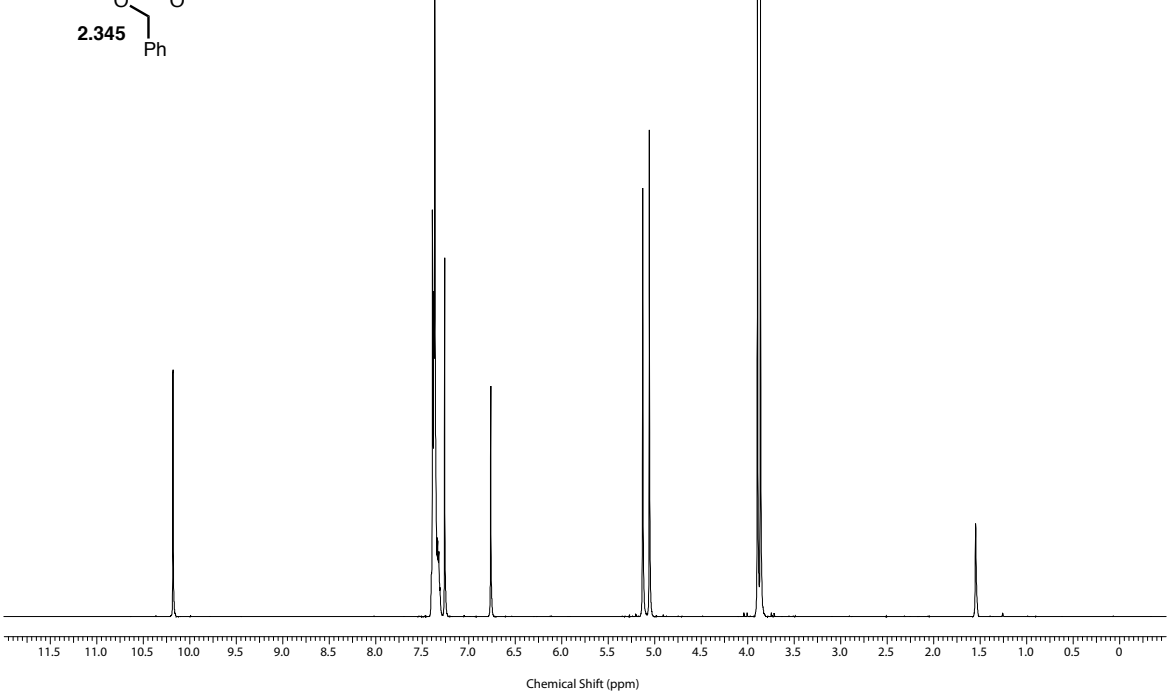
2.343

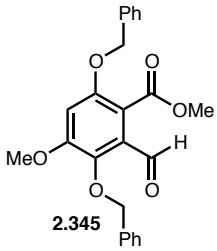


Chemical Shift (ppm)

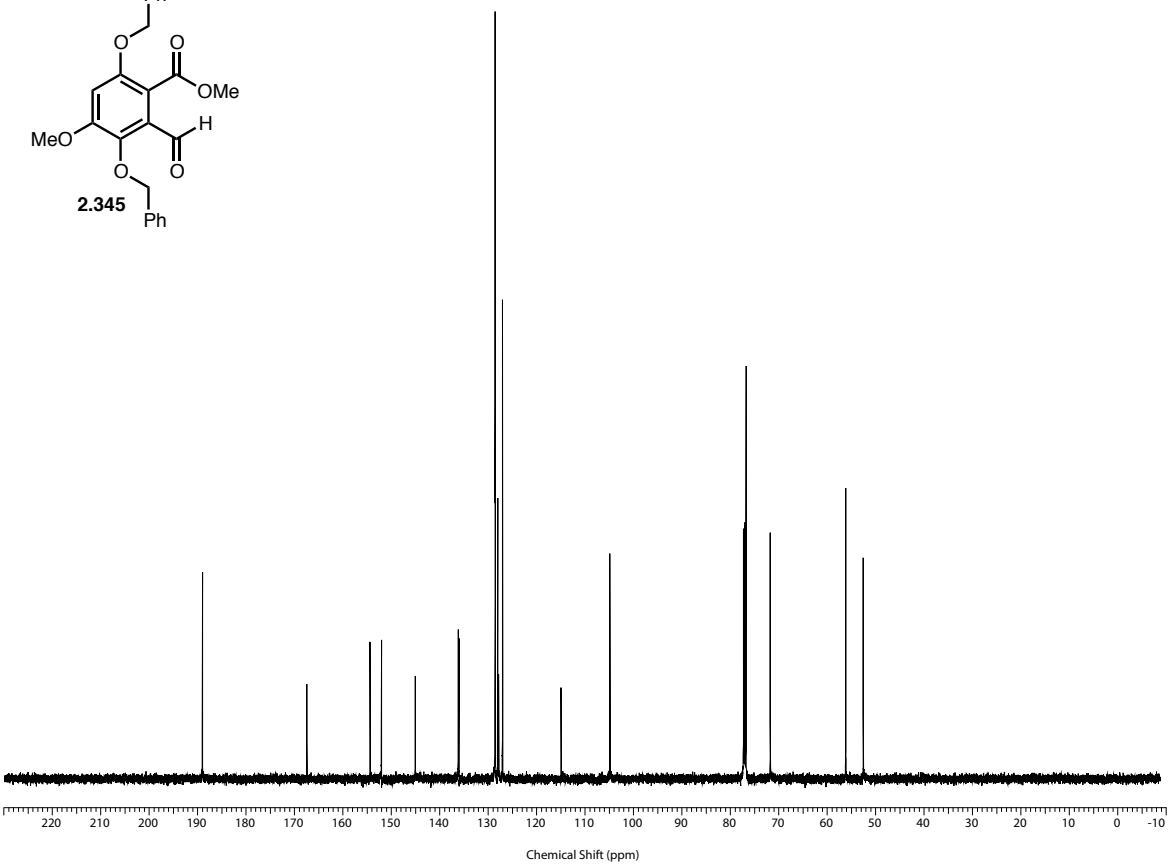

Ph
O
O
OMe
H
MeO
O
O
Ph

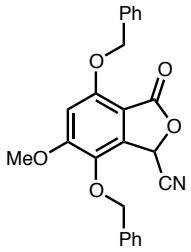
2.345


11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

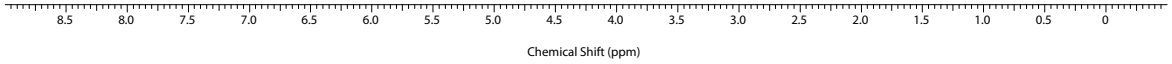

Ph
O
O
OMe
H
MeO
O
O
Ph

2.345


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

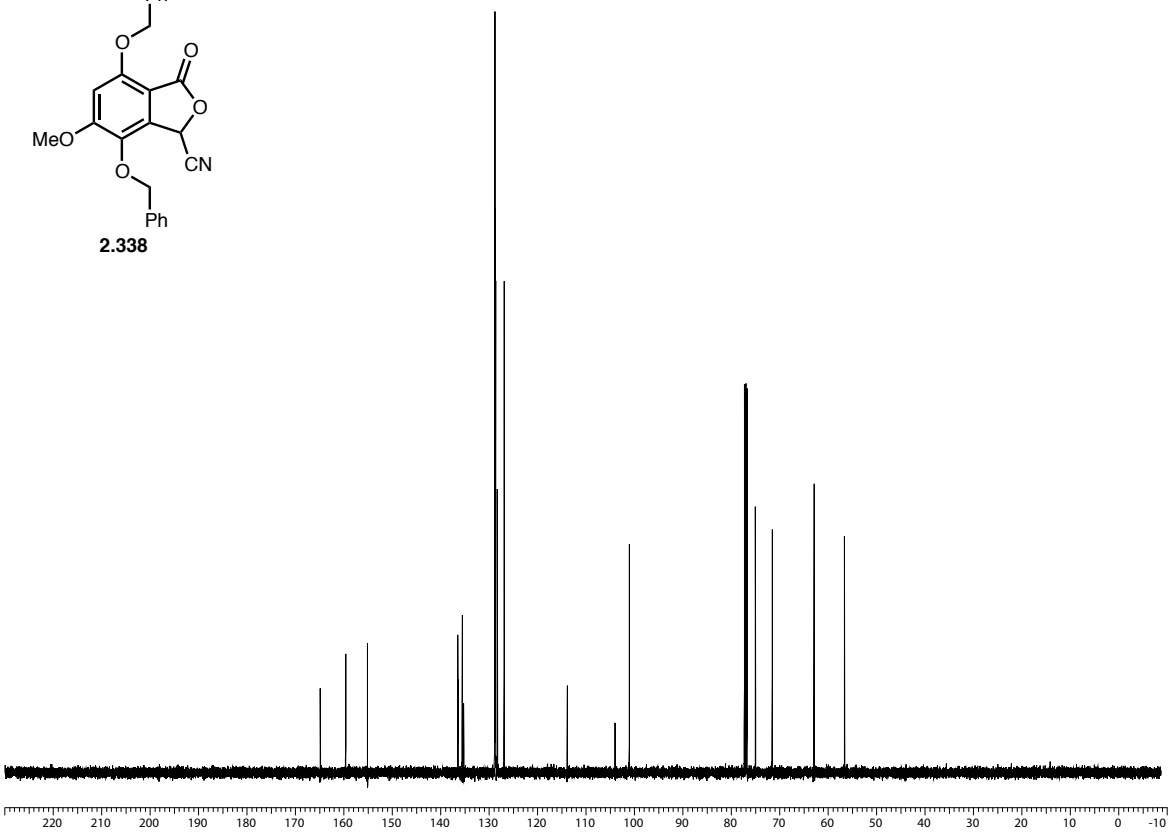


2.338

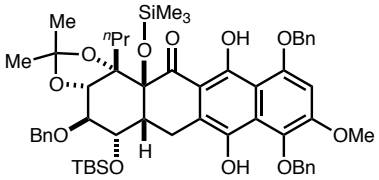


Chemical Shift (ppm)

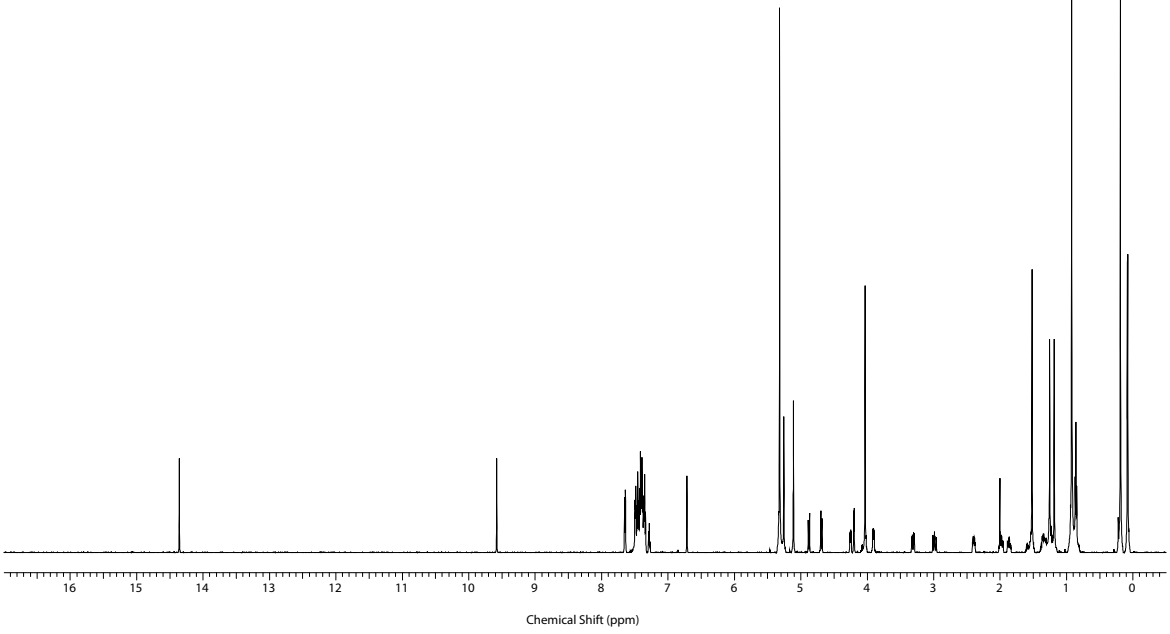
2.338

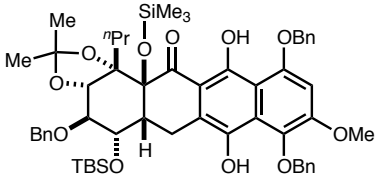


Chemical Shift (ppm)

