I. Catalytic Allylic Oxidation to Generate Vinylogous Acyl Sulfonates From Vinyl Sulfonates II. Synthesis of the Cucumin a Ring System via a 5-Endo-Trig Heck Cyclization

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II. Synthesis of the Cucumin A Ring System via a 5-endo-trig Heck Cyclization

A dissertation presented

by

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Dissertation Advisor: Professor Matthew D. Shair James Karl Tucker

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Abstract

The work presented in the first two chapters of this thesis culminated in a largely unprecedented allylic oxidation. Regioselective formation of vinylogous acyl sulfonates via allylic oxidation of the corresponding vinyl sulfonates was achieved with catalytic iron(III) chloride and stoichiometric *tert*-butyl hydroperoxide. The transformation exhibited tolerance of many different functional groups, including some other allylic and benzylic sites. Results were optimal for substrates with steric protection of the vinyl sulfonate moiety, although other classes of substrates were isolated in reduced yields.

The final chapter of this thesis describes the asymmetric synthesis of the cucumin A (**43**) ring system **174** via the 5-endo-trig Heck cyclization of **173**. Intermediate **173** was derived from enantioenriched **160**, which was forged from building blocks **158** and **159** via the chiral pryrrolidinyl sulfonamide promoter **156**.

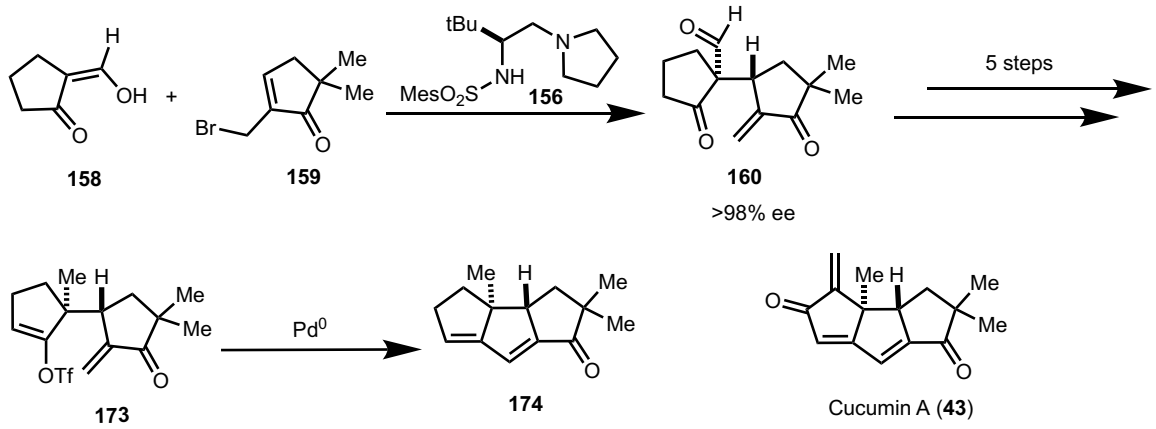

Table of Contents

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I thank the teachers, far too many to discuss in this space, who took an interest in my education while I attended the Kirkwood R7 school district. I remember each of your contributions to the fostering of my scientific inquiries and their clear communication.

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always been intelligent and funny. Ethan Magno, of the Myers lab, has been a thoughtful contributor to discussions of many topics—chemistry, writing, and music, to name a few.

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List of Abbreviations

$(Ph_3P)_4Pd^0$	tetrakis(triphenylphosphine)palladium(0)
$(Ru(p\text{-cymene})Cl_2)_2$	dichloro(p-cymene)ruthenium(II) dimer
3,5-DMP	3,5-dimethylpyrazole
ACN	acetonitrile
AIBN	azobisisobutyronitrile
allyl-$SnBu_3$	allyltributylstannane
Br_2	bromine
BTF	benzotrifluoride
CBr_4	carbon tetrabromide
$CeCl_3$	cerium trichloride
CH_2Cl_2 or DCM	methylene chloride
CH_2O	fomaldehyde
$CHCl_3$	chloroform
$ClC(S)OC_6F_5$	pentafluorophenyl chlorothionoformate
CrO_3	chromium trioxide
Cs_2CO_3	cesium carbonate
CSA	camphorsulfonic acid
CsF	cesium fluoride
$Cu(OAc)_2$	cupric acetate
CuI	cuprous iodide
D-(-)-DET	(2S, 3S)-diethyltartrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide

DMP	Dess-Martin periodinane
DMPE	1,2-Bis(dimethylphosphino)ethane
DMSO	dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalent
Et_3B	triethylborane
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
$Fe(acac)_3$	iron(III) acetylacetonate
$FeCl_2$	iron(II) chloride
$FeCl_3$	iron(III) chloride
$Hg(OAc)_2$	mercuric acetate
HMDS	hexamethyldisilazide
$HSnBu_3$	tri-*n*-butylstannane
IBX	2-iodoxybenzoic acid
iPr_2NEt	ethyl diisopropylamine
K_2CO_3	potassium carbonate
KHMDS	potassium bis(trimethylsilyl)amide
KOAc	potassium acetate
KOH	potassium hydroxide
KOtBu	potassium *tert*-butoxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiCl	lithium chloride
$LiHAl(OtBu)_3$	lithium tri-*tert*-butoxy aluminum hydride
$LiHBEt_3$	lithium triethylborohydride
LLS	longest linear sequence

LTS	linear triquinane sesquiterpene
M.S.	molecular sieves
mCPBA	3-chloroperbenzoic acid
MeOH	methanol
MoOPH	oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide)
MsCl	mesyl chloride
$N_2H_4 \cdot H_2O$	hydrazine monohydrate
Na_2CO_3	sodium carbonate
$Na_2Cr_2O_7$	sodium dichromate
$Na_2S_2O_3$	sodium thiosulfate
$NaBH_4$	sodium borohydride
NaH_2PO_4	sodium phosphate, monobasic
NaOH	sodium hydroxide
NfF	perfluorobutanesulfonyl fluoride
Nf	perfluorobutanesulfonyl
NH_3	ammonia
NHS	*N*-hydroxysuccinimide
Ox	oxidation
$Pd(OH)_2/C$	palladium hydroxide on carbon
$PhB(OH)_2$	phenylboronic acid
PhH	benzene
PhLi	phenyllithium
PhMe	toluene
PhNHLi	lithium anilide
$PhSiH_3$	phenylsilane
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PPAP	polycyclic polyprenylated acylphloroglucinol
PPh_3	triphenylphosphine
pyr	pyridine

quant.	quantitative
Rh_2cap_4	dirhodium tetracaprolactamate
RT	room temperature
s-BuLi	*sec*-Butyllithium
$Sc(OTf)_3$	scandium(III) triflate
SeO_2	selenium dioxide
SJW	St. John's Wort
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBSCl	*tert*-butyl dimethylsilylchloride
tBuOH	*tert*-butanol
Tf_2O	trifluoromethansulfonic anhydride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
$Ti(OiPr)_4$	titanium(IV) isopropoxide
TIPSOTf	triisopropyl trifluoromethanesulfonate
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Chapter 1: Improvement of an Oxidative Step in a PPAP Synthesis Platform

Coworkers: Dr. Brian A. Sparling & Dr. David C. Moebius

Introduction

The following chapter traces the development of my interest in allylic oxidation chemistry in the context of a platform leveraged toward syntheses of analogues of the polyprenylated acylphloroglucinol (PPAP) known as hyperforin. Improvement of the oxidative formation of a vinylogous ester from a methyl-vinyl ether within this route would serve as inspiration for subsequent research pursuits.

Pursuit of Polyprenylated Acylphloroglucinol Synthesis

To date, there are some 717 molecules known as PPAPs.[1] The structures are comprised of an acylphloroglucinol core with varying degrees of oxygenation and a varying number and location of isoprenyl or geranyl linkages.[1] Several members of this class have been the targets of total synthesis, given their challenging structures and interesting bioactivities. One compound of particular interest given its putative antidepressive and anti-inflammatory properties is hyperforin (**1**), a constituent of the folk medicine known as St. John's Wort (SJW).[2] Our lab had developed a bio-inspired, enantioselective route to **1**.[3] Two other closely-related compounds known as seco-hyperforin (**2**) and *ent*-nemorosone (**3**) were also synthesized in our lab through analogous chemistry (**Figure 1.1**).[4] Analogues of **1** to probe the mechanism of its efficacy with regards to depression and improve its safety profile were of interest. In the context of analogue development, a key allylic oxidation step in the course of the syntheses of these molecules defined the first part of my studies.

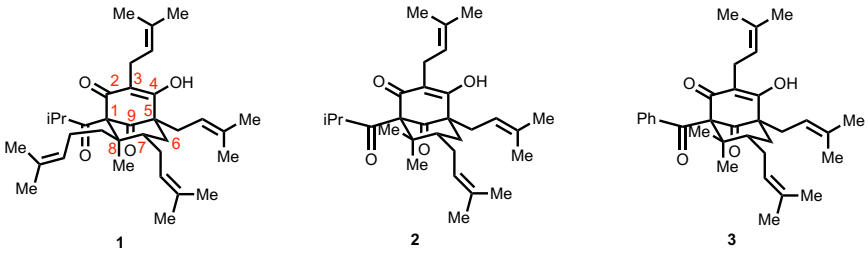
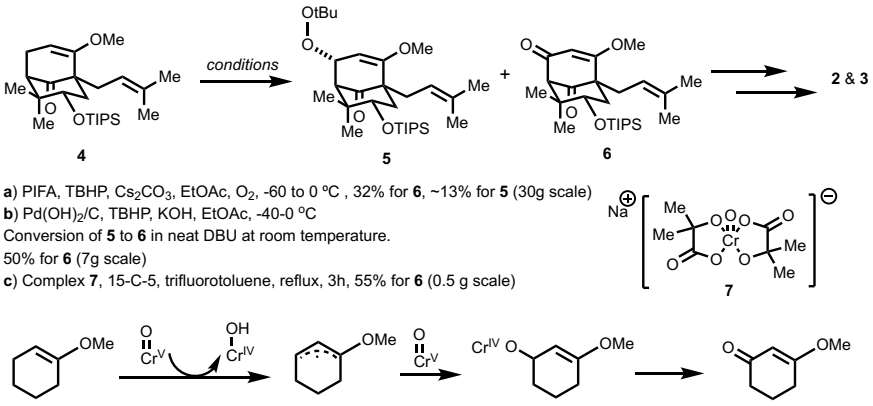


Figure 1.1. The structures of hyperforin (bicycle positions numbered in red), secohyperforin (**2**), and ent-nemorosone (**3**)

Allylic Oxidation Improvement

My studies commenced with improving the route to **2** and **3**. Even with the syntheses accomplished, the low yield and poor reproducibility of the C2 oxidation of intermediate **4** stood athwart the efficiency of the route. Initial conditions **a** based on a protocol developed by Yeung et al. formed a mixture of side product **5** and desired product **6**; additionally, yield of formation of **6** was as low as 18% on scale (**Scheme 1.1**).[5] Application of Corey-Yu oxidation conditions led to a more consistent yield of **6** on scale than before;

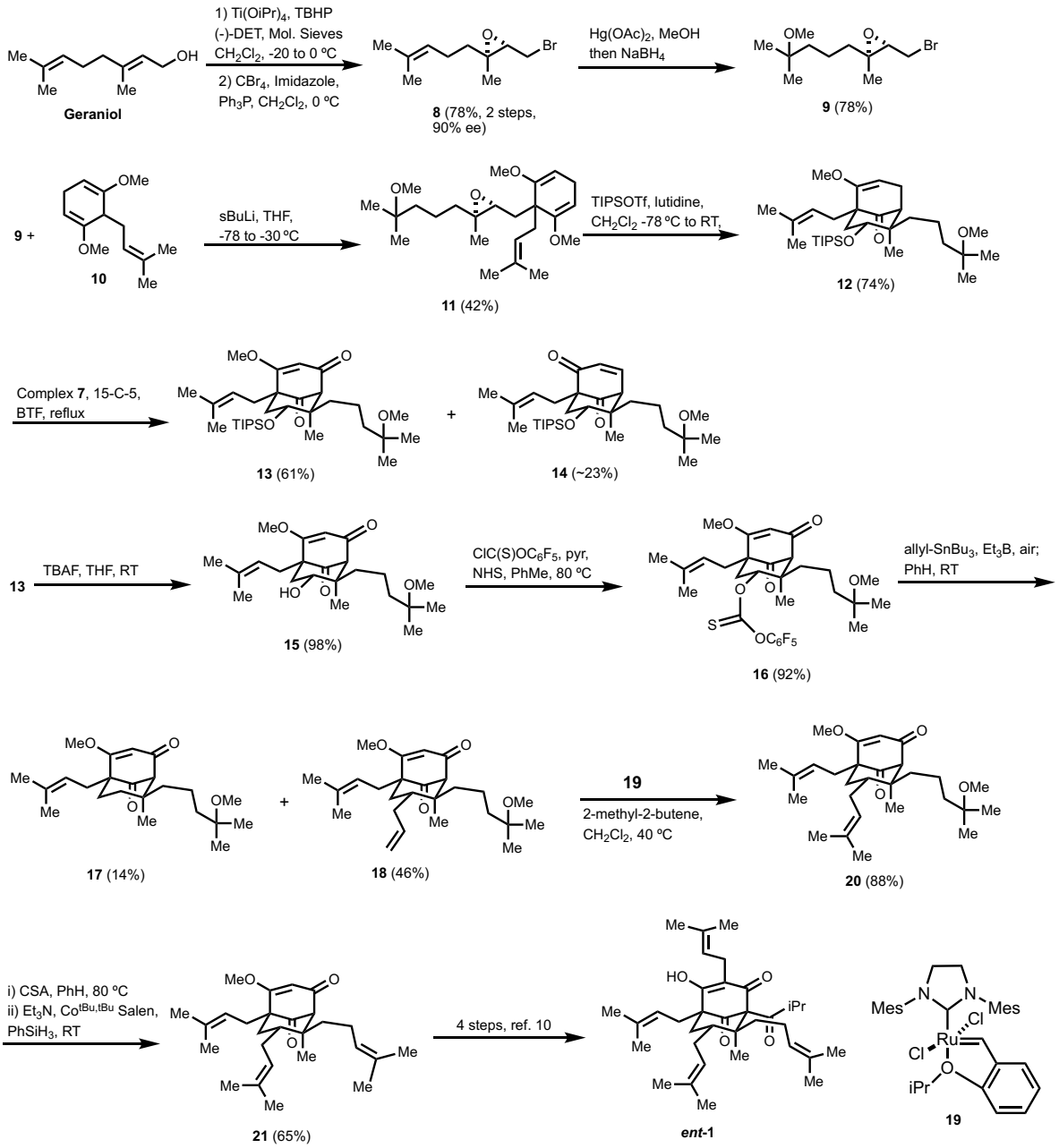
additionally, treatment of a mixture containing **5** in neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) formed **6**, cleanly.[6] The overall yield of **6** from **4** was 50%. Given the improvements in yield and consistency of outcome, conditions **b** were incorporated into the published route.[4] After publication of conditions **b**, further improvement in yield using conditions analogous to those developed by Baran et al. involving chromium (V) reagent **7** was realized with conditions **c**.[7] The relevant mechanism likely involves radical scission of the relevant allylic C-H bond concurrent with the formation of a Cr(IV)-hydroxy species.[7] One other advantage to these conditions is the lack of formation of **5**.



Scheme 1.1. Evolution of the oxidative protocol to furnish **6** from **4** and a mechanistic proposal for conditions **c**

Synthesis of *ent*-Hyperforin

Pursuit of the unnatural enantiomer of **1** was undertaken to interrogate a proposed mechanism of efficacy of **1** and attempt to improve its clinical safety profile (see **Appendix 1** for the full rationale). The synthesis of *ent*-**1** drew on our previous synthesis of **1** while incorporating some improvements (**Scheme 1.2**).[3] Specifically, the TIPSOTf-mediated cyclization protocol discovered during the approach to **2** and **3** extended with facility to the cyclization of **11** to give 3,3,1 bicycle **12** in 74% isolated yield on multigram scale.[4] Given the similarity of A-values between a methyl group (1.74 kcal/mol) and an ethyl group (1.79 kcal/mol), it is unsurprising that the cyclization protocol tolerated the increased steric bulk from a methyl group to a masked homoprenyl moiety during formation of **12**.[8,4] Importantly, oxidation of **12** utilizing complex **7** afforded vinylogous ester **13** in 61% yield on multigram scale. A one-pot methanol extrusion followed by catalytic olefin isomerization drawing on conditions pioneered in the lab of Prof. R. A. Shenvi afforded **21**.[9] Intermediate **21** was formed during the approach to **1** developed by Ting et al. and was advanced to *ent*-**1** via the same chemistry.[10] Characterization data for *ent*-**1** matched those reported.[11,3]



Scheme 1.2. Fifteen step, asymmeytric synthesis of *ent*-**1**

Conclusion and Future Directions

A novel approach to C2 oxidation via Cr(V) reagent **7** has been exploited during an enantioselective, 15-step approach to *ent*-**1**. Additionally, the TIPSOTf-mediated cyclization protocol discovered during the pursuit of **2** and **3** was useful in this context. Further discussion of the biological implications of this work is offered in **Appendix 1**. Development of the allylic oxidation described herein led naturally to the question of which other allylic oxidation methodologies might be worth pursuing, thus informing future research pursuits.

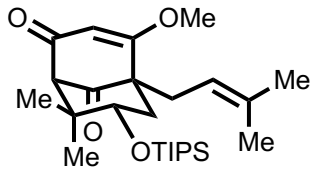
General Experimental Information

General Procedures. All reactions were performed in oven-dried glassware under a positive pressure of dinitrogen unless otherwise noted. Flash column chromatography was performed as described by Still et al.[12] employing silica gel 60 (40-63 μm, Whatman). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F254 plates (Merck).

Materials. Reagents and solvents used herein were purchased from commercial vendors and used as received, with these specifications: Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), 2,6-lutidine, benzotrifluoride (BTF), pyridine, and triethylamine (NEt_3) were sourced from sureseal bottles. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and triisopropylsilyloxy trifluoromethanesulfonate (TIPSOTf) were distilled over calcium hydride at reduced pressure. 5 M CH_2Cl_2 solutions of tert-Butyl hydroperoxide (TBHP) were prepared according to a literature procedure.[13] 5.5 M solutions of TBHP in nonane over 3 Å mol sieves were purchased from Aldrich. Chromium V complex **7** was prepared according to a literature procedure.[14] The molarities of sureseal sec-butyllithium (sBuLi) cyclohexane solutions (Aldrich) were determined by titration with 1,10-phenanthroline as an indicator (average of three determinations). Sureseal THF solutions of tetrabutylammonium fluroide (TBAF) were purchased from Aldrich. 5 M solutions of triethylborane (BEt_3) in PhH were prepared via the addition of neat BEt_3 to PhH. Hoyveda-Grubbs Generation II catalyst (**19**) was purchased from Aldrich. Camphorsulfonic acid (CSA) was recrystallized from EtOAc and dried in a vacuum oven overnight before use.

Instrumentation. ^{1}H NMR spectra were recorded with Varian INOVA-500, Agilent DD2-600, or JEOL-400 spectrometers, are reported in parts per million (δ), and are calibrated using residual non-deuterated solvent as an internal reference: $CDCl_3$, δ 7.26 ($CHCl_3$); C_6D_6, δ 7.16 (C_6H_6). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sx = sextet, m = multiplet; br = broad, or combinations thereof. ^{13}C NMR spectra were recorded with a Varian INOVA-500 or JEOL-400 spectrometer, are reported in parts per million (δ), and are referenced from the central peak of the carbon resonance of the solvent: $CDCl_3$, δ 77.16; C_6D_6, δ 128.06. ^{19}F NMR spectra were recorded with a JEOL-400 or a Varian INOVA-500 spectrometer and are reported in parts per million (δ). Infrared (IR) data were recorded on a Bruker Alpha FT-IR spectrometer outfitted with an Eco-ATR sampling module. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mass spectroscopy using a Thermo Scientific Dionex UltiMate 3000 UHPLC coupled to a Thermo Q Exactive Plus mass spectrometer system equipped with either an HESI-II electrospray ionization source or an APCI probe.

Experimentals



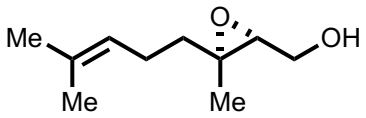
6

(1S,5R,7S)-4-Methoxy-8,8-dimethyl-5-(3-methylbut-2-en-1-yl)-7-((triisopropylsilyl)oxy)bicyclo [3.3.1]non-3-ene-2,9-dione (6):[4]

A colorless EtOAc (30 mL) solution of **4** (6.49 g, 14.9 mmol, 1 equiv) in a 100-mL recovery flask was placed in a -40 ℃ dry ice/ACN bath. In quick succession, potassium hydroxide powder (1.01 g, 17.9 mmol, 1.2 equiv) and palladium hydroxide (20 wt% on carbon, 1.65 g, 3.0 mmol, 0.2 equiv) were added. tert-Butyl hydroperoxide (5.5 M in nonane, 13.5 mL, 74.5 mmol, 5 equiv) was then added dropwise over 35 min. The reaction was then warmed directly to 0 ℃ using an ice/H_2O bath. After stirring at 0 ℃ for 15 h, the reaction mixture was filtered through a plug of SiO_2 (300 mL), rinsing sequentially with EtOAc and 9:1 EtOAc:[2M NH_3 in MeOH]. The combined organic fractions were concentrated in vacuo to a colorless oil. Flash column chromatography (500 mL SiO_2, 98:2 to 96:4 to 94:6 to 92:8 hexane:EtOAc) afforded 1.68 g of **6** as an off-white, waxy solid and 3.93 g of complex mixture of products containing **5**.

The complex mixture containing tert-butyl peroxide **5** was taken up in DBU (75 mL) and stirred at rt for 25 h. The reaction mixture was then diluted with sat. aq. NH_4Cl and extracted thrice with EtOAc. The combined EtOAc fractions were sequentially washed twice with sat. aq. NH_4Cl, once with sat. aq. $NaHCO_3$, once with H_2O, once with brine, dried over Na_2SO_4, and concentrated in vacuo to a dark orange oil. Flash column chromatography (50 mL SiO_2, 98:2 to 9:1 hexane:EtOAc) afforded an additional 1.68 g (3.74 mmol, 25% yield) of **6** as a white, waxy solid. A total of 3.36 g (7.48 mmol, 50% yield) of **6** was obtained.

*For characterization data, consult Sparling et al.[4]



22

((2R,3R)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methanol (22):[3]

A 5 M solution of TBHP in DCM (37.4 mL, 187 mmol, 1.7 equiv) was added to a stirring solution of $Ti(OiPr)_4$ (3.25 mL, 11 mmol, 10 mol %), D-(-)-DET (2.82 mL, 16.5 mmol, 15 mol %) and 4 Å MS (3.4 g) in CH_2Cl_2 (85 mL) in a 250 mL 3-neck round-bottom flask cooled to -22 ℃ in a dry ice/ACN bath (internal temperature). Following completion of the addition, the reaction mixture was stirred with the internal temperature maintained below -20 ℃ for 45 minutes. A solution of geraniol (19.3 mL, 110 mmol, 1 equiv) in CH_2Cl_2 (23 mL) was added dropwise over 40 minutes, such that the internal temperature was maintained below -20 ℃. The reaction was kept below this temperature for 1 h and then allowed to warm to -10 ℃ over 35 minutes. The reaction was quenched with 50 mL water, followed by 30 mL of 30% aqueous NaOH, saturated in NaCl. The resulting emulsion was warmed to room temperature and stirred for 45 minutes. The reaction was diluted with 150 mL MeOH and 30 mL brine and the layers were separated. The aqueous layer was extracted thrice with CH_2Cl_2. The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure to give **22** (19.39 g, ca quantitative) as a clear, colorless oil. The crude material was judged to be free from major impurities and carried directly into the next step. Analysis of the reaction mixture enantiomeric excess was performed as in Sparling et al. stablished the enantiomeric excess of 22 to be >90% ee.[3]

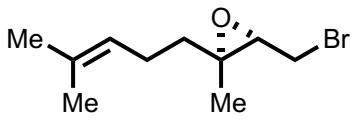
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.12 – 5.04 (m, 1H), 3.82 (dd, J = 12.2, 4.2 Hz, 1H), 3.68 (dd, J = 12.1, 6.7 Hz, 1H), 2.97 (dd, J = 6.7, 4.3 Hz, 1H), 2.15 – 2.03 (m, 2H), 1.74 – 1.63 (m, 4H), 1.61 (d, J = 1.3 Hz, 3H), 1.47 (ddd, J = 13.7, 9.0, 7.4 Hz, 1H), 1.30 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 132.3, 123.5, 63.0, 61.6, 61.3, 38.6, 25.9, 23.8, 17.8, 16.9.

FTIR (thin film) ν_{max}: 3412, 2967, 2927, 2859, 1451, 1384, 1100, 1076, 1033, 864, 814, 551, 459 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{10}H_{18}O_2$, 171.1380; found, 171.1378.

TLC R_f= 0.47 (1:1 hexane:EtOAc).



8

(2R,3S)-3-(bromomethyl)-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane (8):[15]

A solution of **22** (5.00 g, 29.4 mmol, 1 equiv) in CH_2Cl_2 (294 mL) in a 500 mL round-bottom 3-neck flask was cooled to 0 ℃ in an ice-water bath. Imidazole (6.00 g, 88.1 mmol, 3 equiv) was added in one portion, followed by triphenylphosphine (11.55 g 44.0 mmol, 1.5 equiv). Ten minutes later, CBr_4 (14.61 g, 44.0 mmol, 1.5 equiv) was added, and the reaction was protected from light and stirred at 0 ℃. After 2 h, the reaction was concentrated to ca 1/10 volume in vacuo and applied directly to a 15 by 6 cm silica gel column. The column was eluted with 5% (1 L) and then 10% (1 L) EtOAc/hexane, generating 20 100 mL fractions. Fractions 7-12 were combined and concentrated at reduced pressure to give **8** (5.34 g, 22.9 mmol, 78%) as a clear, colorless liquid.

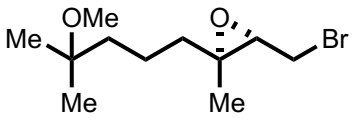
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.10 (dd, J = 8.6, 5.7 Hz, 1H), 3.54 (dd, J = 10.4, 5.9 Hz, 1H), 3.24 (dd, J = 10.4, 7.8 Hz, 1H), 3.08 (dd, J = 7.8, 5.9 Hz, 1H), 2.10 (m, 2H), 1.78 – 1.66 (m, 4H), 1.61 (d, J = 1.4 Hz, 3H), 1.45 (ddd, J = 13.7, 9.1, 7.3 Hz, 1H), 1.31 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 132.4, 123.4, 63.2, 61.6, 38.5, 29.9, 25.8, 23.9, 17.8, 16.2.

FTIR (thin film) ν_{max}: 2968, 2915, 2858, 1450, 1385, 1249, 1217, 1112, 1070, 890, 848, 834, 745, 695, 652, 452, 430 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{10}H_{17}BrO$, 233.0536; found, 233.0533.

TLC R_f= 0.75 (4:1 hexane:EtOAc).



9

(2R,3S)-3-(bromomethyl)-2-(4-methoxy-4-methylpentyl)-2-methyloxirane (9):

A stirring solution of **8** (5.13 g, 22 mmol, 1 equiv) in MeOH (90 mL) was treated with a solution of $Hg(OAc)_2$ (10.50 g, 33 mmol, 1.5 equiv) in MeOH (60 mL). The resulting solution was stirred for 20 minutes at room temperature and then cooled to 0 ℃ with an ice-water bath. To the reaction was added 3N NaOH (36 mL) followed by a solution of $NaBH_4$ (685 mg) in 3N NaOH (36 mL). The reaction was diluted with 100 mL water and extracted thrice with 4:1 hexane:EtOAc. The combined organic layers were washed thrice with water and once with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude residue obtained was applied to a 12 by 4 cm silica gel column and eluted with 5% (0.25 L), then 10% (0.25 L) and finally 20% (0.5 L) EtOAc/hexane. The process generated 38 24 mL fractions, and fractions 15-24 were combined and concentrated at reduced pressure to give **9** (4.52 g, 17.0 mmol, 78%) as a slightly yellow oil.

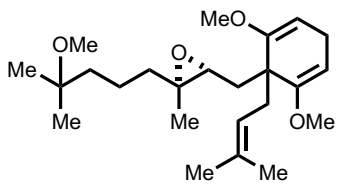
^{1}HNMR (400 MHz; $CDCl_3$) δ: 3.54 (dd, J = 10.4, 5.9 Hz, 1H), 3.25 (dd, J = 10.4, 7.7 Hz, 1H), 3.17 (s, 3H), 3.09 (dd, J = 7.7, 5.9 Hz, 1H), 1.73 – 1.60 (m, 1H), 1.55 – 1.38 (m, 5H), 1.31 (s, 3H), 1.14 (s, 6H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 74.5, 63.3, 61.5, 49.3, 39.9, 38.8, 30.0, 25.1, 19.6, 16.2.

FTIR (thin film) ν_{max}: 2971, 2945, 2909, 2826, 1464, 1431, 1382, 1364, 1258, 1220, 1204, 1148, 1082, 891, 852, 746, 652, 433, 423 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{11}H_{21}BrO_2$, 287.0617; found, 287.0614.

TLC R_f= 0.33 (9:1 hexane:EtOAc).



11

(2R,3R)-3-((2,6-dimethoxy-1-(3-methylbut-2-en-1-yl)cyclohexa-2,5-dien-1-yl)methyl)-2-(4-methoxy-4-methylpentyl)-2-methyloxirane (11):[3,4]

A solution of **10**[3] (3.12 g, 15 mmol, 1 equiv) in THF (75 mL) in a 250 mL two-neck round-bottom flask equipped with a stir bar and an internal thermometer was cooled to -78 ℃ using a dry ice/acetone bath. A solution of sBuLi in cyclohexane (1.42 M, 11.1 mL, 15.75 mmol, 1.05 equiv) was added dropwise over ten minutes, maintaining an internal temperature below -65 ℃. The reaction was warmed to -30 ℃ over 50 minutes and held at that temperature for 20 minutes. The reaction was cooled back to -78 ℃, and a solution of **9** (4.18 g, 15.75 mmol, 1.1 equiv) in THF (16 mL) was added dropwise over 20 minutes such that the internal temperature was kept below -65 ℃. The reaction was held at this temperature for 1.5 h and then was allowed to warm to -20 ℃ over 1.5 h. The reaction was quenched by careful addition of saturated aqueous sodium bicarbonate solution directly to the mixture at this temperature and warmed to room temperature. The reaction mixture was poured into a separatory funnel, and the aqueous layer was extracted thrice with ethyl acetate. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was loaded onto a 12 by 6 cm silica gel plug and eluted with 4% (0.5 L) and then 6% (0.5 L) and then 8% (0.5 L) and finally 10% (1.3 L) EtOAc/hexane. The process generated 106 24 mL fractions. Fractions 63-106 were combined and concentrated at reduced pressure to yield **11** (2.46 g, 6.30 mmol, 42%) as a clear, colorless oil.

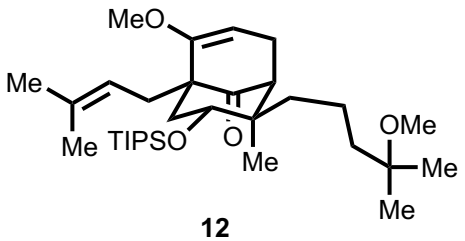
^{1}HNMR (400 MHz; C_6D_6) δ: 5.30 (dd, J = 8.7, 5.8 Hz, 1H), 4.66 (dt, J = 14.6, 3.6 Hz, 2H), 3.26 (s, 3H), 3.20 (s, 3H), 3.00 (s, 3H), 2.91 (dd, J = 7.5, 4.2 Hz, 1H), 2.82 (td, J = 3.6, 2.3 Hz, 2H), 2.75 – 2.59 (m, 2H), 2.41 (dd, J = 13.7, 4.2 Hz, 1H), 2.12 (dd, J = 13.7, 7.5 Hz, 1H), 1.68 (d, J = 1.5 Hz, 3H), 1.63 – 1.56 (m, 4H), 1.51 – 1.42 (m, 2H), 1.41 – 1.29 (m, 4H), 1.26 (s, 3H), 1.03 (s, 6H).

^{13}CNMR (101 MHz; C_6D_6) δ: 154.3, 154.3, 131.9, 121.1, 92.8, 73.8, 60.3, 60.0, 53.9, 53.5, 48.6, 46.3, 40.2, 39.9, 34.8, 34.7, 25.9, 24.8, 24.7, 24.2, 19.8, 17.6, 16.8.

FTIR (thin film) ν_{max}: 2969, 2938, 2826, 1693, 1658, 1451, 1380, 1364, 1222, 1205, 1150, 1122, 1081, 1055, 1032, 973, 951, 849, 778, 750, 688, 433 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{24}H_{40}O_4$, 393.2999; found, 393.2994.

TLC R_f= 0.41 (9:1 hexane:EtOAc).



12

(1S,5S,6R,7R)-2-methoxy-6-(4-methoxy-4-methylpentyl)-6-methyl-1-(3-methylbut-2-en-1-yl)-7-((triisopropylsilyl)oxy)bicyclo[3.3.1]non-2-en-9-one (12):[4]

A solution of **11** (2.35 g, 5.99 mmol, 1 equiv) in CH_2Cl_2 (60 mL) in a 250 mL round bottom flask was cooled to -78 ℃. 2,6-Lutidine (1.47 mL, 12.57 mmol, 2.1 equiv) was added, followed by dropwise addition of TIPSOTf (3.22 mL, 11.98 mmol, 2 equiv). The reaction was allowed to warm slowly to ca 0 ℃ over 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate, and the layers were separated. The aqueous layer was extracted thrice with CH_2Cl_2. The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude material was applied to a 12 by 6 cm silica gel column and eluted with 50% (1 L), and then 75% (0.5 L) and then 100% (1.5 L CH_2Cl_2:hexane). The plug was further eluted with 2% (0.5 L) and then 4% (2.5 L) EtOAc/hexane. The process generated 166 24 mL fractions, and fractions 109-166 were combined and concentrated at reduced pressure to give **12** (2.37 g, 4.42 mmol, 74%) as a clear, colorless, viscous oil.

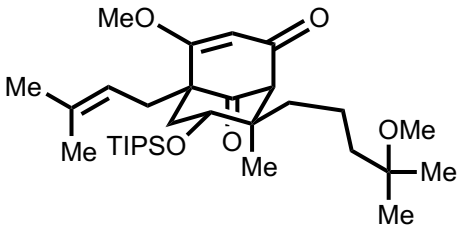
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.06 (t, J = 7.0 Hz, 1H), 4.70 (dd, J = 4.8, 2.4 Hz, 1H), 4.17 (dd, J = 11.1, 5.2 Hz, 1H), 3.47 (s, 3H), 3.17 (s, 3H), 2.35 (m, 4H), 2.21 (dd, J = 14.5, 7.0 Hz, 1H), 2.01 (dd, J = 13.1, 5.2 Hz, 1H), 1.65 (d, J = 1.4 Hz, 3H), 1.63 (d, J = 1.3 Hz, 3H), 1.45 – 1.38 (m, 3H), 1.29 – 1.16 (m, 1H), 1.13 (s, 6H), 1.04 (m, 21H), 1.02 – 0.94 (m, 3H), 0.83 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 212.0, 155.0, 132.7, 120.8, 93.8, 74.7, 74.2, 54.8, 53.8, 52.1, 49.3, 46.4, 41.1, 40.3, 37.7, 29.7, 26.1, 25.1, 25.0, 24.5, 18.4, 18.3, 18.1, 17.1, 16.8, 13.1.

FTIR (thin film) ν_{max}: 2943, 2866, 1724, 1662, 1463, 1381, 1363, 1213, 1190, 1161, 1127, 1100, 1062, 1014, 997, 882, 843, 677, 471, 465, 458, 444, 436, 418, 409 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{32}H_{58}O_4Si$, 535.4177; found, 535.4169.

TLC R_f= 0.43 (9:1 hexane:EtOAc).



13

(1R,5S,7R,8R)-4-methoxy-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-en-1-yl)-7-((triisopropylsilyl)oxy)bicyclo[3.3.1]non-3-ene-2,9-dione (13):[7]

A stirring solution of **12** (2.17 g, 4.06 mmol, 1 equiv) in BTF (81 mL) in a 500 mL recovery flask was charged with **7** (4.79 g, 16.23 mmol, 4 equiv), and then 15-crown-5 (1.61 mL, 8.12 mmol, 2 equiv) was added via syringe. The flask was outfitted with a reflux condenser, and the reaction was heated at reflux with stirring for 4 h. The reaction was cooled to room temperature and passed through a 10 by 6 cm silica gel plug, rinsing with 0.5 L EtOAc, and the eluted organic layer was concentrated at reduced pressure. The residue obtained was applied to an 11 by 6 cm silica gel plug and eluted with 10% (1 L) and then 20% (0.75 L) EtOAc/hexane. The process generated 65 24 mL fractions. Fractions 26-42 were combined and concentrated at reduced pressure to give **14** (ca 80% pure, 0.49 g, 0.93 mmol, 23%). Fractions 43-64 were combined and concentrated at reduced pressure to give **13** (1.35 g, 2.48 mmol, 61%) as a clear, colorless oil.

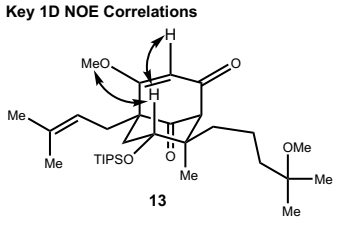
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.65 (s, 1H), 4.97 (tdd, J = 6.1, 3.1, 1.4 Hz, 1H), 3.96 (dd, J = 11.2, 5.2 Hz, 1H), 3.72 (s, 3H), 3.21 (s, 1H), 3.20 (s, 3H), 2.48 (dd, J = 14.6, 6.5 Hz, 1H), 2.37 (dd, J = 14.5, 7.7 Hz, 1H), 2.04 (dd, J = 13.4, 5.2 Hz, 1H), 1.77 (dd, J = 13.3, 11.2 Hz, 1H), 1.69 – 1.60 (m, 8H), 1.51 – 1.41 (m, 1H), 1.33 (ddd, J = 14.1, 10.4, 3.5 Hz, 1H), 1.27 – 1.19 (m, 1H), 1.16 (s, 6H), 1.02 (m, 22H), 0.88 (s, 3H).

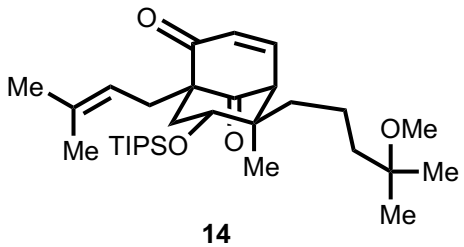
^{13}CNMR (101 MHz; $CDCl_3$) δ: 205.3, 193.3, 177.4, 134.4, 119.1, 105.9, 74.8, 73.2, 69.1, 56.8, 55.9, 49.2, 47.2, 40.2, 39.4, 38.4, 29.5, 26.0, 25.5, 25.0, 18.3, 18.2, 18.1, 17.2, 15.7, 13.0.

FTIR (thin film) ν_{max}: 2943, 2866, 1737, 1655, 1594, 1461, 1363, 1349, 1218, 1195, 1128, 1102, 1055, 1013, 997, 917, 882, 840, 826, 780, 733, 705, 678, 647, 606, 466, 445, 433 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{32}H_{56}O_5Si$, 549.3970; found, 549.3957.

TLC R_f= 0.35 (4:1 hexane:EtOAc).





14

(1R,5S,7R,8R)-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-en-1-yl)-7-((triisopropylsilyl)oxy)bicyclo[3.3.1]non-3-ene-2,9-dione (14):

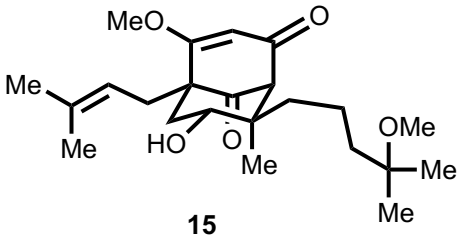
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.05 (dd, J = 9.8, 6.7 Hz, 1H), 6.36 (d, J = 9.8 Hz, 1H), 5.07 (dd, J = 7.5, 5.8 Hz, 1H), 3.88 (dd, J = 11.6, 5.5 Hz, 1H), 3.18 (s, 3H), 3.14 (d, J = 6.7 Hz, 1H), 2.45 (d, J = 7.3 Hz, 2H), 1.96 (dd, J = 13.1, 5.5 Hz, 1H), 1.87 (dd, J = 13.0, 11.7 Hz, 1H), 1.73 – 1.61 (m, 7H), 1.49 – 1.40 (m, 4H), 1.28 – 1.19 (m, 1H), 1.16 (s, 6H), 1.00 (m, 21H), 0.94 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 206.8, 200.6, 146.5, 134.7, 132.3, 119.5, 74.5, 72.0, 66.1, 56.3, 49.3, 45.2, 42.2, 41.1, 39.9, 38.6, 28.9, 26.0, 25.1, 24.9, 18.3, 18.3, 18.1, 17.6, 16.0, 12.9.

FTIR (thin film) ν_{max}: 2967, 2944, 2911, 2867, 1735, 1680, 1464, 1381, 1364, 1235, 1130, 1106, 1070, 998, 882, 858, 826, 683, 674, 646, 447, 416 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{31}H_{54}O_4Si$, 519.3864; found, 519.3850.

TLC R_f= 0.53 (4:1 hexane:EtOAc).



15

(1R,5S,7R,8R)-7-hydroxy-4-methoxy-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (15):[3,4]

A solution of **13** (1.33 g, 2.42 mmol, 1 equiv) in THF (24.2 mL) was treated with TBAF (1 M in THF, 7.3 mL, 7.3 mmol, 3 equiv) and stirred at room temperature for 5 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate and transferred to a separatory funnel. The aqueous layer was extracted thrice with EtOAc. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 12 by 4 cm silica gel plug and eluted with 25% (0.5 L) and then 75% (0.7 L) EtOAc/hexane. The process generated 47 24 mL fractions, and fractions 25-47 were combined and concentrated at reduced pressure to give **15** (0.93 g, 2.37 mmol, 98%) as a clear, colorless oil.

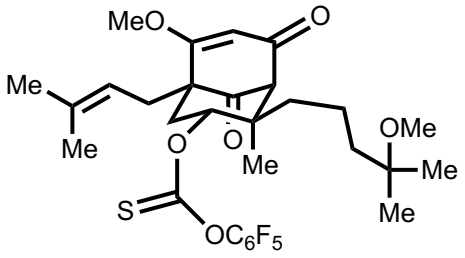
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.65 (s, 1H), 5.01 – 4.93 (m, 1H), 3.80 (dd, J = 11.5, 5.5 Hz, 1H), 3.75 (s, 3H), 3.19 (app s, 4H), 2.49 (dd, J = 14.6, 6.5 Hz, 1H), 2.39 (dd, J = 14.6, 7.5 Hz, 1H), 2.10 (dd, J = 13.4, 5.4 Hz, 1H), 1.82 – 1.70 (m, 3H), 1.67 – 1.56 (m, 8H), 1.50 – 1.31 (m, 3H), 1.30 – 1.21 (m, 2H), 1.15 (s, 6H), 0.88 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 205.2, 193.1, 177.5, 134.5, 119.0, 106.0, 74.8, 72.0, 69.1, 57.0, 56.0, 49.2, 46.1, 40.1, 39.4, 38.3, 29.5, 26.0, 25.5, 25.0, 18.1, 17.3, 15.7.

FTIR (thin film) ν_{max}: 3422, 2970, 2942, 2911, 1735, 1654, 1591, 1459, 1365, 1351, 1279, 1228, 1217, 1188, 1074, 1051, 1026, 974, 918, 845, 828, 793, 758, 731, 706, 663, 647, 612, 562, 546, 492, 467, 439, 420 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{23}H_{36}O_5S$, 391.2490; found, 391.2490.

TLC R_f= 0.16 (1:1 hexane:EtOAc).



16

O-((1R,2R,3R,5S)-6-methoxy-2-(4-methoxy-4-methylpentyl)-2-methyl-5-(3-methylbut-2-en-1-yl)-8,9-dioxobicyclo[3.3.1]non-6-en-3-yl) O-(perfluorophenyl) carbonothioate (16):[3,4]

A solution of **15** (0.91 g, 2.32 mmol, 1 equiv) and NHS (267 mg, 2.32 mmol, 1 equiv) in PhMe (29 mL) in a 500 mL recovery flask was charged with pyridine (0.94 mL, 11.6 mmol, 5 equiv), followed by pentafluorophenylchlorothiono formate (1.86 mL, 11.6 mmol, 5 equiv), both via syringe. The reaction was capped, sealed with teflon tape and parafilm, and heated with stirring in an aluminum shot bath at 80 °C for 3.5 h. The reaction was cooled to room temperature and partitioned between EtOAc (0.2 L) and water (0.1 L) in a separatory funnel. The organic layer was extracted once more with water and once with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude material was applied to a 12 by 6 cm silica gel column and eluted with 2% (0.5 L) and then 5% (0.5 L) and then 10% (0.5 L) and finally 12.5% (1.5 L) EtOAc/hexane. The process generated 113 24 mL fractions; fractions 73-112 were combined and concentrated at reduced pressure to give **16** (1.30 g, 2.15 mmol, 92%) as a golden oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.73 (s, 1H), 5.44 (dd, J = 11.6, 5.4 Hz, 1H), 4.98 (t, J = 7.1 Hz, 1H), 3.80 (s, 3H), 3.29 (s, 1H), 3.20 (s, 3H), 2.62 – 2.39 (m, 3H), 1.92 (app t, J = 12.3 Hz, 1H), 1.68-1.58 (m, 7H), 1.47-1.42 (m, 2H), 1.40 – 1.23 (m, 3H), 1.16 (d, J = 3.0 Hz, 6H), 1.08 (s, 3H).

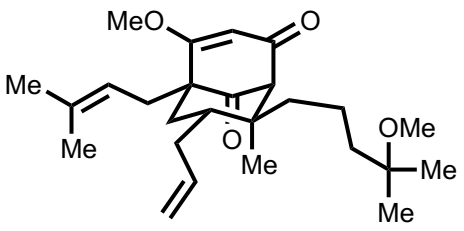
^{13}CNMR (101 MHz; $CDCl_3$) δ: 203.5, 191.9, 191.6, 176.9, 135.1, 118.4, 106.2, 87.1, 74.6, 69.3, 57.4, 55.5, 49.3, 45.5, 39.9, 37.9, 33.9, 29.3, 27.1, 26.1, 25.6, 25.0, 18.1, 17.3, 17.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -152.23 (d, J = 18.7 Hz, 2F), -156.16 (t, J = 21.8 Hz, 1F), -161.67 (t, J = 20.3 Hz, 2F).

FTIR (thin film) ν_{max}: 2971, 2915, 1741, 1658, 1593, 1519, 1462, 1376, 1350, 1328, 1307, 1283, 1265, 1221, 1198, 1150, 1076, 1044, 997, 964, 910, 848, 826, 731, 647, 545, 497, 447, 419 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{30}H_{35}F_5O_6S$, 619.2147; found, 619.2132.

TLC R_f= 0.14 (9:1 hexane:EtOAc).



18

(1R,5S,7R,8S)-7-allyl-4-methoxy-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (18):[3,4]

A solution of **16** (1.24 g, 2.05 mmol, 1 equiv) in PhH (2.3 mL) and allyltributylstannane (6.9 mL) in a 250 mL round bottom flask was charged with BEt_3 (5.0 M in PhH, 0.41 mL, 2.05 mmol, 1 equiv) via syringe. With vigorous stirring (500 rpm) of the reaction mixture ca 1 cm off the center of the plate, the vessel was opened to the atmosphere by removal of the septum and stirred in this way for 30 minutes. The reaction was concentrated partially at reduced pressure and applied directly to a 14 by 5 cm silica gel column. The column was eluted with 2% (1 L), and then 5% (1 L), and then 10% (1 L), and then 12% (1 L) and finally 15% (1.5 L) EtOAc/hexane. The process generated ten 100 mL fractions followed by 170 24 mL fractions. Of these 170 24 mL fractions, fractions 100-137 were combined and concentrated at reduced pressure to give **18** (0.39 g, 0.94 mmol, 46%). Fractions 138-170 were combined and concentrated at reduced pressure to give **17** (0.11 g, 0.29 mmol, 14%).

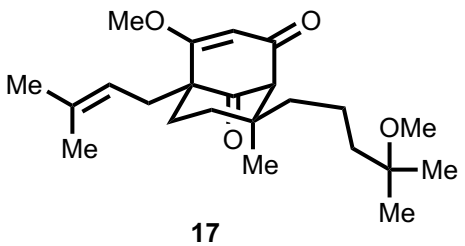
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.71 – 5.58 (m, 2H), 5.05 – 4.92 (m, 3H), 3.73 (s, 3H), 3.20 (s, 3H), 3.14 (s, 1H), 2.45 (dd, J = 14.6, 6.2 Hz, 1H), 2.40 – 2.27 (m, 2H), 1.97 (dd, J = 13.9, 4.5 Hz, 1H), 1.77 – 1.61 (m, 9H), 1.53 – 1.43 (m, 3H), 1.43 – 1.29 (m, 2H), 1.22 – 1.12 (m, 8H), 0.81 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 206.9, 193.9, 177.5, 137.0, 133.9, 119.4, 116.7, 106.4, 74.7, 70.5, 56.9, 49.3, 46.1, 40.0, 39.8, 39.2, 39.0, 33.8, 29.7, 26.0, 25.6, 25.0, 18.0, 17.8, 17.4.

FTIR (thin film) ν_{max}: 2969, 2917, 2856, 2825, 1731, 1652, 1595, 1444, 1365, 1352, 1303, 1277, 1225, 1196, 1172, 1109, 1079, 1056, 993, 913, 845, 828, 794, 774, 732, 663, 645, 595, 547, 485, 446, 433 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{26}H_{40}O_4$, 417.2999; found, 417.2985.

TLC R_f= 0.25 (4:1 hexane:EtOAc).



17

(1R,5R,8S)-4-methoxy-8-(4-methoxy-4-methylpentyl)-8-methyl-5-(3-methylbut-2-en-1-yl) bicyclo[3.3.1]non-3-ene-2,9-dione (17):

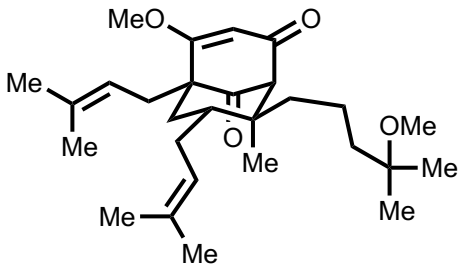
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.72 (s, 1H), 4.96 (dd, J = 7.8, 6.3 Hz, 1H), 3.74 (s, 3H), 3.17 (s, 3H), 2.99 (s, 1H), 2.50 (dd, J = 14.6, 6.2 Hz, 1H), 2.38 (dd, J = 14.5, 7.7 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.73 – 1.61 (m, 7H), 1.51 – 1.46 (m, 1H), 1.40 (m, 2H), 1.36 – 1.29 (m, 2H), 1.24 – 1.18 (m, 3H), 1.14 (d, J = 1.7 Hz, 6H), 0.94 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 206.9, 194.1, 177.1, 133.9, 119.5, 106.3, 74.7, 72.0, 56.8, 49.3, 43.4, 42.2, 40.2, 33.3, 31.9, 29.7, 26.0, 25.5, 25.1, 22.0, 18.1, 17.5.

FTIR (thin film) ν_{max}: 2967, 2926, 2854, 1731, 1655, 1596, 1459, 1366, 1221, 1195, 1153, 1085, 1055, 846 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{23}H_{36}O_4$, 399.2506; found, 399.2497.

TLC R_f= 0.15 (4:1 hexane:EtOAc).



20

(1R,5S,7R,8S)-4-methoxy-8-(4-methoxy-4-methylpentyl)-8-methyl-5,7-bis(3-methylbut-2-en-1-yl)bicyclo[3.3.1]non-3-ene-2,9-dione (20):[3,4]

A solution of **18** (390 mg, 0.94 mmol, 1 equiv) and **19** (88.4 mg, 0.14 mmol, 15 mol %) in CH_2Cl_2 (13 mL) and 2-methyl-2-butene (13 mL) was capped, sealed with teflon tape and parafilm, and heated with stirring at 40 ℃ for 4 h. The reaction was cooled to room temperature and concentrated at reduced pressure. The residue obtained was applied to a 10 by 5 cm silica gel column and eluted with 5% (0.5 L) and then 10% (0.5 L) and then 12% (0.5 L) and then 15% (1 L) and finally 50% (200 mL) EtOAc/hexane. The process generated 105 24 mL fractions, and fractions 65-101 were combined and concentrated at reduced pressure to give **20** (367 mg, 0.825 mmol, 88%) as a slightly brown oil.

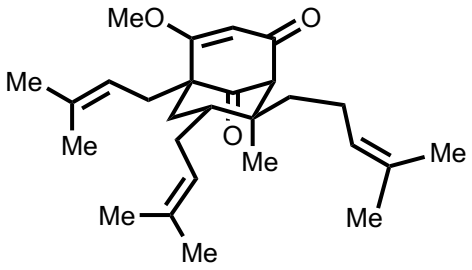
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.68 (s, 1H), 4.96 (m, 2H), 3.73 (s, 3H), 3.20 (s, 3H), 3.13 (s, 1H), 2.45 (dd, J = 14.6, 6.1 Hz, 1H), 2.36 (dd, J = 14.6, 7.7 Hz, 1H), 2.12 (dd, J = 11.7, 6.4 Hz, 1H), 1.93 (dd, J = 13.9, 3.8 Hz, 1H), 1.69 (s, 3H), 1.67 – 1.61 (m, 9H), 1.55 (s, 3H), 1.52 – 1.29 (m, 4H), 1.23 – 1.17 (m, 2H), 1.16 (d, J = 1.7 Hz, 6H), 0.82 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 207.2, 194.0, 177.6, 133.8, 133.2, 122.7, 119.5, 106.4, 74.7, 70.6, 57.0, 56.9, 49.3, 46.2, 40.9, 40.1, 39.4, 39.0, 29.8, 27.8, 26.0, 26.0, 25.6, 25.0, 18.1, 18.0, 17.8, 17.4.

FTIR (thin film) ν_{max}: 2968, 2914, 2856, 2825, 1731, 1653, 1596, 1449, 1366, 1301, 1278, 1221, 1195, 1171, 1109, 1080, 1056, 973, 919, 849, 827, 792, 731, 545, 473, 432, 418 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{28}H_{44}O_4$, 445.3312; found, 445.3299.

TLC R_f= 0.28 (4:1 hexane:EtOAc).



21

(1R,5S,7R,8S)-4-methoxy-8-methyl-5,7-bis(3-methylbut-2-en-1-yl)-8-(4-methylpent-3-en-1-yl) bicyclo[3.3.1]non-3-ene-2,9-dione (21):

A solution of **20** (222 mg, 0.50 mmol, 1 equiv) in PhH (10 mL) was treated with CSA (116 mg, 0.50 mmol, 1 equiv) and the resulting solution was heated at 80 ℃ for 28 h. The reaction was cooled to room temperture and Et_3N (0.14 mL, 1 mmol, 2 equiv) was added. The reaction was stirred for five minutes and then $Co^{(tbu,\ tbu)}$ salen acetate (33 mg, 0.05 mmol, 0.1 equiv) was added, followed by $PhSiH_3$ (62 μL, 0.5 mmol, 1 equiv).[9] The reaction was stirred at room temperature for 20 h and then passed through an SiO_2 plug with EtOAc, rinsing with EtOAc. The residue obtained was purified on an SiO_2 column (2% to 5% to 10% EtOAc in hexane) to afford **21** (134 mg, 0.325 mmol, 65%) as a clear, colorless oil. Characterization data matched those reported.[10]

References

[1] Yang, X.-W.; Grossman, R. B.; Xu, G. *Chemical Reviews* **2018**, *118*, 3508–3558.

[2] Friedland, K.; Harteneck, C. *Reviews of Physiology, Biochemistry and Pharmacology Vol. 169*; Springer, 2015; pp 1–24.

[3] Sparling, B. A.; Moebius, D. C.; Shair, M. D. *Journal of the American Chemical Society* **2012**, *135*, 644–647.

[4] Sparling, B. A.; Tucker, J. K.; Moebius, D. C.; Shair, M. D. *Organic Letters* **2015**, *17*, 3398–3401.

[5] Zhao, Y.; Yeung, Y.-Y. *Organic Letters* **2010**, *12*, 2128–2131.

[6] Yu, J.-Q.; Wu, H.-C.; Corey, E. *Organic Letters* **2005**, *7*, 1415–1417.

[7] Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *Journal of the American Chemical Society* **2014**, *136*, 4909–4912.

[8] Eliel, E. L.; Wilen, S. H. *Stereochemistry of organic compounds*; John Wiley & Sons, 2008.

[9] Crossley, S. W.; Barabé, F.; Shenvi, R. A. *Journal of the American Chemical Society* **2014**, *136*, 16788–16791.

[10] Ting, C. P.; Maimone, T. J. *Journal of the American Chemical Society* **2015**, *137*, 10516–10519.

[11] Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angewandte Chemie International Edition* **2010**, *49*, 1103–1106.

[12] Still, W. C.; Kahn, M.; Mitra, A. *The Journal of Organic Chemistry* **1978**, *43*, 2923–2925.

[13] Hanson, R. M.; Sharpless, K. B. *The Journal of Organic Chemistry* **1986**, *51*, 1922–1925.

[14] Krumpolc, M.; Rocek, J. *Journal of the American Chemical Society* **1979**, *101*, 3206–3209.

[15] Mitani, H.; Matsuo, T.; Kodama, T.; Nishikawa, K.; Tachi, Y.; Morimoto, Y. *Tetrahedron* **2016**, *72*, 7179–7184.

Chapter 2: Catalytic Allylic Oxidation to Generate Vinylogous Acyl Sulfonates from Vinyl Sulfonates

Introduction

Pursuit of the oxidation of a methyl-vinyl ether to a vinylogous ester during PPAP synthesis led to the question of which other substrates would be interesting for the development of allylic oxidation methodology. One class of substrates had been the subject of few studies: vinylogous acyl sulfonates. Vinylogous acyl sulfonates are versatile intermediates for organic synthesis, undergoing a variety of coupling and fragmentation processes.[1] These substrates typically originate from treatment of the corresponding 1,3-dicarbonyl with a weak base and sulfonate electrophile (**Figure 2.1A**). In the case of substrates lacking symmetrical substitution with respect to the 1,3-dicarbonyl, a mixture of products results.[2,3] Moreover, the 1,3-dicarbonyl oxidation state must already be established, limiting the range of vinylogous acyl sulfonates rapidly accessible by this approach (**Figure 2.1C**). A regioselective synthesis of vinylogous acyl sulfonates via allylic oxidation of corresponding vinyl sulfonates would thus increase the diversity of such structures (**Figure 2.1B**).

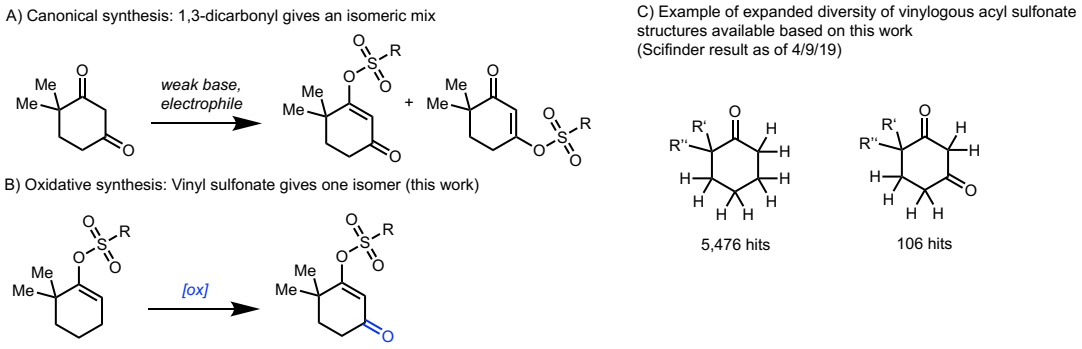
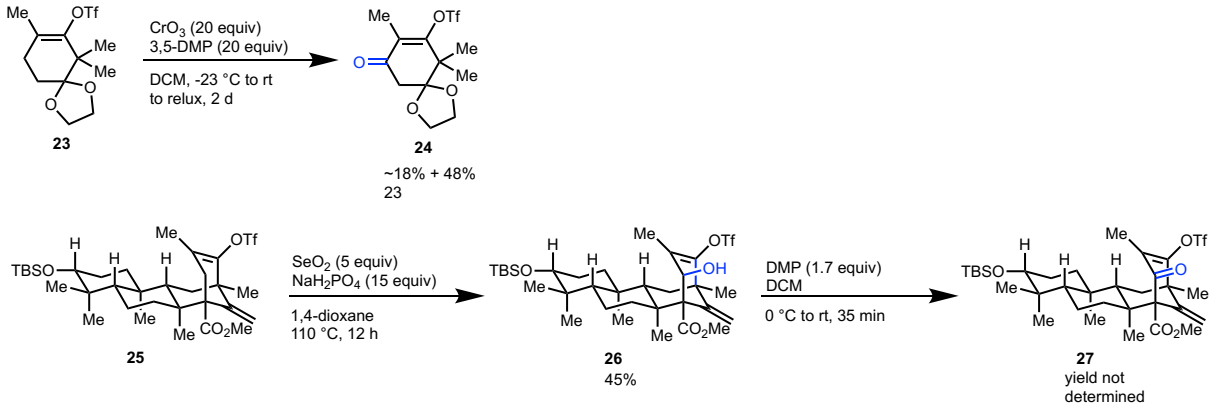


Figure 2.1. Proposed Utility of an Oxidative Approach to Vinylogous Acyl Sulfonates

To date, there are two examples of this oxidation, both of which rely on superstoichiometric quantities of toxic reagents while forming the product in moderate yield (**Scheme 2.1**).[4,5] We sought to effect this transformation with greater facility under more benign conditions.



Scheme 2.1: Known approaches for oxidative vinylogous acyl sulfonate formation from vinyl sulfonates

Results

To study this transformation, we chose readily available vinyl triflate **28a** because it lacked a competing allylic site (**Figure 2.2**). Application of Corey-Yu oxidation conditions and the dirhodium tetracaprolatamate (Rh_2cap_4)-mediated allylic oxidation system developed by Doyle, both known to affect the oxidation of electron-deficient allylic sites, resulted in poor conversion (ca 20-30%) following extended reaction times (**Figure 2.2**).[6,7]

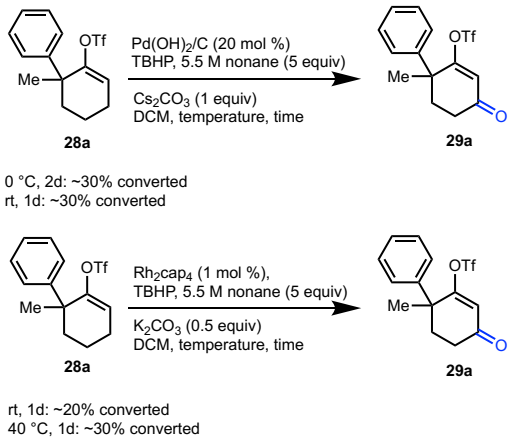
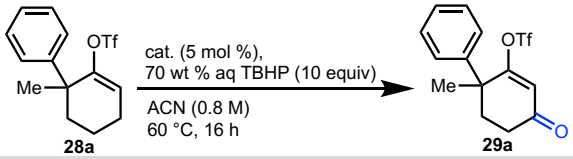


Figure 2.2. Studies directed toward the oxidation of 28a to 29a using known systems

A preponderance of allylic oxidations in other settings are catalytic on a transition metal species in acetonitrile or acetone, with tert-Butyl hydroperoxide (TBHP) as the stoichiometric oxidant.[8,9] We chose to evaluate a series of catalysts with these parameters in place. Under the conditions described above **Table 2.1**, the efficiency of Rh_2cap_4 (entry 1) improved markedly. Catalysis under these conditions based on simple chromium and copper sources also converted **28a** to an acceptable extent. Interestingly, iron(III) acetylacetanoate (iron(III) acac, entry 6) was capable of mediating the transformation in this setting, albeit at a reduced efficiency.[10,11] Use of iron(III) chloride (entry 7) improved upon the efficiency of iron(III) acac and led to an overall superior reaction outcome. Despite being a well-known agent for oxidative C-C bond formation and a variety of allylic C-H bond oxidations, iron (III) chloride is yet to be reported as a catalyst for transformation of olefins to enones, to the best of our knowledge.[12,13,14] The nearest example to its employment as such is as a complex in a polymer-bound Schiff base.[15] We chose to investigate the substrate scope for iron (III) chloride catalysis, given the novelty of the catalyst for this transformation and the improvement of iron over more toxic or costly species often employed to affect allylic oxidations.

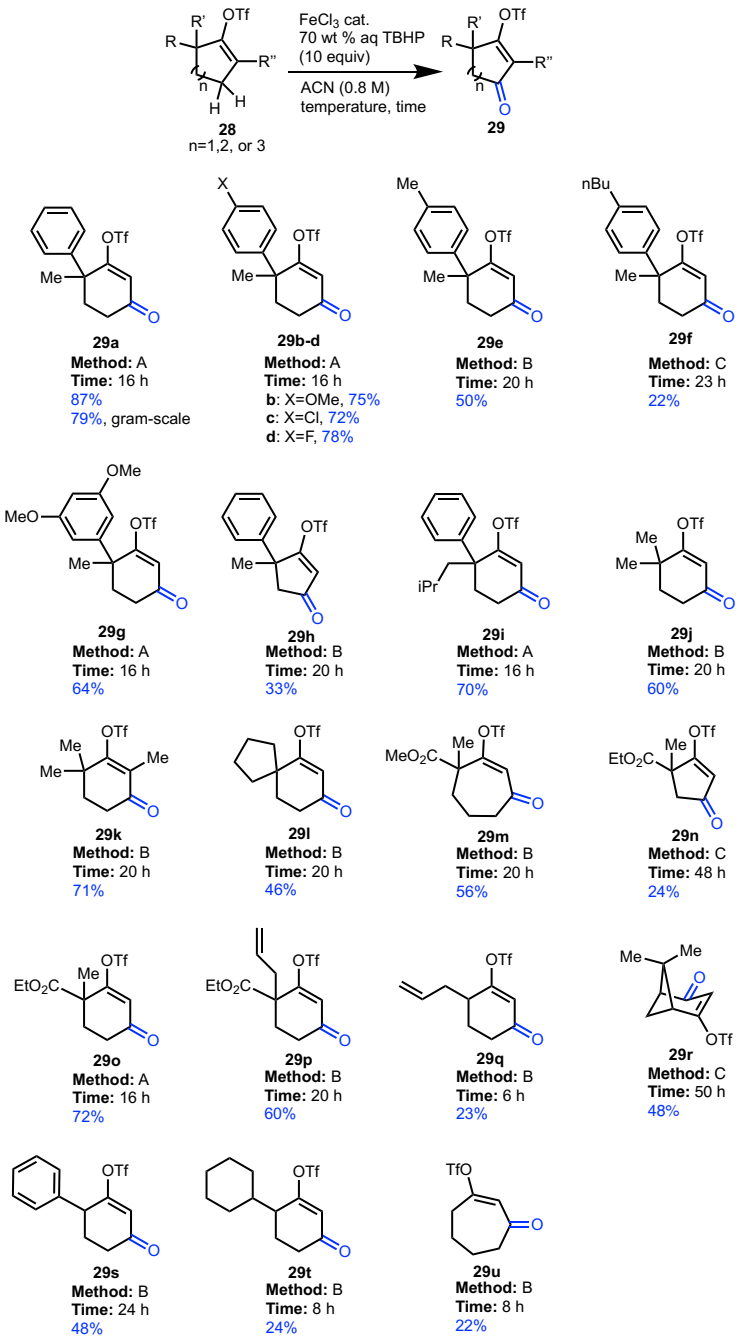


28a 29a

entry	solvent	cat.	nmr yield of **29a** (%)
1	ACN	Rh_2cap_4	63
2	ACN	$Pd(OH)_2/C$	21
3	ACN	Na_2CrO_7	70
4	ACN	CuI	57
5	ACN	$Cu(OAc)_2$	67
6	ACN	$Fe(acac)_3$	35
7	**ACN**	**$FeCl_3$**	**93**
8	Acetone	$FeCl_3$	89
9[a]	ACN	$FeCl_3$	55
10[b]	ACN	$FeCl_3$	63
11	ACN	$FeCl_2$	73
12	ACN	none	ca 10
13[c]	ACN	$FeCl_3$	<5
14	PhH	$FeCl_3$	13[d]
15	EtOAc	$FeCl_3$	16[d]

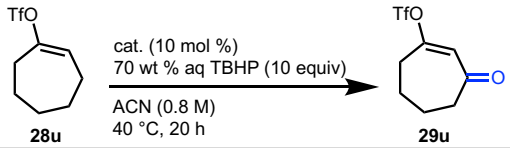
Table 2.1. Experiments concerning catalyst discovery. All yields are based on the use of dimethylsulfone as an internal standard. [a] 40 °C. [b] 5 equiv TBHP. [c] No TBHP. [d] Percent conversion by NMR to **29a** without an internal standard.

The scope for the oxidation of vinyl triflates is shown in **Scheme 2.2**. Aryl ring halide and methoxy substitution as shown for structures **29b-d** and **29g** was well tolerated. The system displayed a window of chemoselectivity for the desired oxidation over another olefin in cases **29p** and **29q**. Products **29e**, **29f** and **29s** were isolated despite containing benzylic centers. Interestingly, the oxidation of six-membered rings occurred with greater facility than that of analogous five-membered rings as shown in the relative ease of formation of **29a** versus **29h** and **29o** versus **29n**. The method scaled well, forming **29a** on gram scale in 79% isolated yield. In many cases, use of elevated catalyst loadings together with extended reaction times at lower temperatures served to improve the yield.



Scheme 2.2. Vinyl triflate substrate scope. Method A: 5 mol % $FeCl_3$, 60 °C Method B: 10 mol % $FeCl_3$, 40 °C Method C: 20 mol % $FeCl_3$, 30 °C

The transformation worked best for structures with quaternary centers immediately adjacent to the triflate. Competitive oxidation of the remaining allylic site of non-quaternary vinylogous acyl triflates was one issue. Additionally, as steric bulk adjacent to the triflate decreased, the yield of vinylogous acyl triflate generally decreased because of its hydrolysis under the reaction conditions. This is unsurprising given the use of acidic iron (III) chloride in a partially aqueous reaction mixture.

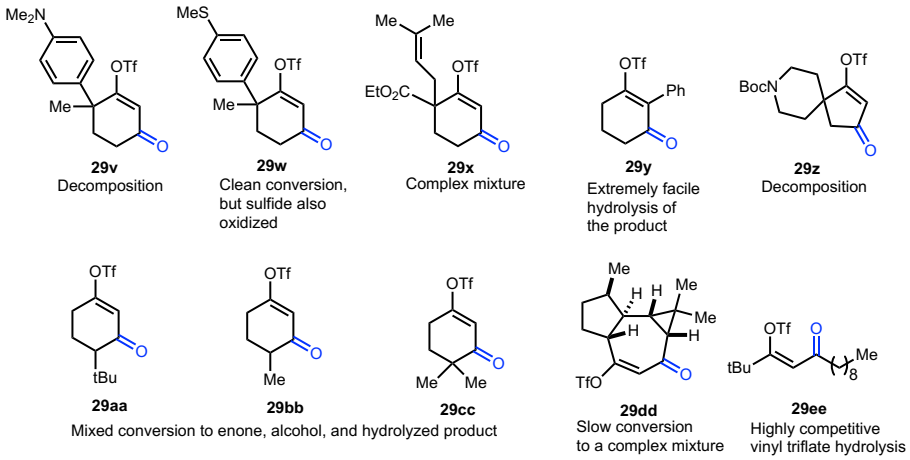


28u 29u

entry	cat.	base	nmr yield of **29u** (%
1	$FeCl_3$	none	23
2	CuI	none	19
3	$Cu(OAc)_2$	none	20
4	$Na_2Cr_2O_7$	none	21
5	Rh_2cap_4	none	21
6	$FeCl_3$	2,6-diphenylpyridine	8
7	$FeCl_3$	Cs_2CO_3	<5
8	$FeCl_3$	KOAc	<5
9[a]	$FeCl_3$	none	19
10[b]	$FeCl_3$	none	17
11[c]	$FeCl_3$	none	ca 20[d]

Table 2.2. Attempts to improve the process for **29u**. All yields are based on the use of dimethylsulfone as an internal standard. [a]Anhydrous conditions. [b] In Acetone. [c]Nonaflate in lieu of triflate. [d] Isolated yield.

Attempts to circumvent these issues in studies of **29u** formation such as buffering with inorganic or amine bases, employing anhydrous reaction conditions, substituting other catalysts, or changing the sulfonate identity failed to improve the reaction outcome. While the system allowed for variance of R" from hydrogen in case **29k**, homoallylic steric bulk was tolerated poorly. Additionally, the process failed for linear substrates and those containing nitrogeneous moieties.



29v Decomposition

29w Clean conversion, but sulfide also oxidized

29x Complex mixture

29y Extremely facile hydrolysis of the product

29z Decomposition

29aa **29bb** **29cc** Mixed conversion to enone, alcohol, and hydrolyzed product

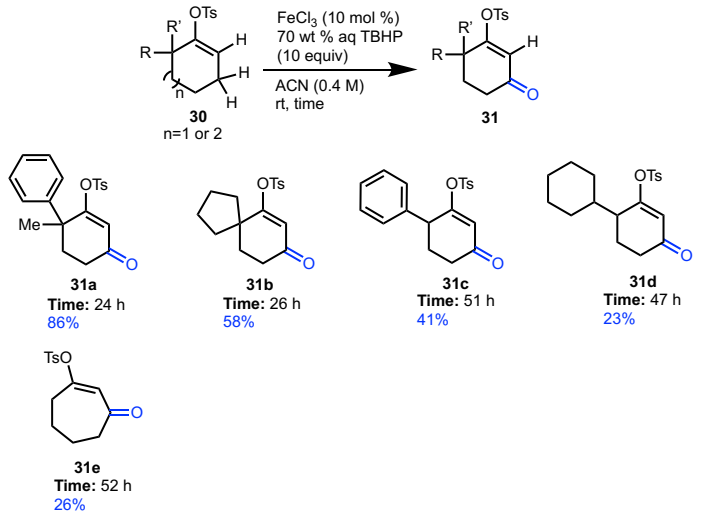
29dd Slow conversion to a complex mixture

29ee Highly competitive vinyl triflate hydrolysis

Figure 2.3. Substrates not tolerated under the reaction conditions & reasons for failure

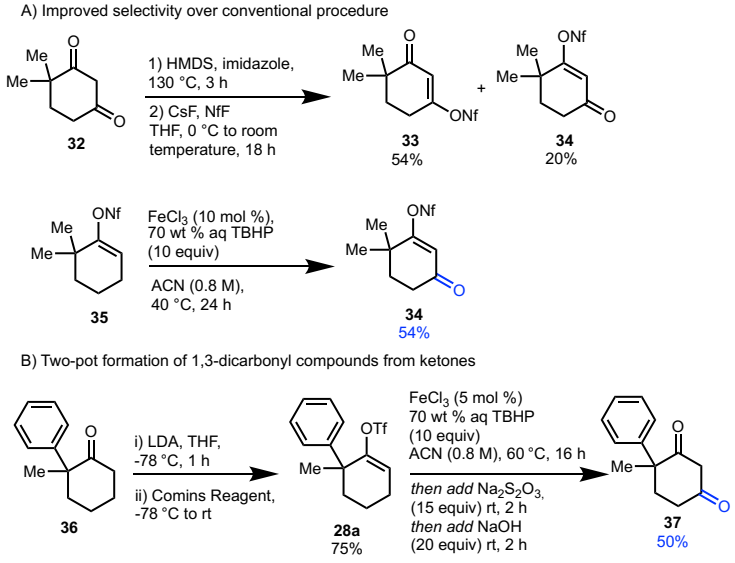
Given the limitations observed with vinyl triflates, we turned our attention to a survey of the oxidation of vinyl tosylates to vinylogous acyl tosylates, and the results are shown in **Scheme 2.3**. The transformation progressed under slightly gentler conditions than in the case of vinyl triflates and delivered the vinylogous acyl tosylate in a similar yield to that of the analogous vinylogous acyl triflate. The slightly more forceful conditions necessary for the oxidation of vinyl triflates might be because the shift on the vinylic proton on a

vinyl triflate is slightly downfield that of the analogous vinyl tosylate. Hydrolysis and overoxidation of the desired products were the issues again as steric bulk immediately adjacent to the tosylate decreased.



Scheme 2.3. Brief survey of vinyl tosylates.

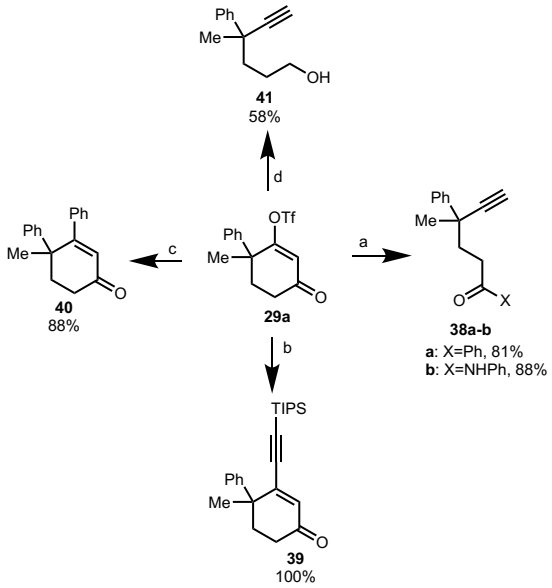
As a demonstration of the proposed utility of this method, we generated vinylogous acyl nonaflate **34** selectively from vinyl nonaflate **35** in 54% yield (**Scheme 2.4A**). Conditions employed in the literature from 1,3-dicarbonyl **32** gave an isomeric mix of products. In fact, these conditions favored vinylogous acyl nonaflate **33** (54% yield) over formation of desired product **34** (20% yield).[3] A second advantage of this oxidation was demonstrated in the two-pot synthesis of 1,3-dicarbonyl compound **37** from ketone **36**, representing an improvement over lengthier sequences typical in the literature (**Scheme 2.4B**).[16,17]



Scheme 2.4. Adavntages associated with an oxidative approach to vinylogous acyl sulfonates

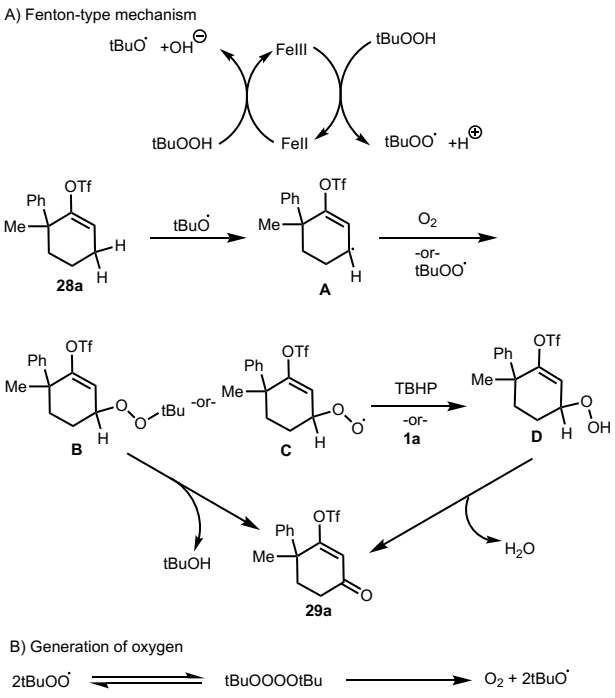
Product **29a** underwent the addition/fragmentation process described by Dudley et al. to generate products **38a-b** in good yield (**Scheme 2.5**).[18] Sterically demanding couplings of **29a** in Sonogashira and

Suzuki reactions formed **39** and **40** in high yield.[19,20] Additionally, formation of alcohol **41** in a hydride-mediated reductive ring opening was achieved in 58% yield.[18] The formation of **38**-**41** serves as a brief illustration of the utility of vinylogous acyl sulfonates for diverse derivatization.