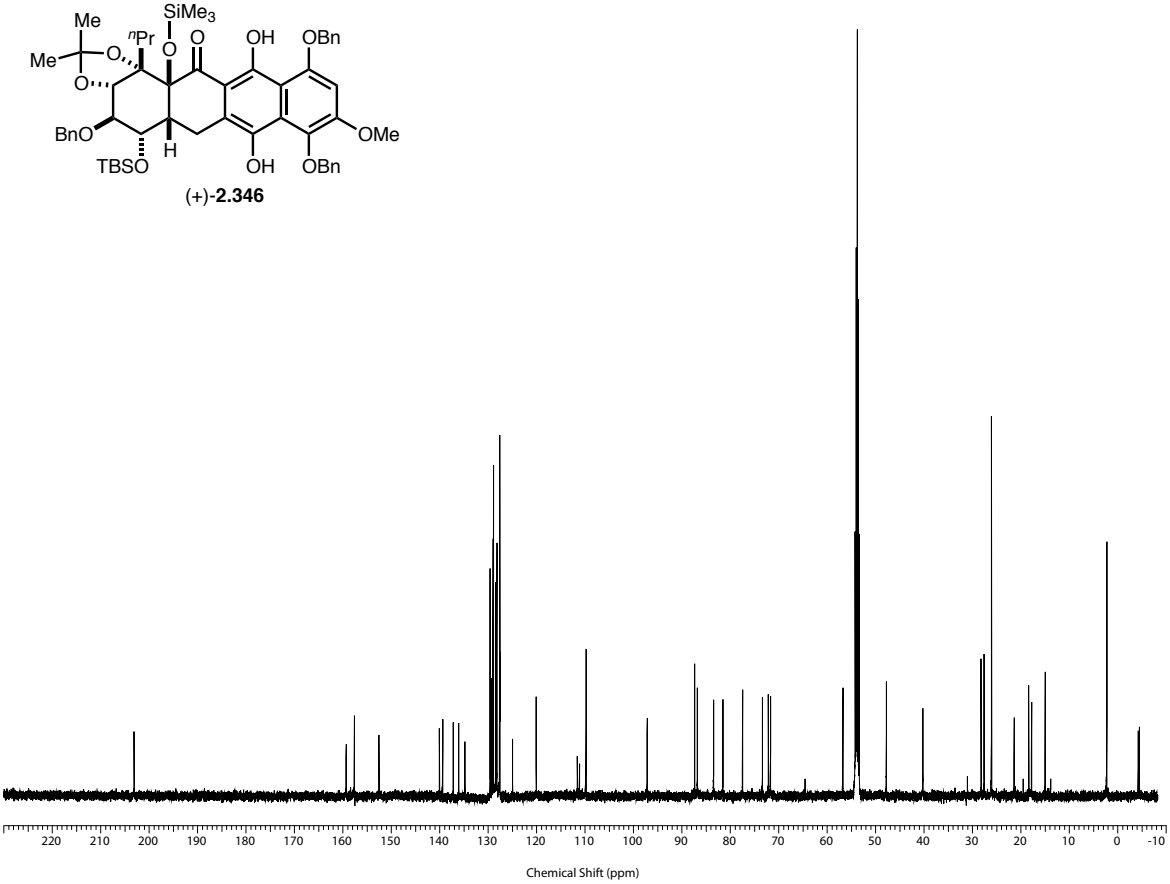

Me
SiMe3
nPr
O
O
OH
OBn
Me
O
O
BnO
H
OMe
TBSO
OH
OBn

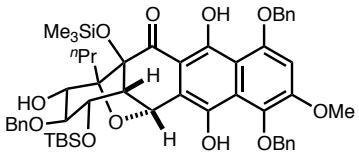
(+)-**2.346**


16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

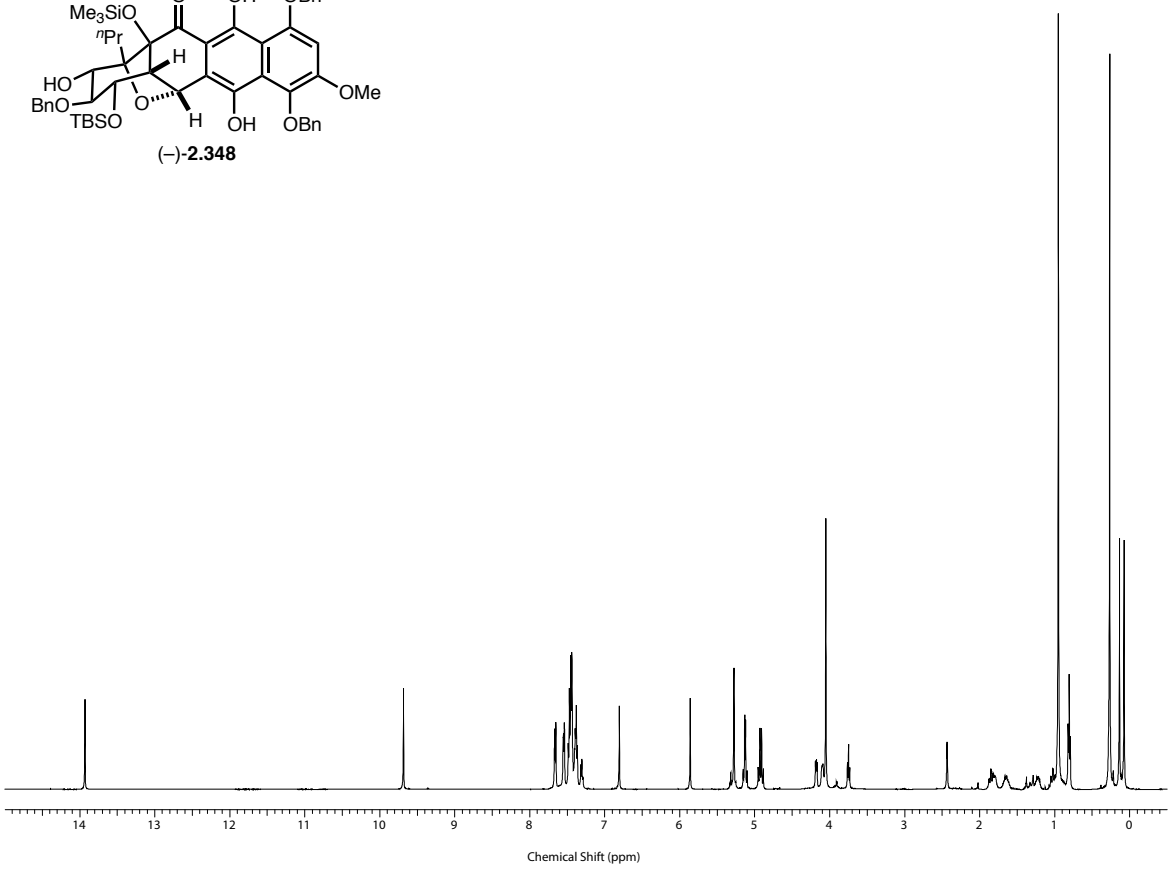

Me
SiMe3
nPr
O
O
OH
OBn
Me
O
O
BnO
H
OMe
TBSO
OH
OBn

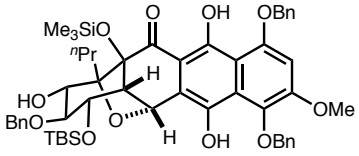
(+)-**2.346**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

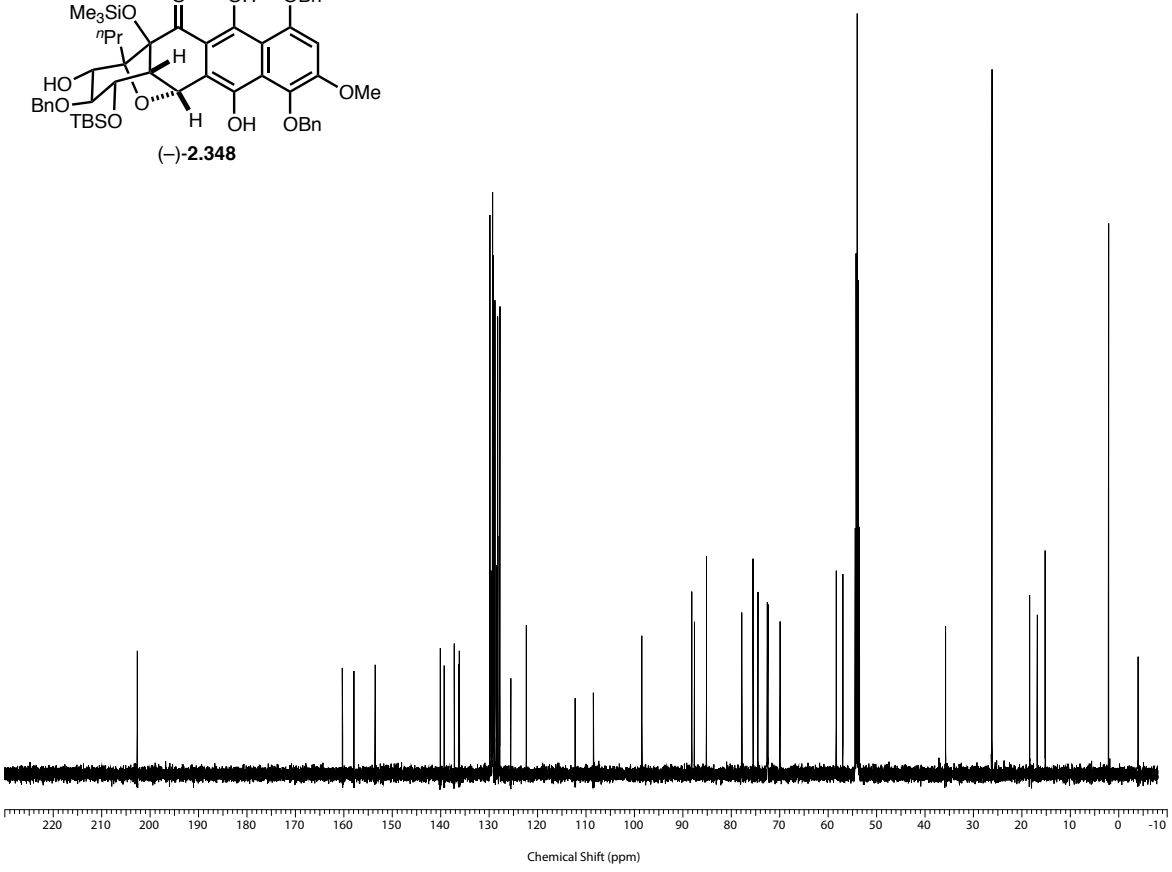

Me3SiO
nPr
O
OH
OBn
H
HO
BnO
TBSO
O
H
OH
OBn
OMe

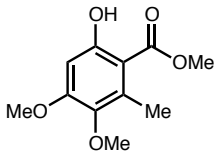
(–)-**2.348**


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

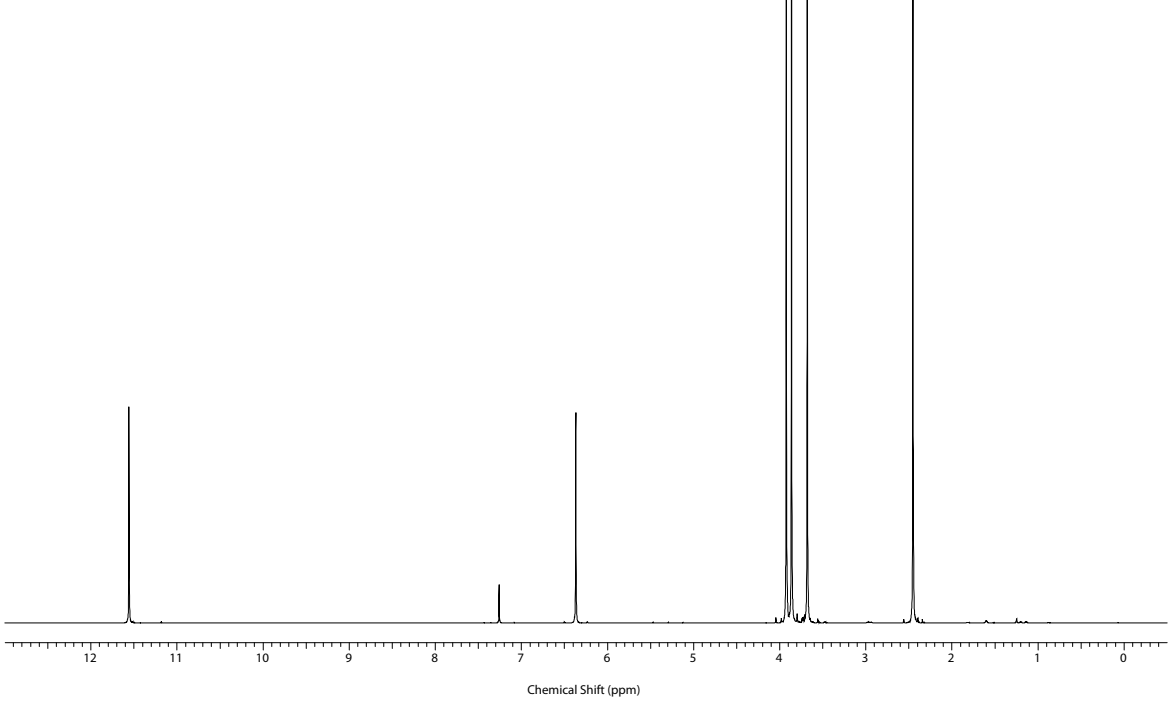

Me3SiO
nPr
O
OH
OBn
H
HO
BnO
TBSO
O
H
OH
OBn
OMe

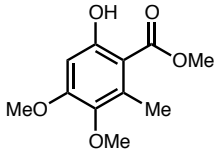
(–)-**2.348**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