Scheme 2.5. Representative derivatization of vinylogous acyl triflate products. Conditions: a: Li-X, THF, -78 to -10 °C over 1 h; then, 60 °C, 30 min. b: $(Ph_3P)_4Pd^0$, CuI, triisopropylsilylacetylene, iPr_2NEt:THF 1:1, 70 °C. c: $(Ph_3P)_4Pd^0$, $PhB(OH)_2$, aq Na_2CO_3, 3:1 PhMe:EtOH, rt. d: $LiHBEt_3$, -78 °C to rt.

Preliminary mechanistic investigations are underway. Substitution of iron (III) chloride with iron (II) chloride or a variety of other transition metal sources still allowed the reaction to proceed (**Table 2.1**). Based on these results, we propose an iron II/III catalytic cycle operating with analogy to the canonical Fenton oxidation pathway first discussed by Haber and Weiss (**Scheme 2.6A**).[21] Performance of the reaction under conditions free from atmospheric oxygen had no effect on yield of the desired product. Analysis of the gas formed by this reaction following its completion by a glowing splint test offered evidence that an oxidizing gas had been generated. Production of oxygen from tert-butyl peroxy radicals (**Scheme 2.6B**) might explain the formation of an oxidizing atmosphere.[22,23] Therefore, we propose that intermediate **A** may combine with either molecular oxygen or tert-butyl peroxy radical to generate intermediates **B** or **C** *en route* to the vinylogous acyl sulfonate. Given the highly reactive tert- butoxy radical postulated by this mechanism, the window of chemoselectivity for the desired transformation over alternative allylic and benzylic positions is surprising.



Scheme 2.6. Mechanistic proposal

Conclusion and Future Directions

We have accomplished the regioselective formation of vinylogous acyl sulfonates through an iron(III) chloride-mediated oxidation of the corresponding vinyl sulfonates. The most favorable vinyl sulfonates for this transformation contained quaternary centers immediately adjacent to the vinyl sulfonate, although other classes of products were isolated at lower yields. The vinylogous acyl sulfonates produced were useful for an assortment of subsequent transformations. Future studies will improve the process for less sterically protected vinyl sulfonates, achieve the oxidation of linear substrates, and address substrates with steric hindrance around the allylic site.

General Experimental Information

General Procedures. All reactions were performed in oven-dried glassware under a positive pressure of dinitrogen unless otherwise noted. Flash column chromatography was performed as described by Still et al.[24] employing silica gel 60 (40-63 μm, Whatman). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F254 plates (Merck).

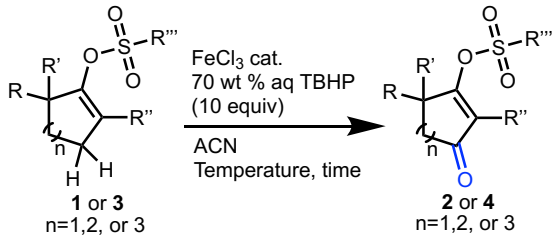
Materials. Reagents and solvents used herein were purchased from commercial vendors and used as received, with these specifications: Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), diisopropylamine, and N-ethyldiisopropylamine were sourced from sureseal bottles. The molarities of sureseal butyllithium hexane solutions (Aldrich) were determined by titration with 1,10-phenanthroline as an indicator (average of three determinations). THF solutions of lithium diisopropylamide (LDA) and lithium anilide were prepared by addition of a hexane solution of butyllithium (1 equiv) to a THF solution of the appropriate amine (1.1 equiv) cooled to –78 ℃ and stirring the solution for 30 min at 0 ºC. Sureseal THF solutions of sodium hexamethyldisilazide (NaHMDS) and lithium triethylborohydride ($LiHBEt_3$) were purchased from Aldrich and used without further modification. Sureseal ethereal solutions of phenyllithium (PhLi) were purchased from Aldrich and used without further modification.

Instrumentation. ^{1}H NMR spectra were recorded with Varian INOVA-500, Agilent DD2-600, or JEOL-400 spectrometers, are reported in parts per million (δ), and are calibrated using residual non-deuterated solvent as an internal reference: $CDCl_3$, δ 7.26 ($CHCl_3$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sx = sextet, m = multiplet; br = broad, or combinations thereof. ^{13}C NMR spectra were recorded with a Varian INOVA-500 or JEOL-400 spectrometer, are reported in parts per million (δ), and are referenced from the central peak of the carbon resonance of the solvent: $CDCl_3$, δ 77.16. ^{19}F NMR spectra were recorded with a JEOL-400 or a Varian INOVA-500 spectrometer and are reported in parts per million (δ). Infrared (IR) data were recorded on a Bruker Alpha FT-IR spectrometer outfitted with an Eco-ATR sampling module. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mass spectroscopy using a Thermo Scientific Dionex UltiMate 3000 UHPLC coupled to a Thermo Q Exactive Plus mass spectrometer system equipped with either an HESI-II electrospray ionization source or an APCI probe.

Experimentals

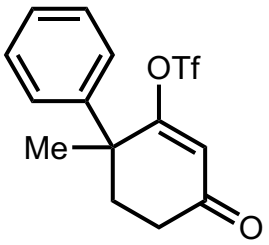
A full description of the syntheses of compounds **28**, **30**, and **35**, including the procurement or synthesis of all precursors thereto, is available in the supporting information of the published version of this work. [25]

Oxidative Synthesis of Vinylogous Acyl Sulfonates



General Sulfonate Oxidation Procedure (A). The following was performed open to air and moisture. A vial equipped with a stir bar was charged with the vinyl sulfonate and acetonitrile. Reactions on vinyl triflates **1** and vinyl nonaflate **8** were performed on a 0.8 M solution in acetonitrile of the substrate. Reactions on vinyl tosylates **3** were performed on a 0.4 M solution in acetonitrile of the substrate. Ten equivalents of TBHP (70% wt solution in water) were added, followed by the proscribed equivalents of iron (III) chloride as a 0.1 M aqueous solution. The vial was closed with a teflon-lined cap, sealed with teflon tape and parafilm, and heated (if necessary) at the indicated temperature for the indicated time in an aluminum shot bath. The reaction was cooled to room temperature and poured into a saturated aqueous sodium thiosulfate solution. The aqueous layer was extracted thrice with EtOAc or ether as indicated. The combined organic fractions were washed with saturated aqueous sodium bicarbonate solution, water, and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. Concentration of EtOAc fractions was performed with a 50 ℃ water bath; of ethereal fractions, a room temperature bath. The residue obtained was separated by silica gel chromatography as described (column reported in "length" by "width") to afford the pure vinylogous acyl sulfonate.

Note on vinyl triflate ^{13}C characterization. In cases in which the carbon quartet (appearing at ca 123, 120, 117, and 114 ppm) of the -CF_3 group is partially visible, the peak(s) associated with this resonance (typically the tallest two at ca 120 and 117 ppm) are reported individually.



1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29a):

General procedure A was executed upon 69.0 mg (0.215 mmol) of **28a**, using 5 mol % $FeCl_3$ at 60 ℃ with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (50 mL) and then 30% (100 mL) EtOAc/hexane. The process generated 12 12 mL fractions. Fractions 7-11 were combined and concentrated at reduced pressure to give **29a** (62.4 mg, 0.187 mmol, 87%) as a clear, colorless oil. Repetition of the same procedure on 1.03 g (3.23 mmol) of **28a** afforded 855 mg (2.56 mmol, 79%) of **29a**.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.45 – 7.35 (m, 2H), 7.35 – 7.29 (m, 3H), 6.31 (s, 1H), 2.47 – 2.36 (m, 1H), 2.35 – 2.22 (m, 3H), 1.72 (s, 3H).

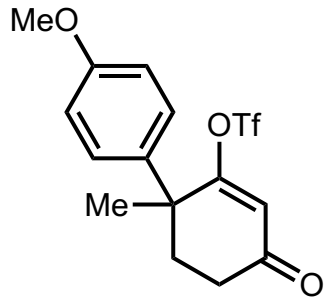
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.3, 170.2, 140.8, 129.2, 127.9, 125.9, 119.8, 118.2, 116.7, 44.7, 38.4, 34.1, 24.7.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.81.

FTIR (thin film) ν_{max}: 2980, 1691, 1632, 1602, 1497, 1461, 1446, 1414, 1325, 1247, 1209, 1134, 1083, 1036, 1017, 941, 917, 899, 877, 852, 805, 762, 756, 700, 609, 579, 552, 534, 508, 445, 432 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{14}F_3O_4S$, 335.0559; found, 335.0559.

TLC R_f= 0.44 (4:1 hexane:EtOAc).



4'-methoxy-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29b):

General procedure A was executed upon 70.8 mg (0.202 mmol) of **28b**, using 5 mol % $FeCl_3$ at 60 °C with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.2 L) EtOAc/hexane. The process generated 23 12 mL fractions. Fractions 13-20 were combined and concentrated at reduced pressure to give **29b** (55.2 mg, 0.151 mmol, 75%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.23 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.28 (s, 1H), 3.81 (s, 3H), 2.41 (dt, J = 16.4, 4.9 Hz, 1H), 2.36 – 2.18 (m, 3H), 1.69 (s, 3H).

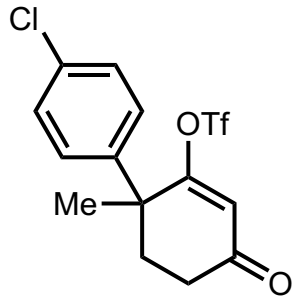
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.5, 170.5, 159.1, 132.6, 127.1, 119.9, 118.1, 116.7, 114.5, 55.5, 44.1, 38.5, 34.1, 24.8.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.81.

FTIR (thin film) ν_{max}: 2937, 2840, 1694, 1631, 1611, 1582, 1514, 1463, 1414, 1383, 1326, 1313, 1298, 1248, 1211, 1187, 1135, 1103, 1076, 1034, 1021, 936, 902, 878, 856, 829, 809, 797, 766, 752, 694, 663, 625, 606, 579, 560, 513, 409 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{15}H_{15}F_3O_5S$, 365.0665; found, 365.0660.

TLC R_f= 0.25 (4:1 hexane:EtOAc).



4'-chloro-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29c):

General procedure A was executed upon 76.1 mg (0.214 mmol) of **28c**, using 5 mol % $FeCl_3$ at 60 °C with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.2 L) EtOAc/hexane. The process generated 24 12 mL fractions. Fractions 14-21 were combined and concentrated at reduced pressure to give **29c** (56.9 mg, 0.154 mmol, 72%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.38 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.31 (s, 1H), 2.48-2.36 (m, 1H), 2.34 – 2.16 (m, 3H), 1.70 (s, 3H).

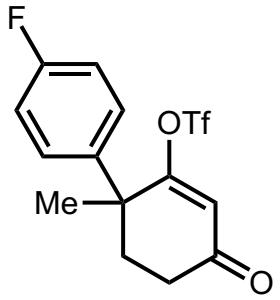
^{13}CNMR (101 MHz; $CDCl_3$) δ: 196.9, 169.5, 139.4, 134.0, 129.4, 127.4, 118.4, 44.4, 38.4, 34.0, 24.6.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.73.

FTIR (thin film) ν_{max}: 2928, 1694, 1632, 1492, 1462, 1415, 1325, 1247, 1210, 1134, 1100, 1072, 1038, 1022, 1011, 940, 902, 877, 854, 825, 804, 758, 733, 687, 598, 579, 550, 523, 478, 409 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{12}ClF_3O_4S$, 369.0170; found, 369.0168.

TLC R_f= 0.28 (4:1 hexane:EtOAc).



4'-fluoro-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29d):

General procedure A was executed upon 69.0 mg (0.204 mmol) of **28d**, using 5 mol % $FeCl_3$ at 60 °C with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.2 L) EtOAc/hexane. The process generated 24 12 mL fractions. Fractions 13-22 were combined and concentrated at reduced pressure to give **29d** (56.2 mg, 0.159 mmol, 78%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.35 – 7.27 (m, 2H), 7.14 – 7.04 (m, 2H), 6.30 (s, 1H), 2.44 (ddd, J = 15.9, 5.8, 3.9 Hz, 1H), 2.32 (dd, J = 8.9, 6.7 Hz, 1H), 2.28 – 2.20 (m, 2H), 1.71 (s, 3H).

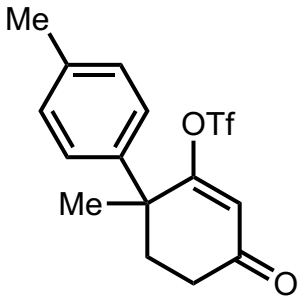
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.0, 169.8, 162.2 (d, J = 249.5 Hz), 136.6 (d, J = 4.0 Hz), 127.8 (d, J = 8.1 Hz), 118.3, 116.1 (d, J = 22.2 Hz), 44.3, 38.5, 34.0, 24.7.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.79, -114.33.

FTIR (thin film) ν_{max}: 2929, 1694, 1632, 1606, 1511, 1462, 1414, 1324, 1211, 1168, 1135, 1091, 1073, 1038, 1022, 1013, 938, 903, 878, 859, 834, 803, 753, 725, 694, 660, 625, 606, 579, 557, 530, 494, 433, 409 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{12}F_4O_4S$, 353.0465; found, 353.0462.

TLC R_f= 0.30 (4:1 hexane:EtOAc).



1,4'-dimethyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29e):

General procedure A was executed upon 69.0 mg (0.207 mmol) of **28e**, using 10 mol % $FeCl_3$ at 40 °C with a 20 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 5% (0.1 L) and then 10% (0.2 L) EtOAc/hexane. The process generated 24 12 mL fractions. Fractions 13-21 were combined and concentrated at reduced pressure to give **29e** (35.9 mg, 0.103 mmol, 50%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.22-7.18 (m, 4H), 6.30 (s, 1H), 2.40 (dt, J = 15.7, 4.1 Hz, 1H), 2.35 (s, 3H), 2.31 (dd, J = 10.7, 5.2 Hz, 1H), 2.28 – 2.20 (m, 2H), 1.69 (s, 3H).

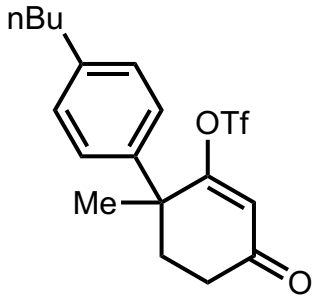
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.5, 170.5, 137.7, 137.6, 129.8, 125.9, 119.9, 118.1, 116.7, 44.4, 38.5, 34.1, 24.8, 21.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.80.

FTIR (thin film) v_{max}: 2926, 1694, 1632, 1515, 1419, 1327, 1314, 1247, 1214, 1137, 1074, 1039, 1025, 1015, 940, 903, 878, 855, 815, 765, 753, 696, 606, 579, 528, 495 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{15}H_{15}F_3O_4S$, 349.0716; found, 349.0712.

TLC R_f= 0.43 (4:1 hexane:EtOAc).



4'-butyl-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29f):

General procedure A was executed upon 74.8 mg (0.199 mmol) of **28f**, using 20 mol % $FeCl_3$ at 30 °C with a 23 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 5% (0.1 L), then 8% (0.2 L) and then 20% (0.25 L) EtOAc/hexane. The process generated 41 12 mL fractions. Fractions 14-18 were combined and concentrated at reduced pressure to give **29f** (17.0 mg, 44 μmol, 22%) as a clear, colorless oil. Fractions 30-39 were combined and concentrated at reduced pressure to give **42** (29.2 mg, 72 μmol, 36%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.24 – 7.16 (m, 4H), 6.29 (s, 1H), 2.61 (t, J = 7.3 Hz, 2H), 2.45 – 2.35 (m, 1H), 2.35 – 2.18 (m, 3H), 1.70 (s, 3H), 1.65-1.54 (m, 2H), 1.43 – 1.29 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).

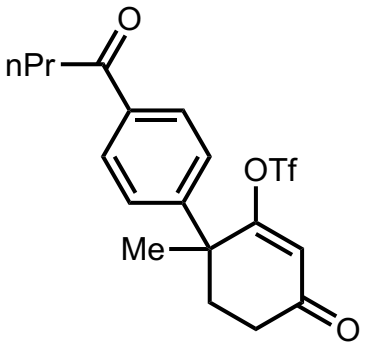
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.5, 170.6, 142.6, 137.8, 129.1, 125.8, 118.1, 44.5, 38.4, 35.2, 34.1, 33.6, 24.8, 22.5, 14.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.80.

FTIR (thin film) ν_{max}: 2958, 2929, 2859, 1693, 1631, 1511, 1459, 1413, 1381, 1364, 1322, 1247, 1210, 1135, 1107, 1075, 1037, 1024, 1013, 941, 901, 878, 854, 830, 804, 754, 696, 607, 577, 533, 508, 445, 409 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{21}F_3O_4S$, 391.1185; found, 391.1181.

TLC R_f = 0.49 (4:1 hexane:EtOAc).



SI-26

4'-butyryl-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (42):

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.99 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 6.34 (s, 1H), 2.94 (t, J = 7.3 Hz, 2H), 2.51 – 2.38 (m, 1H), 2.34 – 2.20 (m, 3H), 1.85 – 1.71 (m, 5H), 1.01 (t, J = 7.4 Hz, 3H).

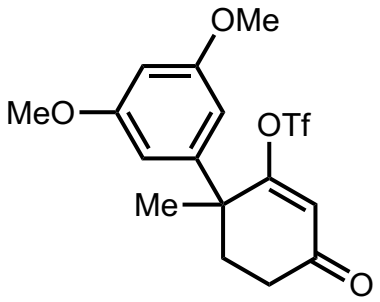
^{13}CNMR (101 MHz; $CDCl_3$) δ: 199.7, 196.8, 169.4, 145.9, 136.7, 128.9, 126.3, 119.8, 118.5, 116.7, 44.9, 40.7, 38.3, 34.0, 24.5, 17.8, 14.0.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.70.

FTIR (thin film) ν_{max}: 2963, 2930, 2875, 1686, 1632, 1607, 1459, 1410, 1366, 1324, 1301, 1247, 1213, 1135, 1105, 1073, 1038, 1024, 1014, 991, 943, 904, 879, 855, 805, 757, 704, 607, 576, 492, 406 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{19}F_3O_5S$, 405.0978; found, 405.0979.

TLC R_f = 0.21 (4:1 hexane:EtOAc).



3',5'-dimethoxy-1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29g):

General procedure A was executed upon 85.0 mg (0.223 mmol) of **28g**, using 5 mol % $FeCl_3$ at 60 °C with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 20% (0.2 L) EtOAc/hexane. The process generated 23 12 mL fractions. Fractions 14-21 were combined and concentrated at reduced pressure to give **29g** (56.4 mg, 0.143 mmol, 64%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.45 (d, J = 2.2 Hz, 2H), 6.41 (t, J = 2.2 Hz, 1H), 6.28 (s, 1H), 3.79 (s, 6H), 2.47 – 2.15 (m, 4H), 1.67 (s, 3H).

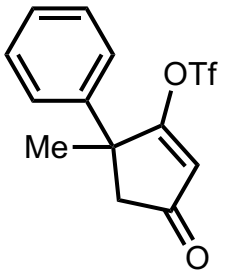
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.4, 170.0, 161.4, 143.3, 119.9, 118.2, 116.7, 104.7, 99.1, 55.5, 44.9, 38.3, 34.2, 24.8.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.80.

FTIR (thin film) v_{max}: 2938, 2841, 1691, 1631, 1595, 1458, 1422, 1326, 1295, 1247, 1205, 1158, 1135, 1092, 1046, 1021, 942, 929, 901, 869, 840, 817, 799, 763, 700, 657, 637, 605, 577, 509, 446 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{16}H_{17}F_3O_6S$, 395.0771; found, 395.0766.

TLC R_f= 0.23 (4:1 hexane:EtOAc).



5-methyl-3-oxo-5-phenylcyclopent-1-en-1-yl trifluoromethanesulfonate (29h):

General procedure A was executed upon 63.1 mg (0.206 mmol) of **28h**, using 10 mol % $FeCl_3$ at 40 ℃ with a 20 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 5% (0.2 L) and then 8% (0.2 L) EtOAc/hexane. The process generated 46 9 mL fractions. Fractions 28-38 were combined and concentrated at reduced pressure to give **29h** (21.5 mg, 67 μmol, 33%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.39 (t, J = 7.7 Hz, 2H), 7.34 – 7.26 (m, 3H), 6.25 (s, 1H), 2.87 (d, J = 18.7 Hz, 1H), 2.75 (d, J = 18.7 Hz, 1H), 1.81 (s, 3H).

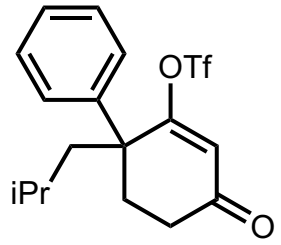
^{13}CNMR (101 MHz; $CDCl_3$) δ: 201.9, 181.4, 140.6, 129.3, 128.0, 125.6, 120.0, 116.8, 115.5, 53.6, 48.5, 23.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -72.77.

FTIR (thin film) ν_{max}: 2925, 2853, 1727, 1616, 1498, 1432, 1381, 1300, 1286, 1214, 1130, 1082, 1057, 1030, 1003, 943, 923, 911, 835, 809, 763, 731, 700, 665, 607, 585, 540, 509, 488, 445 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{11}F_3O_4S$, 321.0403; found, 321.0400.

TLC R_f= 0.38 (4:1 hexane:EtOAc).



1-isobutyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29i):

General procedure A was executed upon 74.1 mg (0.204 mmol) of **28i**, using 5 mol % $FeCl_3$ at 60 ℃ with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.15 L) EtOAc/hexane. The process generated 20 12 mL fractions. Fractions 13-18 were combined and concentrated at reduced pressure to give **29i** (54.2 mg, 0.144 mmol, 70%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.42 – 7.35 (m, 2H), 7.34-7.27 (m, 3H), 6.35 (s, 1H), 2.55 – 2.34 (m, 2H), 2.28 – 2.15 (m, 2H), 2.06 – 1.91 (m, 2H), 1.80 (dp, J = 11.8, 6.3 Hz, 1H), 1.01 (dd, J = 16.5, 6.7 Hz, 6H).

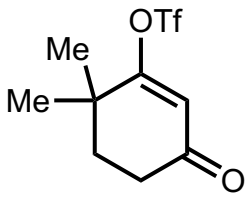
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.4, 170.0, 141.1, 129.1, 127.8, 126.3, 119.8, 118.3, 116.4, 49.2, 46.5, 34.1, 34.0, 25.7, 25.1, 24.3.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.84.

FTIR (thin film) ν_{max}: 2961, 2874, 1691, 1628, 1601, 1512, 1497, 1467, 1447, 1413, 1369, 1327, 1246, 1213, 1168, 1134, 1070, 1035, 984, 917, 858, 835, 807, 757, 725, 700, 639, 616, 597, 566, 539, 517, 482 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{17}H_{19}F_3O_4S$, 377.1029; found, 377.1027.

TLC R_f= 0.45 (4:1 hexane:EtOAc).



6,6-dimethyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (29j):

General procedure A was executed upon 58.7 mg (0.225 mmol) of **28j**, using 10 mol % $FeCl_3$ at 40 °C with a 20 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 20% (0.2 L) ether/pentane. The process generated 22 12 mL fractions. Fractions 15-22 were combined and concentrated at reduced pressure to give **29j** (36.9 mg, 0.136 mmol, 60%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.01 (s, 1H), 2.53 – 2.48 (m, 2H), 1.99 – 1.94 (m, 2H), 1.31 (s, 6H).

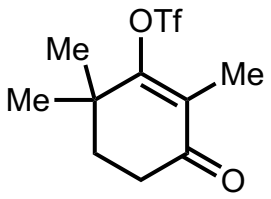
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.5, 172.9, 116.3, 36.3, 35.9, 34.1, 25.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.69.

FTIR (thin film) ν_{max}: 2927, 1693, 1633, 1418, 1326, 1248, 1213, 1137, 1041, 1022, 936, 920, 882, 811, 760, 711, 606, 577, 532 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_9H_{11}F_3O_4S$, 273.0403; found, 273.0401.

TLC R_f= 0.33 (4:1 hexane:EtOAc).



2,6,6-trimethyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (29k):

General procedure A was executed upon 61.4 mg (0.223 mmol) of **28k**, using 10 mol % $FeCl_3$ at 40 °C with a 20 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 20% (0.2 L) ether/pentane. The process generated 23 12 mL fractions. Fractions 12-18 were combined and concentrated at reduced pressure to give **29k** (45.7 mg, 0.160 mmol, 71%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 2.58 – 2.54 (m, 2H), 1.96 – 1.86 (m, 5H), 1.31 (s, 6H).

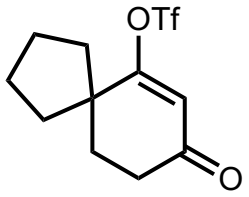
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.7, 168.4, 127.4, 120.3, 117.1, 37.0, 36.7, 34.0, 25.2, 10.4.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -72.62.

FTIR (thin film) ν_{max}: 2973, 2936, 1692, 1647, 1451, 1408, 1379, 1371, 1333, 1297, 1242, 1207, 1136, 1100, 1051, 1003, 916, 883, 799, 764, 710, 672, 609, 574, 544, 503 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{10}H_{13}F_3O_4S$, 287.0559; found, 287.0556.

TLC R_f= 0.48 (4:1 hexane:EtOAc).



8-oxospiro[4.5]dec-6-en-6-yl trifluoromethanesulfonate (29l):

General procedure A was executed upon 61.4 mg (0.216 mmol) of **28l**, using 10 mol % $FeCl_3$ at 40 °C with a 20 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.25 L) ether/pentane. The process generated 27 12 mL fractions. Fractions 17-25 were combined and concentrated at reduced pressure to give **29l** (29.5 mg, 99 μmol, 46%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.02 (s, 1H), 2.51 – 2.43 (m, 2H), 2.05 – 1.93 (m, 4H), 1.87 – 1.68 (m, 6H).

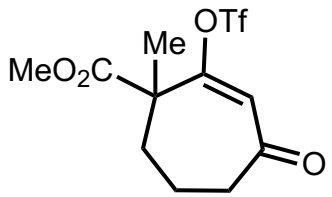
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.6, 172.4, 116.1, 46.7, 36.0, 34.8, 34.3, 25.9.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.76.

FTIR (thin film) ν_{max}: 2959, 2874, 1690, 1630, 1449, 1415, 1345, 1331, 1247, 1213, 1137, 1080, 1031, 987, 963, 918, 869, 810, 760, 650, 603, 579, 517 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{11}H_{13}F_3O_4S$, 299.0559; found, 299.0559.

TLC R_f= 0.43 (4:1 hexane:EtOAc).



methyl 1-methyl-4-oxo-2-(((trifluoromethyl)sulfonyl)oxy)cyclohept-2-ene-1-carboxylate (29m):

General procedure A was executed upon 64.3 mg (0.203 mmol) of **28m**, using 10 mol % $FeCl_3$ at 40 ℃ with a 20 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.25 L) EtOAc/hexane. The process generated 27 12 mL fractions. Fractions 18-27 were combined and concentrated at reduced pressure to give **29m** (37.4 mg, 0.113 mmol, 56%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.16 (s, 1H), 3.80 (s, 3H), 2.82 – 2.58 (m, 2H), 2.39 – 2.26 (m, 1H), 1.98-1.85 (m, 3H), 1.56 (s, 3H).

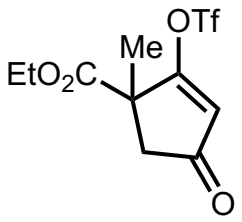
^{13}CNMR (101 MHz; $CDCl_3$) δ: 198.9, 172.2, 162.0, 123.2, 119.9, 116.7, 54.2, 53.3, 43.7, 37.0, 23.6, 18.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -74.49.

FTIR (thin film) ν_{max}: 2956, 1743, 1672, 1643, 1457, 1417, 1385, 1345, 1247, 1210, 1180, 1136, 1103, 1066, 997, 978, 870, 823, 804, 759, 671, 608, 576, 550, 515 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{11}H_{13}F_3O_6S$, 331.0458; found, 331.0455.

TLC R_f= 0.20 (4:1 hexane:EtOAc).



ethyl 1-methyl-4-oxo-2-(((trifluoromethyl)sulfonyl)oxy)cyclopent-2-ene-1-carboxylate (29n):

General procedure A was executed upon 65.9 mg (0.220 mmol) of **28n**, using 20 mol % $FeCl_3$ at 30 °C with a 48 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.2 L) EtOAc/hexane. The process generated 47 9 mL fractions. Fractions 22-35 were combined and concentrated at reduced pressure to give **29n** (16.6 mg, 52 μmol, 24%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.19 (s, 1H), 4.30 – 4.14 (m, 2H), 2.97 (d, J = 18.4 Hz, 1H), 2.49 (d, J = 18.4 Hz, 1H), 1.61 (s, 3H), 1.39 – 1.16 (m, 3H).

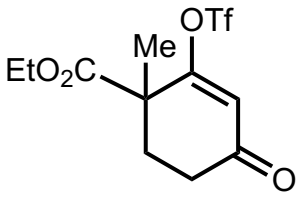
^{13}CNMR (101 MHz; $CDCl_3$) δ: 199.9, 177.3, 170.6, 120.1, 117.0, 116.6, 62.8, 51.3, 47.9, 21.1, 14.0.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -72.74.

FTIR (thin film) ν_{max}: 2923, 2853, 1733, 1621, 1434, 1381, 1368, 1308, 1274, 1214, 1186, 1132, 1068, 1020, 941, 899, 857, 821, 805, 762, 699, 605, 580, 532, 502, 458 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{10}H_{11}F_3O_6S$, 317.0301; found, 317.0299.

TLC R_f= 0.31 (4:1 hexane:EtOAc).



ethyl 1-methyl-4-oxo-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-2-ene-1-carboxylate (29o):

General procedure A was executed upon 68.1 mg (0.215 mmol) of **28o**, using 5 mol % $FeCl_3$ at 60 ℃ with a 16 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 20% (0.15 L) EtOAc/hexane. The process generated 20 12 mL fractions. Fractions 11-18 were combined and concentrated at reduced pressure to give **29o** (51.1 mg, 0.155 mmol, 72%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.13 (s, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.58 – 2.46 (m, 3H), 2.10 – 1.95 (m, 1H), 1.55 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H).

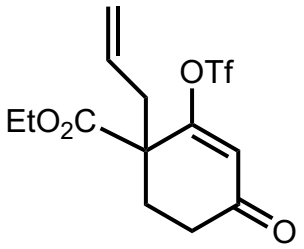
^{13}CNMR (101 MHz; $CDCl_3$) δ: 196.5, 171.1, 166.2, 118.1, 62.8, 47.7, 34.4, 33.5, 21.8, 14.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.92.

FTIR (thin film) ν_{max}: 2985, 2929, 1737, 1694, 1637, 1422, 1384, 1367, 1325, 1249, 1212, 1188, 1136, 1099, 1043, 1028, 945, 905, 859, 802, 763, 684, 608, 517, 423 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{11}H_{13}F_3O_6S$, 331.0458; found, 331.0455.

TLC R_f= 0.33 (4:1 hexane:EtOAc).



ethyl 1-allyl-4-oxo-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-2-ene-1-carboxylate (29p):

General procedure A was executed upon 73.2 mg (0.213 mmol) of **28p**, using 10 mol % $FeCl_3$ at 40 °C with a 20 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.2 L) EtOAc/hexane. The process generated 23 12 mL fractions. Fractions 12-18 were combined and concentrated at reduced pressure to give **29p** (45.7 mg, 0.127 mmol, 60%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ 6.14 (s, 1H), 5.69 (dddd, J = 16.4, 10.6, 7.7, 6.9 Hz, 1H), 5.29 – 5.17 (m, 2H), 4.27 (m, 2H), 2.76 – 2.61 (m, 2H), 2.55 – 2.48 (m, 2H), 2.43 (dt, J = 13.8, 4.5 Hz, 1H), 2.20 – 2.07 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H).

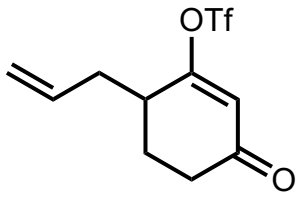
^{13}CNMR (101 MHz; $CDCl_3$) δ: 196.6, 170.3, 164.8, 130.8, 121.4, 119.9, 119.0, 116.7, 62.9, 51.1, 39.5, 34.4, 29.8, 14.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -74.13.

FTIR (thin film) v_{max}: 2927, 1737, 1694, 1636, 1426, 1368, 1331, 1283, 1248, 1211, 1180, 1137, 1043, 1016, 989, 920, 881, 858, 803, 759, 642, 600, 551, 518 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{15}F_3O_6S$, 357.0614; found, 357.0612.

TLC R_f= 0.40 (4:1 hexane:EtOAc).



6-allyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (29q):

General procedure A was executed upon 112.7 mg (0.417 mmol) of **28q**, using 10 mol % $FeCl_3$ at 40 ℃ with a 6 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.5 L) ether/pentane. The process generated 53 9 mL fractions. Fractions 27-43 were combined and concentrated at reduced pressure to give **29q** (27.7 mg, 99 μmol, 23%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.07 (s, 1H), 5.76 (dddd, J = 17.4, 9.7, 7.7, 6.5 Hz, 1H), 5.24 – 5.13 (m, 2H), 2.85 – 2.75 (m, 1H), 2.63 – 2.46 (m, 2H), 2.45 – 2.30 (m, 2H), 2.18 (ddt, J = 14.3, 9.2, 5.2 Hz, 1H), 2.02 – 1.91 (m, 1H).

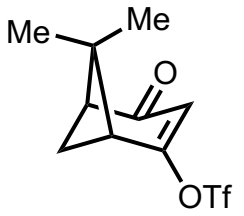
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.4, 169.4, 133.6, 120.1, 119.2, 119.0, 116.9, 38.0, 35.0, 34.3, 25.2.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.42.

FTIR (thin film) ν_{max}: 2925, 2854, 1692, 1639, 1423, 1366, 1348, 1330, 1312, 1247, 1209, 1137, 1033, 995, 975, 900, 872, 801, 759, 604, 576, 506, 491 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{10}H_{11}F_3O_4S$, 285.0403; found, 285.0403.

TLC R_f= 0.44 (4:1 hexane:EtOAc).



(1R,5S)-6,6-dimethyl-4-oxobicyclo[3.1.1]hept-2-en-2-yl trifluoromethanesulfonate (29r):

General procedure A was executed upon 59.1 mg (0.219 mmol) of **28r**, using 20 mol % $FeCl_3$ at 30 ℃ with a 50 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 10 by 3 cm silica gel column and eluted with 7.5% (0.5 L) ether/pentane. The process generated 55 9 mL fractions. Fractions 33-52 were combined and concentrated at reduced pressure to give **29r** (29.8 mg, 0.105 mmol, 48%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.86 (d, J = 2.0 Hz, 1H), 2.99 (dt, J = 9.8, 5.7 Hz, 1H), 2.74 (dd, J = 5.7, 2.0 Hz, 2H), 2.34 (d, J = 9.8 Hz, 1H), 1.57 (s, 3H), 1.15 (s, 3H).

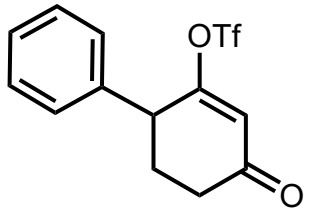
^{13}CNMR (101 MHz; $CDCl_3$) δ: 200.2, 174.4, 120.1, 116.9, 112.0, 57.8, 55.0, 48.9, 41.1, 26.3, 22.2.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.18.

FTIR (thin film) ν_{max}: 2965, 2927, 1697, 1625, 1470, 1428, 1392, 1375, 1332, 1278, 1247, 1211, 1137, 1081, 1066, 1000, 981, 910, 896, 866, 831, 796, 764, 749, 727, 677, 605, 574, 530, 502, 483, 428 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{10}H_{11}F_3O_4S$, 285.0403; found, 285.0403.

TLC R_f= 0.48 (4:1 hexane:EtOAc).



4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (29s):

General procedure A was executed upon 132.8 mg (0.434 mmol) of **28s**, using 10 mol % $FeCl_3$ at 40 ℃ with a 24 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.4 L) EtOAc/hexane. The process generated 56 9 mL fractions. Fractions 30-49 were combined and concentrated at reduced pressure to give **29s** (66.5 mg, 0.208 mmol, 48%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.45 – 7.31 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 6.28 (s, 1H), 4.06 – 3.97 (m, 1H), 2.58 – 2.39 (m, 3H), 2.23 – 2.07 (m, 1H).

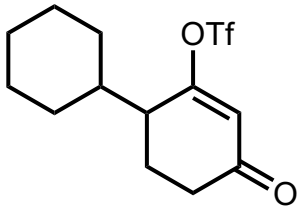
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.3, 167.3, 136.8, 129.4, 128.3, 127.9, 120.3, 45.1, 34.3, 30.6.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.53.

FTIR (thin film) ν_{max}: 2926, 1690, 1640, 1602, 1495, 1455, 1423, 1365, 1325, 1245, 1210, 1135, 1075, 1042, 1003, 977, 928, 899, 878, 797, 759, 701, 651, 605, 519, 508, 488 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{11}F_3O_4S$, 321.0403; found, 321.0405.

TLC R_f= 0.43 (4:1 hexane:EtOAc).



4-oxo-[1,1'-bi(cyclohexan)]-2-en-2-yl trifluoromethanesulfonate (29t):

General procedure A was executed upon 106.2 mg (0.340 mmol) of **28t**, using 10 mol % $FeCl_3$ at 40 °C with an 8 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 8% (0.3 L) EtOAc/hexane. The process generated 25 12 mL fractions. Fractions 15-24 were combined and concentrated at reduced pressure to give **29t** (25.4 mg, 78 μmol, 24%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.07 (s, 1H), 2.60 (q, J = 5.7 Hz, 1H), 2.52 (ddd, J = 17.2, 8.6, 5.1 Hz, 1H), 2.39 (ddd, J = 17.2, 8.4, 5.3 Hz, 1H), 2.11 (ddt, J = 14.0, 8.7, 5.4 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.90 – 1.75 (m, 3H), 1.75 – 1.59 (m, 3H), 1.39 – 1.18 (m, 3H), 1.18 – 1.03 (m, 2H).

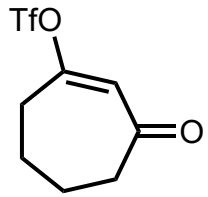
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.8, 170.0, 120.1, 119.6, 116.9, 44.1, 39.2, 35.1, 31.2, 29.3, 26.7, 26.5, 26.2, 22.5.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.50.

FTIR (thin film) v_{max}: 2929, 2855, 1691, 1636, 1451, 1423, 1246, 1209, 1169, 1137, 1029, 992, 911, 889, 805, 757, 606, 575 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{17}F_3O_4S$, 327.0872; found, 327.0874.

TLC R_f= 0.53 (4:1 hexane:EtOAc).



3-oxocyclohept-1-en-1-yl trifluoromethanesulfonate (29u):

General procedure A was executed upon 123.5 mg (0.506 mmol) of **28u**, using 10 mol % $FeCl_3$ at 40 ℃ with an 8 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 0% (0.1 L) and then 1% (0.1 L) and finally 2% (0.1 L) EtOAc/PhH. The process generated 36 12 mL fractions. Fractions 25-30 were combined and concentrated at reduced pressure to give **29u** (28.6 mg, 0.111 mmol, 22%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.11 (s, 1H), 2.80 (t, J = 6.0 Hz, 2H), 2.73 – 2.67 (m, 2H), 1.98 (p, J = 5.9 Hz, 1H), 1.94-1.85 (m, 2H).

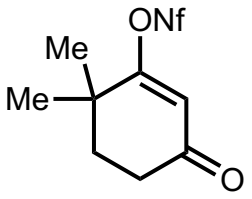
^{13}CNMR (101 MHz; $CDCl_3$) δ: 199.6, 164.6, 124.1, 120.1, 117.0, 43.7, 34.5, 24.4, 21.6.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.53.

FTIR (thin film) ν_{max}: 2935, 2873, 1673, 1655, 1455, 1419, 1367, 1312, 1246, 1203, 1135, 1035, 988, 915, 866, 789, 757, 606, 572, 512, 453, 421 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_8H_9F_3O_4S$, 259.0246; found, 259.0246.

TLC R_f= 0.50 (4:1 hexane:EtOAc).



6,6-dimethyl-3-oxocyclohex-1-en-1-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (34):

General procedure A was executed upon 88.7 mg (0.220 mmol) of **35**, using 10 mol % $FeCl_3$ at 40 ℃ with a 24 h reaction time. After workup with ether, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 25% (0.2 L) ether/pentane. The process generated 22 12 mL fractions. Fractions 14-19 were combined and concentrated at reduced pressure to give **34** (50.0 mg, 0.118 mmol, 54%) as a clear, colorless oil. Characterization data were consistent with those published.[3]

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.03 (s, 1H), 2.51 (t, J = 7.4, 2H), 1.97 (t, J = 7.4, 2H), 1.31 (s, 6H).

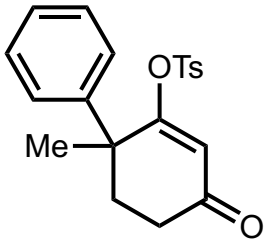
^{13}CNMR (101 MHz; $CDCl_3$) δ: 197.5, 173.1, 116.3, 36.4, 36.0, 34.1, 25.1.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -80.49 (t, J = 10.0 Hz, 3F), -109.08 (t, J = 14.0 Hz, 2F), -120.77 (m, 2F), -125.67 (m, 2F).

FTIR (thin film) ν_{max}: 2927, 1694, 1631, 1474, 1418, 1370, 1353, 1326, 1291, 1228, 1199, 1143, 1126, 1039, 1020, 955, 936, 920, 884, 794, 769, 749, 736, 710, 699, 651, 635, 588, 575, 539, 529, 483, 453 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{12}H_{11}F_9O_4S$, 423.0307; found, 423.0307.

TLC R_f= 0.36 (4:1 hexane:EtOAc).



1-methyl-4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl 4-methylbenzenesulfonate (31a):

General procedure A was executed upon 71.7 mg (0.210 mmol) of **30a**, using 10 mol % $FeCl_3$ at room temperature with a 24 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 20% (0.1 L) and then 40% (0.2 L) EtOAc/hexane. The process generated 22 12 mL fractions. Fractions 11-15 were combined and concentrated at reduced pressure to give **31a** (64.7 mg, 0.182 mmol, 86%) as an off-white solid.

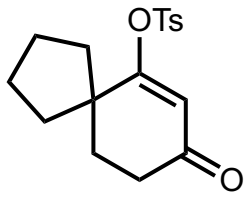
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.71 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.29 – 7.22 (m, 3H), 7.20 – 7.14 (m, 2H), 6.36 (s, 1H), 2.45 (s, 3H), 2.27 (td, J = 11.6, 11.1, 4.7 Hz, 1H), 2.19 – 2.08 (m, 3H), 1.55 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 198.7, 170.6, 146.3, 142.0, 132.7, 130.2, 128.8, 128.5, 127.3, 126.1, 115.0, 44.5, 38.4, 34.0, 25.1, 21.9.

FTIR (thin film) ν_{max}: 2926, 1681, 1618, 1597, 1496, 1458, 1446, 1417, 1380, 1364, 1328, 1295, 1212, 1195, 1180, 1137, 1111, 1083, 1062, 1024, 942, 897 , 851, 815, 801, 781, 763, 744, 701, 668, 647, 607, 596, 575, 548 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{20}H_{20}O_4S$, 357.1155; found, 357.1155.

TLC R_f= 0.18 (4:1 hexane:EtOAc).



8-oxospiro[4.5]dec-6-en-6-yl 4-methylbenzenesulfonate (31b):

General procedure A was executed upon 66.3 mg (0.216 mmol) of **30b**, using 10 mol % $FeCl_3$ at room temperature with a 26 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (200 mL) and then 20% (400 mL) EtOAc/hexane. The process generated 69 9 mL fractions. Fractions 40-57 were combined and concentrated at reduced pressure to give **31b** (39.9 mg, 0.125 mmol, 58%) as an off-white solid.

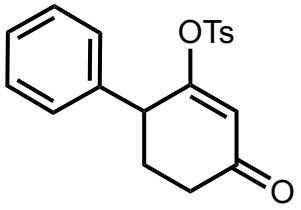
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.84 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 5.99 (s, 1H), 2.47 (s, 3H), 2.36 (t, J = 6.7 Hz, 2H), 1.86 (m, 4H), 1.74-1.59 (m, 4H), 1.58 – 1.50 (m, 2H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 198.9, 173.1, 146.2, 132.9, 130.3, 128.3, 113.1, 46.6, 36.0, 34.8, 34.3, 26.0, 21.9.

FTIR (thin film) v_{max}: 2954, 2869, 1673, 1615, 1597, 1448, 1379, 1363, 1331, 1311, 1294, 1223, 1193, 1178, 1107, 1082, 1064, 1019, 990, 917, 869, 815, 802, 787, 750, 715, 670, 642, 601, 574, 548, 517 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{17}H_{20}O_4S$, 321.1155; found, 321.1155.

TLC R_f= 0.18 (4:1 hexane:EtOAc).



4-oxo-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl 4-methylbenzenesulfonate (31c):

General procedure A was executed upon 66.1 mg (0.201 mmol) of **30c**, using 10 mol % $FeCl_3$ at room temperature with a 51 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.2 L) and then 20% (0.4 L) EtOAc/hexane. The process generated 68 9 mL fractions. Fractions 41-60 were combined and concentrated at reduced pressure to give **31c** (28.0 mg, 82 μmol, 41%) as an off-white solid.

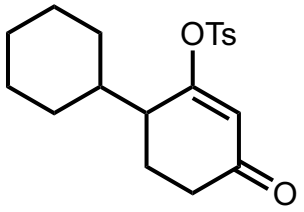
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.62 (d, J = 8.4 Hz, 2H), 7.30-7.24 (m, 5H), 7.07-7.01 (m, 2H), 6.21 (s, 1H), 3.81 (t, J = 4.9 Hz, 1H), 2.45 (s, 3H), 2.43 – 2.26 (m, 3H), 2.08 – 1.96 (m, 1H).

^{13}CNMR (101 MHz; $CDCl_3$) δ 198.6, 167.6, 146.2, 137.9, 132.4, 130.1, 129.0, 128.4, 128.0, 127.6, 117.4, 44.6, 33.6, 30.1, 21.9.

FTIR (thin film) ν_{max}: 2924, 2854, 1685, 1628, 1597, 1494, 1454, 1379, 1363, 1328, 1296, 1241, 1194, 1179, 1107, 1085, 1066, 1033, 1018, 979, 928, 900, 879, 815, 758, 738, 701, 670, 646, 623, 607, 587, 569, 548, 521, 501 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{18}O_4S$, 343.0999; found, 343.0999.

TLC R_f= 0.18 (4:1 hexane:EtOAc).



4-oxo-[1,1'-bi(cyclohexan)]-2-en-2-yl 4-methylbenzenesulfonate (31d):

General procedure A was executed upon 142.6 mg (0.430 mmol) of **30d**, using 10 mol % $FeCl_3$ at room temperature with a 47 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 14 by 5 cm silica gel column and eluted with 1% (0.4 L), then 2% (0.4 L) and finally 3% (0.6 L) EtOAc/PhH. The process generated 64 12 mL and then 64 9 mL fractions. Fractions 101-128 were combined and concentrated at reduced pressure to give **31d** (34.3 mg, 98 μmol, 23%) as a yellow semisolid.

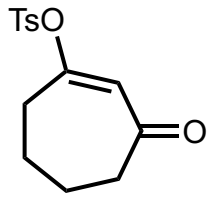
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.82 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 5.86 (s, 1H), 2.53 – 2.35 (m, 6H), 2.32-2.21 (m, 1H), 2.03 – 1.85 (m, 2H), 1.84 – 1.61 (m, 2H), 1.54-1.48 (m, 2H), 1.35 – 0.95 (m, 6H).

^{13}CNMR (126 MHz; $CDCl_3$) δ: 199.0, 170.5, 146.2, 132.8, 130.1, 128.4, 117.1, 43.8, 39.1, 35.2, 31.3, 29.4, 26.8, 26.6, 26.3, 22.4, 22.0.

FTIR (thin film) ν_{max}: 2927, 2853, 1682, 1623, 1598, 1450, 1380, 1331, 1308, 1194, 1180, 1076, 909, 889, 815, 803, 768, 746, 707, 692, 669, 569, 549 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{24}O_4S$, 349.1468; found, 349.1465.

TLC R_f= 0.23 (4:1 hexane:EtOAc).



3-oxocyclohept-1-en-1-yl 4-methylbenzenesulfonate (31e):

General procedure A was executed upon 55.5 mg (0.208 mmol) of **30e**, using 10 mol % $FeCl_3$ at room temperature with a 52 h reaction time. After workup with EtOAc, the crude residue obtained was loaded onto an 8 by 4 cm silica gel column and eluted with 1% (0.2 L) , then 2% (0.2 L) and then 3% (0.4 L) EtOAc/PhH. The process generated 91 9 mL fractions. Fractions 62-77 were combined and concentrated at reduced pressure to give **31e** (15.4 mg, 55 μmol, 26%) as a yellow oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 5.70 (s, 1H), 2.69 – 2.64 (m, 2H), 2.61-2.56 (m, 2H), 2.46 (s, 3H), 1.90 – 1.73 (m, 4H).

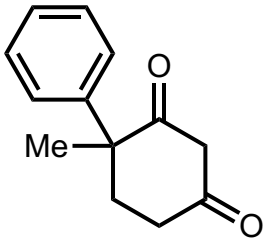
^{13}CNMR (101 MHz; $CDCl_3$) δ 201.1, 165.4, 146.0, 132.8, 130.2, 128.4, 122.9, 43.4, 34.4, 24.3, 21.9, 21.6.

FTIR (thin film) ν_{max}: 2928, 2870, 1667, 1644, 1597, 1454, 1420, 1374, 1308, 1266, 1191, 1178, 1155, 1121, 1093, 1064, 1048, 1018, 915, 857, 816, 740, 686, 666, 567, 552 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{16}O_4S$, 281.0842; found, 281.0841.

TLC R_f= 0.19 (4:1 hexane:EtOAc).

Synthesis of Vinylogous Acyl Sulfonate Derivatives



4-methyl-4-phenylcyclohexane-1,3-dione (37):

A modification of general procedure A was executed upon 76.1 mg (0.237 mmol) of **29a**, using 5 mol % $FeCl_3$ at 60 ℃ with a 16 h reaction time. After this timeframe, the reaction was cooled to room temperature, treated with 883 mg (3.56 mmol, 15 equiv) of powdered sodium thiosulfate pentahydrate, and stirred at room temperature for 2 h. Then, 10% aqueous NaOH was added (1.9 mL, 4.74 mmol, 20 equiv) and the mixture was stirred at room temperature for 2 h. The reaction was poured into a saturated ammonium chloride solution, and the aqueous layer was extracted thrice with EtOAc. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 2:1 (250 mL) EtOAc/hexane. The process generated 20 12 mL fractions. Fractions 8-19 were combined and concentrated at reduced pressure to give **37** (24.2 mg, 0.119 mmol, 50%) as a white solid.

*The behavior of this compound in $CDCl_3$ is as a ~7:1 ratio of diketone to enol isomers; only the diketone resonances are reported in the NMR data.

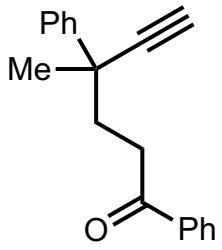
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.40 (t, J = 7.6, 2H), 7.31 (td, J = 6.6, 1.9 Hz, 1H), 7.22 (dd, J = 7.4, 1.8 Hz, 2H), 3.51 (d, J = 16.7 Hz, 1H), 3.36 (d, J = 16.7 Hz, 1H), 2.71 (ddd, J = 14.8, 5.4, 3.5 Hz, 1H), 2.66 – 2.53 (m, 2H), 1.87 (ddd, J = 14.8, 13.1, 5.0 Hz, 1H), 1.41 (s, 3H).

^{13}CNMR (126 MHz; $CDCl_3$) δ: 205.5, 203.7, 140.9, 129.6, 127.7, 125.9, 57.3, 53.2, 37.8, 29.9, 27.3.

FTIR (thin film) ν_{max}: 2924, 2854, 1720, 1577, 1495, 1456, 1445, 1408, 1377, 1359, 1339, 1302, 1269, 1244, 1200, 1189, 1157, 1103, 1079, 1029, 908, 868, 847, 763, 732, 698, 545 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{14}O_2$, 203.1067; found, 203.1068.

TLC R_f= 0.36 (1:3 hexane:EtOAc).



4-methyl-1,4-diphenylhex-5-yn-1-one (38a):[18]

A 1.8 M solution of PhLi in ether (55 μL, 98 μmol, 0.95 equiv) was added dropwise to a stirring solution of **29a** (34.6 mg, 0.103 mmol, 1 equiv) in THF (1 mL) cooled to -78 ℃ in a dry ice/acetone bath. The reaction was allowed to warm to -10 ℃ over 60 minutes and then removed from the bath. Fifteen minutes after removal from the cooling bath, the reaction was placed in a 60 ℃ aluminum shot bath and stirred at that temperature for 30 minutes. The reaction was then cooled to room temperature and poured into a saturated sodium bicarbonate solution, and the aqueous layer was extracted thrice with EtOAc. The combined organic fractions were washed with brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 2% (50 mL) and then 5% (150 mL) EtOAc/hexane. The process generated 15 12 mL fractions. Fractions 8-13 were combined and concentrated at reduced pressure to give **38a** (21.9 mg, 83 μmol, 81%) as a clear, colorless oil.

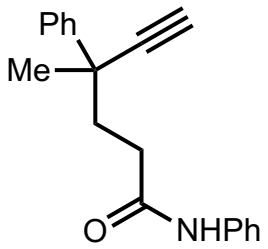
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.88 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.27 – 7.23 (m, 1H), 3.20 (ddd, J = 17.0, 10.4, 5.8 Hz, 1H), 2.76 (ddd, J = 17.0, 10.5, 5.5 Hz, 1H), 2.47 (s, 1H), 2.37 – 2.20 (m, 2H), 1.66 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 200.1, 144.0, 137.0, 133.1, 128.7, 128.6, 128.2, 126.9, 126.1, 88.7, 72.7, 40.3, 37.9, 35.4, 31.1.

FTIR (thin film) ν_{max}: 3297, 2973, 2928, 2854, 1685, 1598, 1581, 1492, 1448, 1413, 1377, 1362, 1316, 1293, 1244, 1212, 1180, 1158, 1141, 1076, 1028, 1002, 983, 762, 742, 700, 690, 643, 592, 568 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{18}O$, 263.1430; found, 263.1431.

TLC R_f= 0.70 (4:1 hexane:EtOAc).



4-methyl-N,4-diphenylhex-5-ynamide (38b):[18]

A freshly prepared 0.5 M solution of lithium anilide in THF (0.42 mL, 0.208 mmol, 2.1 equiv) was added dropwise to a stirring solution of **29a** (33.1 mg, 99 μmol, 1 equiv) in THF (0.4 mL) cooled to -78 ℃ in a dry ice/acetone bath. Following the addition, the reaction was stirred at -78 ℃ for ten minutes, 0 ℃ for ten minutes, room temperature for 30 minutes, and finally 60 ℃ for 30 minutes. The reaction was then cooled to room temperature and poured into a saturated ammonium chloride solution, and the aqueous layer was extracted thrice with EtOAc. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 5% (0.1 L) and then 10% (0.5 L) EtOAc/hexane. The process generated 44 12 mL fractions. Fractions 21-40 were combined and concentrated at reduced pressure to give **38b** (24.5 mg, 88 μmol, 89%) as a yellow oil.

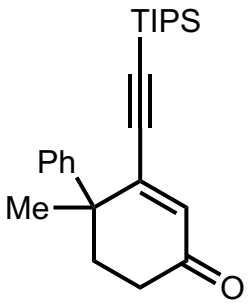
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.56 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.30 – 7.21 (m, 3H), 7.12-7.03 (m, 2H), 2.57 – 2.47 (m, 1H), 2.47 (s, 1H), 2.31-2.23 (m, 2H), 2.18-2.09 (m, 1H), 1.63 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 170.9, 143.8, 138.0, 129.1, 128.6, 127.0, 126.1, 124.3, 119.8, 88.5, 72.8, 40.3, 38.9, 34.2, 30.9.

FTIR (thin film) ν_{max}: 3294, 3199, 3138, 3060, 2973, 2926, 2854, 1657, 1618, 1598, 1544, 1498, 1442, 1378, 1325, 1307, 1276, 1252, 1198, 1176, 1157, 1141, 1099, 1076, 1029, 964, 904, 840, 755, 698, 642, 598, 544, 506, 436 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{19}NO$, 278.1539; found, 278.1540.

TLC R_f= 0.38 (4:1 hexane:EtOAc).



1-methyl-6-((triisopropylsilyl)ethynyl)-2,3-dihydro-[1,1'-biphenyl]-4(1H)-one (39):[19]

A vial containing a stir bar was charged with tetrakis(triphenylphosphine)palladium(0) (5.2 mg, 4.5 μmol, 0.05 equiv) and cuprous iodide (2.6 mg, 13.5 μmol, 0.15 equiv). The vial was evacuated and backfilled thrice with dinitrogen, and THF (0.25 mL) was added via syringe. A solution of triisopropylsilylacetylene (30 μL, 0.135 mmol, 1.5 equiv) and **29a** (30.1 mg, 90 μmol, 1 equiv) in THF (0.25mL) and N-ethyldiisopropylamine (0.45mL) was then added with a syringe, followed by a 0.1 mL THF wash. The vial was sealed with a teflon-lined cap, teflon tape, and parafilm and heated in a 70 ℃ aluminum shot bath for 14 h. The reaction was cooled to room temperature and loaded directly onto an 8 by 3 cm silica gel column followed by elution with 5% (50 mL) and then 10% (100 mL) EtOAc/hexane. The process generated 13 12 mL fractions. Fractions 6-10 were combined and concentrated at reduced pressure to give **39** (33.0 mg, 90 μmol, 100%) as a clear, colorless oil.

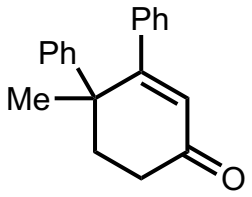
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.37 (d, J = 7.1 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.23 (t, J = 7.1 Hz, 1H), 6.41 (s, 1H), 2.44 – 2.09 (m, 4H), 1.70 (s, 3H), 0.99-0.95 (m, 21H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 198.8, 149.8, 144.5, 133.9, 128.5, 126.9, 126.7, 105.5, 104.8, 43.9, 38.8, 34.7, 27.3, 18.6, 11.2.

FTIR (thin film) ν_{max}: 2942, 2891, 2864, 1676, 1579, 1462, 1445, 1328, 1306, 1262, 1210, 1121, 1072, 996, 882, 760, 692, 675, 661, 626, 461 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{24}H_{34}OSi$, 367.2452; found, 367.2452.

TLC R_f= 0.60 (4:1 hexane:EtOAc).



1'-methyl-5',6'-dihydro-[1,1':2',1"-terphenyl]-4'(1'H)-one (40):[20]

A 10 mL recovery flask open to ambient atmosphere containing a solution of **29a** (35.5 mg, 0.106 mmol, 1 equiv) in 3:1 PhMe:ethanol (2.8 mL) was charged sequentially with phenylboronic acid (19.4 mg, 0.159 mmol, 1.5 equiv), a 2.0 M aqueous solution of sodium carbonate (0.48 mL, 0.954 mmol, 9 equiv), and finally tetrakis(triphenylphosphine)palladium(0) (6.2 mg, 5.3 μmol, 0.05 equiv). The reaction was sparged with dinitrogen for 2 minutes and stirred at room temperature for 3 hours. The mixture was diluted with ether and then washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 20% (0.25 L) ether/hexane. The process generated 27 12 mL fractions. Fractions 16-24 were combined and concentrated at reduced pressure to give **40** (24.5 mg, 94 μmol, 88%) as a white solid.

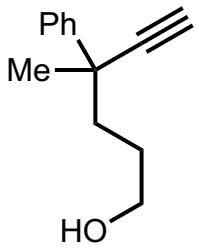
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.48 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.34 – 7.26 (m, 2H), 7.24 (t, J = 7.3 Hz, 2H), 7.13 (d, J = 7.1 Hz, 2H), 6.43 (s, 1H), 2.41 – 2.28 (m, 3H), 2.16 – 2.03 (m, 1H), 1.54 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 199.9, 166.0, 143.7, 139.2, 129.7, 129.0, 128.8, 128.3, 127.9, 127.0, 126.9, 43.8, 42.0, 34.2, 28.1.

FTIR (thin film) ν_{max}: 2929, 2854, 1670, 1596, 1569, 1493, 1456, 1444, 1414, 1381, 1329, 1309, 1262, 1238, 1209, 1149, 1077, 1069, 1028, 995, 967, 911, 890, 850, 763, 732, 699, 579, 552, 485, 436 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{18}O$, 263.1430; found, 263.1430.

TLC R_f= 0.41 (4:1 hexane:EtOAc).



4-methyl-4-phenylhex-5-yn-1-ol (41):[18]

A 1.0 M solution of $LiHBEt_3$ in THF (0.23 mL, 0.226 mmol, 2.2 equiv) was added dropwise to a stirring solution of **29a** (34.3 mg, 0.103 mmol, 1 equiv) in THF (0.41 mL) cooled to -78 ℃ in a dry ice/acetone bath. Following the addition, the reaction was stirred at -78 ℃ for ten minutes, 0 ℃ for ten minutes, and finally room temperature for 3 h. The reaction was poured into a saturated ammonium chloride solution, and the aqueous layer was extracted thrice with EtOAc. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The crude residue obtained was loaded onto an 8 by 3 cm silica gel column and eluted with 10% (0.1 L) and then 15% (0.1 L) and finally 20% (0.2 L) EtOAc/hexane. The process generated 30 12 mL fractions. Fractions 23-28 were combined and concentrated at reduced pressure to give **41** (12.0 mg, 60 μmol, 58%) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.54 (d, J = 8.1 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 2.42 (s, 1H), 1.95 – 1.84 (m, 2H), 1.78-1.65 (m, 2H), 1.62 (s, 3H), 1.50 – 1.37 (m, 1H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 144.7, 128.4, 126.7, 126.1, 89.3, 71.9, 63.1, 40.4, 40.4, 30.5, 29.1.

FTIR (thin film) ν_{max}: 3300, 2927, 2855, 1492, 1446, 1413, 1376, 1317, 1254, 1215, 1056, 1023, 910, 764, 732, 698, 634, 587, 570, 512, 484 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{13}H_{16}O$, 189.1274; found, 189.1275.

TLC R_f= 0.20 (4:1 hexane:EtOAc).

References

[1] Chassaing, S.; Specklin, S.; Weibel, J.-M.; Pale, P. *Tetrahedron* **2012**, *68*, 7245–7273.

[2] Martinez, A.; Fernandez, A.; Alvarez, R.; Munoz, G. *Anales De Quimica Serie C-Quimica Organica Y Bioquimica* **1981**, *77*, 28–30.

[3] Batsomboon, P.; Gold, B. A.; Alabugin, I. V.; Dudley, G. B. *Synthesis* **2012**, *44*, 1818–1824.

[4] Danishefsky, S. J.; Bornmann, W. G.; Queneau, Y.; Magee, T. V.; Krol, W. J.; Masters, J. J.; Jung, D. K. Total synthesis of taxol and analogues thereof. 1996; US Patent 5,488,116.

[5] Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. *Journal of the American Chemical Society* **2017**, *139*, 1790–1793.

[6] Yu, J.-Q.; Wu, H.-C.; Corey, E. *Organic Letters* **2005**, *7*, 1415–1417.

[7] Catino, A. J.; Forslund, R. E.; Doyle, M. P. *Journal of the American Chemical Society* **2004**, *126*, 13622–13623.

[8] Nakamura, A.; Nakada, M. *Synthesis* **2013**, *45*, 1421–1451.

[9] Weidmann, V.; Maison, W. *Synthesis* **2013**, *45*, 2201–2221.

[10] Kimura, M.; Muto, T. *Chemical and Pharmaceutical Bulletin* **1979**, *27*, 109–112.

[11] Kimura, M.; Muto, T. *Chemical and Pharmaceutical Bulletin* **1980**, *28*, 1836–1841.

[12] Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chemical Reviews* **2004**, *104*, 6217–6254.

[13] Bauer, I.; Knölker, H.-J. *Chemical Reviews* **2015**, *115*, 3170–3387.

[14] Sarhan, A. A.; Bolm, C. *Chemical Society Reviews* **2009**, *38*, 2730–2744.

[15] Islam, S. M.; Paul, S.; Roy, A. S.; Banerjee, S.; Ghosh, K.; Dey, R. C.; Santra, S. *Transition Metal Chemistry* **2013**, *38*, 675–682.

[16] Cole, K. P.; Hsung, R. P. *Organic Letters* **2003**, *5*, 4843–4846.

[17] Krueger, A. C. *Bioorganic Medicinal Chemistry Letters* **2007**, *17*, 2289–2292.

[18] Kamijo, S.; Dudley, G. B. *Journal of the American Chemical Society* **2006**, *128*, 6499–6507.

[19] Nakatsuji, H.; Ueno, K.; Misaki, T.; Tanabe, Y. *Organic Letters* **2008**, *10*, 2131–2134.

[20] Luo, Y.; Carnell, A. J. *Angewandte Chemie International Edition* **2010**, *49*, 2750–2754.

[21] Haber, F.; Weiss, J. *Proceedings of the Royal Society of London. Series A-Mathematical and Physical Sciences* **1934**, *147*, 332–351.

[22] Kirsch, L. J.; Parkes, D. A. *Journal of the Chemical Society, Faraday Transactions 1: Physical Chemistry in Condensed Phases* **1981**, *77*, 293–307.

[23] Bartlett, P. D.; Günther, P. *Journal of the American Chemical Society* **1966**, *88*, 3288–3294.

[24] Still, W. C.; Kahn, M.; Mitra, A. *The Journal of Organic Chemistry* **1978**, *43*, 2923–2925.

[25] Tucker, J. K.; Shair, M. D. *Organic Letters* **2019**, *21*, 2473–2476.

Chapter 3: Enantioselective Synthesis of the Cucumin A Ring System via a 5-endo-trig Heck Cyclization

Introduction

With the allylic oxidation conditions in the previous chapter developed, application of the process to the multistep synthesis of a target was a logical next step. The target chosen was a natural product known as cucumin A. Although the oxidative chemistry developed in the previous chapter was not useful in this context, pursuit of this synthesis became interesting in its own right on account of how the ring system was constructed–via an anti-Baldwin 5-endo-trig Heck cyclization.

Linear Triquinane Sesquiterpene Overview

The linear triquinane sesquiterpenes (LTSs) encompass any and all compounds composed of 15 carbons in total containing three consecutive five-member rings arranged as shown in **Figure 3.1**. There are 8 LTS carbon skeletons that bear a variety of oxidation patterns, giving way to a diverse array of natural products. As of 2018, at least 118 compounds within the LTS umbrella were known.[1] Overall, many members within this class of natural products display cytotoxic, antimicrobial, or anti-inflammatory activities.[1] The two most common carbon skeletons appearing within this class of natural products, the hirsutanes and capnellenes, are shown below (**Figure 3.1**).

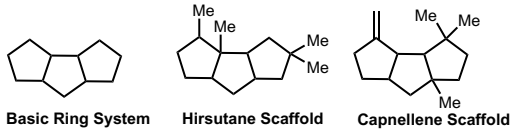


Figure 3.1. Common linear triquinane scaffolds

Identification of Cucumin A as a Synthetic Target

Within the hirsutane subset of LTSs, I identified a series of eight compounds containing a diene within the "A" and "B" rings and became interested in accomplishing their total syntheses, given this unique oxidation state (**Figure 3.2**). Specifically, I decided to target the formation cucumin A (**43**), named for the *Macrocystidia cucumis* mushroom from which it was isolated. This natural product exhibited cytotoxicity against an array of bacterial and fungal cell lines. Notably, **43** exhibited greater potency against some of the lines studied in this context than **44**, suggesting the Michael acceptor on the A ring is important for cytotoxicity.[2]

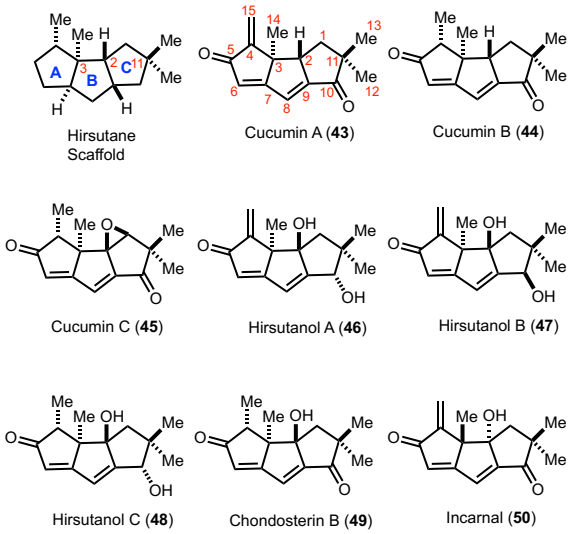
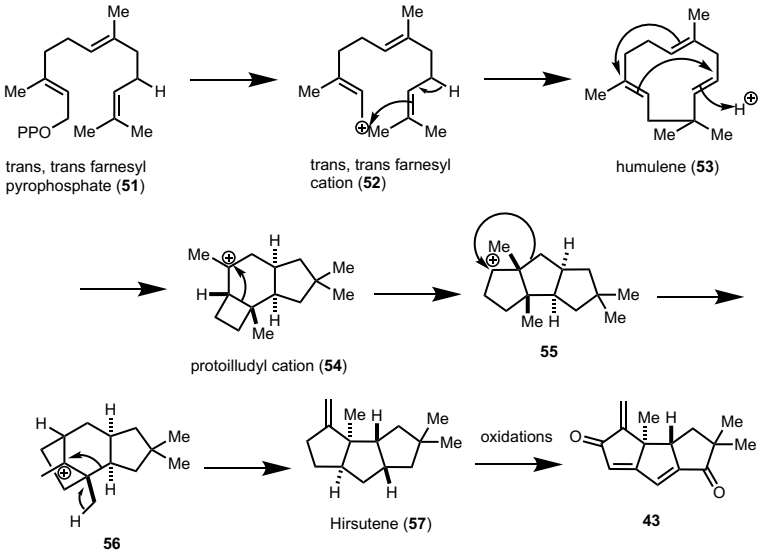


Figure 3.2. A subset of oxidized hirsutanes bearing an A/B ring diene. Numbering of the carbons of Cucumin A is presented in red.

Biogenesis

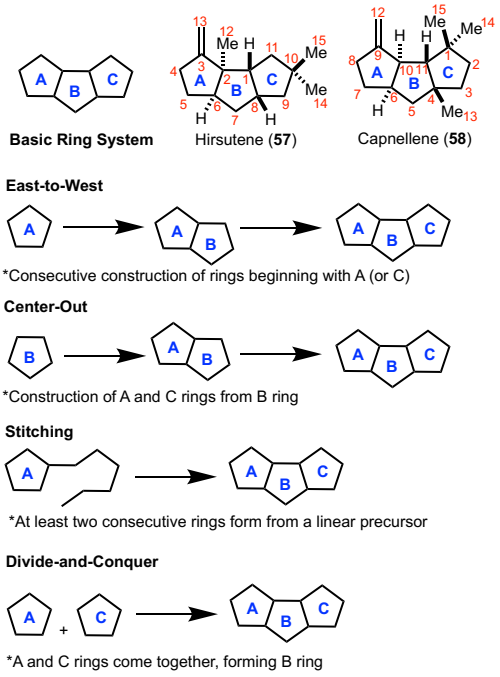
One point of inspiration for synthetic approaches to a target is the postulated biosynthesis of said target. A reasonable explanation for the formation of **43** is via the oxidation of a hirsutene (**57**) scaffold (**Scheme 3.1**). Hirsutene is thought to be derived ultimately from trans, trans-farnesyl pyrophosphate (**51**).[3] This structure ionizes and undergoes transannular cyclization followed by a series of carbocationic shifts to give **57**.[4] Following cyclization, a series of oxidations of **57** would lead to **43**.[2]



Scheme 3.1. Postulated biosynthesis of cucumin A (**43**)

Past Approaches to Linear Triquinane Sesquiterpene Synthesis

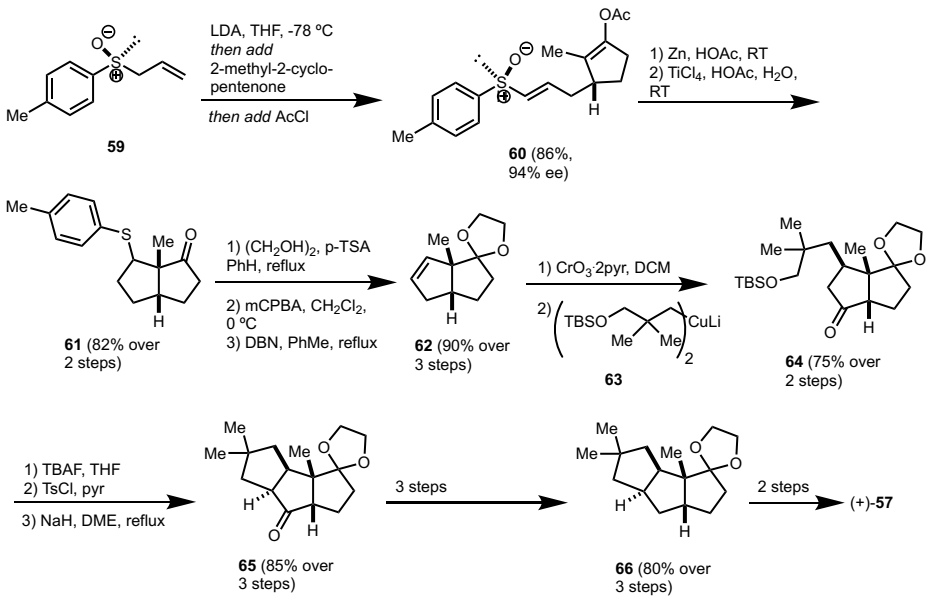
No approach to **43** is known. Nonetheless, the chemical literature is rich with synthetic routes to LTSs from which lessons learned may inform an approach to **43**.[5,6,1] This section addresses the approaches to the two of the most common targets for LTS syntheses: hirsutene (**57**) and capnellene (**58**). At least one representative synthesis for each of these two natural products is discussed for the four general approaches: east-to-west, center-out, stitching, and divide-and-conquer (**Scheme 3.2**). The ultimate end of this survey is to contextualize the pursuit of **43**. Sequences described in this section may be racemic or enantioselective.



Scheme 3.2. Description of generalized approaches to **57** and **58**. The carbons of **57** and **58** are numbered in red.

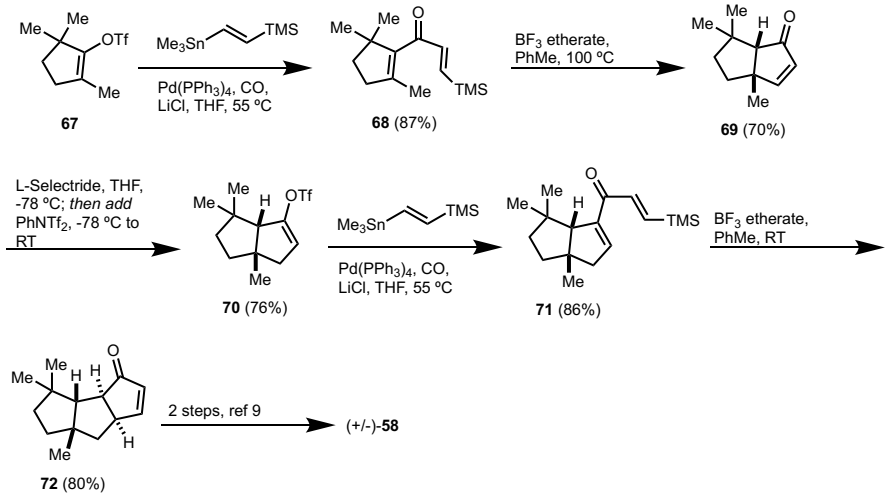
East-to-West

An exemplary east-to-west approach to **57** came from the lab of Prof. D. H. Hua.[7] The approach leveraged the addition of the lithium sulfinallyl ion of chiral sulfoxide **59** to 2-methyl-2-cyclopentenone followed by a series of annulative steps. The process achieved the enantioselective synthesis of **57** in a 16 step longest-linear-sequence (LLS) (**Scheme 3.3**).