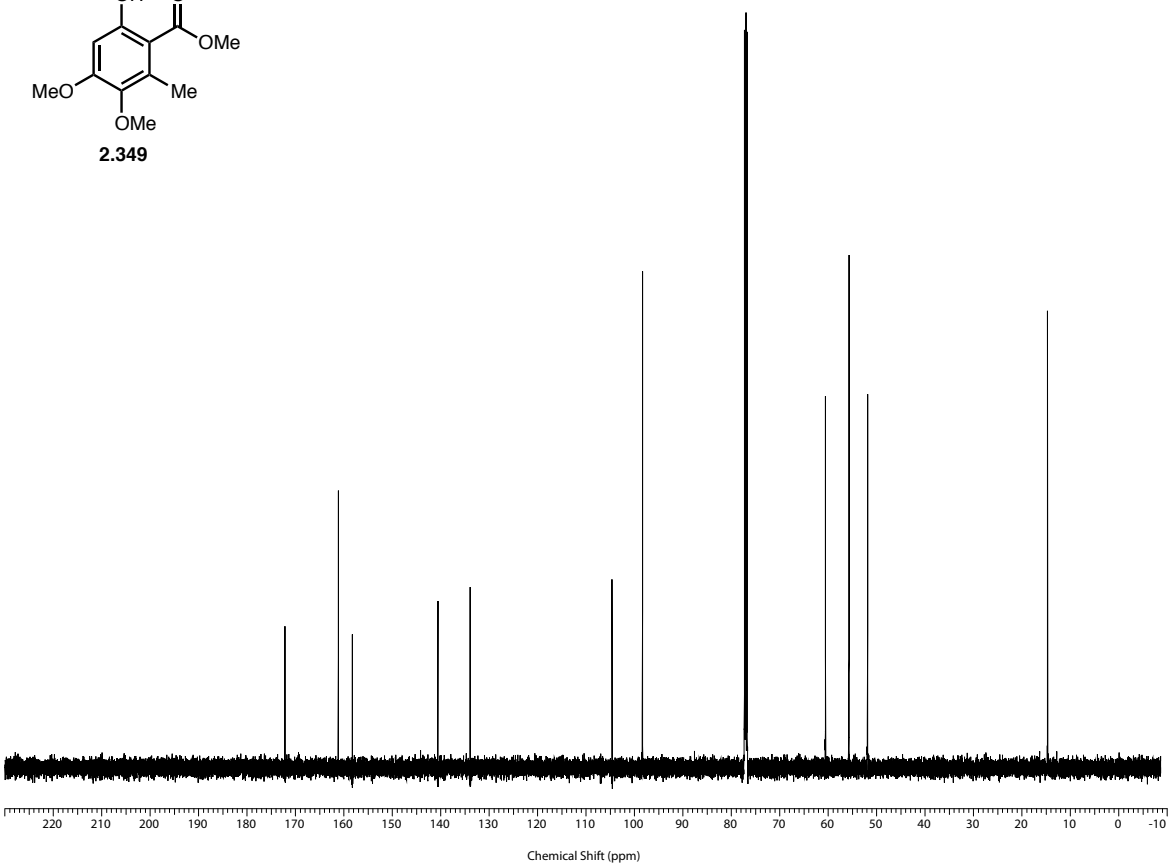

OH
O
OMe
MeO
Me
OMe

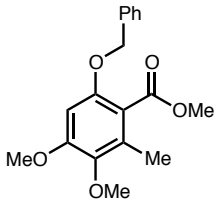
2.349


12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

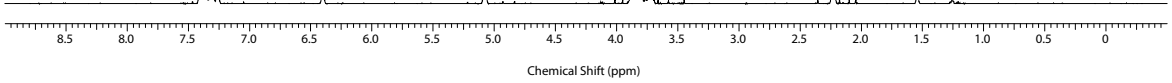

OH
O
OMe
MeO
Me
OMe

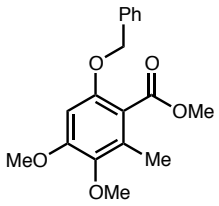
2.349


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

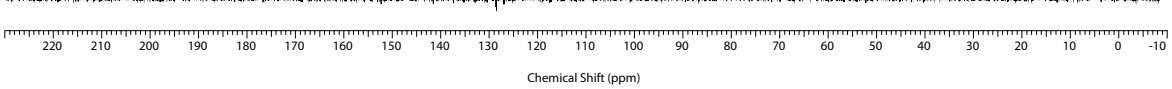

Ph
O
O
OMe
MeO
Me
OMe

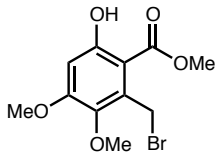
2.350


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

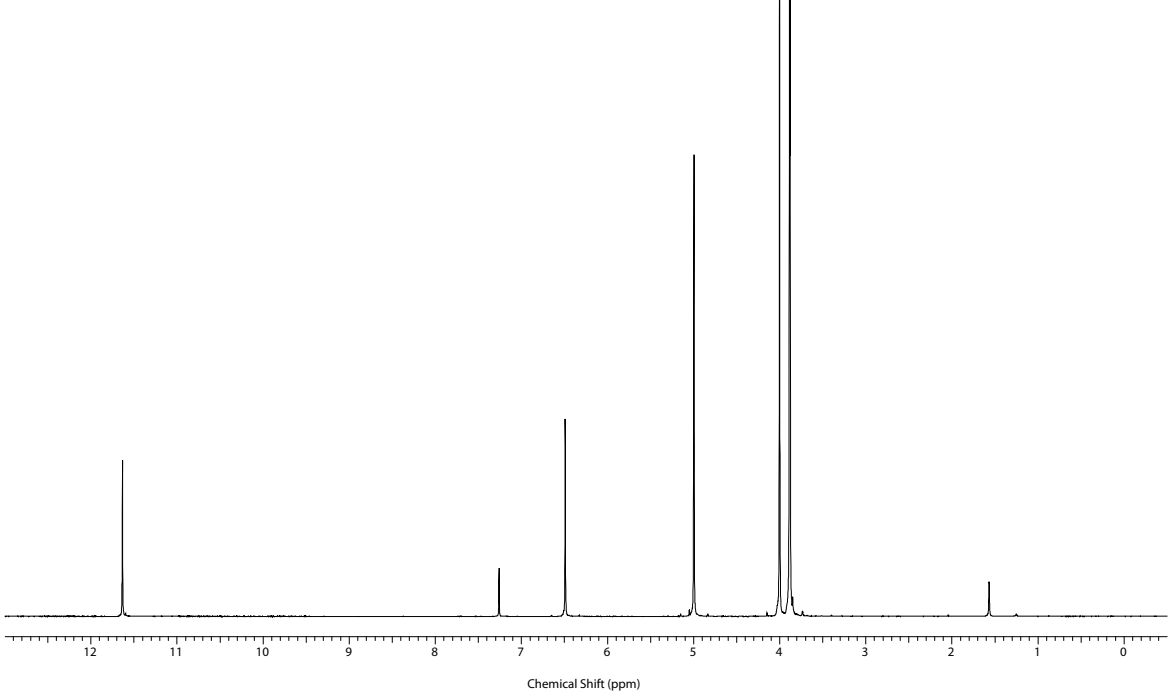

Ph
O
O
OMe
MeO
Me
OMe

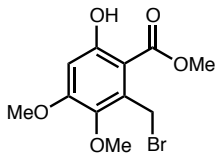
2.350


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

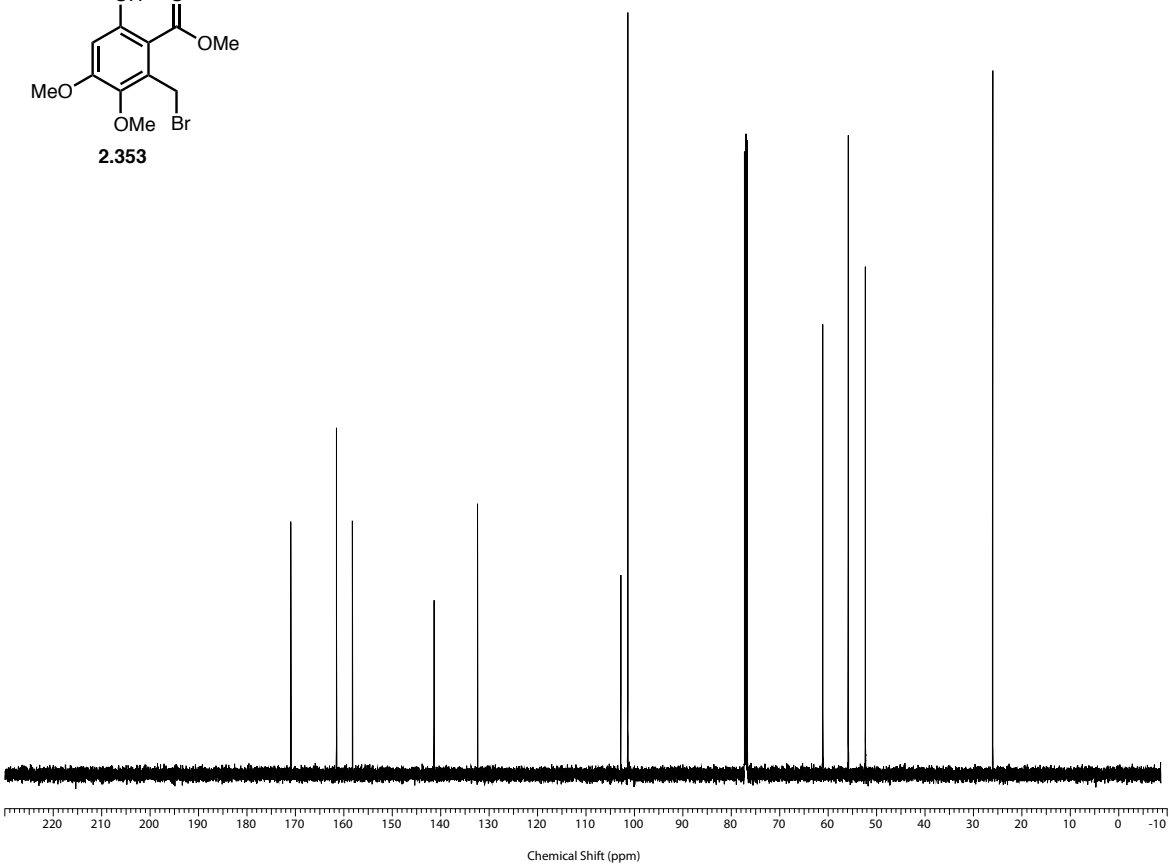

OH
O
OMe
MeO
OMe
Br

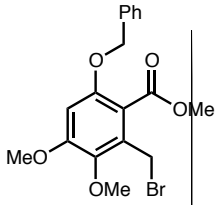
2.353


12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

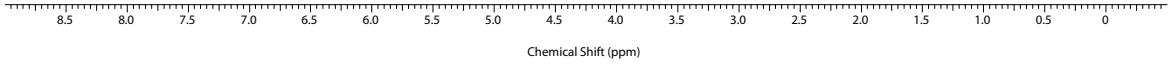

OH
O
OMe
MeO
OMe
Br

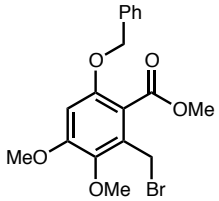
2.353


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

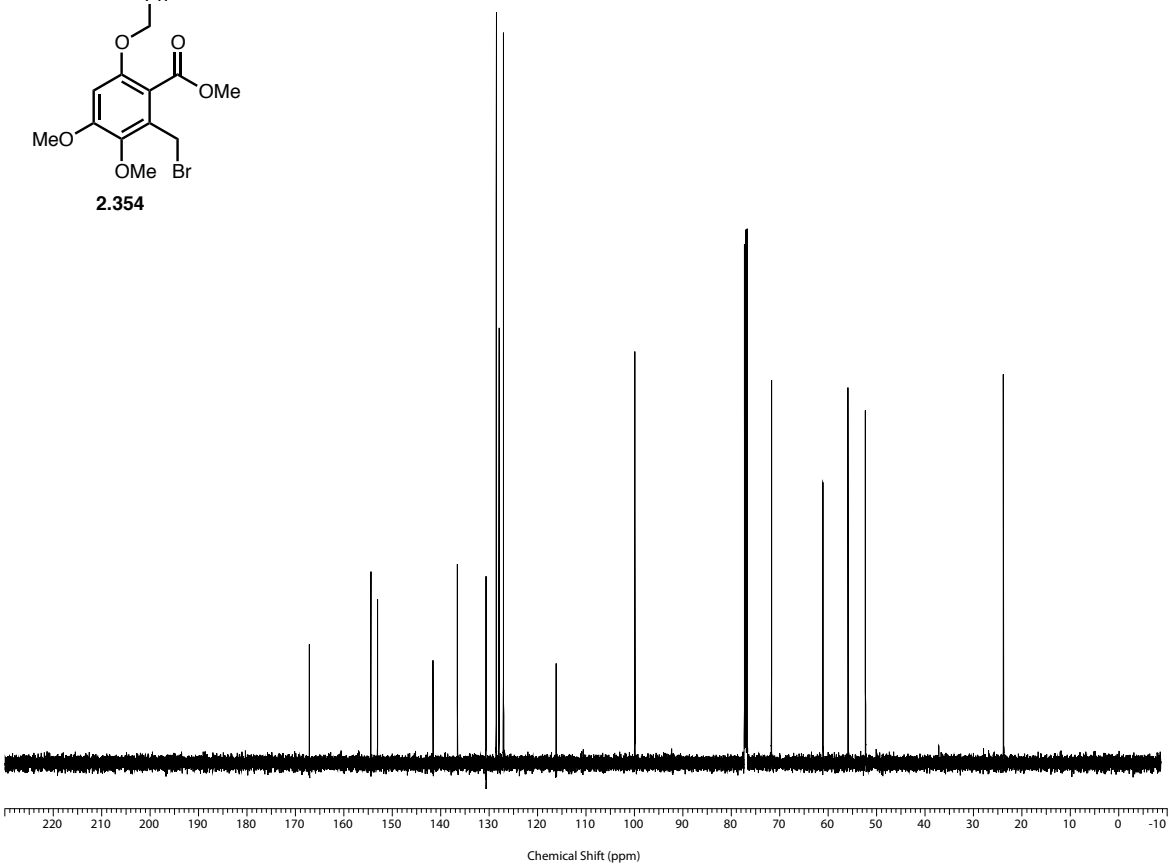

Ph
O
O
OMe
MeO
OMe
Br

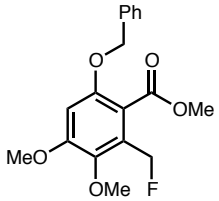