Scheme 3.3. Asymmetric approach to (+)-hirsutene via a chiral sulfoxide

The lab of Prof. J. K. Stille reported an 8-step approach to racemic **58** involving iterative carbonylative Stille couplings followed by Nazarov cyclizations (**Scheme 3.4**).[8] This approach bears some resemblance to that reported by Paquette et al. to construct the same natural product.[9]

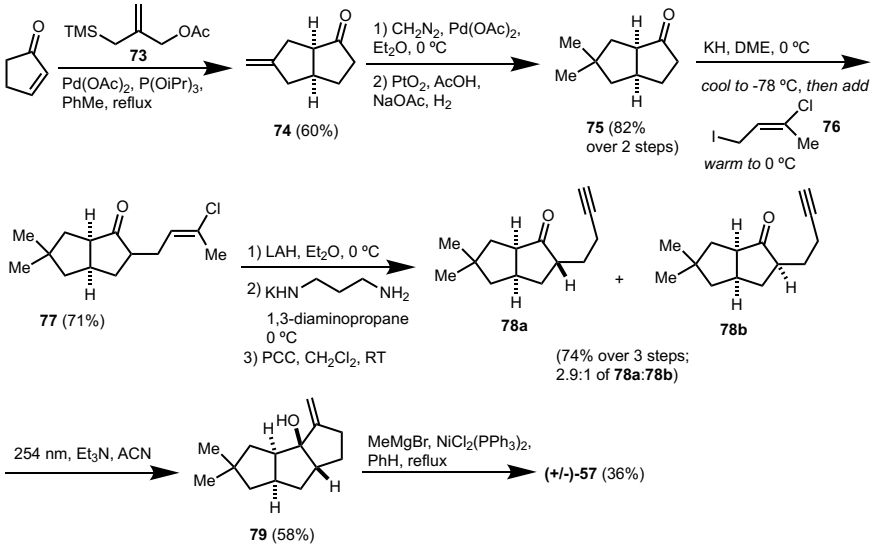


Scheme 3.4. Racemic approach to capnellene via iterative nazarov cyclizations

Center-Out

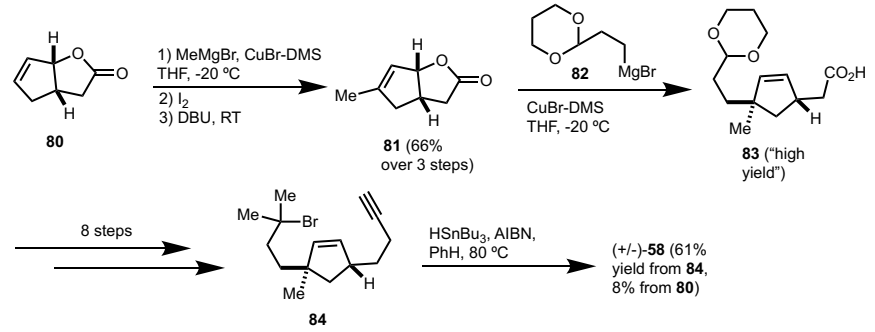
A rapid center-out approach to racemic **57** came from the lab of Prof. J. Cossy (**Scheme 3.5**).[10] The first ring formation stemmed from a palladium-catalyzed 3+2 annulation of cyclopentenone and **73**. Completion of the tricycle occurred via application of photoreductive cyclization conditions to the mixture of **78a** and **78b**. Notably, **78b** failed to cyclize under these conditions on account of steric encumbrance, so intermediate

79 was isolated as the lone product. Overall, the title compound **57** was rendered in a 9 step LLS.



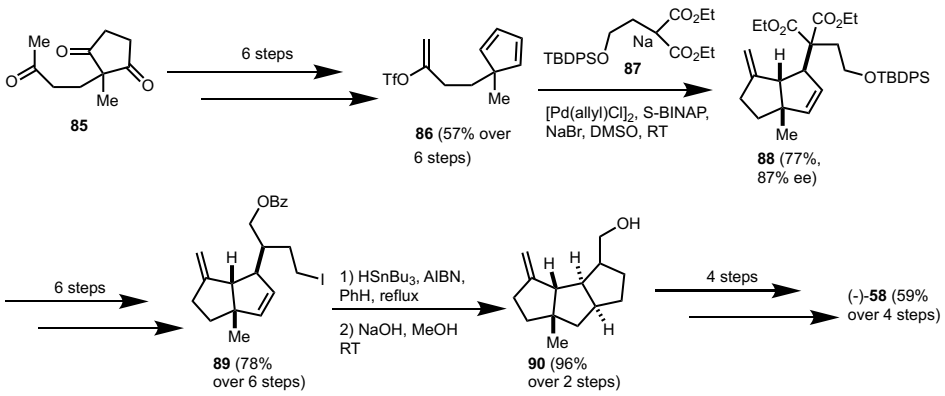
Scheme 3.5. Center-out approach to hirsutene

The radical-mediated approach to racemic **58** via penultimate **84** developed by Prof. D. P. Curran and coworkers is one of the most acclaimed routes to this structure (**Scheme 3.6**).[11] Overall, the synthesis progressed in 13 steps, LLS, from lactone **80**. An enantioselective approach to **58** inspired by this mode of cyclization later was developed in the lab of Prof. A. I. Meyers.[12]



Scheme 3.6. A radical-mediated approach to racemic capnellene

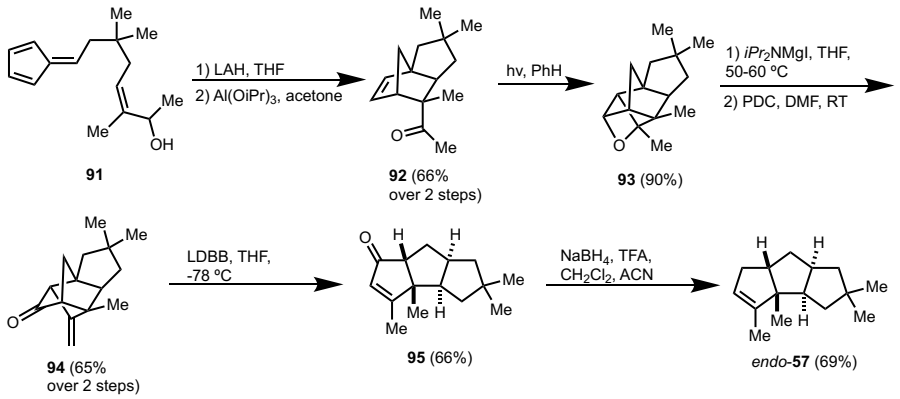
A palladium-catalyzed, asymmetric approach to (-)-**58** came from the lab of Prof. M. Shibasaki (**Scheme 3.7**).[13] The palladium pi-allyl intermediate formed upon cyclization of vinyl triflate **86** underwent attack by malonate nucleophile **87** to afford bicyclic intermediate **88** with 87% ee. The overall route to (-)-**58** was achieved from **85** in 19 steps, LLS.



Scheme 3.7. Palladium-catalyzed, asymmetric center-out approach to capnellene

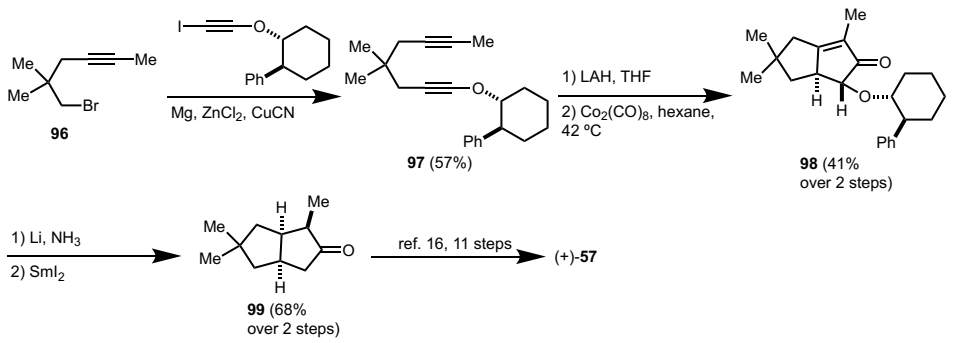
Stitching

Formation of endo-**57** from linear precursor **91** was described by V. K. Rawal et al. (**Scheme 3.8**).[14] Diels-Alder adduct **92** underwent an intramolecular Paterno-Buchi reaction to form oxetane **93**. Opening of **93**, followed by oxidation and a second base-mediated fragmentation, afforded the completed tricyclic system **95**. The formation of endo-**57** from **91** occurred in a sequence of 7 steps.



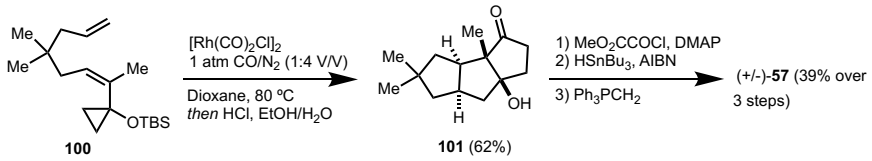
Scheme 3.8. A Diels-Alder-based, stitching-mediated, racemic approach to *endo*-**57**

An asymmetric approach to **(+)-57** via an enantioselective Pauson-Khand reaction through the influence of a chiral auxiliary has been developed (**Scheme 3.9**).[15] The bicyclic intermediate **99** sufficed for a claim of the formal synthesis of (+)-**57** in a LLS of 16 steps from **96**.[16]



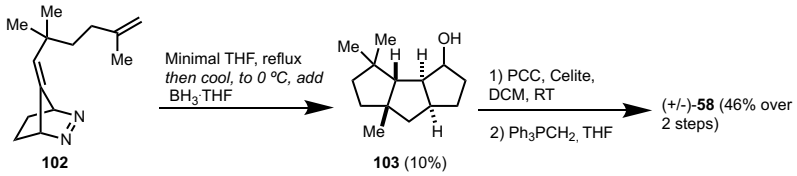
Scheme 3.9. Pauson-Khand-mediated enantioselective approach to (+)-**57**

A Rhodium-mediated cascade from linear precursor **100** served as a rapid means for the synthesis of racemic **57** as reported by the lab of Prof. Z. Yu (**Scheme 3.10**).[17] Formation of **100** required several steps, but its conversion to **57** occurred over just 4 steps, including formation of all three rings in one pot.



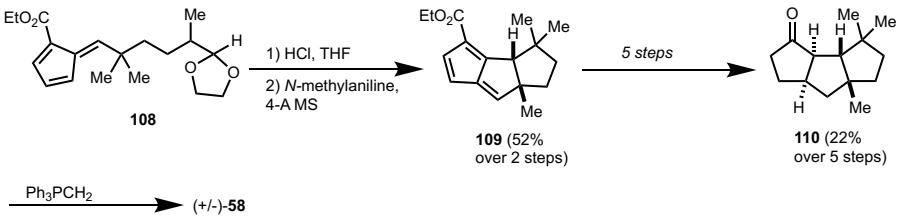
Scheme 3.10. Simultaneous formation of all three rings of (+/-)-**57** from a sngle linear precursor

The rapid approach to **58** from diazine precursor **102** was disclosed from the lab of Prof. J. L. Petersen (**Scheme 3.11**).[18] Although the yield of intermediate **103** was low, completion of the approach to racemic **58** was accomplished in just from 3 steps from **102**.



Scheme 3.11. Diazine-mediated approach to racemic capnellene

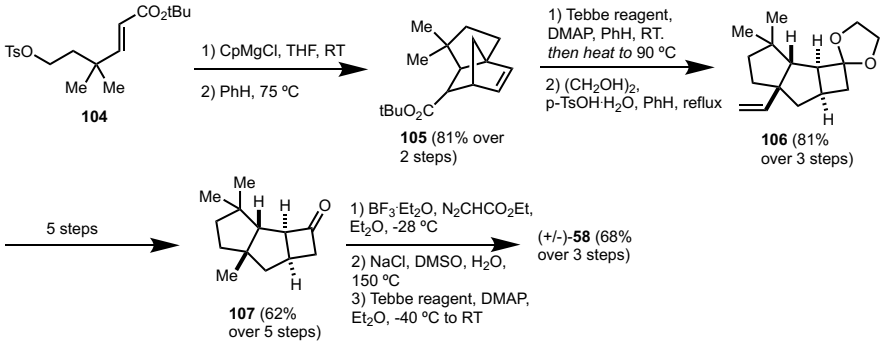
Similar in many respects to the approach just described, work disclosed from the lab of Prof. K. N. Houk led to the generation of racemic **58** from linear precursor **108** (**Scheme 3.12**).[19] The synthesis progressed in 8 steps from this starting material.



Scheme 3.12. Generation of racemic capnellene from a linear ester-substituted fulvene

In an approach from the lab of R. H. Grubbs, a Diels-Alder reaction followed by an olefin metathesis

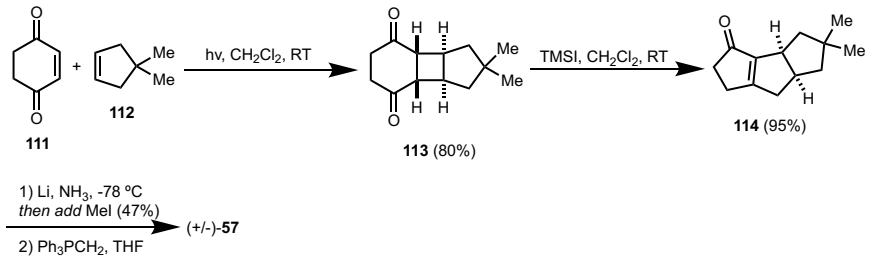
cascade furnished tricyclic intermediate **106** from precursor **104** (**Scheme 3.13**).[20] Following functional group interconversions and ring expansion, the formation of **58** was accomplished from **104** in 12 steps.



Scheme 3.13. An olefin metathesis cascade to racemic capnellene

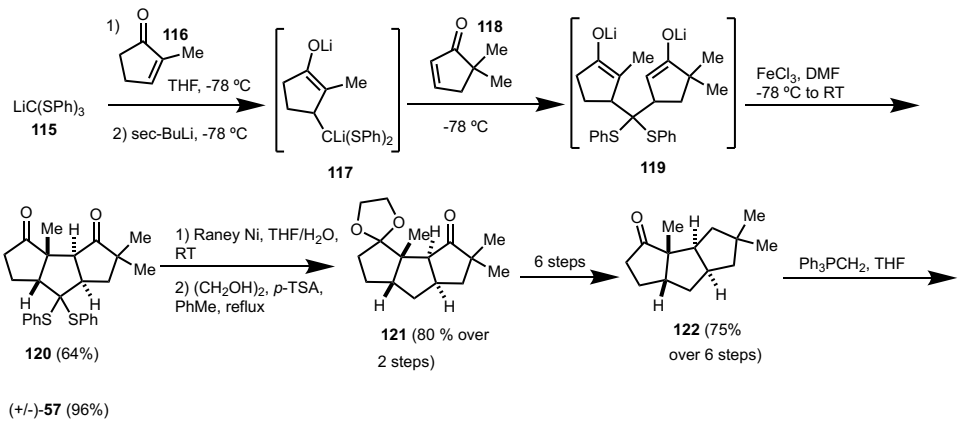
Divide and Conquer

An exceptionally short synthesis of racemic **57** from simple precursors **111** and **112** over just 4 synthetic operations was disclosed by the lab of Prof. M. Oda (**Scheme 3.14**).[21] Following the 2+2 addition of these two materials to form **113**, fragmentation mediated by TMSI delivered tricyclic intermediate **114** in 95% yield.



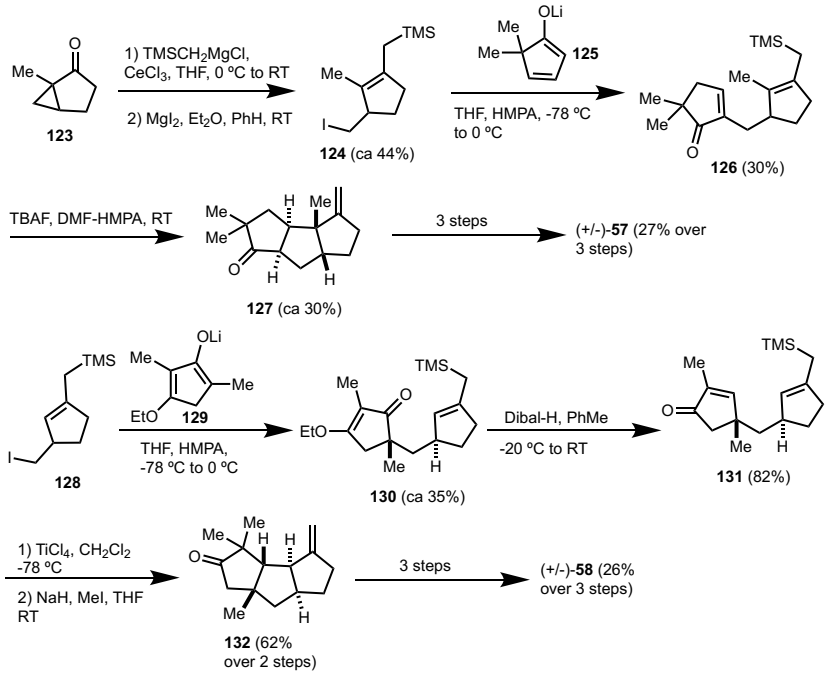
Scheme 3.14. A rapid approach to racemic hirsutene from two simple building blocks

Exploitation of a [2+1+2] cyclopentannulation process utilizing building blocks **115**, **116**, and **118** led to a rapid assembly of the tricyclic hirsutene ring system as reported by Prof. T. Cohen (**Scheme 3.15**).[22] The synthesis of natural product was achieved in a 10 step LLS.



Scheme 3.15. Generation of hirsutene via a [2+1+2] cyclopentannulation process

An approach to racemic **57** and **58** via a formal homoiodo allylsilane annulation was disclosed by the lab of W. L. Li (**Scheme 3.16**).[23] Generation of **racemic 57** was accomplished in a 7 step LLS from cyclopropane **123**. By analogy, formation of **racemic 58** was achieved from the analogous cyclopropane precursor of **128** in a 9 step LLS. This successful approach is reminiscent of a previous attempted approach to LTSs.[24]

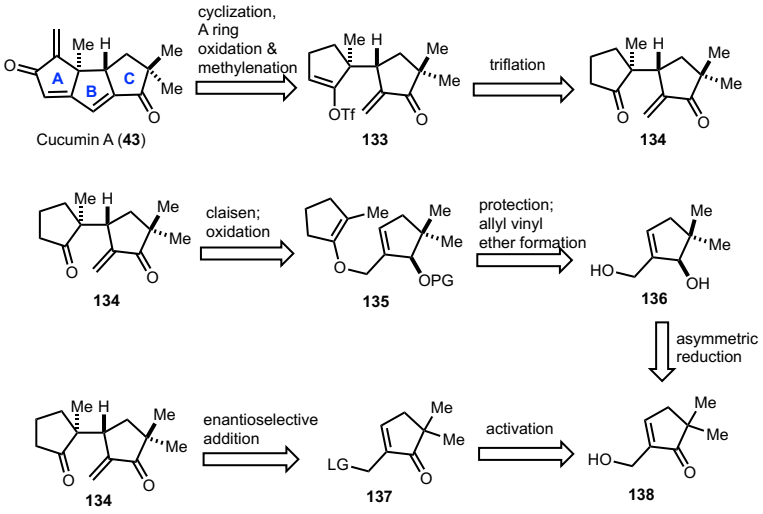


Scheme 3.16. Generation of racemic hirsutene and capnellene via a formal homoiodo allylsilane annulation approach

Cucumin A Retrosynthesis

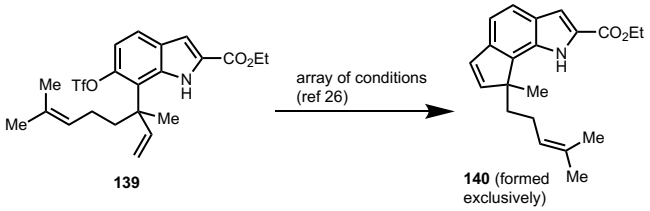
Asymmetric retrosynthetic disconnection of **43** progressed within the divide-and-conquer paradigm, with a focus on route convergence (**Scheme 3.17**). Center-out and east-to-west approaches often require lengthier

sequences, with the approach of Prof. J. K. Stille to **58** as a notable exception.[8] While the somewhat biomimetic stitching approaches from linear precursors may indeed be rapid and dramatic, the formation of the linear precursors themselves often requires lengthy synthetic sequences. Furthermore, formation of the A, B-ring diene motif and oxidation state of **43** would require multiple synthetic operations following cyclization.



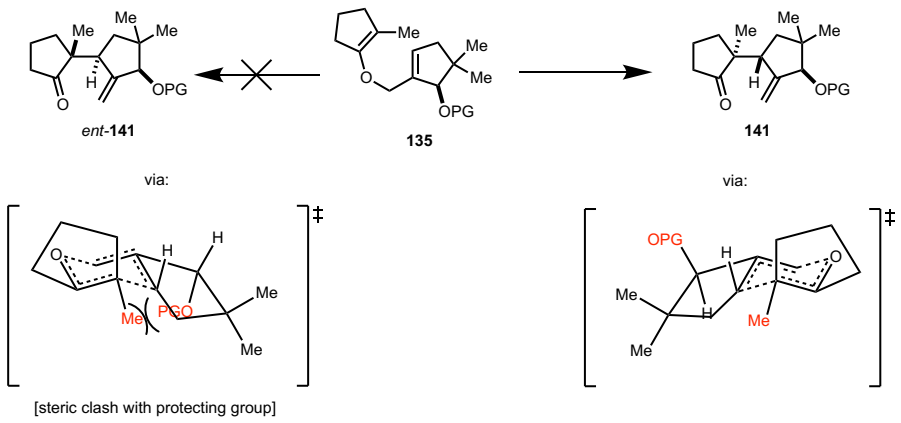
Scheme 3.17. Retrosynthesis of cucumin A (**43**)

I envisioned synthesis of the diene motif via a 5-endo-trig Mizoroki-Heck cyclization of vinyl triflate **133**, which would originate from dione **134**. Alternately, oxidation of vinyl triflate **133** via the conditions developed in the previous chapter followed by a Heck cyclization of the resultant vinylogous acyl sulfonate could also have been possible. Some precedent exists for palladium(0)-catalyzed, 5-endo-trig Mizoroki-Heck cyclizations, including one system in which this cyclization progressed in preference to a 6-exo-trig cyclization (Scheme 3.18).[25,26] Additionally, a handful of oxidative palladium(II)-catalyzed 5-endo-trig Fujiwara-Moritani-Heck cyclizations are known.[27,28,29,30]



Scheme 3.18. Preference for a 5-endo Heck cyclization over a 6-exo cyclization

Formation of **134** was envisioned via a Claisen reaction of **135**, which would be formed from diol **136** (**Scheme 3.17**, middle sequence). Stereocontrol of the Claisen reaction outcome might be possible via the "-OPG" biasing element of **135** such that structure **141** forms exclusively (**Scheme 3.19**).

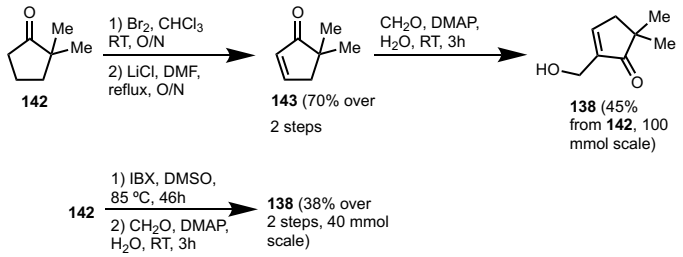


Scheme 3.19. Proposed rationale for a stereoselective Claisen cyclization

Alternately, dione **134** is a retron for an addition-elimination sequence utilizing **137** and an appropriate nucleophile (**Scheme 3.17**, bottom sequence). Thus, the formal annulation to form the tricyclic ring system could be accomplished in multiple ways. Ultimately, all disconnections work back to alcohol **138**.

Study of a Claisen Approach

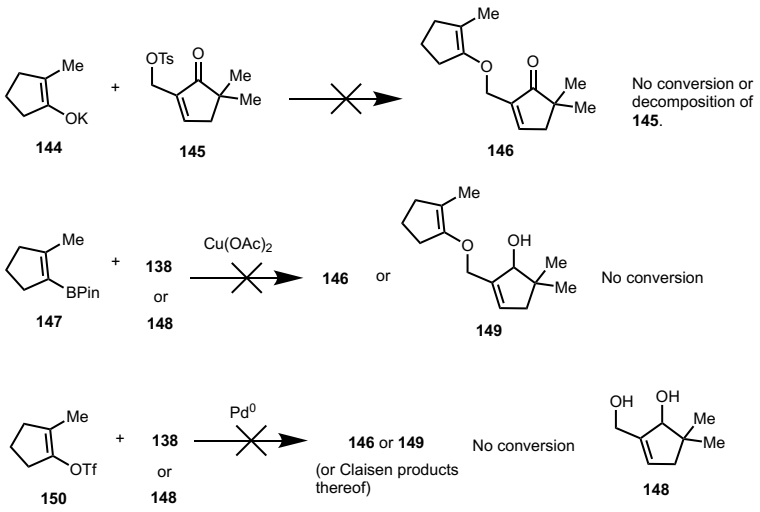
The formation of **138** was possible via two different methods, both on multigram scale. Although intermediate **143** was available in principle commercially, its prohibitive cost necessitated genesis of the route from **1**42. A bromination-elimination sequence followed by a Morita-Bayliss-Hillman (MBH) reaction (**Scheme 3.20**, upper sequence) afforded **138** in 45% yield over 3 steps.[31,32,33] Alternately, a Nicolau oxidation-(MBH) sequence afforded 138 in 38% yield over 2 steps (**Scheme 3.20**, lower sequence).[34,33] Both approaches were applicable to the formation of pure **138** on multigram scale.



Scheme 3.20. Useful approaches to alcohol **138**

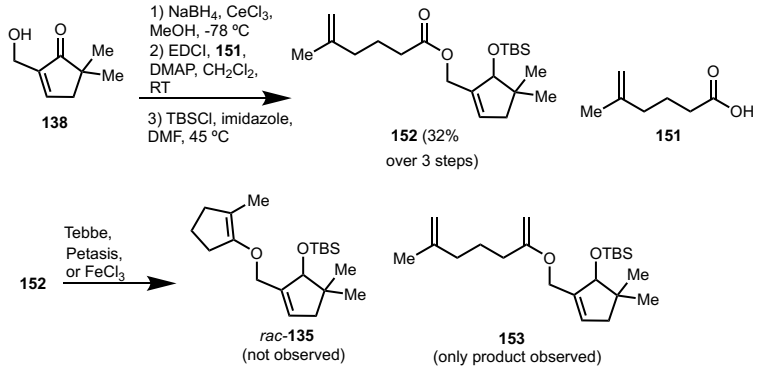
The initial pursuit of Claisen precursor **135** occurred with a racemic route; enantioselective carbonyl reduction was to be pursued if success in the racemic context transpired. Formation of the allyl vinyl ether linkage present in **135** was troublesome. Alkylation of tosylate **145** with equilibrated potassium enolate **144** under a variety of conditions failed to produce **146** (**Scheme 3.21**).[35] Attempts to couple vinyl boronate **147** and alcohols **138** or **148** (formation of **148** in **Scheme 3.22**) in a process developed in the lab of Prof.

C. A. Merlic failed to progress.[36] Linkage of vinyl triflate **150** with **138 or 148** under conditions described by Prof. S. L. Buchwald also failed (**Scheme 3.21**).[37]



Scheme 3.21. Initial attempts to form a racemic Claisen precursor

A second approach to **135** began with the formation of **152** from **138** in 32% yield over 3 steps.[38,39] Attempts to cyclize **152** to allyl-vinyl ether **135** via protocols developed by Nicolau[40], Ranier[41], and Schindler[42] all failed; the only structure observed during any of these efforts was **153**. Attempts to cyclize **153** to **135** with a variety of ruthenium-based olefin metathesis catalysts also failed. At this juncture, pursuit of an addition-elimination sequence began.

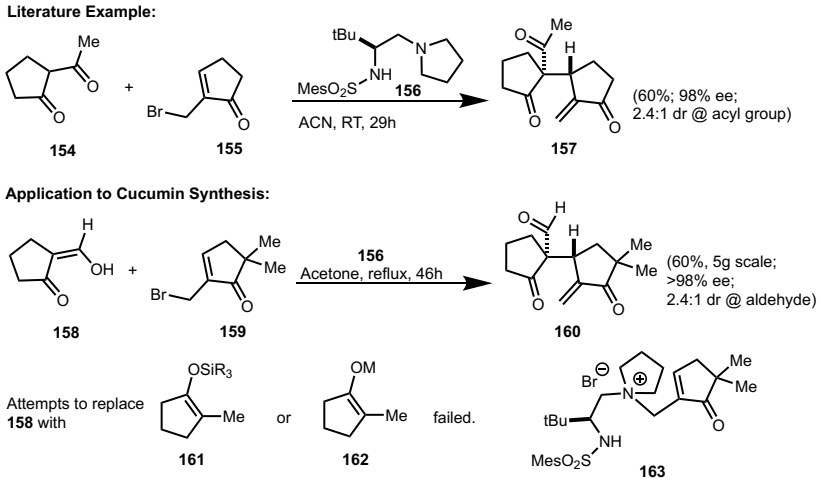


Scheme 3.22. Attempts to form a racemic Claisen precursor via carbonyl-olefin metathesis

Chiral Pyrrolidinyl Sulfonamide Application

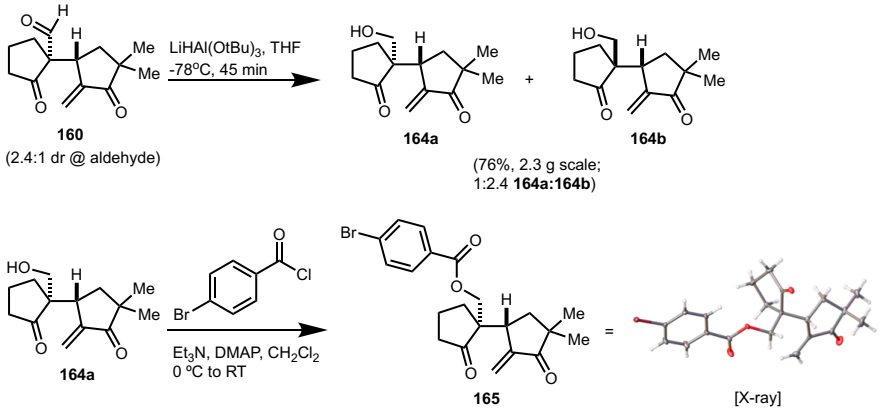
A highly enantioselective addition-elimination procedure was reported for the formation of **157** from **154** and **155** via a chiral pyrrolidinyl sulfonamide (CPS) promoter **156**.[43] Under quite similar conditions, the coupling of **158**[44] and **159**[45] to form structure **160** transpired in 60% yield with greater than 98% enantioselectivity and a 2.4:1 diastereomeric ratio at the aldehydic position (**Scheme 3.23**). These two diastereomers are quite

sensitive, requiring rapid purification; thus, their separation from one another was not pursued. Consistent with the proposed mechanism of such a transformation, mixing of only **156** and **159** led to the formation of quaternary ammonium salt **163**, where the mixing of only **156** and **158** led to no other observable adduct.[43] An array of attempts to replace **158** with enolsilanes **161** in coupling with **159** failed, as did attempts to add equilibrated enolates **162** into salt adduct **163**. Therefore, it was clear that reduction of the aldehyde moiety in **160** would be the next problem to solve.



Scheme 3.23. Connection of A and C rings via a CPS promoter

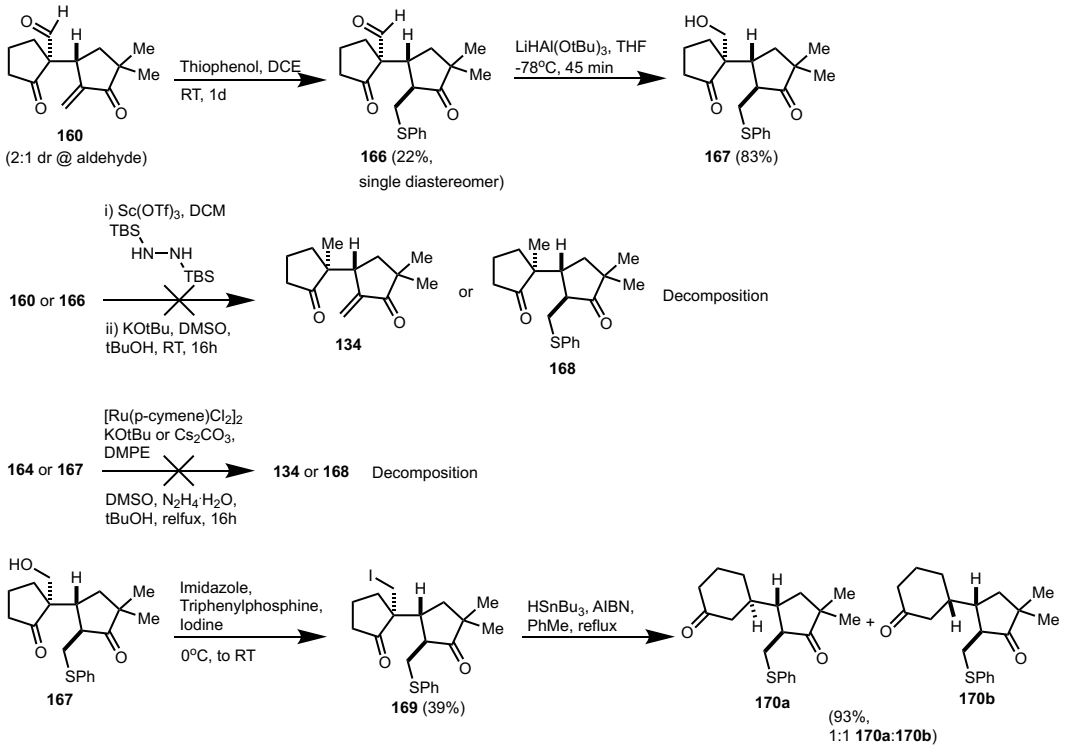
Chemoselective reduction of the aldehyde of **160** occurred with $LiHAl(OtBu)_3$ to afford partially separable minor diastereomer **164a** and major diastereomer **164b** (**Scheme 3.24**).[46] Esterification of minor diastereomer **164a** yielded adduct **165**, the crystals of which were suitable for diffraction.[47] Crystallographic evidence supported the conclusion that the CPS-promoted reaction favored the undesired diastereomer; however, given the high level of enantioinduction in **160** and easy access to **158** (1 step) and **159** (3-4 steps) from commercial materials at multigram scale, pursuit of cucumin A via this route continued.



Scheme 3.24. Solution of the stereochemical outcome of the CPS addition

Pursuit of Deoxygenation

The next task at hand was transformation of the neopentyl aldehyde moiety in **160** to a methyl group. Subjection of **160** or **166**[48] to the deoxygenation procedure described by the lab of Prof. A. G. Myers failed to deliver desired adducts **134** or **168**.[49] Treatment of **164** or **167** under the conditions described by the lab of Prof. C. Li likewise failed.[50] Subjection of iodide **169** to radical scission in the presence of $HSnBu_3$[51] failed to promote formation of **168**; instead, Dowd-Beckwith products **170a-b** formed in 93% yield.[52] The lesson of the studies here described is that radical-mediated reduction of the neopentyl primary aldehyde in **160** or derivatives thereof is intractable; hydride-mediated reduction would be the next pursuit.

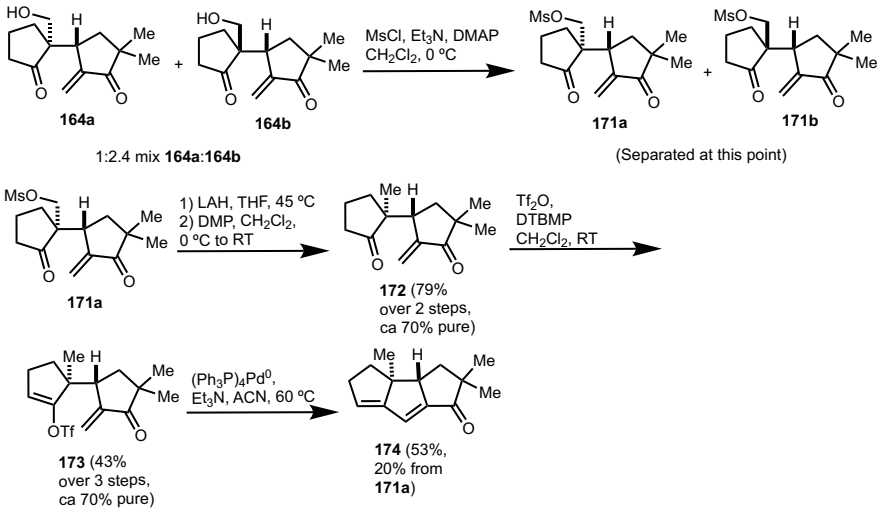


Scheme 3.25. Unsuccessful attempts to deoxygenate

Successful Route to a 5-endo-trig Heck Cyclization

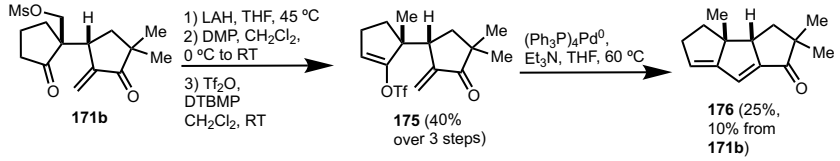
The mixture of alcohols **164a-b** underwent mesylation to afford the mixture of adducts **171a-b**[53]; preparative separation of these two products was successful, and well over 1 gram of **171a** has been isolated to date (**Scheme 3.26**). Reduction of mesylate **171a** with LAH followed by DMP oxidation of the resulting diols was the best way to produce dione **172** (structure **134** in **Scheme 3.17**), despite its impure isolation.[54] Attempts to displace the mesylate or alternative activating groups without reducing either of the two carbonyls of **171a** all met with failure. Formation of vinyl triflate **173** (structure **133** in **Scheme 3.17**) with

Tf_2O and DTBMP from **172** proceeded in 54% yield (**Scheme 3.26**).[55,56] All other conditions employed to tackle this problem such as canonical hard enolization/triflimide quench led only to decomposition of **172** to a complex mixture.[57] Notably, structure **173** decomposed under the conditions developed for oxidative vinylogous acyl sulfonate formation described in the previous chapter; presence of the enone moiety was the culprit for this failure.[58] Nonetheless, the formal annulation proposed transpired via the intramolecular Heck reaction of 173. Use of $(Ph_3P)_3Pd^0$ and Et_3N in ACN at 60 ℃ led to formation of **174** in 53% yield from **173** and 20% yield from **171a** (**Scheme 3.26**).[59] Employment of inorganic bases, other palladium sources, or alternative phosphine ligands truncated the observed reactivity greatly. Completion of **174** achieves the goal of establishing the carbocylic framework of cucumin A.



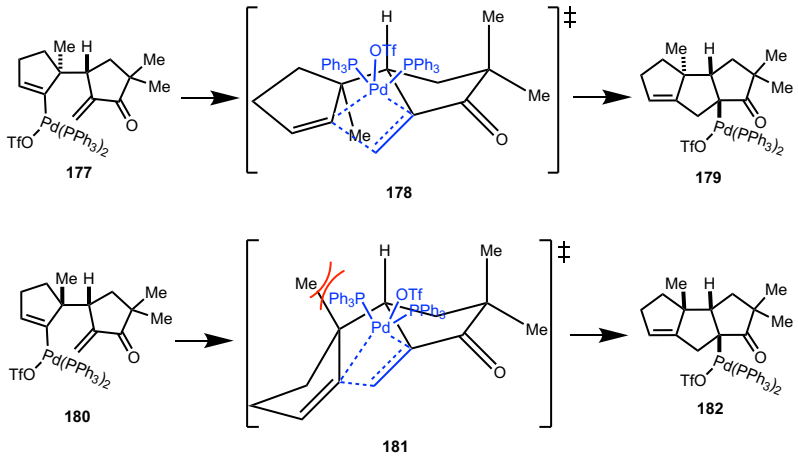
Scheme 3.26. Successful approach to the cucumin A ring system **174**

Major mesylate diastereomer **171b** underwent the analogous sequence described previously to form vinyl triflate **175** in 40% yield over 3 steps (**Scheme 3.27**). Interestingly, the analogous Heck reaction on this substrate was less successful than the cyclization of **173**. Only through switch of the reaction solvent to THF was **176** isolated in low yield; employment of ACN gave little to no product (**Scheme 3.27**).