2.354


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

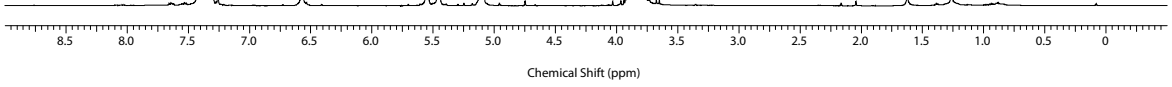

Ph
O
O
OMe
MeO
OMe
Br

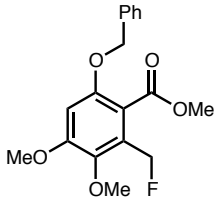
2.354


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

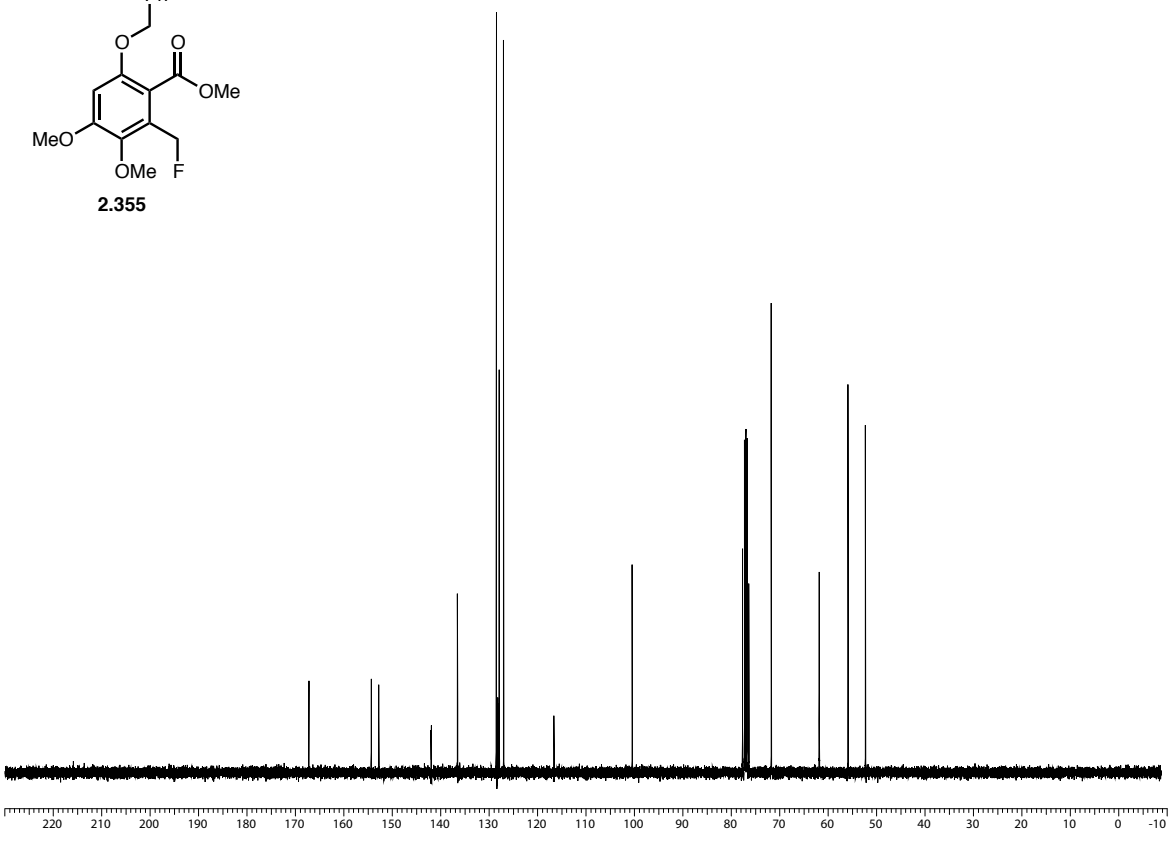

Ph
O
O
OMe
MeO
OMe
F

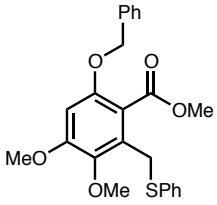
2.355


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

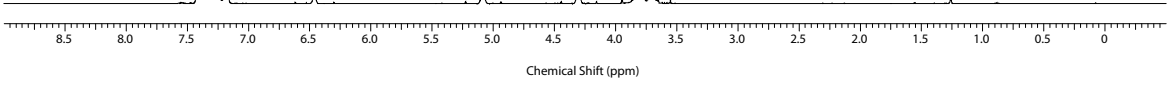

Ph
O
O
OMe
MeO
OMe
F

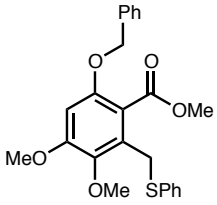
2.355


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

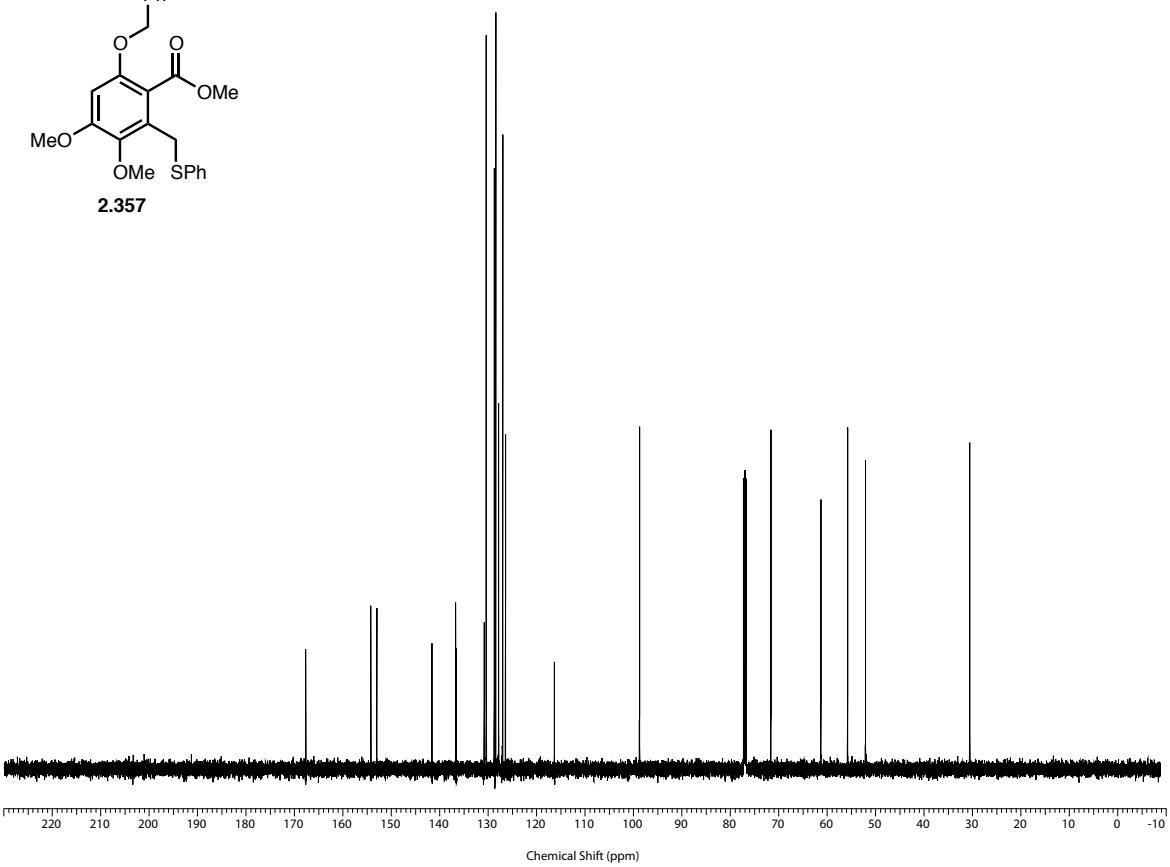

Ph
O
O
OMe
MeO
OMe
SPh

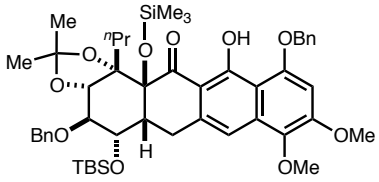
2.357


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

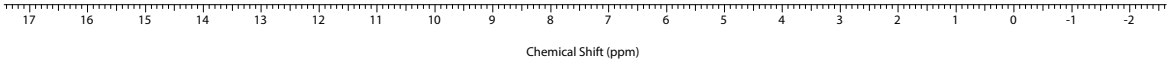

Ph
O
O
OMe
MeO
OMe
SPh

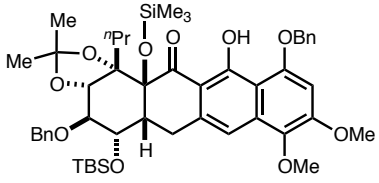
2.357


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

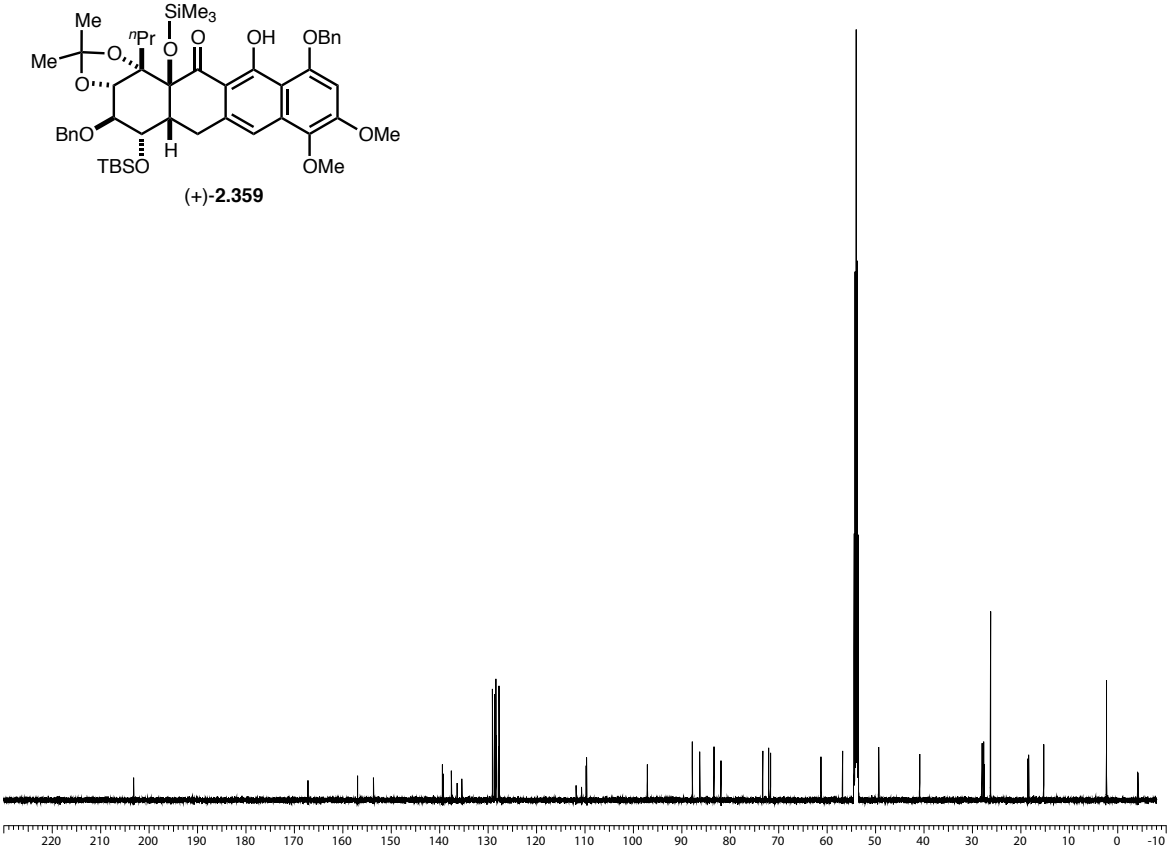

Me
SiMe3
nPr
O
OH
OBn
Me
O
O
BnO
OMe
H
TBSO
OMe

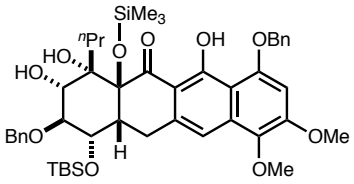
(+)-**2.359**


17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)

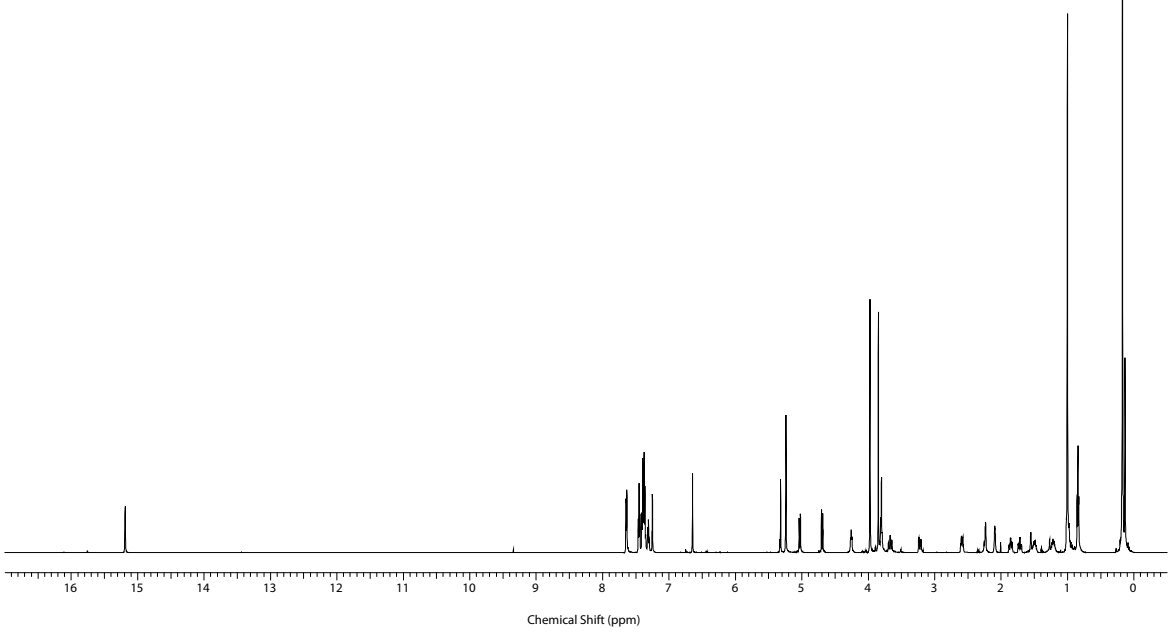

Me
SiMe3
nPr
O
OH
OBn
Me
O
O
BnO
OMe
H
TBSO
OMe

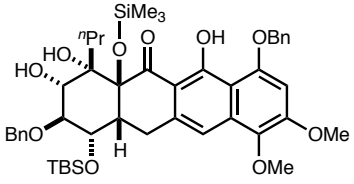
(+)-**2.359**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

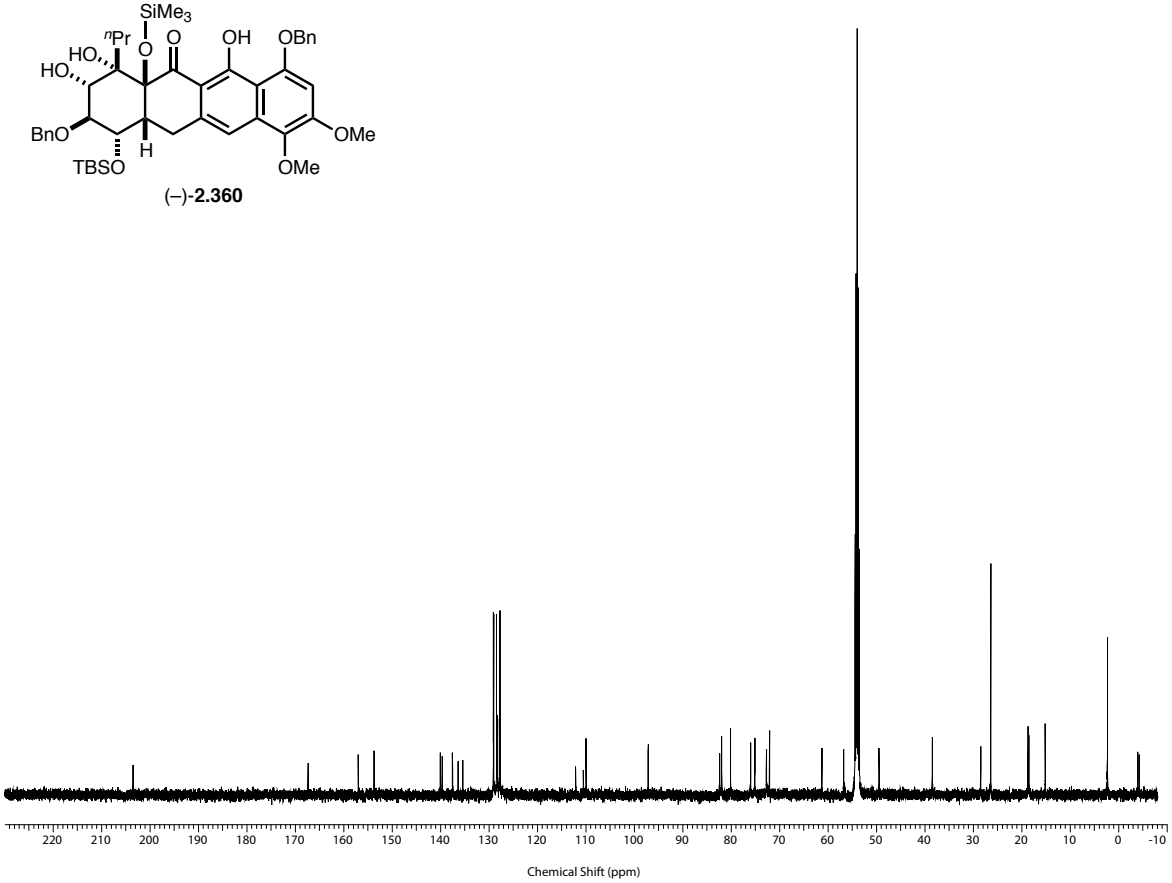

SiMe3
nPr
O
O
OH
OBn
HO
HO
BnO
H
OMe
TBSO
OMe

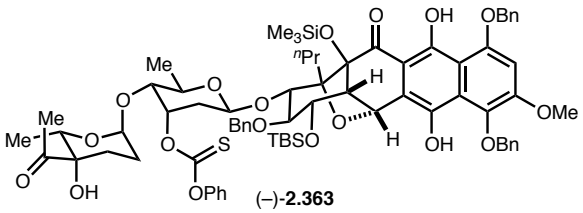
(–)-**2.360**


16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

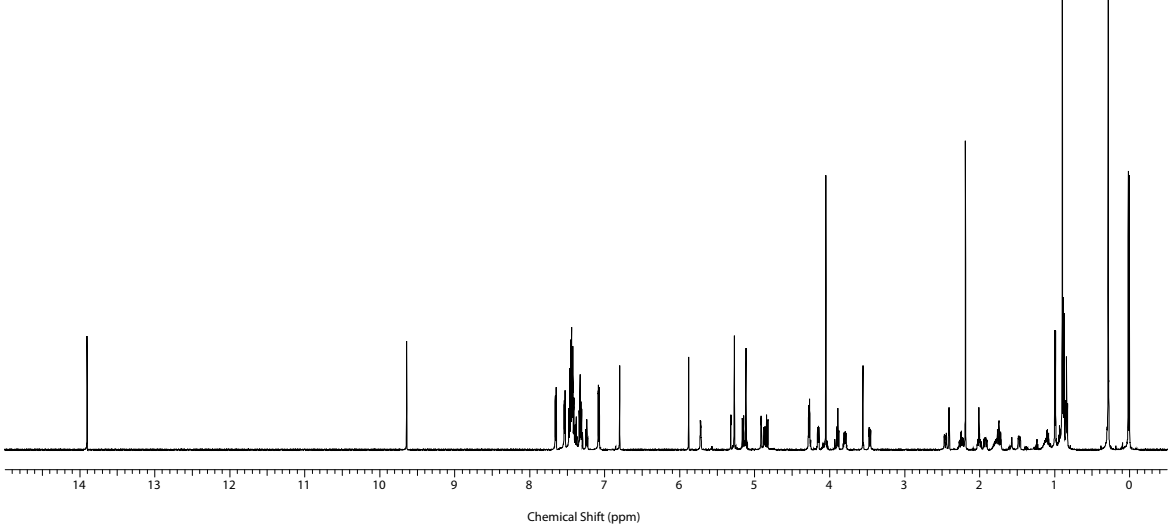

SiMe3
nPr
O
O
OH
OBn
HO
HO
BnO
H
OMe
TBSO
OMe

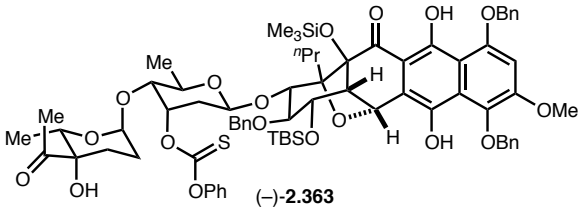
(–)-**2.360**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