Scheme 3.27. Heck cyclization of the vinyl triflate derived from **171b** to form **176**

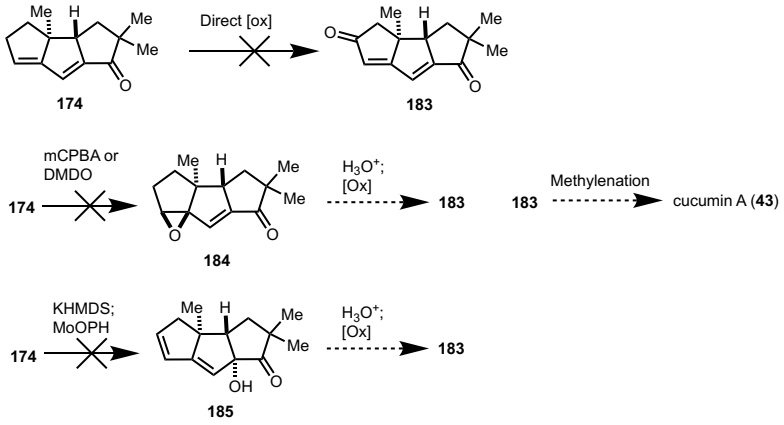
An explanation of the difference in the success of the Heck reactions of **173** and **175** is offered in **Scheme 3.28**. During the cyclization of **175**, transition state structure **181** picks up an additional syn-pentane-like clash *en route* to palladium sigma complex **182**. This clash would be absent in transition state structure **178** during the cyclization of **173**. The likelihood of the reaction proceeding through a trans-(5-5)-bicyclic analogue of either **179** or **182** is relatively low (**Scheme 3.28**).[60]



Scheme 3.28. Rationalizing the different facilities of the Heck reactions of **173** and **175**

A-Ring Oxidation

With ring system **174** in place, the next task at hand was introduction of the final oxygen atom on the A ring to give penultimate **183**. Oxidation of the allylic site directly (**Scheme 3.29**, top sequence), whether by SeO_2[61,62], Cr(VI) reagents[63,64], or the Corey-Yu oxidation,[65] has failed to produce **183** thus far. We hypothesized that structures such as **184** or **185** could serve as stepping stones to **183** via acid-catalyzed rearrangement followed by further oxidation (**Scheme 3.29**, middle and bottom sequences).[66,67] However, attempts at the formation of **184** and **185** have been fruitless to this point.



Scheme 3.29. Attempts to form cucumin A penultimate **183** via oxidation of **174**

Conclusion and Future Directions

The ring system of cucumin A, intermediate **174**, has been synthesized in a 10-step LLS from commercial materials via a CPS-mediated addition-elimination sequence followed by a 5-endo-trig Heck cyclization.

Further investigation into the differential facilities of Heck reactions of **173** versus **175** via calculations of the relevant transition states will be an enlightening pursuit. Further studies concerning the formation of **183** are ongoing.

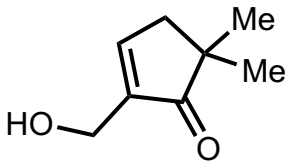
General Experimental Information

General Procedures. All reactions were performed in oven-dried glassware under a positive pressure of dinitrogen unless otherwise noted. Flash column chromatography was performed as described by Still *et. al.*[68] employing silica gel 60 (40-63 μm, Whatman). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F254 plates (Merck).

Materials. Reagents and solvents used herein were purchased from commercial vendors and used as received, with these specifications: Bromine (Br_2), Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), dimethylformamide (DMF), thiophenol, 1,2-dichloroethane (DCE), pyridine, acetonitrile (ACN) and triethylamine (Et_3N) were sourced from sureseal bottles. Aside from these, all other solvents used herein were reagent grade with no protection from air/moisture. 2-iodoxybenzoic acid (IBX) was sourced from Oakwood as a 30 wt % solid. Dry lithium chloride (LiCl) was purchased from Aldrich and used without further modification. Sureseal Tebbe reagent solutions (0.50 M in PhMe) were purchased from Aldrich. Lithium tris(tert-butoxy) aluminum hydride ($LiHAl(OtBu)_3$) was purchased from Alfa Aesar and stored in a drybox in between uses. Sureseal lithium aluminum hydride (LAH) solutions (1.0 M in THF) were purchased from Aldrich. Dess-Martin Periodinane (DMP) was purchased from Oakwood. 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was purchased from Oakwood. Triflic anhydride (Tf_2O) was purchased and used as received. Tetrakis(triphenylphosphine)palladium(0) ($(Ph_3P)_4Pd^0$) was purchased from Strem and stored at -80 ℃ in between uses.

Instrumentation. ^1H NMR spectra were recorded with Varian INOVA-500, Agilent DD2-600, or JEOL-400 spectrometers, are reported in parts per million (δ), and are calibrated using residual non-deuterated solvent as an internal reference: $CDCl_3$, δ 7.26 ($CHCl_3$); C_6D_6, δ 7.16 (C_6H_6). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicities are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sx = sextet, m = multiplet; br = broad, or combinations thereof. ^{13}C NMR spectra were recorded with a Varian INOVA-500 or JEOL-400 spectrometer, are reported in parts per million (δ), and are referenced from the central peak of the carbon resonance of the solvent: $CDCl_3$, δ 77.16. ^{19}F NMR spectra were recorded with a JEOL-400 or a Varian INOVA-500 spectrometer and are reported in parts per million (δ). Infrared (IR) data were recorded on a Bruker Alpha FT-IR spectrometer outfitted with an Eco-ATR sampling module. High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mass spectroscopy using a Thermo Scientific Dionex UltiMate 3000 UHPLC coupled to a Thermo Q Exactive Plus mass spectrometer system equipped with either an HESI-II electrospray ionization source or an APCI probe.

Experimentals



2-(hydroxymethyl)-5,5-dimethylcyclopent-2-en-1-one (138):

A stirring solution of 2,2-dimethylcyclopentanone (5.0 mL, 40 mmol, 1 equiv) in DMSO (200 mL) in a 500 mL recovery flask open to the air was charged with IBX (30 wt %, 56 g, 60 mmol, 1.5 equiv). The flask was capped, sealed with teflon tape and parafilm, and heated to 85 ℃ with stirring for 44 h.[34] The reaction was cooled to room temperature and treated with 100 mL pentane and 100 mL water, followed by stirring for five minutes. The reaction mixture was filtered through a Whatman grade 42 filter paper-equipped Buchner funnel (pentane washes). Following transfer of the filtered reaction mixture to a separatory funnel (pentane washes), the layers were separated. The aqueous layer was extracted ten times with 70 mL pentane. The combined organic fractions were washed four times with water (200 mL), dried over sodium sulfate, filtered, and concentrated at reduced pressure with a room temperature water bath, affording 3.18 g of crude 5,5-dimethylcyclopent-2-en-1-one (28.4 mmol assumed for the next step). This material was transferred to a 500 mL recovery flask and suspended in water (57 mL). A solution of formaldehyde (37% aqueous, 4.70 mL, 42.5 mmol, 1.5 equiv) was added, followed by DMAP (697 mg, 5.7 mmol, 0.2 equiv).Basavaiah *et al.*[33] The resulting mixture was stirred vigorously off-center at room temperature for 2 h. The reaction was poured into a separatory funnel containing 100 mL water and 100 mL EtOAc, and the layers were separated. The aqueous layer was extracted twice more with EtOAc. The combined organic layers were dried over sodium sulfate , filtered, and concentrated at reduced pressure. The residue obtained was applied to a 13 by 4 cm silica gel column and eluted with 33% EtOAc/hexane (1.3 L), generating 51 24 mL fractions. Fractions 20-48 were combined and concentrated at reduced pressure to give **138** (2.11 g, 15.1 mmol, 38% from 2,2-dimethylcyclopentanone) as a slightly yellow liquid.

In an alternative procedure[31,32], a solution of Br_2 (5.2 mL, 100 mmol, 1 equiv) in $CHCl_3$ (100 mL) was added to a stirring solution of 2,2-dimethylcyclopentanone (12.6 mL, 100 mmol, 1 equiv) in $CHCl_3$ (250 mL) in a 500 mL recovery flask over 3 h via a pressure-equalizing addition funnel. After stirring at room temperature for 20 h, the reaction mixture was transferred to a separatory funnel and washed twice with 1 L saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was transferred to a 500 mL recovery flask equipped with a stir bar and treated with dry LiCl (11.44 g, 270 mmol, 2.7 equiv). The flask was evacuated and

backfilled once with dinitrogen, and then dry DMF (132 mL) was added. The flask was outfitted with a reflux condenser, and the reaction was stirred at reflux in a copper shot bath for 17h. The reaction was cooled to room temperature and diluted with 2.5 L H_2O. The aqueous layer was extracted 10 times with 300 mL pentane. The combined organic fraction were dried over sodium sulfate, filtered, and concentrated at reduced pressure (bath temperature <30 ℃) to give 5,5-dimethylcyclopent-2-en-1-one (7.59 g, 68.9 mmol, 69%) as a slightly brown liquid. To this intermediate in a 500 mL recovery flask equipped with a stir bar was added water (138 mL). A solution of formaldehyde (37% aqueous, 8.4 mL, 75.8 mmol, 1.1 equiv) was added, followed by DMAP (421 mg, 3.45 mmol, 0.05 equiv).[33] The resulting mixture was stirred vigorously off-center at room temperature for 3 h. The reaction was poured into a separatory funnel containing 200 mL water and 200 mL EtOAc, and the layers were separated. The aqueous layer was extracted twice more with EtOAc. The combined organic layers were dried over sodium sulfate , filtered, and concentrated at reduced pressure. The residue obtained was purified with analogy to the process described above to give **138** (6.29 g, 44.9 mmol, 65%) as a yellow oil. The yield from 2,2-dimethylcyclopentanone was 45%.

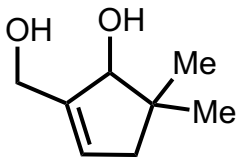
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.40 (tt, J = 2.8, 1.3 Hz, 1H), 4.37 (m, 2H), 2.49 (m, br, 3H), 1.11 (s, 6H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 214.3, 155.9, 142.3, 58.1, 44.1, 44.0, 25.0.

FTIR (thin film) ν_{max}: 3433, 2962, 2927, 2868, 1685, 1637, 1466, 1436, 1382, 1360, 1346, 1305, 1286, 1253, 1211, 1154, 1068, 1036, 995, 980, 958, 932, 902, 837, 763, 676, 663, 610, 582, 545 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_8H_{12}O_2$, 163.0730; found, 163.0726.

TLC R_f= 0.36 (1:1 hexane:EtOAc).



2-(hydroxymethyl)-5,5-dimethylcyclopent-2-en-1-ol (148):[38]

A stirring solution of **138** (280 mg, 2 mmol, 1 equiv) in methanol (10 mL) in a 50 mL recovery flask was charged with $CeCl_3 \cdot 7H_2O$ (986 mg, 4 mmol, 2 equiv), and the resulting mixture was stirred for 5 minutes. The reaction was then cooled to -78 ℃ in a dry ice/acetone bath, and $NaBH_4$ (84 mg, 2.2 mmol, 1.1 equiv) was added in three portions. The reaction was stirred at this temperature for 80 minutes and then warmed to 0 ℃, whereupon 4 mL of saturated aqueous NH_4Cl were added. The reaction was then poured into a separatory funnel containing water, and the aqueous layer was extracted four times with EtOAc. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 10 by 3 cm silica gel and eluted with 75% EtOAc/hexane (0.4 L), generating 21 20 mL fractions. Fractions 9-21 were combined and concentrated at reduced pressure to give **148** (209 mg, 1.47 mmol, 74%) as a clear, viscous, colorless oil.

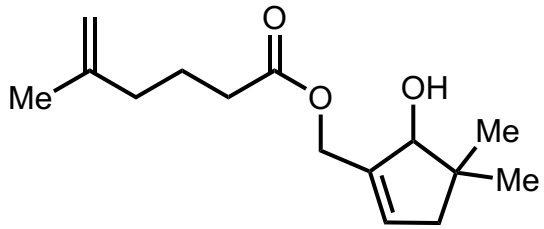
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.73 (m, 1H), 4.30 (m, 2H), 4.24 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 1.92 (br s, 2H), 1.08 (s, 3H), 1.06 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 143.6, 129.4, 85.4, 61.3, 45.6, 42.6, 28.3, 22.5.

FTIR (thin film) ν_{max}: 3321, 2954, 2922, 2899, 2867, 2846, 1466, 1382, 1363, 1288, 1043, 998, 684, 640 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_8H_{14}O_2$, 165.0886; found, 165.0884.

TLC R_f= 0.18 (1:1 hexane:EtOAc).



(5-hydroxy-4,4-dimethylcyclopent-1-en-1-yl)methyl 5-methylhex-5-enoate (186):[39]

A stirring solution of **148** (209 mg, 1.47 mmol, 1 equiv) and **151** (188 mg, 1.47 mmol, 1 equiv) in CH_2Cl_2 was charged with EDCI·HCl (338 mg, 1.76 mmol, 1.2 equiv) followed by DMAP (few crystals), and the reaction was stirred at room temperature for 22 h. EDCI·HCl (338 mg, 1.76 mmol, 1.2 equiv) and DMAP (few crystals) were added once more, and the reaction was stirred for 19 h. The reaction was poured into a separatory funnel containing 1N HCl and the layers were separated. The aqueous layer was extracted thrice more with CH_2Cl_2. The combined organic fractions were washed with 1N HCl, saturated aqueous sodium bicarbonate, and brine sequentially, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 10 by 4 cm silica gel column and eluted with 5% (0.2 L), then 10% (0.2 L) and finally 15% (0.4 L) EtOAc/hexane. The process generated 39 20 mL fractions. Fractions 26-36 were combined and concentrated at reduced pressure to give **186** (201 mg, 0.80 mmol, 54%) as a clear, colorless oil.

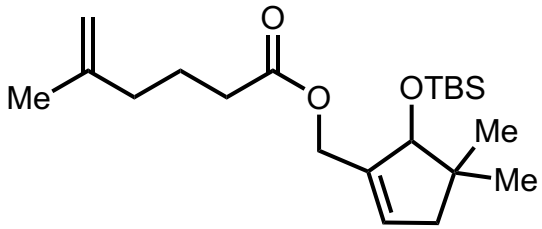
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.81 (m, 1H), 4.79 – 4.71 (m, 2H), 4.69 – 4.61 (m, 2H), 4.11 (m, 1H), 2.33 (t, J = 7.5 Hz, 2H), 2.23 (m, 1H), 2.13 – 2.01 (m, 3H), 1.95 (m, 1H), 1.83 – 1.73 (m, 2H), 1.71 (t, J = 1.1 Hz, 3H), 1.07 (s, 3H), 1.05 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 174.0, 144.8, 140.2, 132.0, 110.9, 84.1, 61.5, 45.5, 42.4, 37.2, 33.8, 28.3, 22.9, 22.6, 22.3.

FTIR (thin film) ν_{max}: 3434, 2954, 2934, 2868, 2848, 1735, 1650, 1523, 1450, 1376, 1364, 1310, 1225, 1148, 1112, 1048, 999, 965, 888, 821, 797, 748, 697, 544, 446, 429, 406 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{15}H_{24}O_3$, 275.1618; found, 275.1614.

TLC R_f= 0.32 (4:1 hexane:EtOAc).



(5-((tert-butyldimethylsilyl)oxy)-4,4-dimethylcyclopent-1-en-1-yl)methyl 5-methylhex-5-enoate (152):

To a solution of **186** (201 mg, 0.80 mmol, 1 equiv) in DMF (8 mL) was added imidazole (163 mg, 2.40 mmol, 3 equiv), followed by TBSCl (241 mg, 1.60 mmol, 2 equiv). The flask was capped, sealed with teflon tape and parafilm, and heated to 45 ℃ with stirring for 17 h. The reaction was cooled to room temperature, poured into a separatory funnel containing 1N HCl, and extracted thrice with ethyl acetate. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to an 8 by 4 cm silica gel column and eluted with 10% (0.25 L) and then 40% (0.6 L) CH_2Cl_2/hexane. The process generated 33 24 mL fractions, and fractions 17-32 were combined and concentrated at reduced pressure to give **152** (236 mg, 0.64 mmol, 80%) as a clear, colorless oil.

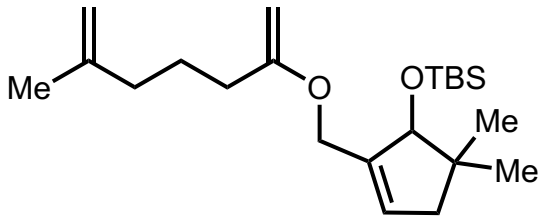
^{1}HNMR (400 MHz; $CDCl_3$) δ: 5.71 (m, 1H), 4.73 (m, 1H), 4.70 – 4.63 (m, 2H), 4.56 – 4.50 (m, 1H), 4.27 (m, 1H), 2.32 (m, 2H), 2.22 – 2.13 (m, 1H), 2.11 – 2.02 (m, 3H), 1.84 – 1.74 (m, 2H), 1.71 (t, J = 1.0 Hz, 3H), 1.08 (s, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 173.5, 144.9, 140.2, 129.8, 110.8, 84.0, 61.4, 45.7, 43.2, 37.2, 33.8, 28.2, 26.1, 23.6, 22.9, 22.4, 18.3, -3.9, -4.6.

FTIR (thin film) ν_{max}: 2955, 2929, 2897, 2857, 1739, 1651, 1463, 1382, 1363, 1308, 1290, 1251, 1189, 1148, 1114, 1095, 1070, 1007, 966, 939, 888, 866, 836, 799, 773, 671, 423 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{21}H_{38}O_3Si$, 389.2482; found, 389.2476.

TLC R_f= 0.73 (9:1 hexane:EtOAc).



tert-butyl((5,5-dimethyl-2-(((6-methylhepta-1,6-dien-2-yl)oxy)methyl)cyclopent-2-en-1-yl) oxy)dimethylsilane (153):

A stirring solution of **152** (76.4 mg, 0.208 mmol, 1 equiv) and pyridine (50 uL, 0.62 mmol, 3 equiv) in THF (2.1 mL) was cooled to 0 ℃ in an ice-water bath, and Tebbe reagent solution (0.50 M in PhMe, 1 mL, 0.5 mmol, 2.4 equiv) was added dropwise. The bath was removed and the reaction was stirred at room temperature for 2 h. The reaction was applied to an 8 by 3 cm basic alumina plug directly and eluted with 70 mL hexane, generating 8 9 mL fractions. Fractions 2-6 were combined and concentrated at reduced pressure to give **153** (75 mg, 0.206 mmol, 99%) as a yellow oil.

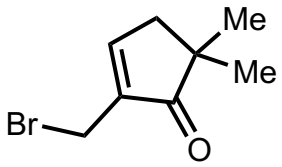
^{1}HNMR (400 MHz; C_6D_6) δ: 5.65 (m, 1H), 4.80 (m, 2H), 4.36 – 4.26 (m, 3H), 4.06 – 4.00 (m, 2H), 2.20 (m, 2H), 2.11 (m, 1H), 2.00 (t, J = 7.6 Hz, 2H), 1.97 – 1.91 (m, 1H), 1.81 – 1.72 (m, 2H), 1.63 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.00 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H).

^{13}CNMR (101 MHz; C_6D_6) δ: 163.3, 145.5, 141.7, 128.8, 113.3, 110.6, 84.2, 81.6, 64.6, 45.8, 43.2, 35.2, 28.2, 26.2, 25.8, 23.8, 22.4, 18.5, -4.0, -4.6.

FTIR (thin film) ν_{max}: 2955, 2929, 2898, 2857, 1651, 1597, 1463, 1382, 1374, 1363, 1329, 1257, 1208, 1151, 1113, 1095, 1072, 1011, 982, 964, 939, 888, 868, 836, 799, 774, 732, 669, 442, 418 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{22}H_{40}O_2Si$, 365.2870; found, 365.2867.

TLC R_f= 0.87 (9:1 hexane:EtOAc).



2-(bromomethyl)-5,5-dimethylcyclopent-2-en-1-one (159):[45]

A stirring solution of **138** (3.92 g, 28.0 mmol, 1 equiv) in dry ether (56 mL) in a 500 mL recovery flask was cooled to 0 ℃ and PBr_3 (1.35 mL, 14.0 mmol, 0.5 equiv) was added dropwise. After stirring for 15 minutes at 0 ℃, the reaction was treated with 14.6 mL methanol via syringe and then concentrated at reduced pressure, with a 35 ℃ water bath. The residue obtained was applied to a 12 by 4 cm silica gel column and eluted with 10% EtOAc/hexane (0.55 L), generating 23 24 mL fractions. Fractions 8-19 were combined and concentrated at reduced pressure to give **159** (4.93 g, 24.4 mmol, 87%) and a slightly yellow liquid.

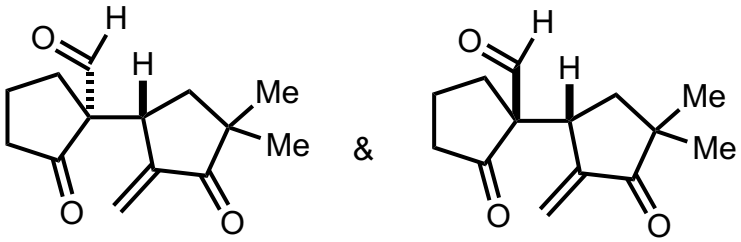
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.57 (m, 1H), 4.05 (m, 2H), 2.50 (m, 2H), 1.12 (s, 6H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 210.9, 159.0, 140.1, 44.0, 43.7, 25.0, 22.4.

FTIR (thin film) ν_{max}: 2962, 2926, 2867, 1704, 1633, 1466, 1430, 1380, 1361, 1342, 1320, 1305, 1258, 1213, 1010, 992, 958, 930, 831, 670, 606, 560, 534 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_8H_{11}BrO$, 203.0066; found, 203.0064.

TLC R_f= 0.50 (4:1 hexane:EtOAc).



160a **160b**

(1S,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentane)]-1-carbaldehyde (160a) and

(1R,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentane)]-1-carbaldehyde (160b):[43]

A solution of **159** (5.89 g, 29.2 mmol, 1 equiv) in acetone (292 mL) in a 500 mL recovery flask equipped with a stir bar and open to the air was charged with **158**[44] (3.93 g, 35.0 mmol, 1.2 equiv) and **156**[43] (10.30 g, 29.2 mmol, 1 equiv). The flask was outfitted with a reflux condenser and heated at reflux with stirring for 23 h. The reaction was cooled to room temperature and hexane (200 mL) was added; stirring at room temperature was continued for three more hours. The reaction was filtered, and the white solid composed of the HBr salt of **156**, **187**, was dried under high vacuum to give recovery of the auxiliary (9.44 g, 21.8 mmol, 75% recovery). The filtrate was concentrated at reduced pressure and the residue obtained was applied to a 16 by 6 cm column. The column was eluted over twenty minutes with 10% (1 L) and then 12.5% (2 L) EtOAc/hexane, generating 30 100 mL fractions. Fractions 11-23 were combined and concentrated at reduced pressure to give a 2.4:1 mixture of **160b** and **160a** (4.12 g, 17.6 mmol, 60%, ca 95% pure) as a white wax. The two compounds described are quite sensitive and must be purified rapidly; as such, further exploration of their separation was not undertaken.

FTIR (thin film, mix of both compounds) ν_{max}: 2962, 2928, 2869, 1726, 1709, 1633, 1466, 1406, 1383, 1364, 1318, 1275, 1257, 1190, 1145, 1110, 1056, 1043, 1029, 1005, 944, 799, 591, 548 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{14}H_{18}O_3$, 235.1329; found, 235.1325.

TLC R_f= 0.33 (4:1 hexane:EtOAc).

(1S,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentane)]-1-carbaldehyde (160a)

^{1}HNMR (400 MHz; $CDCl_3$; selected resonances) δ: 9.59 (d, J = 1.3 Hz, 1H), 6.08 (d, J = 3.3 Hz, 1H), 5.09 (d, J = 3.6 Hz, 1H), 3.81 (ddt, J = 11.8, 7.4, 3.1 Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 213.2, 208.6, 198.5, 143.7, 120.2, 70.6, 44.5, 39.7, 39.2, 37.5, 24.6, 24.5, 23.7, 19.5.

(1R,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentane)]-1-carbaldehyde (160b)

^{1}HNMR (400 MHz; $CDCl_3$; selected resonances) δ: 9.41 (d, J = 1.4 Hz, 1H), 6.19 (d, J = 3.2 Hz, 1H), 5.09 (d, J = 2.8 Hz, 2H), 3.89 (ddt, J = 11.2, 8.0, 3.0 Hz, 1H), 1.12 (s, 3H), 1.05 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 214.3, 208.7, 196.6, 142.6, 121.3, 71.9, 44.6, 39.7, 38.8, 38.2, 24.9, 24.1, 23.4, 19.3.

A racemic sample of this product was generated by performance of the reaction with Et_3N in lieu of **156**. HPLC conditions: Chiralcel OJ-H column (Diacel); 90/10 hexane/2-propanol; Flow rate 1.0 mL/min; λ = 230 nm; 25.7 min (minor), 29.8 min (minor), 36.1 min (major), 41.8 min (major). According to relative integration of the peaks, the enantioselective reaction progressed with greater than 98% ee.

Figure 3.3. Racemic reaction:

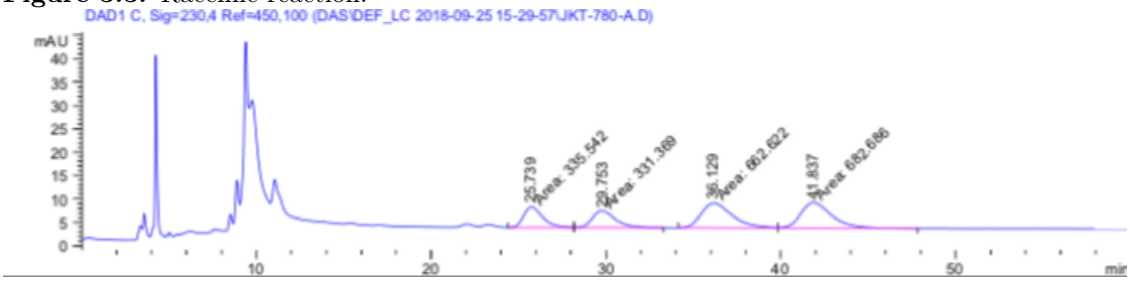
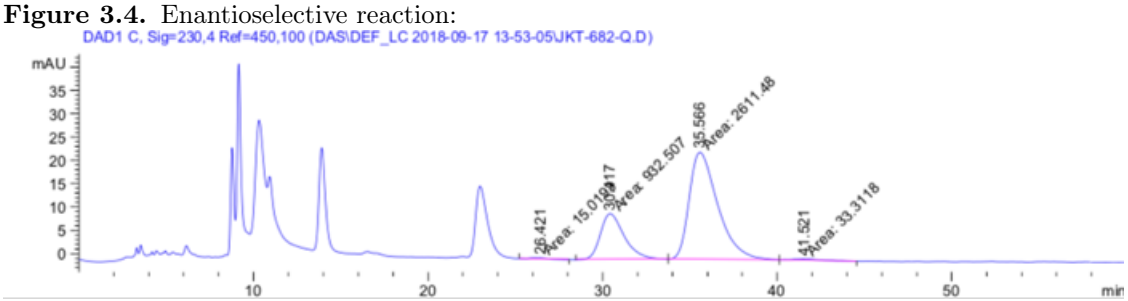
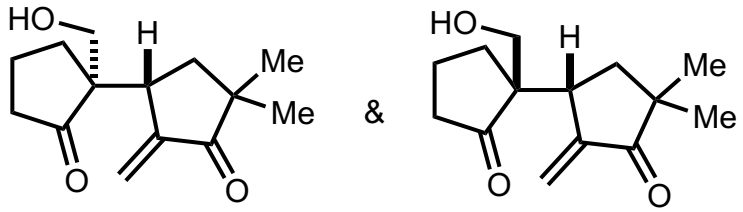


Figure 3.4. Enantioselective reaction:





164a **164b**

(1S,1'R)-1-(hydroxymethyl)-4',4'-dimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (164a) and

(1R,1'R)-1-(hydroxymethyl)-4',4'-dimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (164b):[46]

A stirring solution of **160a** and **b** (1:2 **160a**:**160b**, 2.26 g, 9.65 mmol, 1 equiv) in THF (483 mL) in a 3 L 2-neck round-bottom flask was cooled to -78 ℃ in a dry ice/acetone bath. A solution of $LiHAl(OtBu)_3$ (2.94 g, 11.57 mmol, 1.2 equiv) in THF (82 mL) was added dropwise to the reaction mixture over 25 minutes. The reaction was stirred at this temperature for 45 more minutes. Following this timeframe, 180 mL of MeOH were added via syringe pump at a rate of 2 mL/minute. The reaction was then warmed to 0 ℃, and 560 mL ether followed by 390 mL 5% aqueous AcOH were added. The reaction mixture was warmed to room temperature and poured into a separatory funnel containing saturated aqueous sodium bicarbonate (0.65L) and EtOAc (0.33 L). The layers were separated and the aqueous layer was extracted twice more with 0.33 L EtOAc. The combined organic fractions were washed with brine and concentrated at reduced pressure. The residue obtained was applied to a 14 by 5 cm silica gel column. The column was eluted with 25% (1 L) and then 50% (1 L) EtOAc/hexane, producing five 100 mL fractions and 57 24 mL fractions. Of the final 57 fractions, fractions 25-43 were combined and concentrated at reduced pressure to give a 1:2.4 mixture of **164a** and **164b** (1.73 g, 7.33 mmol, 76% yield).

The following separation then occurred: A ca 100 mg sample of the diastereomeric mix was separated by reverse-phase preparative HPLC through use of a Kromasil 100-10-C18 column with dimensions of 250 by 21.2 mm. A gradient elution of 95% 0.1% TFA in H_2O/5% 0.1% TFA in ACN to 30% 0.1% TFA in H_2O/70% 0.1% TFA in ACN was employed over 60 minutes at a flow rate of 10 mL/minute. Then, the column was flushed with 5% 0.1% TFA in H_2O/95% 0.1% TFA in ACN for 10 minutes at a flow rate of 10 mL/minute. Peak-based collection (λ=254 nm) of 5 mL fractions led to a partial separation of **164a** (retention time=63.1 min) and **164b** (retention time=61.0 min). Fractions collected were each assayed for purity through use of an Accucore aQ 100 by 2.1 mm analytical column. A gradient elution of 95% 0.1% TFA in H_2O/5% 0.1% TFA in ACN to 5% 0.1% TFA in H_2O/95% 0.1% TFA in ACN was employed over 7 minutes at a flow rate of 0.650 mL/minute, followed by elution at the same rate with 5% 0.1% TFA in H_2O/95% 0.1% TFA

in ACN for 1 minute. UV detection (λ=254 nm) indicated with fractions were pure for **164a (retention time=4.04 min)** or **164b** (retention time=3.99 min), and the two bands were combined and concentrated at reduced pressure to give both pure compounds.

(1S,1'R)-1-(hydroxymethyl)-4',4'-dimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (164a)

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.18 (d, J = 3.2 Hz, 1H), 5.48 (d, J = 2.8 Hz, 1H), 3.86 (d, J = 11.3 Hz, 1H), 3.77 (d, J = 11.3 Hz, 1H), 3.37 (ddt, J = 11.0, 7.8, 3.1 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.26 – 2.17 (m, 1H), 2.00 – 1.86 (m, 5H), 1.81 (dd, J = 12.3, 7.8 Hz, 1H), 1.36 (app t, J = 11.9 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 222.9, 210.0, 144.7, 120.8, 65.4, 55.7, 44.4, 39.9, 38.2, 37.4, 28.8, 25.0, 23.7, 19.6.

FTIR (thin film) ν_{max}: 3456, 2962, 2871, 1786, 1725, 1630, 1465, 1405, 1383, 1363, 1322, 1259, 1161, 1042, 953, 918, 876, 801, 771, 731, 647, 620, 595, 557, 451 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{14}H_{20}O_3$, 259.1305; found, 259.1299.

TLC R_f= 0.35 (1:1 hexane:EtOAc).

(1R,1'R)-1-(hydroxymethyl)-4',4'-dimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (164b):

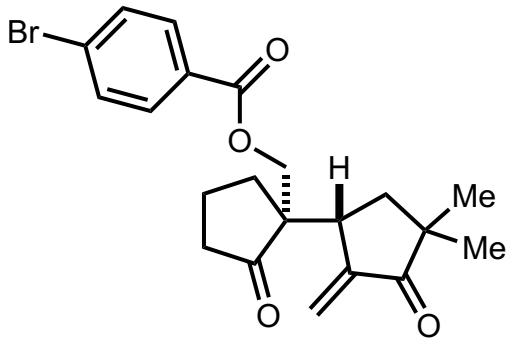
^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.14 (d, J = 3.2 Hz, 1H), 5.01 (d, J = 2.8 Hz, 1H), 3.61 (m, 2H), 3.57 (ddd, J = 11.2, 7.3, 4.1 Hz, 1H), 2.59 – 2.46 (m, 1H), 2.35 – 2.25 (m, 1H), 2.02 (dd, J = 12.6, 8.1 Hz, 1H), 1.98 – 1.84 (m, 4H), 1.73 – 1.60 (m, 1H), 1.38 (app t, J = 11.9 Hz, 1H), 1.15 (s, 3H), 1.04 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 224.0, 210.1, 144.5, 120.5, 64.9, 56.4, 44.5, 40.0, 38.2, 37.9, 27.8, 25.1, 23.5, 19.3.

FTIR (thin film) ν_{max}: 3435, 2961, 2929, 2871, 1724, 1631, 1465, 1407, 1363, 1252, 1163, 1109, 1051, 1027, 942, 803, 734, 621, 589, 549, 451, 424 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{14}H_{20}O_3$, 259.1305; found, 259.1299.

TLC R_f= 0.35 (1:1 hexane:EtOAc).



((1S,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentan)]-1-yl)methyl 4-bromobenzoate (165):[47]

A solution of **164a** (10.2 mg, 43 μmol, 1.0 equiv) in CH_2Cl_2 (0.86 mL) was cooled to 0 °C in an ice-water bath, and Et_3N (12 μL, 86 μmol, 2.0 equiv) was added. Then para-bromobenzoylchloride (10.3 mg, 47 μmol, 1.1 equiv) followed by DMAP (5.3 mg, 43 μmol, 1.0 equiv) was added, and the mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was poured into saturated aqueous sodium bicarbonate and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated at reduced pressure. The residue obtained was loaded onto a 6 by 2 cm silica plug and eluted with 10% (25 mL) and then 20% (100 mL) EtOAc/hexane, generating 16 9 mL fractions. Fractions 8-12 were concentrated at reduced pressure to give **165** (12.7 mg, 43 μmol, 70%) as a white solid. This material was dissolved in a minimal amount of diethyl ether and layered with isooctane, which gave crystals suitable for diffraction following slow evaporation.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.86 – 7.79 (m, 2H), 7.60 (d, J = 8.6 Hz, 2H), 6.25 (d, J = 3.1 Hz, 1H), 5.64 (d, J = 2.9 Hz, 1H), 4.74 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 11.1 Hz, 1H), 3.18 (ddd, J = 11.0, 7.7, 3.1 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.29 (ddd, J = 19.5, 13.4, 7.9 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.06 – 1.93 (m, 3H), 1.89 (ddd, J = 12.4, 7.6, 2.8 Hz, 1H), 1.44 (app t, J = 12.0, Hz, 2H), 1.14 (s, 3H), 1.05 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 219.5, 209.4, 165.7, 144.1, 132.1, 131.2, 128.7, 128.6, 121.1, 67.8, 53.9, 44.3, 39.4, 39.3, 38.3, 29.2, 24.8, 23.7, 19.5.

FTIR (thin film) ν_{max}: 2961, 2927, 2870, 1728, 1632, 1590, 1484, 1465, 1398, 1379, 1267, 1198, 1173, 1114, 1102, 1069, 1050, 1012, 957, 848, 756, 683, 511, 477, 466, 451, 408 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{21}H_{23}BrO_4$, 419.0852; found, 419.0857.

TLC R_f= 0.15 (7:1 hexane:EtOAc).