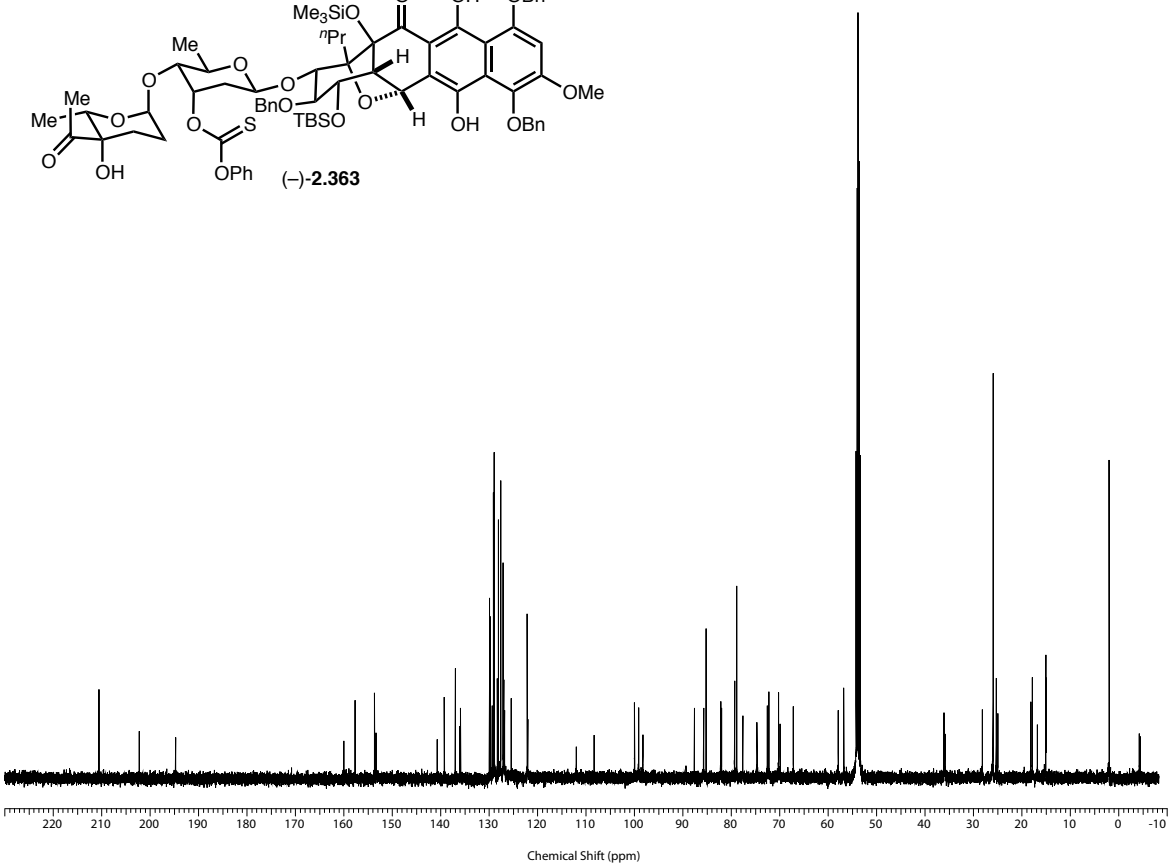

Me3SiO
nPr
O
OH
OBn
Me
H
OMe
Me
BnO
TBSO
O
H
OH
OBn
O
S
OPh
OH

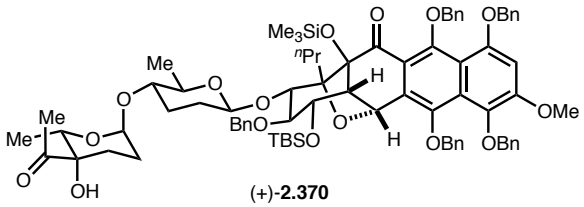
(–)-**2.363**


14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

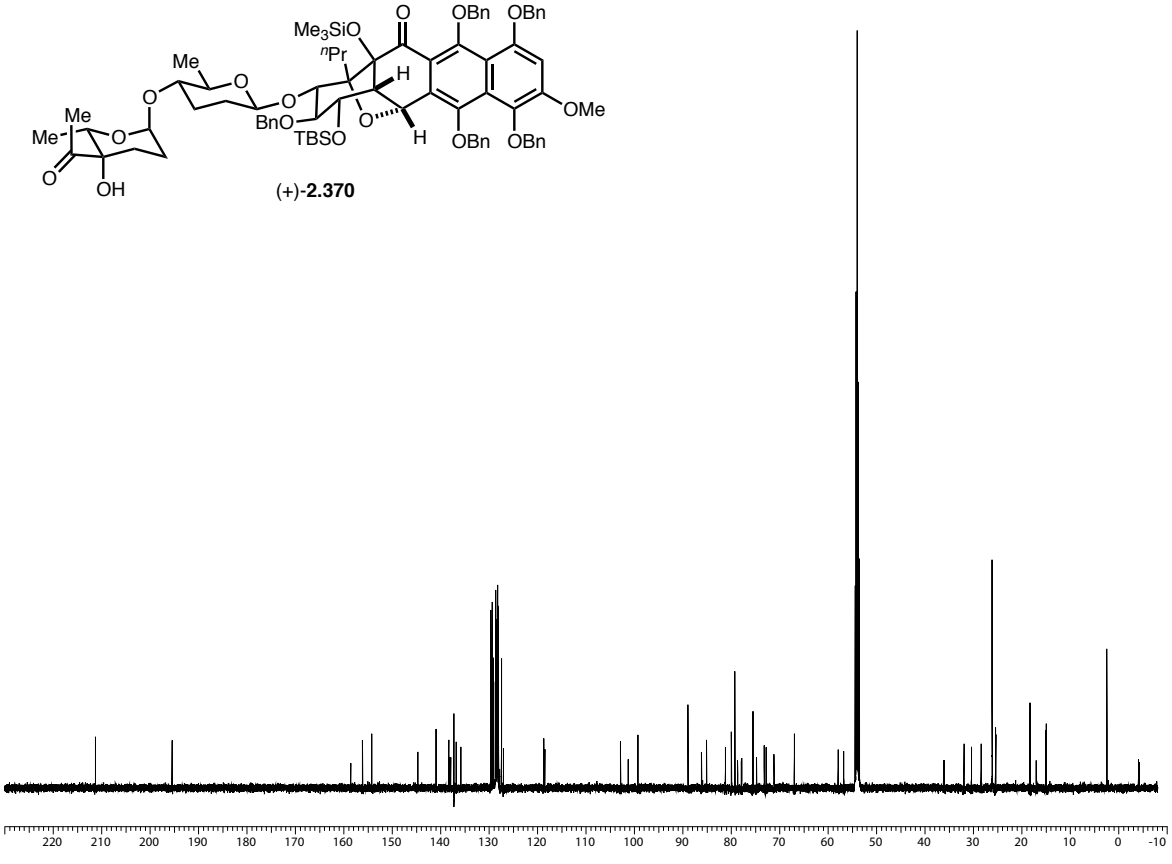

Me3SiO
nPr
O
OH
OBn
Me
H
OMe
Me
BnO
TBSO
O
H
OH
OBn
O
S
OPh
OH

(–)-**2.363**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


Me3SiO
nPr
O
OBn
OBn
Me
H
O
O
O
BnO
TBSO
O
H
OBn
OBn
OMe
Me
Me
O
O
OH

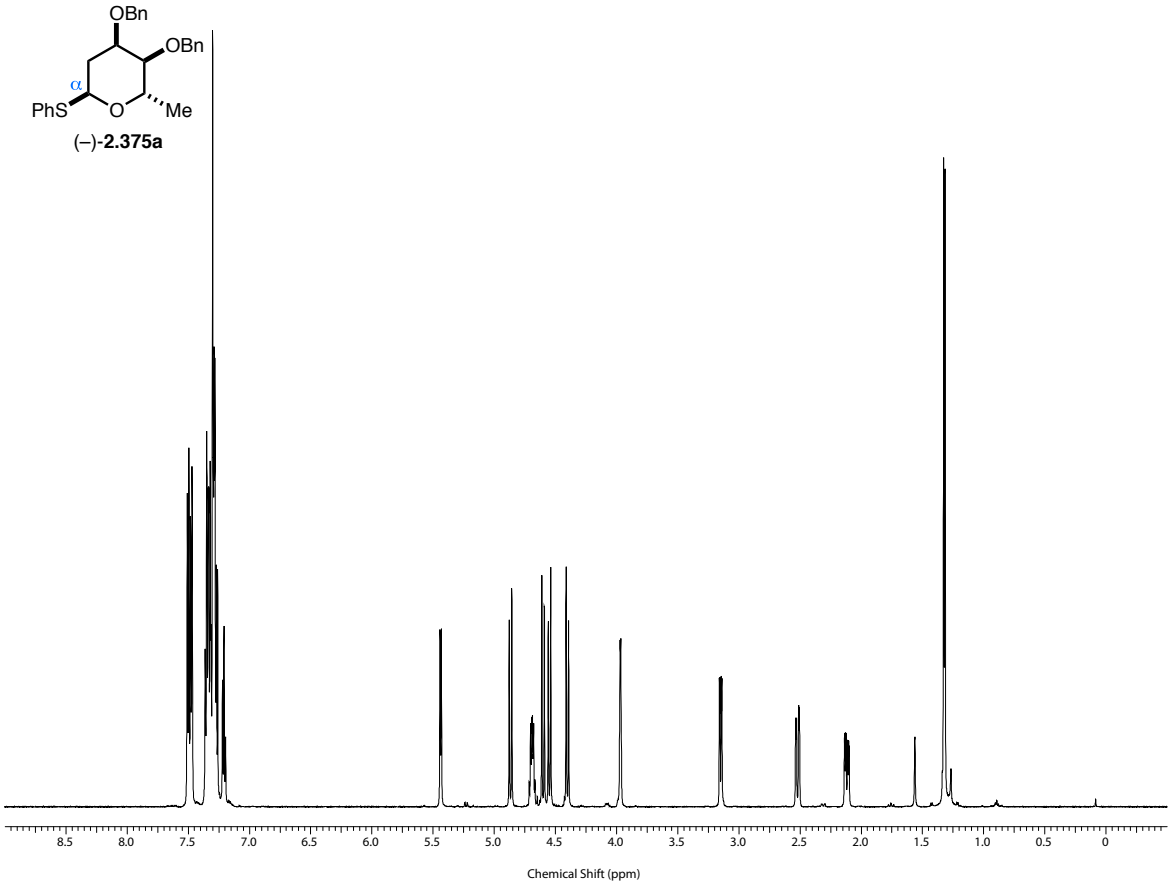
(+)-**2.370**

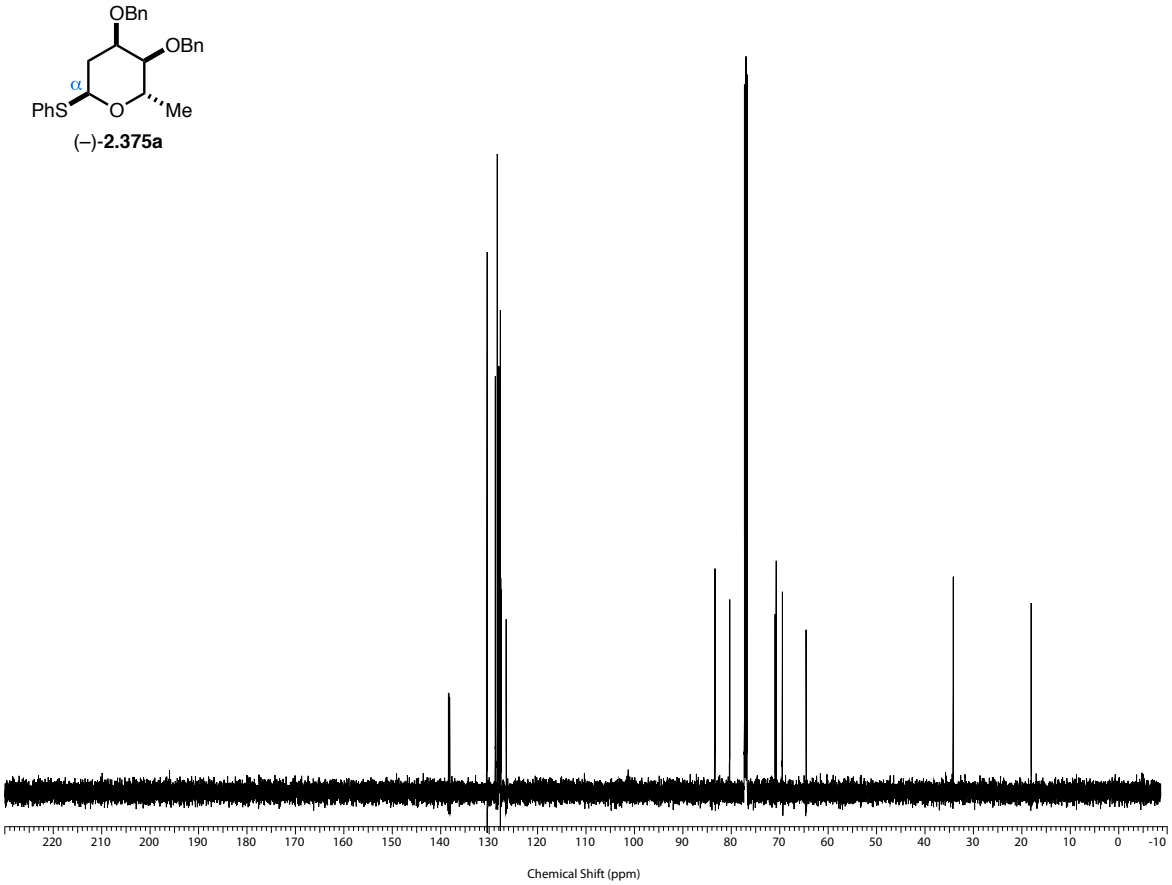

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

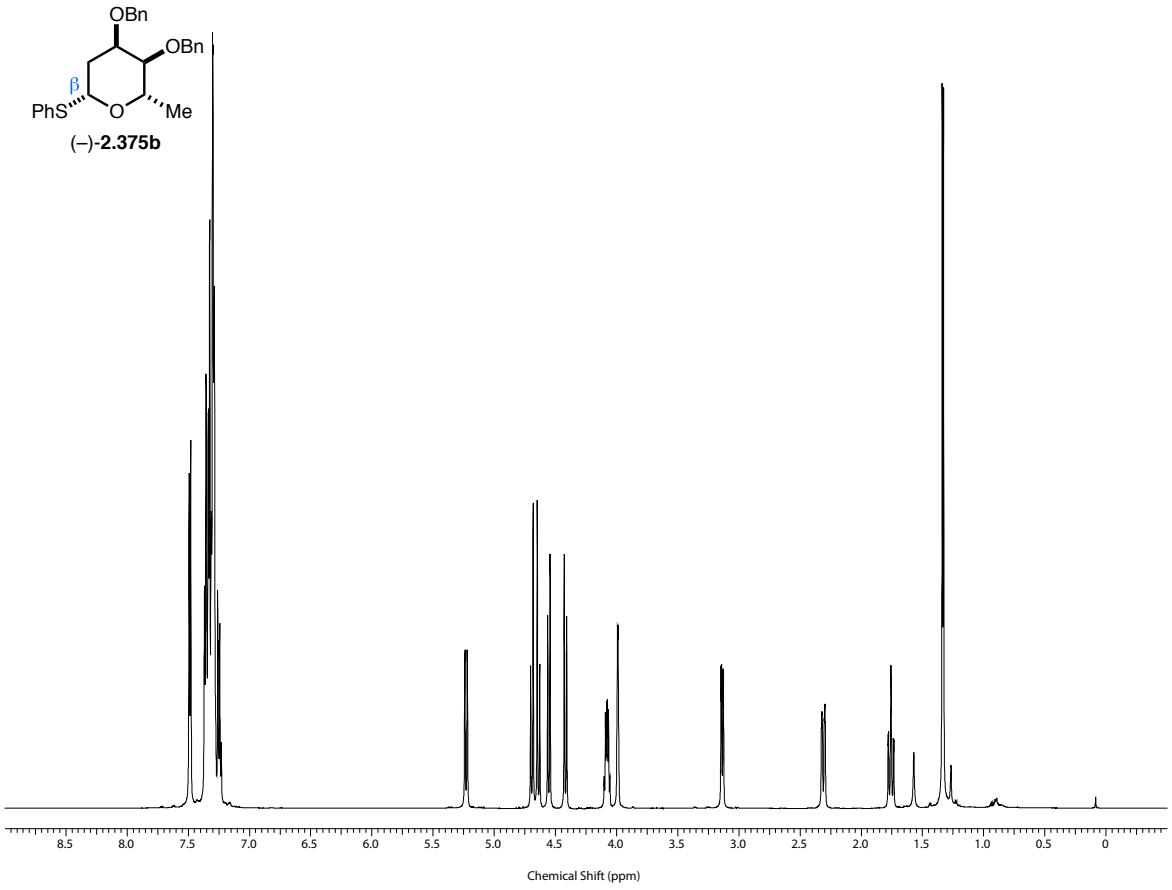
Me3SiO
nPr
O
OBn
OBn
Me
H
O
O
O
BnO
TBSO
O
H
OBn
OBn
OMe
Me
Me
O
O
OH

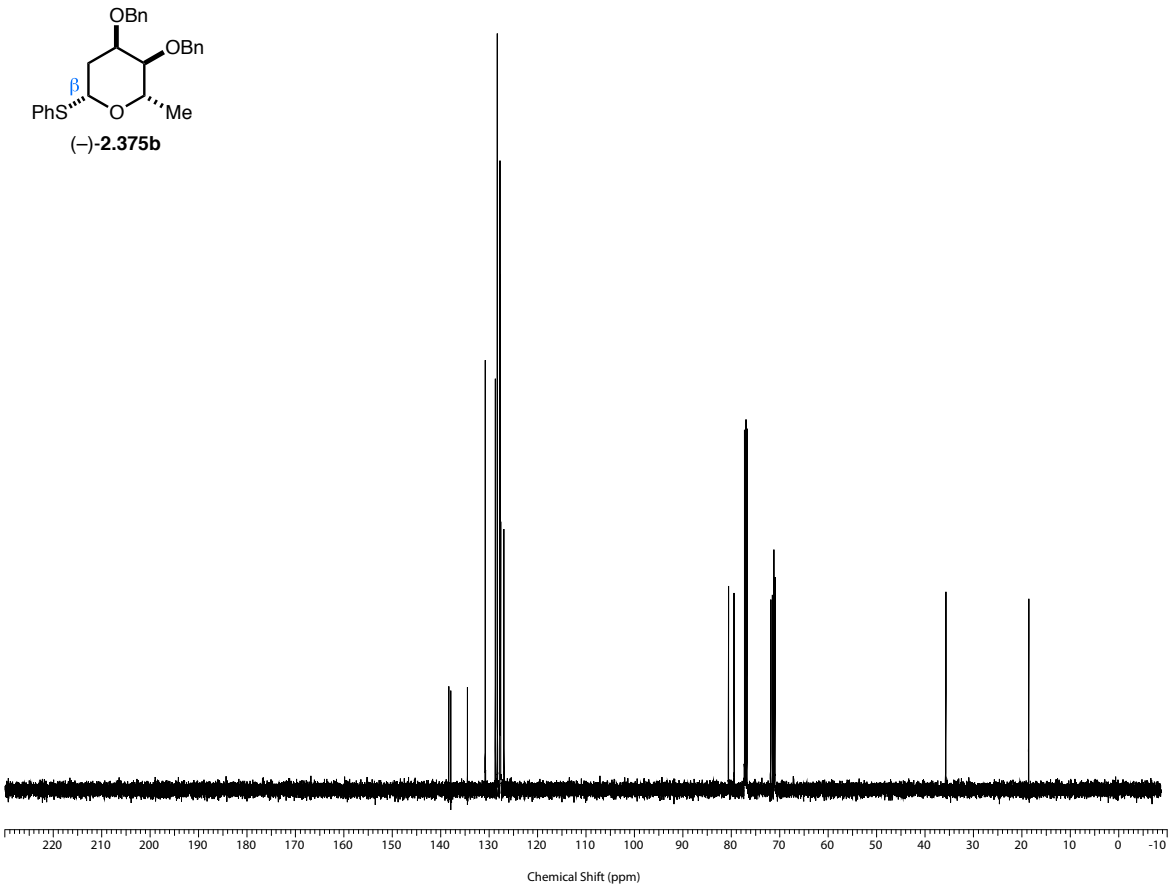
(+)-**2.370**

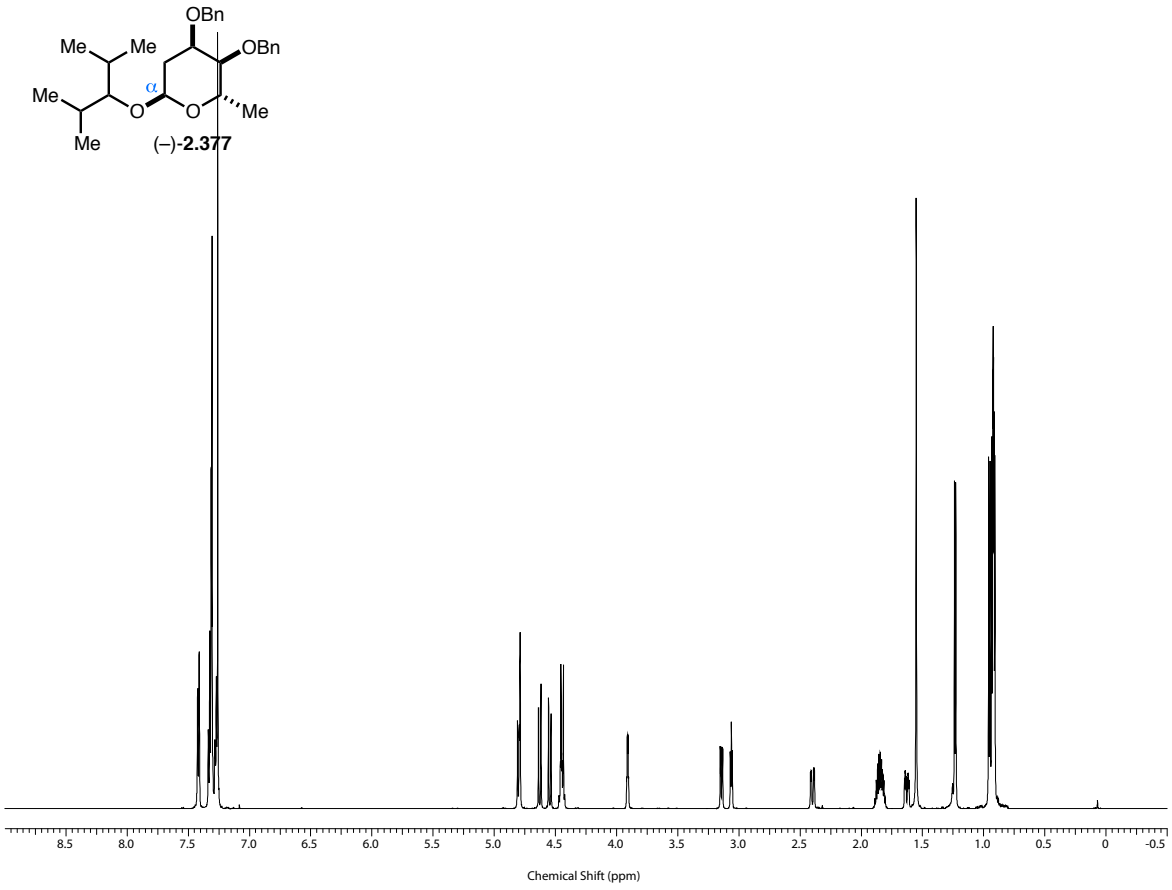
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

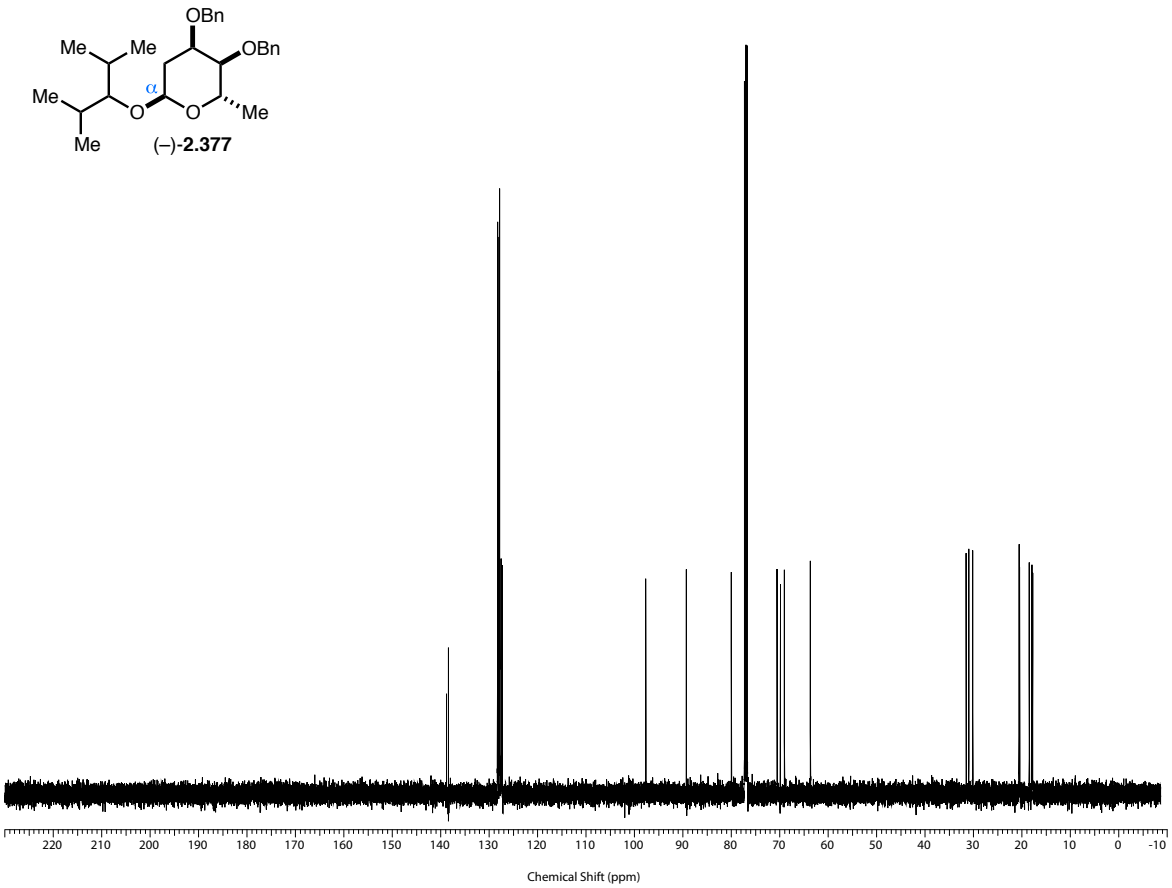

OBn
OBn
α
PhS
O
Me
(–)-2.375a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

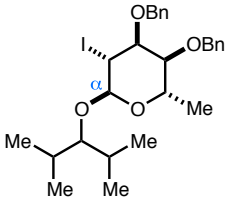

OBn
OBn
α
PhS
O
Me
(–)-2.375a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)


OBn
OBn
β
PhS
O
Me
(–)-2.375b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

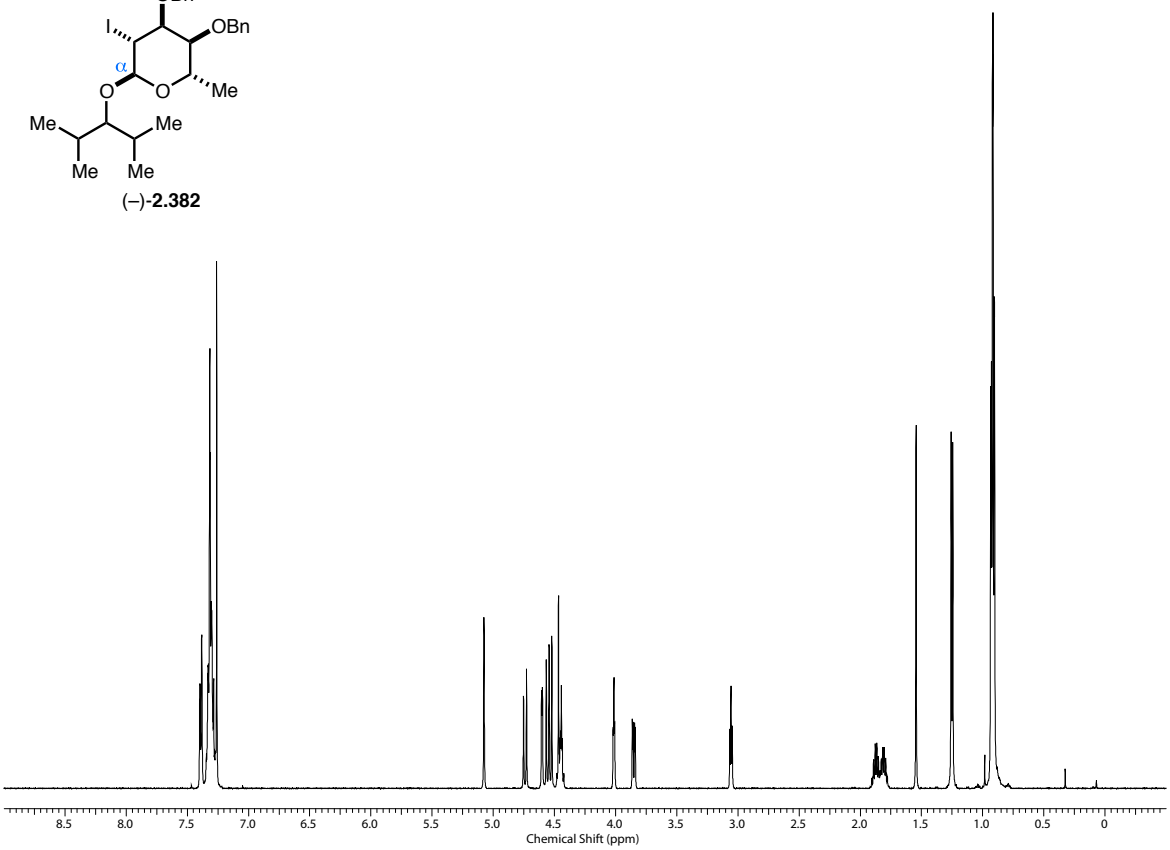

OBn
OBn
β
PhS
O
Me
(–)-2.375b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

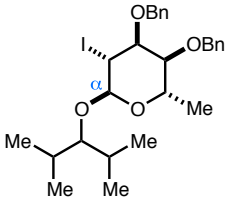

OBn
Me
Me
OBn
α
Me
O
O
Me
Me
(–)-2.377
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)


OBn
Me
Me
OBn
α
Me
O
O
Me
Me
(–)-2.377
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