X-ray Crystallography: *Performed by Dr. Shao-Liang Zhang.* From a crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II CCD diffractometer ($Mo_{K\alpha}$ radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen

flow apparatus. The collection method involved 0.5 scans in ω at 28° in *2θ*. Data integration down to 0.78 Å resolution was carried out using SAINT V8.37A (Bruker diffractometer, 2016) with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2016). The structure was solved by the Intrinsic Phasing methods and refined by least-squares methods again F^2 using SHELXT-2014 and SHELXL-2014 with OLEX 2 interface.[69,70,71] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in **Table 3.1**, and geometric parameters are shown in **Table 3.2**. The Ortep plots produced with SHELXL-2014 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 3.1. 165 crystallography experimental details

	JKT-779c
Crystal data	
Chemical formula	$C_{21}H_{23}BrO_4$
M_r	419.30
Crystal system, space group	Triclinic, *P*1
Temperature (K)	100
a, *b*, *c* (Å)	5.8557 (4), 9.5475 (7), 9.6957 (7)
α, β, γ (°)	69.188 (2), 74.611 (2), 86.544 (2)
V (Å^3)	488.18 (6)
Z	1
Radiation type	Mo *K*α
μ (mm^{-1})	2.13
Crystal size (mm)	0.18 × 0.12 × 0.10
Data collection	
Diffractometer	Bruker D8 goniometer with CCD area detector
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.556, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	20040, 4321, 4237
R_{int}	0.031
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.644
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.023, 0.045, 1.08
No. of reflections	4321
No. of parameters	264
No. of restraints	17
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.18, -0.24
Absolute structure	Flack x determined using 2014 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	-0.012 (3)

Computer programs: SAINT 8.37A (Bruker-AXS, 2015), SHELXT2014, SHELXL2014, Bruker SHELXTL.[69,70]

Table 3.2. 165 crystallography geometric parameters (Å, º)

Br1—C3	1.901 (3)	C15—C16	1.511 (8)
O1—C7	1.350 (3)	C16—O4	1.217 (8)
O1—C8	1.452 (3)	C16—C17	1.528 (8)
O2—C7	1.201 (3)	C17—C20	1.525 (9)
O3—C10	1.214 (3)	C17—C21	1.543 (9)
C1—C2	1.391 (4)	C17—C18	1.544 (10)
C1—C6	1.393 (4)	C18—H18A	0.9900
C1—H1	0.9500	C18—H18B	0.9900
C2—C3	1.381 (4)	C19—H19A	0.9500
C2—H2	0.9500	C19—H19B	0.9500
C3—C4	1.378 (4)	C20—H20A	0.9800
C4—C5	1.378 (4)	C20—H20B	0.9800
C4—H4	0.9500	C20—H20C	0.9800
C5—C6	1.392 (4)	C21—H21A	0.9800
C5—H5	0.9500	C21—H21B	0.9800
C6—C7	1.492 (4)	C21—H21C	0.9800
C8—C9	1.532 (3)	C14A—C15A	1.525 (19)
C8—H8A	0.9900	C14A—C18A	1.57 (2)
C8—H8B	0.9900	C14A—H14A	1.0000
C9—C10	1.530 (4)	C15A—C19A	1.33 (2)
C9—C13	1.542 (4)	C15A—C16A	1.486 (19)
C9—C14A	1.545 (4)	C16A—O4A	1.230 (19)
C9—C14	1.545 (4)	C16A—C17A	1.491 (18)
C10—C11	1.506 (4)	C17A—C20A	1.53 (2)
C11—C12	1.522 (4)	C17A—C18A	1.53 (2)
C11—H11A	0.9900	C17A—C21A	1.56 (2)
C11—H11B	0.9900	C18A—H18C	0.9900
C12—C13	1.540 (4)	C18A—H18D	0.9900
C12—H12A	0.9900	C19A—H19C	0.9500
C12—H12B	0.9900	C19A—H19D	0.9500
C13—H13A	0.9900	C20A—H20D	0.9800
C13—H13B	0.9900	C20A—H20E	0.9800
C14—C15	1.517 (8)	C20A—H20F	0.9800
C14—C18	1.553 (9)	C21A—H21D	0.9800
C14—H14	1.0000	C21A—H21E	0.9800
C15—C19	1.332 (10)	C21A—H21F	0.9800

Table 3.2, continued

C7—O1—C8	117.2 (2)	O4—C16—C17	124.2 (7)
C2—C1—C6	120.1 (3)	C15—C16—C17	108.6 (6)
C2—C1—H1	120.0	C20—C17—C16	112.9 (9)
C6—C1—H1	120.0	C20—C17—C21	111.2 (8)
C3—C2—C1	118.6 (3)	C16—C17—C21	107.5 (7)
C3—C2—H2	120.7	C20—C17—C18	111.1 (9)
C1—C2—H2	120.7	C16—C17—C18	101.9 (7)
C4—C3—C2	122.1 (3)	C21—C17—C18	111.9 (14)
C4—C3—Br1	118.3 (2)	C17—C18—C14	104.1 (8)
C2—C3—Br1	119.5 (2)	C17—C18—H18A	110.9
C3—C4—C5	119.0 (2)	C14—C18—H18A	110.9
C3—C4—H4	120.5	C17—C18—H18B	110.9
C5—C4—H4	120.5	C14—C18—H18B	110.9
C4—C5—C6	120.4 (3)	H18A—C18—H18B	108.9
C4—C5—H5	119.8	C15—C19—H19A	120.0
C6—C5—H5	119.8	C15—C19—H19B	120.0
C5—C6—C1	119.8 (3)	H19A—C19—H19B	120.0
C5—C6—C7	117.8 (2)	C17—C20—H20A	109.5
C1—C6—C7	122.4 (2)	C17—C20—H20B	109.5
O2—C7—O1	124.2 (2)	H20A—C20—H20B	109.5
O2—C7—C6	124.7 (2)	C17—C20—H20C	109.5
O1—C7—C6	111.1 (2)	H20A—C20—H20C	109.5
O1—C8—C9	110.35 (19)	H20B—C20—H20C	109.5
O1—C8—H8A	109.6	C17—C21—H21A	109.5
C9—C8—H8A	109.6	C17—C21—H21B	109.5
O1—C8—H8B	109.6	H21A—C21—H21B	109.5
C9—C8—H8B	109.6	C17—C21—H21C	109.5
H8A—C8—H8B	108.1	H21A—C21—H21C	109.5
C10—C9—C8	107.0 (2)	H21B—C21—H21C	109.5
C10—C9—C13	104.3 (2)	C15A—C14A—C9	122.0 (14)
C8—C9—C13	114.0 (2)	C15A—C14A—C18A	100.5 (15)
C10—C9—C14A	108.6 (2)	C9—C14A—C18A	111.4 (16)
C8—C9—C14A	108.0 (2)	C15A—C14A—H14A	107.3
C13—C9—C14A	114.5 (2)	C9—C14A—H14A	107.3
C10—C9—C14	108.6 (2)	C18A—C14A—H14A	107.3

Table 3.2, continued

C8—C9—C14	108.0 (2)	C19A—C15A—C16A	129 (3)
C13—C9—C14	114.5 (2)	C19A—C15A—C14A	122 (4)
O3—C10—C11	126.1 (3)	C16A—C15A—C14A	108.9 (14)
O3—C10—C9	124.3 (3)	O4A—C16A—C15A	120.2 (18)
C11—C10—C9	109.6 (2)	O4A—C16A—C17A	128 (2)
C10—C11—C12	104.2 (2)	C15A—C16A—C17A	111.3 (15)
C10—C11—H11A	110.9	C16A—C17A—C20A	111 (2)
C12—C11—H11A	110.9	C16A—C17A—C18A	102.2 (16)
C10—C11—H11B	110.9	C20A—C17A—C18A	119 (2)
C12—C11—H11B	110.9	C16A—C17A—C21A	106 (2)
H11A—C11—H11B	108.9	C20A—C17A—C21A	108 (2)
C11—C12—C13	104.4 (2)	C18A—C17A—C21A	109 (3)
C11—C12—H12A	110.9	C17A—C18A—C14A	108.9 (17)
C13—C12—H12A	110.9	C17A—C18A—H18C	109.9
C11—C12—H12B	110.9	C14A—C18A—H18C	109.9
C13—C12—H12B	110.9	C17A—C18A—H18D	109.9
H12A—C12—H12B	108.9	C14A—C18A—H18D	109.9
C12—C13—C9	106.2 (2)	H18C—C18A—H18D	108.3
C12—C13—H13A	110.5	C15A—C19A—H19C	120.0
C9—C13—H13A	110.5	C15A—C19A—H19D	120.0
C12—C13—H13B	110.5	H19C—C19A—H19D	120.0
C9—C13—H13B	110.5	C17A—C20A—H20D	109.5
H13A—C13—H13B	108.7	C17A—C20A—H20E	109.5
C15—C14—C9	114.1 (6)	H20D—C20A—H20E	109.5
C15—C14—C18	103.5 (6)	C17A—C20A—H20F	109.5
C9—C14—C18	115.7 (8)	H20D—C20A—H20F	109.5
C15—C14—H14	107.7	H20E—C20A—H20F	109.5
C9—C14—H14	107.7	C17A—C21A—H21D	109.5
C18—C14—H14	107.7	C17A—C21A—H21E	109.5
C19—C15—C16	117.1 (15)	H21D—C21A—H21E	109.5
C19—C15—C14	135.6 (15)	C17A—C21A—H21F	109.5
C16—C15—C14	107.1 (5)	H21D—C21A—H21F	109.5
O4—C16—C15	127.2 (6)	H21E—C21A—H21F	109.5
C6—C1—C2—C3	-0.3 (4)	C18—C14—C15—C19	-154 (3)

Table 3.2, continued

C1—C2—C3—C4	-0.2 (4)	C9—C14—C15—C16	147.4 (10)
C1—C2—C3—Br1	-179.7 (2)	C18—C14—C15—C16	20.8 (18)
C2—C3—C4—C5	0.4 (5)	C19—C15—C16—O4	-2 (3)
Br1—C3—C4—C5	179.8 (2)	C14—C15—C16—O4	-177.7 (14)
C3—C4—C5—C6	0.0 (5)	C19—C15—C16—C17	179 (2)
C4—C5—C6—C1	-0.5 (5)	C14—C15—C16—C17	2.5 (17)
C4—C5—C6—C7	176.2 (3)	O4—C16—C17—C20	36.1 (17)
C2—C1—C6—C5	0.7 (5)	C15—C16—C17—C20	-144.1 (12)
C2—C1—C6—C7	-175.8 (2)	O4—C16—C17—C21	-86.8 (15)
C8—O1—C7—O2	-6.8 (4)	C15—C16—C17—C21	93.0 (13)
C8—O1—C7—C6	171.6 (2)	O4—C16—C17—C18	155.4 (17)
C5—C6—C7—O2	2.7 (4)	C15—C16—C17—C18	-24.8 (17)
C1—C6—C7—O2	179.3 (3)	C20—C17—C18—C14	157.8 (13)
C5—C6—C7—O1	-175.7 (2)	C16—C17—C18—C14	37.3 (18)
C1—C6—C7—O1	0.9 (4)	C21—C17—C18—C14	-77.2 (15)
C7—O1—C8—C9	112.8 (2)	C15—C14—C18—C17	-36.4 (19)
O1—C8—C9—C10	57.5 (3)	C9—C14—C18—C17	-162.0 (11)
O1—C8—C9—C13	-57.3 (3)	C10—C9—C14A—C15A	-158.5 (19)
O1—C8—C9—C14A	174.17 (19)	C8—C9—C14A—C15A	85.9 (19)
O1—C8—C9—C14	174.17 (19)	C13—C9—C14A—C15A	-42.4 (19)
C8—C9—C10—O3	54.7 (3)	C10—C9—C14A—C18A	-40 (3)
C13—C9—C10—O3	175.9 (2)	C8—C9—C14A—C18A	-156 (3)
C14A—C9—C10—O3	-61.6 (3)	C13—C9—C14A—C18A	76 (3)
C14—C9—C10—O3	-61.6 (3)	C9—C14A—C15A—C19A	-40 (6)
C8—C9—C10—C11	-125.2 (2)	C18A—C14A—C15A—C19A	-164 (6)
C13—C9—C10—C11	-4.1 (3)	C9—C14A—C15A—C16A	144 (2)
C14A—C9—C10—C11	118.5 (2)	C18A—C14A—C15A—C16A	20 (4)
C14—C9—C10—C11	118.5 (2)	C19A—C15A—C16A—O4A	2 (8)
O3—C10—C11—C12	-156.6 (3)	C14A—C15A—C16A—O4A	178 (3)
C9—C10—C11—C12	23.4 (3)	C19A—C15A—C16A—C17A	179 (6)
C10—C11—C12—C13	-33.1 (3)	C14A—C15A—C16A—C17A	-5 (4)
C11—C12—C13—C9	31.3 (3)	O4A—C16A—C17A—C20A	36 (4)
C10—C9—C13—C12	-16.7 (3)	C15A—C16A—C17A—C20A	-141 (3)
C8—C9—C13—C12	99.6 (3)	O4A—C16A—C17A—C18A	164 (4)
C14A—C9—C13—C12	-135.3 (2)	C15A—C16A—C17A—C18A	-13 (4)
C14—C9—C13—C12	-135.3 (2)	O4A—C16A—C17A—C21A	-82 (4)
C10—C9—C14—C15	-166.2 (8)	C15A—C16A—C17A—C21A	101 (3)

Table 3.2, continued

C8—C9—C14—C15	78.2 (8)	C16A—C17A—C18A—C14A	26 (5)
C13—C9—C14—C15	-50.1 (8)	C20A—C17A—C18A—C14A	149 (3)
C10—C9—C14—C18	-46.2 (11)	C21A—C17A—C18A—C14A	-86 (4)
C8—C9—C14—C18	-161.9 (11)	C15A—C14A—C18A—C17A	-29 (5)
C13—C9—C14—C18	69.9 (11)	C9—C14A—C18A—C17A	-160 (3)
C9—C14—C15—C19	-28 (3)		

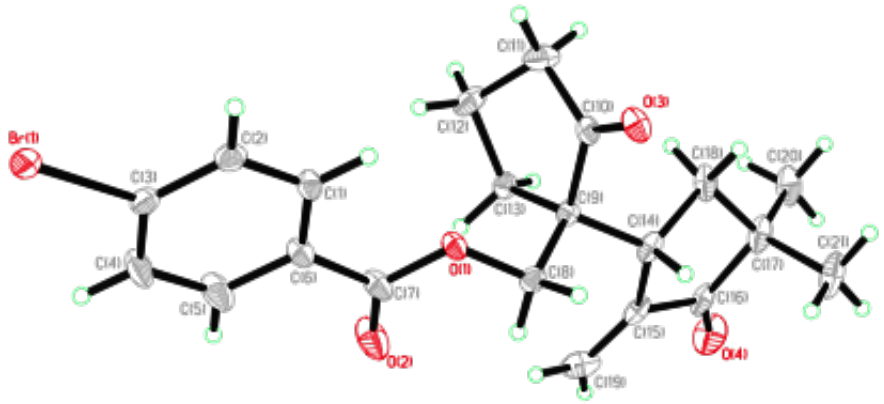


Figure 3.5. Perspective views showing 50% probability displacement

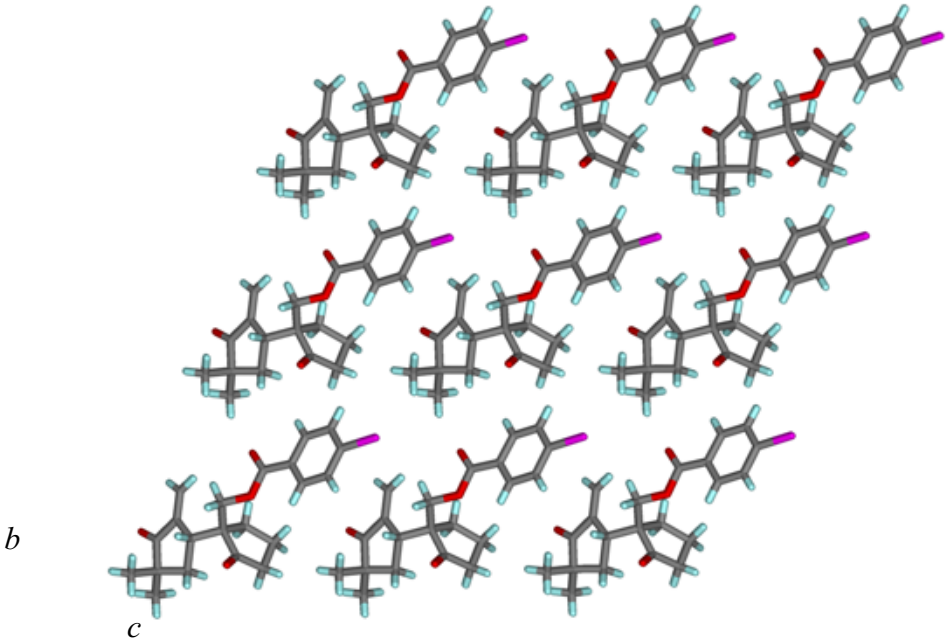
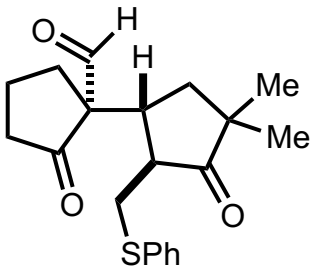


Figure 3.6. Three-dimensional supramolecular architecture viewed along the a-axis direction



(1S,1'R,2'S)-4',4'-dimethyl-2,3'-dioxo-2'-((phenylthio)methyl)-[1,1'-bi(cyclopentane)]-1-carbaldehyde (166):[48]

To a stirring solution of a 1:2.4 mixture of 160a:160b (184 mg, 0.785 mmol, 1.0 equiv) in DCE (7.9 mL) was added thiophenol (0.16 mL, 1.57 mmol, 2.0 equiv) via syringe. The reaction was stirred at room temperature for 42 h and then concentrated at reduced pressure. The residue obtained was applied to a 9 by 5 cm silica gel plug and eluted with 5% (0.2 L) and then 10% (0.4 L) and finally 12.5% (0.6 L) EtOAc/hexane. The process generated 16 20 mL fractions followed by 104 12 mL fractions. Fractions 69-96 were combined and concentrated at reduced pressure to give **166** (60.0 mg, 0.174 mmol, 22%) as a clear, colorless oil.

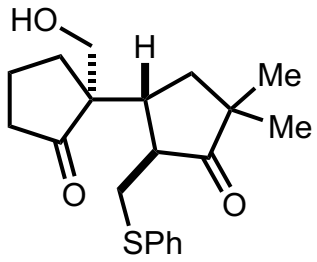
^{1}HNMR (400 MHz; $CDCl_3$) δ: 9.41 (d, J = 1.2 Hz, 1H), 7.34 (dd, J = 8.2, 1.5 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 1H), 3.37 – 3.26 (m, 2H), 2.92 (dd, J = 13.2, 4.6 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.41 – 2.32 (m, 1H), 2.23 – 2.10 (m, 2H), 2.03 (dtt, J = 12.2, 7.0, 3.0 Hz, 1H), 1.92 – 1.71 (m, 3H), 1.37 (app t, J = 12.1 Hz, 1H), 1.10 (s, 3H), 1.06 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 219.2, 213.5, 198.1, 135.5, 130.2, 129.2, 126.8, 70.6, 50.8, 44.3, 39.6, 38.3, 38.0, 32.0, 24.8, 24.2, 24.1, 19.6.

FTIR (thin film) ν_{max}: 2964, 2928, 2869, 1740, 1709, 1481, 1466, 1439, 1405, 1383, 1319, 1275, 1143, 1114, 1059, 1025, 1002, 975, 947, 791, 743, 692, 484, 475 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{20}H_{24}O_3S$, 345.1519; found, 345.1519.

TLC R_f= 0.26 (4:1 hexane:EtOAc).



(1S,1'R,2'S)-1-(hydroxymethyl)-4',4'-dimethyl-2'-((phenylthio)methyl)-[1,1'-bi(cyclopentane)]-2,3'-dione (167):[46]

A stirring solution of **166** (60.0 mg, 0.174 mmol, 1 equiv) in THF (8.7 mL) was cooled to -78 ℃ in a dry ice/acetone bath. A solution of $LiHAl(OtBu)_3$ (53 mg, 0.209 mmol, 1.2 equiv) in THF (1.7 mL) was added dropwise to the reaction mixture over 10 minutes. The reaction was stirred at this temperature for 45 more minutes. Following this timeframe, 3.3 mL of MeOH were added dropwise via syringe over 5 minutes. The reaction was then warmed to 0 ℃, and 11 mL ether followed by 8 mL 5% aqueous AcOH were added. The reaction mixture was warmed to room temperature and poured into a separatory funnel containing saturated aqueous sodium bicarbonate and EtOAc. The layers were separated and the aqueous layer was extracted twice more with EtOAc. The combined organic fractions were washed with brine and concentrated at reduced pressure. The residue obtained was applied to an 11 by 3 cm silica gel column. The column was eluted with 33% (0.12 L) and then 50% (0.24 L) EtOAc/hexane, producing 42 9 mL fractions. Fractions 25-34 were combined and concentrated at reduced pressure to give **167** (50.0 mg, 0.144 mmol, 83% yield) as a clear, colorless oil.

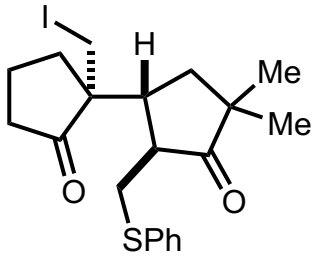
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.40 – 7.35 (m, 2H), 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.66 (d, J = 11.4 Hz, 1H), 3.41 (dd, J = 12.9, 3.4 Hz, 1H), 3.28 (dd, J = 12.9, 5.0 Hz, 1H), 2.82 (td, J = 11.8, 6.3 Hz, 1H), 2.44 – 2.34 (m, 2H), 2.31 – 2.19 (m, 2H), 2.01 – 1.91 (m, 3H), 1.84 (dtd, J = 8.1, 6.8, 1.9 Hz, 1H), 1.74 (dd, J = 12.4, 6.3 Hz, 1H), 1.46 (app t, J = 12.2 Hz, 1H), 1.10 (s, 3H), 1.02 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 222.9, 220.8, 136.1, 130.0, 129.1, 126.6, 65.5, 55.0, 50.7, 44.4, 39.5, 38.5, 37.6, 34.1, 28.9, 24.8, 24.2, 19.4.

FTIR (thin film) ν_{max}: 3480, 2963, 2931, 2868, 1734, 1481, 1466, 1439, 1160, 1060, 1025, 742, 691, 432, 418, 410 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{20}H_{26}O_3S$, 369.1495; found, 369.1486.

TLC R_f= 0.49 (1:1 hexane:EtOAc).



(1R,1'R,2'S)-1-(iodomethyl)-4',4'-dimethyl-2'-((phenylthio)methyl)-[1,1'-bi(cyclopentane)]-2,3'-dione (169):[72]

A stirring solution of **167** (79 mg, 0.228 mmol, 1 equiv) in THF (4.6 mL) was cooled to 0 ℃ in an ice-water bath. In quick succession, imidazole (59 mg, 0.87 mmol, 3.8 equiv), Ph_3P (163 mg, 0.62 mmol, 2.7 equiv) and finally I_2 (150 mg, 0.59 mmol, 2.6 equiv) were added. The reaction was allowed to warm to room temperature and stirred for 14 h. The reaction was quenched with saturated aqueous sodium thiosulfate and extracted thrice with Et_2O. The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 7 by 4 cm silica gel column and eluted with 5% (0.15 L) and then 10% (0.15 L) and finally 15% (0.3 L) EtOAc/hexane, generating 68 9 mL fractions. Fractions 43-63 were combined and concentrated at reduced pressure to give **169** (40.5 mg, 88 μmol, 39%) as a yellow oil.

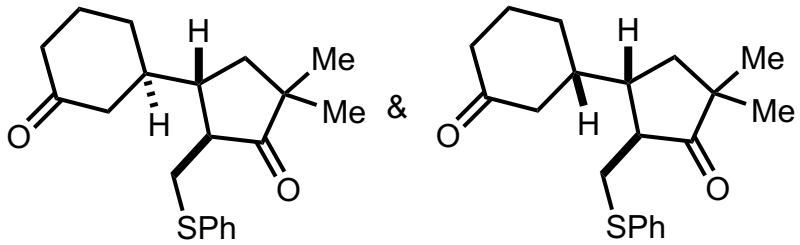
^{1}HNMR (400 MHz; $CDCl_3$) δ: 7.40 – 7.36 (m, 2H), 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 3.45 – 3.39 (m, 2H), 3.30 – 3.25 (m, 2H), 2.64 (td, J = 11.7, 6.4 Hz, 1H), 2.43 – 2.33 (m, 2H), 2.29 – 2.19 (m, 1H), 2.19 – 2.05 (m, 2H), 2.05 – 1.90 (m, 2H), 1.87 (dd, J = 12.5, 6.4 Hz, 1H), 1.72 (app t, J = 12.2 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 220.2, 218.8, 136.0, 130.2, 129.2, 126.8, 53.1, 50.5, 44.3, 41.3, 38.9, 38.8, 34.6, 33.2, 24.7, 24.0, 18.8, 11.7.

FTIR (thin film) ν_{max}: 2961, 2927, 2867, 1736, 1481, 1466, 1438, 1402, 1382, 1261, 1210, 1146, 1096, 1057, 1025, 742, 691 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{20}H_{25}IO_2S$, 457.0693; found, 457.0687.

TLC R_f= 0.66 (3:2 hexane:EtOAc).



170a **170b**

(R)-3-((1S,2S)-4,4-dimethyl-3-oxo-2-((phenylthio)methyl)cyclopentyl)cyclohexan-1-one (170a) and

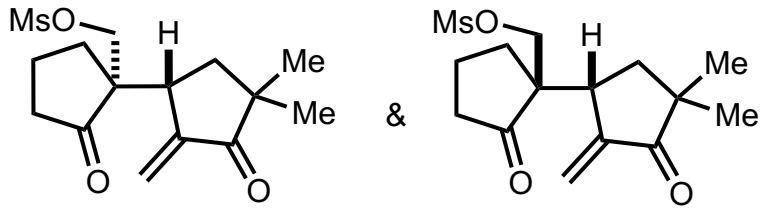
(S)-3-((1S,2S)-4,4-dimethyl-3-oxo-2-((phenylthio)methyl)cyclopentyl)cyclohexan-1-one (170b):[51]

To a stirring solution of **169** (19.5 mg, 43 μmol, 1.0 equiv) in PhMe (0.43 mL) at reflux in a copper shot bath was added a solution of $HSnBu_3$ (35 μL, 0.129 mmol, 3 equiv) and AIBN (3.5 mg, 22 μmol, 0.5 equiv) in PhMe (0.43 mL) dropwise via syringe over 10 minutes. The reaction was stirred at this temperature for 10 more minutes and then cooled to RT and concentrated at reduced pressure. The residue obtained was applied to a 7 by 3 cm silica gel column and eluted with 5% (0.1 L) and then 10% (0.1 L) and finally 20% (0.3 L) EtOAc/hexane, generating 58 9 mL fractions. Fractions 38-52 were combined and concentrated at reduced pressure to give **170ab** (13.1 mg, 40 μmol, 93%, 1:1 mix of inseparable diastereomers) as a clear, colorless oil.

FTIR (thin film, both compounds) ν_{max}: 2957, 2925, 2864, 1735, 1710, 1583, 1481, 1466, 1439, 1381, 1361, 1345, 1315, 1265, 1229, 1196, 1157, 1087, 1070, 1055, 1025, 1000, 978, 954, 869, 741, 692, 510, 474 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{20}H_{26}O_2S$, 331.1726; found, 331.1720.

TLC R_f= 0.22 (4:1 hexane:EtOAc).



171a **171b**

((1S,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentan)]-1-yl)methyl methanesulfonate (171a) and ((1R,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentan)]-1-yl)methyl methanesulfonate (171b):[53]

A stirring solution of 1:2.4 **164a** and **164b** (2.56 g, 10.83 mmol, 1 equiv) and DMAP (66 mg, 0.54 mmol, 5 mol %) in CH_2Cl_2 (217 mL) in a 500 mL recovery flask was cooled to 0 ℃ in an ice-water bath. Et_3N (1.96 mL, 14.08 mmol, 1.3 equiv) was added via syringe, followed by the dropwise addition of MsCl (1.09 mL, 14.08 mmol, 1.3 equiv) via syringe. The reaction was stirred at 0 ℃ for 3 h and then poured into 2N HCl (0.15 L). The layers were separated and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was loaded onto a 12 by 5 cm silica plug and eluted with 25% (1 L) and then 50% (0.75 L) EtOAc/hexane, producing five 100 mL fractions and 49 24 mL fractions. Of the final 49 fractions, fractions 21-39 were combined and concentrated at reduced pressure to give a 1:2.4 mixture of **171a**:**171b** (2.91 g, 9.21 mmol, 85% yield). The diastereomers were separated at this stage by successive rounds of purification, a representative example of which follows:

Two 120 gram silica cartridges (20 μM mesh) were connected in series to an Interchim puriflash system and packed in hexane (flow rate=80 mL/min). Then, a 1.50 gram sample of a 2:1 mixture of **171b:171a** dissolved in minimal CH_2Cl_2 was loaded onto the top of the upper column. The material was eluted using a linear gradient from 0% to 50% EtOAc/hexane over 60 minutes at a flow rate of 45 mL/min and then eluted with 50% EtOAc/hexane at a flow rate of 45 mL/min for 12 minutes. Presence of the products was evidenced by UV detection (λ=254 nm). The process generated 132 25 mL fractions. Fractions 116-125 were assayed for purity using the same analytical HPLC method as described for the previous compounds. The two compounds had the following retention times according to this method: **171a** retention time=3.94 min and **171b** retention time=3.87 min. Overall, fractions 109-115 were pure **171a**, 120-132 were pure **171b**, and 116-119 were mixed. Fractions 116-119 were concentrated at reduced pressure to give 450 mg of mixed product, which was subjected to the exact same protocol as was just described. At the conclusion of these two runs, 421 mg of **171a** were isolated, 949 mg of **171b** were isolated, and only 20 mg remained mixed.

((1S,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentan)]-1-yl)methyl methanesulfonate (171a)

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.22 (d, J = 3.2 Hz, 1H), 5.57 (d, J = 2.8 Hz, 1H), 4.42 (d, J = 9.7 Hz, 1H), 4.36 (d, J = 9.7 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.98 (s, 3H), 2.44 – 2.27 (m, 2H), 2.27-2.14 (m, 1H), 2.05 – 1.90 (m, 3H), 1.84 (dd, J = 12.3, 7.6 Hz, 1H), 1.44 (app t, J = 12.0 Hz, 1H), 1.13 (s, 3H), 1.01 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 219.0, 208.9, 143.5, 121.4, 72.2, 53.6, 44.2, 39.3, 39.1, 38.2, 37.3, 28.8, 24.7, 23.6, 19.2.

FTIR (thin film) ν_{max}: 2964, 2871, 1725, 1631, 1466, 1407, 1354, 1260, 1198, 1173, 1110, 1050, 1036, 953, 882, 855, 813, 734, 616, 590, 528, 477 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{15}H_{22}O_5S$, 337.1080; found, 337.1075.

TLC R_f= 0.45 (1:1 hexane:EtOAc).

((1R,1'R)-4',4'-dimethyl-2'-methylene-2,3'-dioxo-[1,1'-bi(cyclopentan)]-1-yl)methyl methanesulfonate(171b):

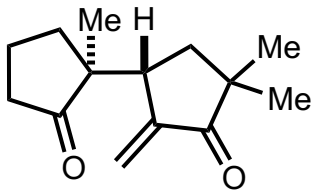
^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.17 (d, J = 3.2 Hz, 1H), 5.10 (d, J = 2.8 Hz, 1H), 4.22 (m, 2H), 3.32 (ddt, J = 11.1, 8.1, 3.0 Hz, 1H), 3.00 (s, 3H), 2.54 – 2.43 (m, 1H), 2.36 – 2.25 (m, 1H), 2.07 – 1.89 (m, 5H), 1.46 (dd, J = 12.7, 11.3 Hz, 1H), 1.15 (s, 3H), 1.02 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 219.6, 209.1, 143.2, 121.5, 72.0, 54.8, 44.4, 39.6, 39.2, 38.4, 37.6, 27.8, 25.1, 23.4, 19.0.

FTIR (thin film) ν_{max}: 2963, 2870, 1725, 1631, 1466, 1410, 1354, 1275, 1255, 1173, 1110, 1053, 955, 883, 855, 827, 734, 663, 648, 624, 590, 528, 479, 448 cm^{-1}.

HRMS-APCI-TOF (m/z): $[M+Na]^+$ calculated for $C_{15}H_{22}O_5S$, 337.1080; found, 337.1075.

TLC R_f= 0.45 (1:1 hexane:EtOAc).



(1S,1'R)-1,4',4'-trimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (172):

To a stirring solution of 171a (380 mg, 1.21 mmol, 1.0 equiv) in THF (24 mL) was added LAH (6.1 mL, 1M in THF, 5.0 equiv) at room temperature. The reaction was placed in a 45 ℃ copper shot bath and stirred for 6 h. The reaction was cooled to 0 ℃ in an ice-water bath and quenched via careful addition of saturated aqueous sodium bicarbonate. The reaction was then poured into a separatory funnel containing more saturated aqueous sodium bicarbonate and EtOAc and the layers were separated. The aqueous layer was extracted twice more with EtOAc, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was solvated in CH_2Cl_2 (24 mL) and cooled to 0 ℃ in an ice-water bath. DMP (2.05 g, 4.18 mmol, 4.0 equiv) was added, and the reaction was maintained at 0 ℃ for one hour. The bath was removed, and the reaction was stirred at RT for 2 h. The reaction was quenched with saturated aqueous sodium thiosulfate and the layers were separated. The aqueous layer was extracted twice more with CH_2Cl_2, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to an 8 by 4 cm silica gel column which was eluted with 5% (0.25 L) and then 10% (0.5 L) EtOAc/hexane, generating 37 20 mL fractions. Fraction 24 was concentrated individually for full characterization data. Overall, fractions 22-35 were combined and concentrated at reduced pressure to give **172** (220 mg, 0.96 mmol, 79%, ca 70% pure) as a clear, colorless oil.

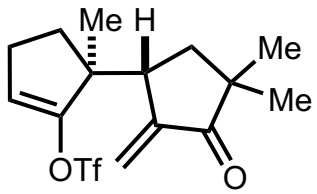
^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.18 (d, J = 3.3 Hz, 1H), 5.64 (dt, J = 2.4, 1.1 Hz, 1H), 3.05 (dddd, J = 12.2, 7.6, 3.2, 1.2 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.19 – 2.10 (m, 1H), 2.01 – 1.93 (m, 2H), 1.88 – 1.81 (m, 3H), 1.32 (app t, J = 11.7 Hz, 1H), 1.20 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 221.9, 210.4, 145.0, 120.9, 50.9, 44.3, 41.7, 38.5, 38.4, 33.3, 25.0, 23.7, 21.1, 18.7.

FTIR (thin film) ν_{max}: 2961, 2929, 2869, 1726, 1630, 1458, 1407, 1381, 1362, 1259, 1196, 1165, 1109, 1067, 1050, 1009, 942, 801, 547, 516 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{20}O_2$, 221.1537; found, 221.1536.

TLC R_f= 0.39 (4:1 hexane:EtOAc).



(1S,1'S)-1,4',4'-trimethyl-2'-methylene-3'-oxo-[1,1'-bi(cyclopentan)]-2-en-2-yl trifluoromethanesulfonate(173):[56]

To a stirring room temperature solution of **172** (189 mg, 0.82 mmol, 1.0 equiv) and DTBMP (674 mg, 3.28 mmol, 4.0 equiv) in CH_2Cl_2 (4.1 mL) was added Tf_2O (0.55 mL, 3.28 mmol, 4.0 equiv) via syringe. After stirring at room temperature for 21 h, the reaction was poured into a separatory funnel containing saturated aqueous sodium bicarbonate and CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to an 11 by 5 cm silica gel column and eluted with 20% (0.3 L), then 30% (0.3 L), then 40% (0.3 L) and finally 50% (0.75L) CH_2Cl_2/hexane, generating 5 100 mL and then 54 20 mL fractions. Of these last 54 fractions, fraction 24 was concentrated individually for full characterization data. Then, 32-52 were combined and concentrated at reduced pressure to give **173** (156 mg, 0.44 mmol, 54%, ca 70% pure) as a clear, colorless oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.18 (d, J = 3.2 Hz, 1H), 5.63 (t, J = 2.6 Hz, 1H), 5.48 (d, J = 2.8 Hz, 1H), 2.92 (ddt, J = 10.9, 7.7, 3.0 Hz, 1H), 2.43 (dddd, J = 16.6, 9.1, 6.2, 2.5 Hz, 1H), 2.31 (dddd, J = 16.6, 9.6, 3.9, 2.8 Hz, 1H), 1.89 – 1.82 (m, 2H), 1.75 (ddd, J = 13.5, 9.4, 3.8 Hz, 1H), 1.44 (s, 3H), 1.28 – 1.23 (m, 1H), 1.14 (s, 3H), 1.05 (s, 3H).

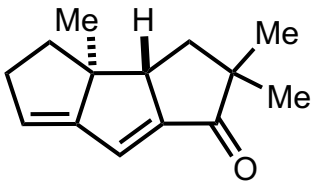
^{13}CNMR (101 MHz; $CDCl_3$) δ: 210.2, 153.1, 144.9, 121.6, 120.1, 117.0, 113.6, 49.4, 44.3, 43.3, 38.8, 31.0, 25.9, 25.3, 25.0, 23.8.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.73.

FTIR (thin film) ν_{max}: 2964, 2931, 2869, 1729, 1658, 1633, 1459, 1421, 1382, 1333, 1250, 1211, 1141, 1047, 946, 926, 910, 853, 608, 517 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{15}H_{19}F_3O_4S$, 353.1029; found, 353.1030.

TLC R_f= 0.33 (9:1 hexane:EtOAc).



(3aS,3bS)-2,2,3b-trimethyl-2,3,3a,3b,4,5-hexahydro-1H-cyclopenta[a]pentalen-1-one (174):

A recovery flask containing **173** (156 mg, ca 70% pure, 0.44 mmol assumed, 1 equiv assumed) and a stir bar was charged with $(Ph_3P)_4Pd^0$ (103 mg, 89 μmol, 0.2 equiv). The flask was evacuated and backfilled thrice with nitrogen, and ACN (8.8 mL) was added, followed by Et_3N (0.31 mL, 2.22 mmol, 5.0 equiv), both via syringe. The resulting mixture was capped, sealed with teflon tape and parafilm, and placed in a 60 ℃ copper shot bath with stirring for 14 h. The reaction was cooled to room temperature and poured into saturated aqueous sodium bicarbonate and Et_2O. The layers were shaken and separated, and the aqueous layer was extracted twice more with Et_2O. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 6 by 4 cm silica gel column and eluted with 50% (0.1 L) and then 100% (0.3 L) CH_2Cl_2/hexane, generating 32 12 mL fractions. Fractions 11-22 were combined and concentrated at reduced pressure to give **174** (47.8 mg, 0.23 mmol, 53%) as a yellow oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.71 (d, J = 3.2 Hz, 1H), 5.65 (t, J = 2.6 Hz, 1H), 3.05 – 2.94 (m, 1H), 2.88 – 2.76 (m, 1H), 2.61 (dddt, J = 16.3, 5.6, 3.7, 1.9 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.77 (dd, J = 12.2, 7.3 Hz, 1H), 1.64 (t, J = 12.1 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 4H), 0.92 (s, 3H).

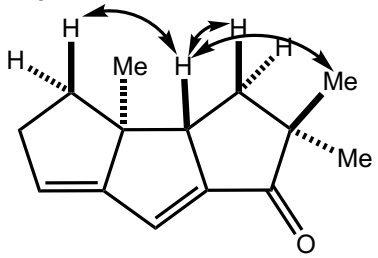
^{13}CNMR (101 MHz; $CDCl_3$) δ: 208.4, 163.6, 154.8, 125.6, 122.4, 60.0, 51.6, 51.6, 38.4, 36.9, 36.9, 25.0, 24.4, 18.9.

FTIR (thin film) ν_{max}: 2956, 2930, 2865, 1739, 1704, 1579, 1458, 1379, 1367, 1296, 1266, 1186, 1172, 1144, 1125, 1108, 1095, 992, 955, 938, 882, 789, 781, 658, 476 cm^{-1}.

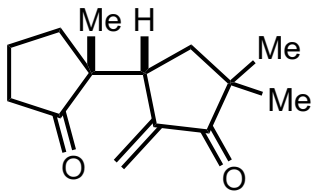
HRMS-APCI-TOF (m/z): $[M+H]^+$ calculated for $C_{14}H_{18}O$, 203.1430; found, 203.1428.

TLC R_f= 0.45 (9:1 hexane:EtOAc).

Key 1D NOE Correlations



174



(1R,1'R)-1,4',4'-trimethyl-2'-methylene-[1,1'-bi(cyclopentane)]-2,3'-dione (188):

To a stirring solution of **171b** (941 mg, 2.99 mmol, 1.0 equiv) in THF (60 mL) was added LAH (15 mL, 1M in THF, 5.0 equiv) at room temperature. The reaction was placed in a 45 ℃ copper shot bath and stirred for 6 h. The reaction was cooled to 0 ℃ in an ice-water bath and quenched via careful addition of saturated aqueous sodium bicarbonate. The reaction was then poured into a separatory funnel containing more saturated aqueous sodium bicarbonate and EtOAc and the layers were separated. The aqueous layer was extracted twice more with EtOAc, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was solvated in CH_2Cl_2 (60 mL) and cooled to 0 ℃ in an ice-water bath. DMP (5.07 g, 11.96 mmol, 4.0 equiv) was added, and the reaction was maintained at 0 ℃ for one hour. The bath was removed, and the reaction was stirred at RT for 2 h. The reaction was quenched with saturated aqueous sodium thiosulfate and the layers were separated. The aqueous layer was extracted twice more with CH_2Cl_2, and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to an 10 by 5 cm silica gel column which was eluted with 5% (0.5 L) and then 10% (1.0 L) EtOAc/hexane, generating 58 24 mL fractions. Fractions 29-42 were combined and concentrated at reduced pressure to give 188 (448 mg, 1.95 mmol, 65%) as a clear, colorless oil.

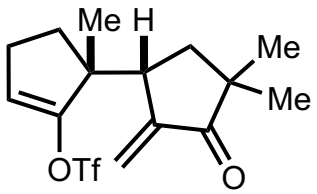
^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.13 (d, J = 3.3 Hz, 1H), 5.00 (d, J = 2.9 Hz, 1H), 3.27 (ddt, J = 11.3, 8.0, 3.1 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.23 – 2.11 (m, 1H), 2.01 – 1.95 (m, 2H), 1.92 – 1.85 (m, 2H), 1.68 – 1.62 (m, 1H), 1.39 (t, J = 12.1 Hz, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).

^{13}CNMR (101 MHz; $CDCl_3$) δ: 223.0, 210.3, 144.6, 120.9, 51.9, 44.4, 41.7, 38.8, 38.7, 30.9, 25.0, 23.5, 21.6, 18.6.

FTIR (thin film) ν_{max}: 2961, 2927, 2870, 1726, 1631, 1458, 1409, 1251, 1213, 1054, 1035, 1010, 940 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{20}O_2$, 221.1536; found, 221.1536.

TLC R_f= 0.39 (4:1 hexane:EtOAc).



(1R,1'S)-1,4',4'-trimethyl-2'-methylene-3'-oxo-[1,1'-bi(cyclopentan)]-2-en-2-yl trifluoromethanesulfonate(175):[56]

To a stirring room temperature solution of **188** (448 mg, 1.95 mmol, 1.0 equiv) and DTBMP (1.60 g, 7.78 mmol, 4.0 equiv) in CH_2Cl_2 (9.7 mL) was added Tf_2O (01.31 mL, 7.78 mmol, 4.0 equiv) via syringe. After stirring at room temperature for 20 h, the reaction was poured into a separatory funnel containing saturated aqueous sodium bicarbonate and CH_2Cl_2. The layers were separated and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic fractions were dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 12 by 6 cm silica gel column and eluted with 20% (0.5 L), then 30% (0.5 L), then 40% (0.5 L) and finally 50% (1 L) CH_2Cl_2/hexane, generating 5 200 mL and then 60 24 mL fractions. Of these last 60 fractions, 32-52 were combined and concentrated at reduced pressure to give **175** (416 mg, 1.19 mmol, 61%) as a clear, slightly yellow oil.