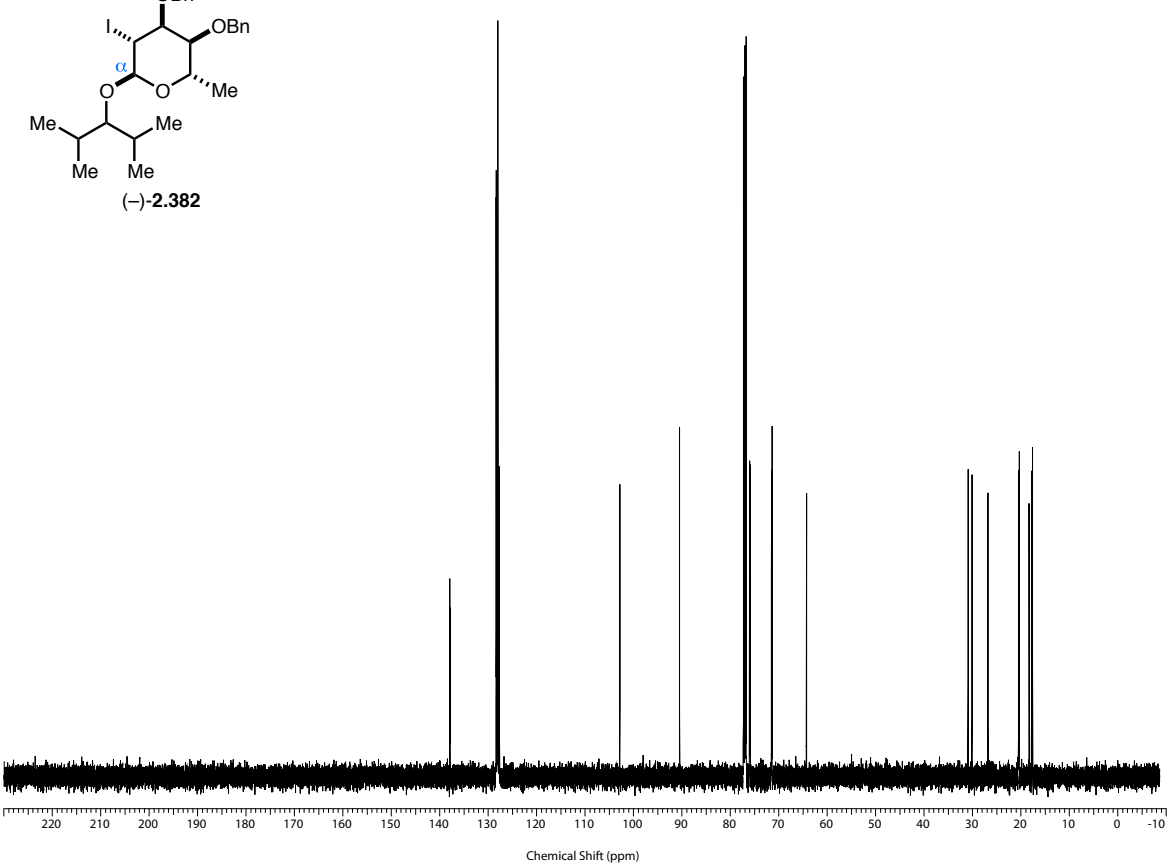

OBn
I
OBn
α
O
O
Me
Me
Me
Me
Me

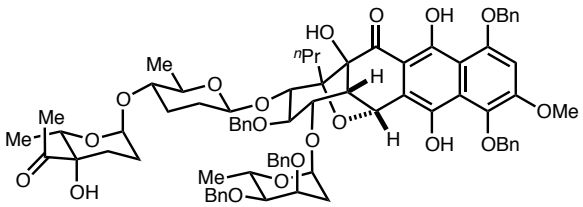
(–)-**2.382**


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

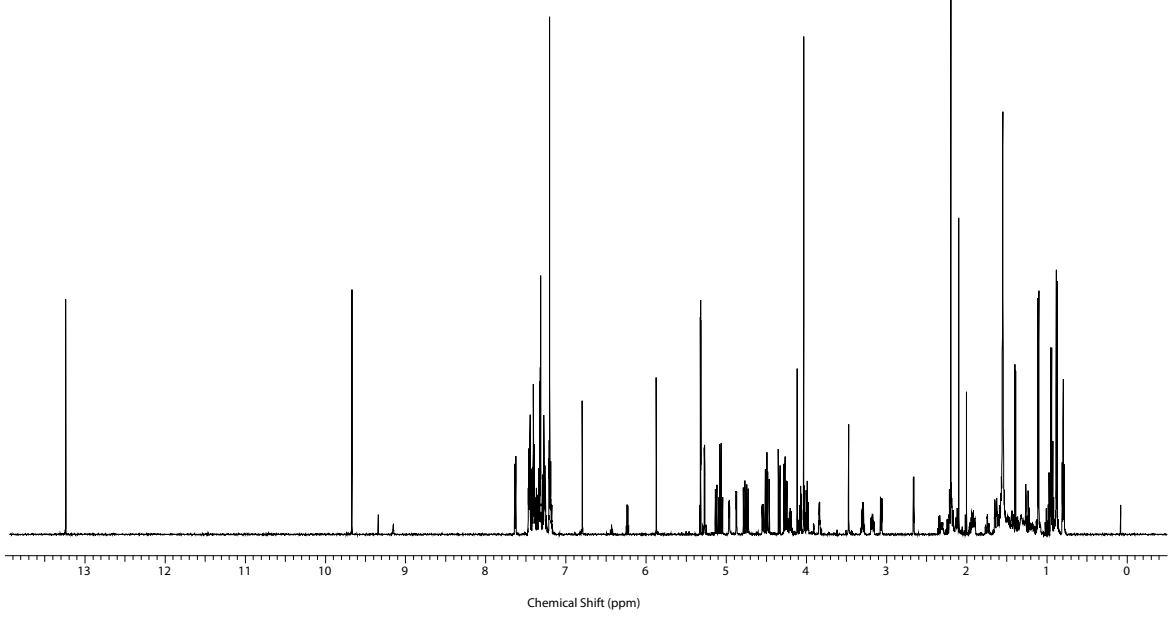

OBn
I
OBn
α
O
O
Me
Me
Me
Me
Me

(–)-**2.382**


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

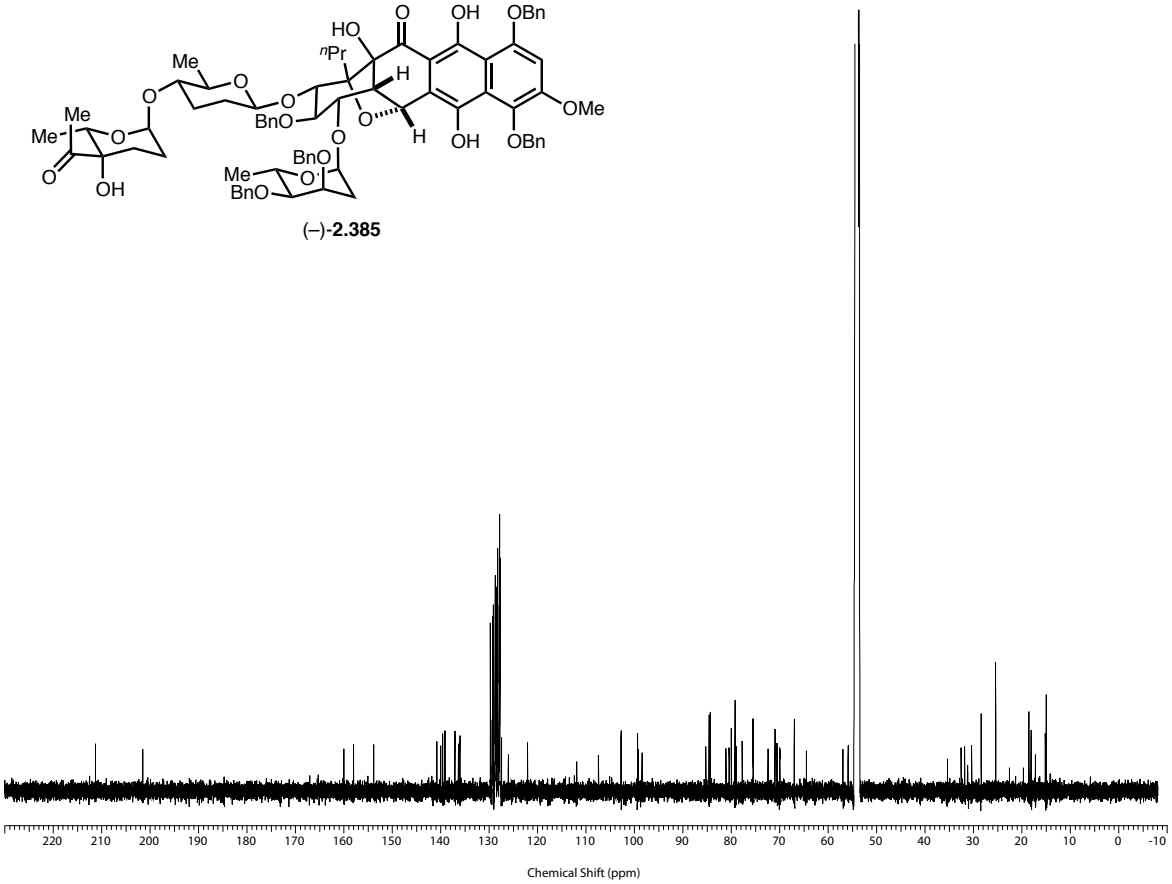

HO
O
OH
OBn
nPr
Me
H
O
OMe
Me
Me
O
BnO
O
H
OH
OBn
O
BnO
Me
BnO
O
O
OH

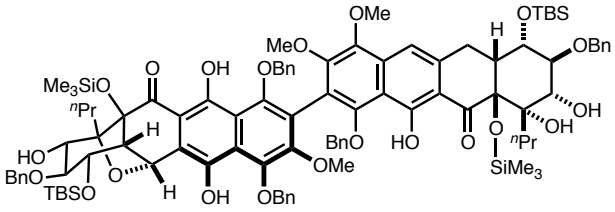
(–)-**2.385**


13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

HO
O
OH
OBn
nPr
Me
H
O
OMe
Me
Me
O
BnO
O
H
OH
OBn
O
BnO
Me
BnO
O
O
OH

(–)-**2.385**

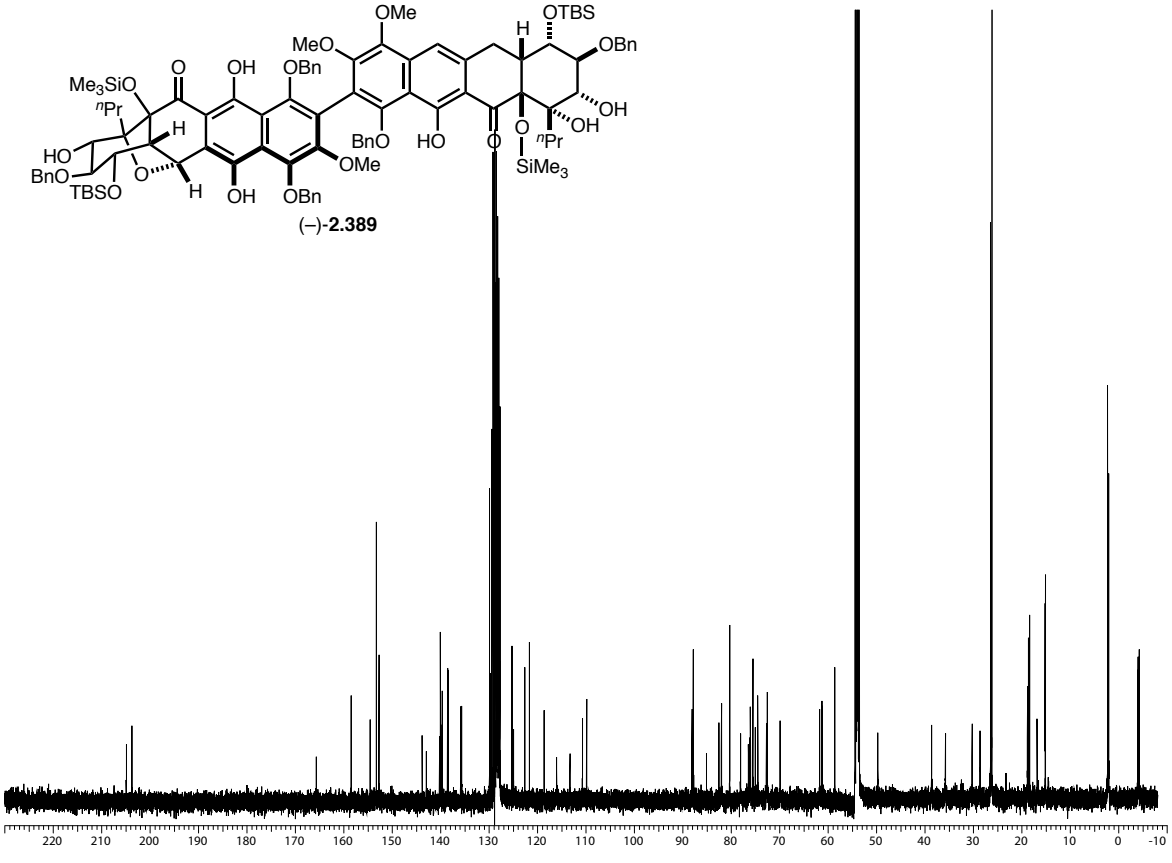

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



(–)-**2.389**

Chemical Shift (ppm)

(–)-**2.389**



Chemical Shift (ppm)