^{1}HNMR (400 MHz; $CDCl_3$) δ: 6.21 (d, J = 3.2 Hz, 1H), 5.66 (t, J = 2.6 Hz, 1H), 5.46 (dd, J = 2.8, 0.7 Hz, 1H), 2.92 (ddt, J = 11.1, 7.9, 3.0 Hz, 1H), 2.41 (dddd, J = 16.5, 9.1, 6.3, 2.5 Hz, 1H), 2.25 (dddd, J = 16.4, 9.7, 3.6, 2.7 Hz, 1H), 1.95 (dd, J = 12.7, 8.0 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.64 (ddd, J = 13.0, 9.3, 3.6 Hz, 1H), 1.44 – 1.35 (m, 1H), 1.24 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H).

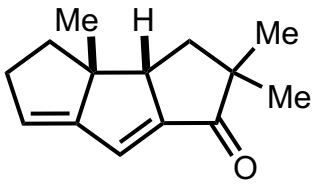
^{13}CNMR (101 MHz; $CDCl_3$) δ: 210.1, 153.3, 144.4, 121.6, 121.6, 120.2, 117.0, 114.3, 49.7, 44.3, 41.0, 39.0, 30.1, 25.6, 25.2, 23.9, 23.6.

^{19}FNMR (400 MHz; $CDCl_3$) δ: -73.62.

FTIR (thin film) ν_{max}: 2964, 2931, 2871, 1728, 1656, 1631, 1455, 1420, 1381, 1364, 1333, 1249, 1207, 1139, 1108, 1092, 1046, 1015, 946, 925, 911, 866, 840, 803, 767, 669, 606, 580, 515 cm^{-1}.

HRMS-ESI (m/z): $[M+NH_4]^+$ calculated for $C_{15}H_{19}F_3O_4S$, 370.1298; found, 370.1294.

TLC R_f= 0.33 (9:1 hexane:EtOAc).



(3aS,3bR)-2,2,3b-trimethyl-2,3,3a,3b,4,5-hexahydro-1H-cyclopenta[a]pentalen-1-one (176):

A recovery flask containing **175** (81 mg, 0.23 mmol, 1 equiv) and a stir bar was charged with $(Ph_3P)_4Pd^0$ (53 mg, 46 μmol, 0.2 equiv). The flask was evacuated and backfilled thrice with nitrogen, and THF (4.6 mL) was added, followed by Et_3N (0.16 mL, 1.15 mmol, 5.0 equiv), both via syringe. The resulting mixture was capped, sealed with teflon tape and parafilm, and placed in a 60 ℃ copper shot bath with stirring for 6 h. The reaction was cooled to room temperature and poured into saturated aqueous sodium bicarbonate and Et_2O. The layers were shaken and separated, and the aqueous layer was extracted twice more with Et_2O. The combined organic fractions were washed with water and brine, dried over sodium sulfate, filtered, and concentrated at reduced pressure. The residue obtained was applied to a 9 by 3 cm column and eluted with 50% (0.1 L) and then 100% (0.2 L) CH_2Cl_2/hexane, generating 36 9 mL fractions. Fractions 21-31 were combined and concentrated at reduced pressure to give **176** (11.6 mg, 58 μmol, 25%) as a slightly yellow oil.

^{1}HNMR (600 MHz; $CDCl_3$) δ: 6.63 (d, J = 2.2 Hz, 1H), 5.79 (dd, J = 3.9, 2.3 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.53 – 2.46 (m, 1H), 1.80 (dd, J = 11.4, 6.6 Hz, 1H), 1.77 – 1.74 (m, 2H), 1.23 (app t, J = 3.5 Hz, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H).

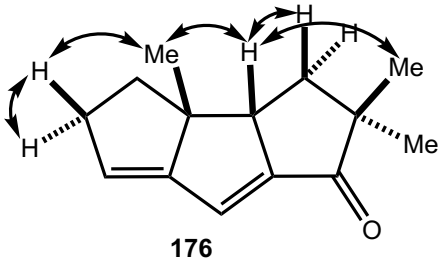
^{13}CNMR (101 MHz; $CDCl_3$) δ: 208.6, 161.0, 154.9, 126.0, 125.8, 52.6, 52.1, 48.8, 38.3, 36.5, 35.4, 26.5, 25.0, 24.5.

FTIR (thin film) ν_{max}: 2955, 2925, 2860, 1744, 1712, 1560, 1455, 1379, 1362, 1266, 1240, 1183, 1165, 1124, 1098, 1069, 1011, 978, 939, 888, 793 cm^{-1}.

HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{14}H_{18}O$, 203.1430; found, 203.1433.

TLC R_f= 0.45 (9:1 hexane:EtOAc).

Key 1D NOE Correlations



176

References

[1] Y. Qiu, W.-J. Lan, H.-J. Li, L.-P. Chen, *Molecules* **2018**, *23*, 2095.

[2] V. Hellwig, J. Dasenbrock, S. Schumann, W. Steglich, K. Leonhardt, T. Anke, *European Journal of Organic Chemistry* **1998**, *1998*, 73–79.

[3] G. A. Cordell, *Chemical Reviews* **1976**, *76*, 425–460.

[4] K. Hayano, Y. Ohfune, H. Shirahama, T. Matsumoto, *Helvetica Chimica Acta* **1981**, *64*, 1347–1364.

[5] F. Le Bideau, M. Kousara, L. Chen, L. Wei, F. Dumas, *Chemical Reviews* **2017**, *117*, 6110–6159.

[6] G. Mehta, A. Srikrishna, *Chemical Reviews* **1997**, *97*, 671–720.

[7] D. H. Hua, S. Venkataraman, R. A. Ostrander, G. Z. Sinai, P. J. McCann, M. J. Coulter, M. R. Xu, *The Journal of Organic Chemistry* **1988**, *53*, 507–515.

[8] G. Crisp, W. J. Scott, J. K. Stille, *Journal of the American Chemical Society* **1984**, *106*, 7500–7506.

[9] L. A. Paquette, K. E. Stevens, *Canadian Journal of Chemistry* **1984**, *62*, 2415–2420.

[10] J. Cossy, D. Belotti, J. Pete, *Tetrahedron Letters* **1987**, *28*, 4547–4550.

[11] D. P. Curran, M.-H. Chen, *Tetrahedron Letters* **1985**, *26*, 4991–4994.

[12] A. Meyers, S. Bienz, *The Journal of Organic Chemistry* **1990**, *55*, 791–798.

[13] T. Ohshima, K. Kagechika, M. Adachi, M. Sodeoka, M. Shibasaki, *Journal of the American Chemical Society* **1996**, *118*, 7108–7116.

[14] V. H. Rawal, A. Fabré, S. Iwasa, *Tetrahedron Letters* **1995**, *36*, 6851–6854.

[15] J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M. A. Pericas, A. Greene, *Journal of the American Chemical Society* **1990**, *112*, 9388–9389.

[16] S. Nozoe, J. Furukawa, U. Sankawa, S. Shibata, *Tetrahedron Letters* **1976**, *17*, 195–198.

[17] Y. Wang, Z.-X. Yu, *Accounts of Chemical Research* **2015**, *48*, 2288–2296.

[18] R. D. Little, G. L. Carroll, J. L. Petersen, *Journal of the American Chemical Society* **1983**, *105*, 928–932.

[19] Y. Wang, D. Mukherjee, D. Birney, K. Houk, *The Journal of Organic Chemistry* **1990**, *55*, 4504–4506.

[20] J. R. Stille, R. H. Grubbs, *Journal of the American Chemical Society* **1986**, *108*, 855–856.

[21] M. Iyoda, T. Kushida, S. Kitami, M. Oda, *Journal of the Chemical Society Chemical Communications* **1986**, 1049–1050.

[22] K. Ramig, M. A. Kuzemko, K. McNamara, T. Cohen, *The Journal of Organic Chemistry* **1992**, *57*, 1968–1969.

[23] S.-J. Shen, W.-D. Z. Li, *The Journal of Organic Chemistry* **2013**, *78*, 7112–7120.

[24] G. Majetich, J. Defauw, *Tetrahedron* **1988**, *44*, 3833–3849.

[25] H. Iida, Y. Yuasa, C. Kibayashi, *The Journal of Organic Chemistry* **1980**, *45*, 2938–2942.

[26] P. Vital, P.-O. Norrby, D. Tanner, *Synlett* **2006**, *2006*, 3140–3144.

[27] B. Åkermark, J. D. Oslob, U. Heuschert, *Tetrahedron Letters* **1995**, *36*, 1325–1326.

[28] H. Hagelin, J. D. Oslob, B. Åkermark, *Chemistry–A European Journal* **1999**, *5*, 2413–2416.

[29] H.-J. Knölker, N. O'Sullivan, *Tetrahedron* **1994**, *50*, 10893–10908.

[30] S. R. Kandukuri, J. A. Schiffner, M. Oestreich, *Angewandte Chemie International Edition* **2012**, *51*, 1265–1269.

[31] J. Milic, H. Schirmer, B. L. Flynn, M. Noltemeyer, A. de Meijere, *Synlett* **2002**, *2002*, 0875–0878.

[32] J.-C. Han, L.-Z. Liu, Y.-Y. Chang, G.-Z. Yue, J. Guo, L.-Y. Zhou, C.-C. Li, Z. Yang, *The Journal of Organic Chemistry* **2013**, *78*, 5492–5504.

[33] D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chemical Reviews* **2003**, *103*, 811–892.

[34] K. Nicolaou, Y.-L. Zhong, P. Baran, *Journal of the American Chemical Society* **2000**, *122*, 7596–7597.

[35] R. K. Boeckman, M. del Rosario Rico Ferreira, L. H. Mitchell, P. Shao, *Journal of the American Chemical Society* **2002**, *124*, 190–191.

[36] R. E. Shade, A. M. Hyde, J.-C. Olsen, C. A. Merlic, *Journal of the American Chemical Society* **2010**, *132*, 1202–1203.

[37] G. Nordmann, S. L. Buchwald, *Journal of the American Chemical Society* **2003**, *125*, 4978–4979.

[38] G.-B. Liu, J.-L. Xu, M. Geng, R. Xu, R.-R. Hui, J.-W. Zhao, Q. Xu, H.-X. Xu, J.-X. Li, *Bioorganic Medicinal Chemistry Letters* **2010**, *18*, 2864–2871.

[39] H. Bruss, H. Schuster, R. Martinez, M. Kaiser, A. P. Antonchick, H. Waldmann, *Beilstein Journal of Organic Chemistry* **2014**, *10*, 194–208.

[40] K. Nicolaou, M. H. Postema, C. F. Claiborne, *Journal of the American Chemical Society* **1996**, *118*, 1565–1566.

[41] K. Iyer, J. D. Rainier, *Journal of the American Chemical Society* **2007**, *129*, 12604–12605.

[42] J. R. Ludwig, P. M. Zimmerman, J. B. Gianino, C. S. Schindler, *Nature* **2016**, *533*, 374.

[43] J. Xu, X. Fu, R. Low, Y.-P. Goh, Z. Jiang, C.-H. Tan, *Chemical Communications* **2008**, 5526–5528.

[44] A. G. Myers, P. M. Harrington, E. Y. Kuo, *Journal of the American Chemical Society* **1991**, *113*, 694–695.

[45] H.-K. Yim, Y. Liao, H. N. Wong, *Tetrahedron* **2003**, *59*, 1877–1884.

[46] M. S. Reddy, H. Zhang, S. Phoenix, P. Deslongchamps, *Chemistry–An Asian Journal* **2009**, *4*, 725–741.

[47] T. Ling, C. Chowdhury, B. A. Kramer, B. G. Vong, M. A. Palladino, E. A. Theodorakis, *The Journal of Organic Chemistry* **2001**, *66*, 8843–8853.

[48] K. Yaji, M. Shindo, *Tetrahedron* **2010**, *66*, 9808–9813.

[49] M. E. Furrow, A. G. Myers, *Journal of the American Chemical Society* **2004**, *126*, 5436–5445.

[50] X.-J. Dai, C.-J. Li, *Journal of the American Chemical Society* **2016**, *138*, 5433–5440.

[51] T. Yoshizumi, H. Miyazoe, Y. Sugimoto, H. Takahashi, O. Okamoto, *Synthesis* **2005**, *2005*, 1593–1600.

[52] P. Dowd, S. C. Choi, *Journal of the American Chemical Society* **1987**, *109*, 6548–6549.

[53] J. F. King, *Accounts of Chemical Research* **1975**, *8*, 10–17.

[54] S. Krishnamurthy, H. C. Brown, *The Journal of Organic Chemistry* **1976**, *41*, 3064–3066.

[55] M. Hanack, G. Auchter, *Journal of the American Chemical Society* **1985**, *107*, 5238–5245.

[56] K. Michalak, J. Wicha, *The Journal of Organic Chemistry* **2011**, *76*, 6906–6911.

[57] D. L. Comins, A. Dehghani, C. J. Foti, S. P. Joseph, *Organic Syntheses* **1997**, 77.

[58] J. K. Tucker, M. D. Shair, *Organic Letters* **2019**, *21*, 2473–2476.

[59] K. F. McClure, S. J. Danishefsky, *Journal of the American Chemical Society* **1993**, *115*, 6094–6100.

[60] M. Köck, A. Grube, I. B. Seiple, P. S. Baran, *Angewandte Chemie International Edition* **2007**, *46*, 6586–6594.

[61] M. Elkin, S. M. Szewczyk, A. C. Scruse, T. R. Newhouse, *Journal of the American Chemical Society* **2017**, *139*, 1790–1793.

[62] T. Tahara, U. Streit, H. E. Pelish, M. D. Shair, *Organic Letters* **2017**, *19*, 1538–1541.

[63] P. Kok, P. J. De Clercq, M. E. Vandewalle, *The Journal of Organic Chemistry* **1979**, *44*, 4553–4557.

[64] C.-C. Li, C.-H. Wang, B. Liang, X.-H. Zhang, L.-J. Deng, S. Liang, J.-H. Chen, Y.-D. Wu, Z. Yang, *The Journal of Organic Chemistry* **2006**, *71*, 6892–6897.

[65] J.-Q. Yu, H.-C. Wu, E. Corey, *Organic Letters* **2005**, *7*, 1415–1417.

[66] J. A. Faraldos, J.-L. Giner, *The Journal of Organic Chemistry* **2002**, *67*, 4659–4666.

[67] N. Hashimoto, A. Kanda, *Organic Process Research Development* **2002**, *6*, 405–406.

[68] W. C. Still, M. Kahn, A. Mitra, *The Journal of Organic Chemistry* **1978**, *43*, 2923–2925.

[69] G. M. Sheldrick, *Acta Crystallographica Section A: Foundational Advances* **2014**, *70*, C1437.

[70] G. M. Sheldrick, *Acta Crystallographica Section C: Structural Chemistry* **2015**, *71*, 3–8.

[71] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. Howard, H. Puschmann, *Journal of Applied Crystallography* **2009**, *42*, 339–341.

[72] D. L. Clive, M. P. Pham, R. Subedi, *Journal of the American Chemical Society* **2007**, *129*, 2713–2717.

Appendix 1: Rationale to Pursue *ent*-Hyperforin

Background

An ongoing program in the lab at the time of my arrival was the development of truncated analogues of **1** to avoid the metabolic liabilities associated therewith while maintaining its efficacy against depression. The following section explores the rationale of this analogue program further and traces the evolution of my idea to render the unnatural enantiomer of **1** to address concerns of safety and mechanism of efficacy.

Depression Treatment Limitations

Major depressive disorder (MDD) affects about 6.7 percent of the U.S. population age 18 and older, and more than two-thirds of patients have an inadequate response to initial treatment with selective serotonin-reuptake inhibitors (SSRIs).[1,2] As such, physicians face the dilemma whether to increase dose, switch treatments, or add agents to augment the antidepressant effect of SSRIs. Augmentation comes with an increased risk for adverse events.[2] Furthermore, withdrawal symptoms after discontinuation of SSRIs are well-documented.[3] Therefore, given the widespread occurrence of MDD and the limitations of existing treatments, additional therapeutic options are needed.

Efficacy of St. John's Wort

In a systematic review of 29 studies encompassing 5,489 patients with mild to moderate depression, Linde et al. compared treatment with various extracts of SJW for 4 to 12 weeks to treatment with placebo or standard antidepressants (active comparators). Overall, SJW was superior to placebo, was as effective as standard antidepressants, and had fewer side effects than standard antidepressants.[4] Additionally, Fava et al. found that in patients with mild to moderate depression (n=135), SJW was significantly more effective than fluoxetine (Prozac) and showed a trend toward statistically significant superiority over placebo. The authors concluded that the "total evidence from the accumulated trials in Europe and the United States continues to suggest that SJW agents may offer antidepressant efficacy for some individuals with mild to moderate depression."[5]

Hyperforin is Responsible for the Efficacy of St. John's Wort

Preclinical studies performed with mice and rats showed that (1) hyperforin content of the SJW extacts administered correlated directly with antidepressive behavior and (2) pure hyperforin was superior to SJW as an antidepressant. Studies in the clinic were consistent with these preclinical *in vivo* models.[6,7] Laakmann et al. found that in patients with mild to moderate depression (n=147), those who received SJW containing a higher percent hyperforin experienced a larger reduction in depression.[8,9]

Hyperforin as a Protonophore for Clinical Efficacy

Protonophore activity may account for the antidepressant activity of hyperforin. Since the discovery that hyperforin is the chief antidepressant component of SJW, numerous studies have centered on elucidating its mechanism of action.[10] Experiments *in vitro* on isolated murine synaptosomes showed that hypeforin was able to inhibit the uptake of multiple neurotransmitters in a dose-dependent fashion.[11] Since most pharmaceutical antidepressants work through targeting the reuptake of only single neurotransmitters, hyperforin appeared to show potential for a novel mechanistic approach for the treatment of depression.

Hyperforin elevates intracellular sodium, which disrupts the sodium gradient needed for uptake of neurotransmitters.[12,13] In 2007, hyperforin was reported to elevate intracellular sodium by selective activation of transient receptor potential protein 6 (TRPC6), a nonselective cation channel, thereby providing a mechanism for the antidepressant activity of hyperforin.[14] More recently, in 2014, hyperforin was instead reported to act as a protonophore to inhibit neurotransmitter reuptake *in vitro*.[15] This effect of proton conductance appears to depend only on membrane potential and pH gradient and not on the presence of specific channel proteins including TRPC6.[14] Key antidepressant effects of proton shuttling by hyperforin across the plasma membrane and vesicles are:

• Increased intracellular Na^+, which inhibits neurotransmitter uptake by Na^+ co-transport. Decreased pH in the cytosol activates the plasma membrane Na^+/H^+ exchanger to pump protons out of the cell in exchange for sodium cations.

• Loss of an H^+ gradient in neurotransmitter vesicles, which impairs vesicular uptake, storage and release of neurotransmitters.

The Liability Associated with Hyperforin Administration

Hyperforin usage as an antidepressant is limited by the potential for adverse drug-drug interactions. Hyperforin binds directly to the pregnane X receptor (PXR), a transcription factor that regulates expression of CYP3A4 and other enzymes involved in xenobiotic metabolism (**Figure A1.1,** panel **A**).[16] Treatment of primary human hepatocytes with hyperforin induced CYP3A4 expression.[17] Additionally, CYP2C9 was induced when HepG2 cells were treated with hyperforin.[18] CYP3A4 and CYP2C9 metabolize 50% and 20% of all known drugs, respectively.[19] Furthermore, in a clinical study in healthy volunteers, administration of SJW dramatically altered the pharmacokinetics of probes for CYP3A4 and CYP2D6.[20] The prevalence of depression and various co-morbidities requiring pharmacological treatment increases with age, so CYP induction represents a serious limitation on usage of hyperforin, especially for elderly patients.

The Promise of *ent*-Hyperforin (*ent*-1)

Separation of the beneficial anti-depressant activity of hyperforin from its adverse PXR activation is necessary. Hyperforin has a clear safety limitation to its widespread use as an antidepressant–the chiral pairing between hyperforin and PXR. A proposed antidepressant mechanism of hyperforin, however, involves interaction with a non-chiral target, 'H^+', rather than a chiral target like PXR. Therefore, the enantiomer of hyperforin, ent-hyperforin (*ent*-**1**), will have the same protonophore activity as hyperforin but would be expected to have a different affinity for PXR. As shown in **Figure A1.1, panel B**, positioning *ent*-**1** in the same orientation as **1** in the PXR binding pocket would eliminate key hydrogen bonding and hydrophobic interactions (in red), particularly with the isopropyl ketone at C1 and the prenyl chains at C5 and C8.

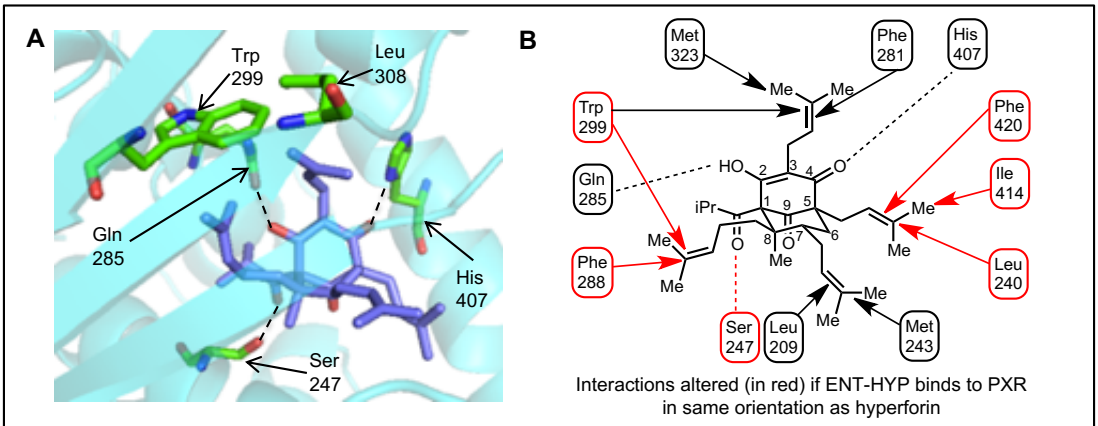


Figure A1.1. (**A**) Crystal structure of human PXR (cyan with certain residues in stick representation) in complex with hyperforin (purple, stick representation), with three hydrogen bonds (dashed lines) between the C1 isopropyl ketone and Ser247 and the vinylygous acid with Gln 285 and His 407. Nonpolar residues targeted for point mutation (Trp 299 and Leu 308) are also indicated. (**B**) Two dimensional rendering of the PXR-hyperforin interaction, showcasing all nonpolar interactions with the prenyl sidechains (barbed arrows) and the hydrogen-bonding network (dashed lines). Note that the vinylygous acid is the tautomer of structures drawn previously. Indicated in red are interactions that would be altered if ENT-HYP binds to PXR in the same orientation as hyperforin.

As precedent for enantiomeric compounds having different PXR affinities, only one enantiomer of the anticoagulant drug warfarin, R-warfarin, is associated with PXR and the upregulation of CYP3A4 and CYP2C9 mRNA target genes of PXR.[21] In addition, the affinity of hyperforin for PXR is sensitive to single PXR amino acid substitutions. For example, PXR (W299M) reduced hyperforin affinity by 3-fold and hyperforin had no observable affinity for PXR (L308F).[16,22] Each of these residues form key hydrophobic interactions with C3 and C8 substituents of **1**, but *ent*-**1** will not position substituents to maintain these contacts properly, thereby reducing affinity. Taken together, these results suggest that *ent*-**1** is not expected to have the same high affinity for PXR as **1**.

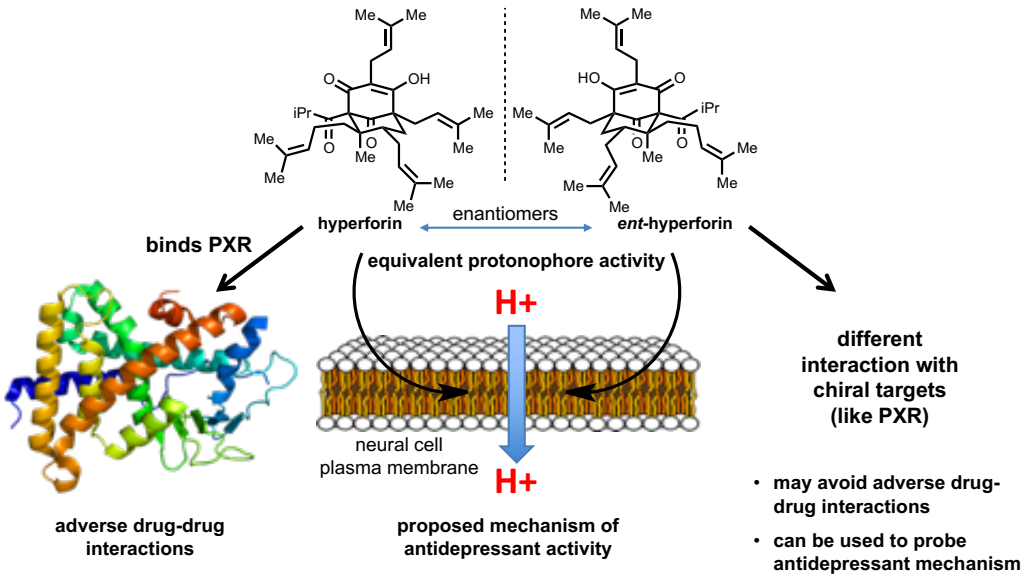


Figure A1.2. Overall project rationale. *Ent*-hyperforin is the mirror image of hyperforin. It will have equivalent protonophore activity as hyperforin but may avoid unfavorable PXR binding. We propose to synthesize and test *ent*-hyperforin for antidepressant activity and PXR binding, with the results guiding the discovery of hyperforin-like antidepressant leads with reduced PXR binding.

Ent-1 is not available from SJW or natural sources. Therefore, synthesis of *ent*-**1** could lead to a test of the protonophore mechanism for the antidepressant activity of **1**. (**Figure A1.2**) If it demonstrates hyperforin-like antidepressant activity *in vivo* and has reduced PXR binding, it will represent a highly attractive preclinical lead for treatment of depression.

Evaluation of *ent*-Hyperforin and Future Directions

The evaluation of the affinity of *ent*-**1** for human PXR *in vitro* was accomplished using a competitive binding assay (LanthaScreen TR-FRET PXR Competitive Binding Assay, ThermoFisher Scientific). Where the affinity of **1** in this assay was 108 nM, the affinity of *ent*-**1** was 717 nM, a seven-fold shift. Evaluation of *ent*-**1** in other *in vitro* or *in vivo* experiments would be a useful pursuit to ascertain whether a protonophore mechanism of action is implicated for the clinical efficacy of **1**.

References

[1] Kessler, R. C.; Chiu, W. T.; Demler, O.; Walters, E. E. *Archives of General Psychiatry* **2005**, *62*, 617–627.

[2] others,, et al. *Psychiatry Research* **2015**, *229*, 760–770.

[3] Fava, G. A.; Gatti, A.; Belaise, C.; Guidi, J.; Offidani, E. *Psychotherapy and Psychosomatics* **2015**, *84*, 72–81.

[4] Linde, K.; Berner, M. M.; Kriston, L. *Cochrane database of Systematic reviews* **2008**,

[5] Fava, M.; Alpert, J.; Nierenberg, A. A.; Mischoulon, D.; Otto, M. W.; Zajecka, J.; Murck, H.; Rosenbaum, J. F. *Journal of Clinical Psychopharmacology* **2005**, *25*, 441–447.

[6] Bhattacharya, S.; Chakrabarti, A.; Chatterjee, S. *Pharmacopsychiatry* **1998**, *31*, 22–29.

[7] Chatterjee, S.; Nöldner, M.; Koch, E.; Erdelmeier, C. *Pharmacopsychiatry* **1998**, *31*, 7–15.

[8] Laakmann, G.; Dienel, A.; Kieser, M. *Phytomedicine* **1998**, *5*, 435–442.

[9] Laakmann, G.; Schüle, C.; Baghai, T.; Kieser, M. *Pharmacopsychiatry* **1998**, *31*, 54–59.

[10] Chatterjee, S.; Bhattacharya, S.; Wonnemann, M.; Singer, A.; Müller, W. *Life Sciences* **1998**, *63*, 499–510.

[11] Müller, W.; Singer, A.; Wonnemann, M.; Hafner, U.; Rolli, M.; Schäfer, C. *Pharmacopsychiatry* **1998**, *31*, 16–21.

[12] Wonnemann, M.; Singer, A.; Müller, W. *Neuropsychopharmacology* **2000**, *23*, 188–197.

[13] Singer, A.; Wonnemann, M.; Müller, W. *Journal of Pharmacology and Experimental Therapeutics* **1999**, *290*, 1363–1368.

[14] Leuner, K.; Kazanski, V.; Müller, M.; Essin, K.; Henke, B.; Gollasch, M.; Harteneck, C.; Müller, W. E. *The FASEB Journal* **2007**, *21*, 4101–4111.

[15] Sell, T. S.; Belkacemi, T.; Flockerzi, V.; Beck, A. *Scientific Reports* **2014**, *4*, 7500.

[16] Watkins, R. E.; Maglich, J. M.; Moore, L. B.; Wisely, G. B.; Noble, S. M.; Davis-Searles, P. R.; Lambert, M. H.; Kliewer, S. A.; Redinbo, M. R. *Biochemistry* **2003**, *42*, 1430–1438.

[17] Moore, L. B.; Goodwin, B.; Jones, S. A.; Wisely, G. B.; Serabjit-Singh, C. J.; Willson, T. M.; Collins, J. L.; Kliewer, S. A. *Proceedings of the National Academy of Sciences* **2000**, *97*, 7500–7502.

[18] Chen, Y.; Ferguson, S. S.; Negishi, M.; Goldstein, J. A. *Journal of Pharmacology and Experimental Therapeutics* **2004**, *308*, 495–501.

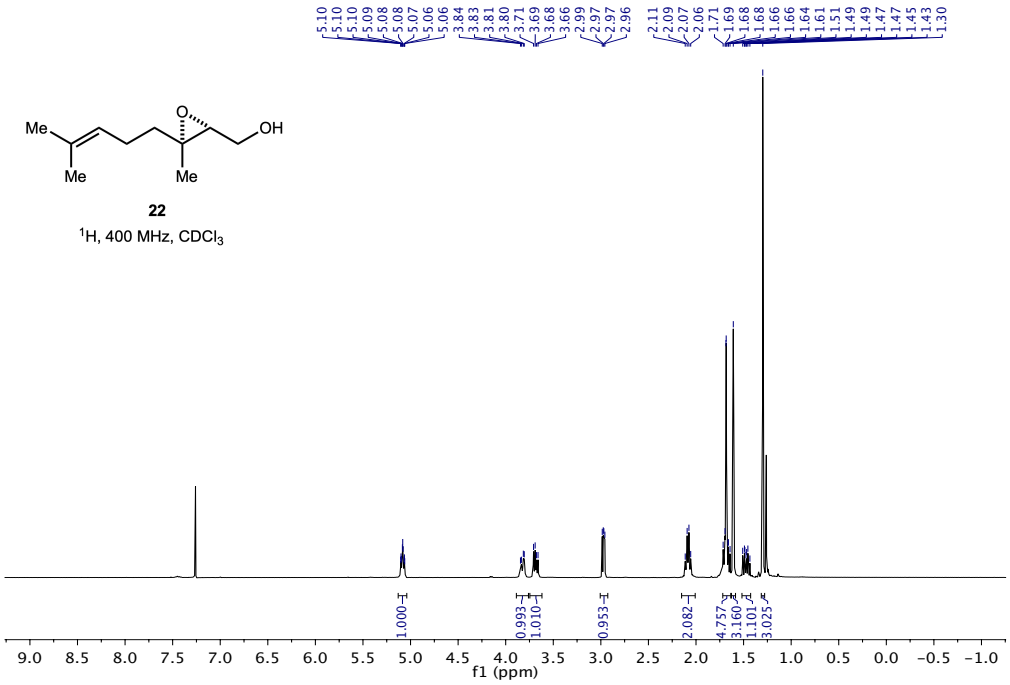
[19] Zanger, U. M.; Schwab, M. *Pharmacology & therapeutics* **2013**, *138*, 103–141.

[20] Markowitz, J. S.; Donovan, J. L.; DeVane, C. L.; Taylor, R. M.; Ruan, Y.; Wang, J.-S.; Chavin, K. D. *Jama* **2003**, *290*, 1500–1504.

[21] Rulcova, A.; Prokopova, I.; Krausova, L.; Bitman, M.; Vrzal, R.; Dvorak, Z.; Blahos, J.; Pavek, P. *Journal of Thrombosis and Haemostasis* **2010**, *8*, 2708–2717.

[22] Tirona, R. G.; Leake, B. F.; Podust, L. M.; Kim, R. B. *Molecular Pharmacology* **2004**, *65*, 36–44.

Appendix 2: Catalogue of Spectra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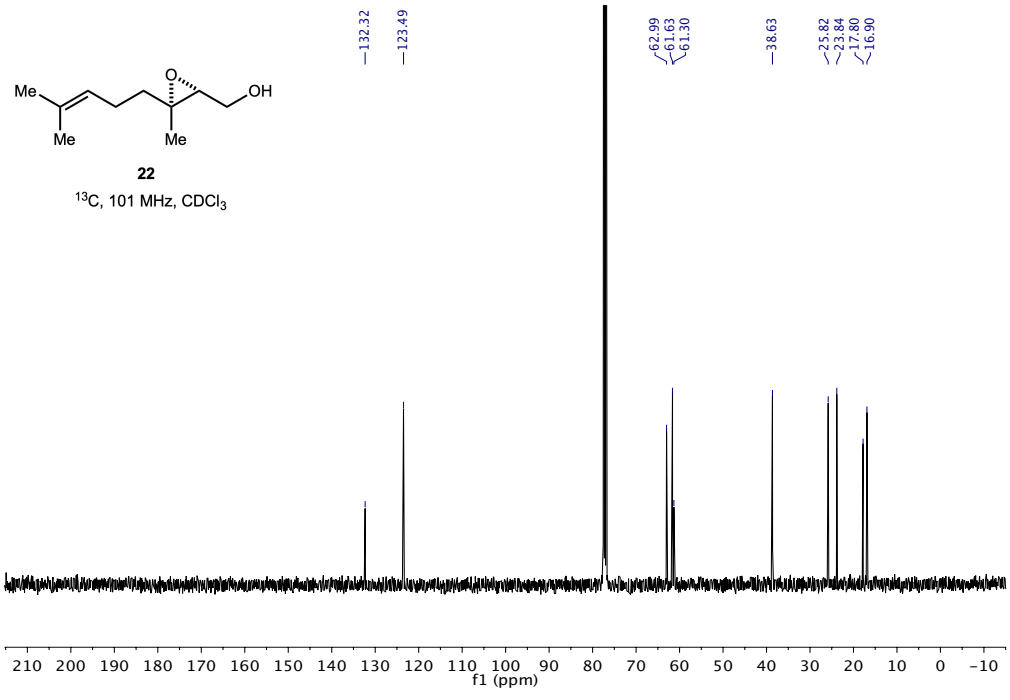
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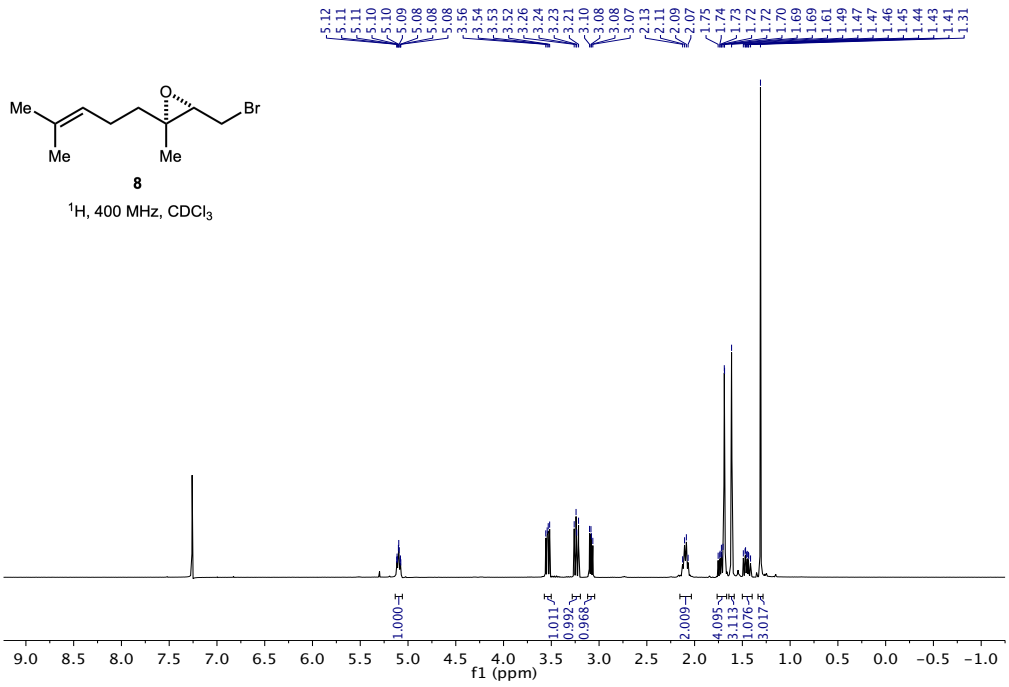
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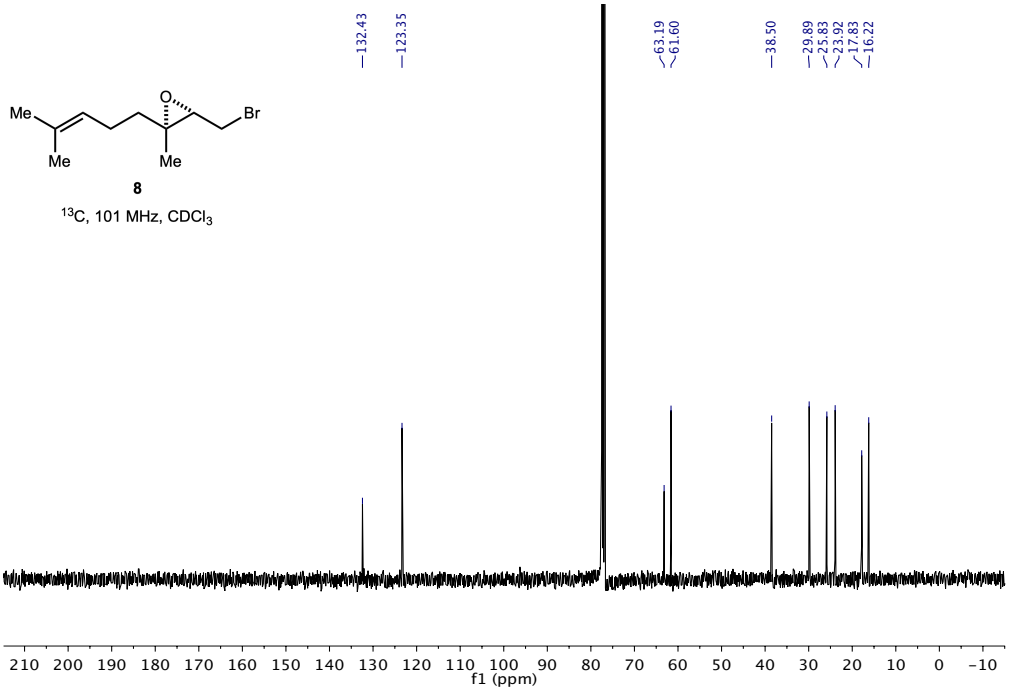
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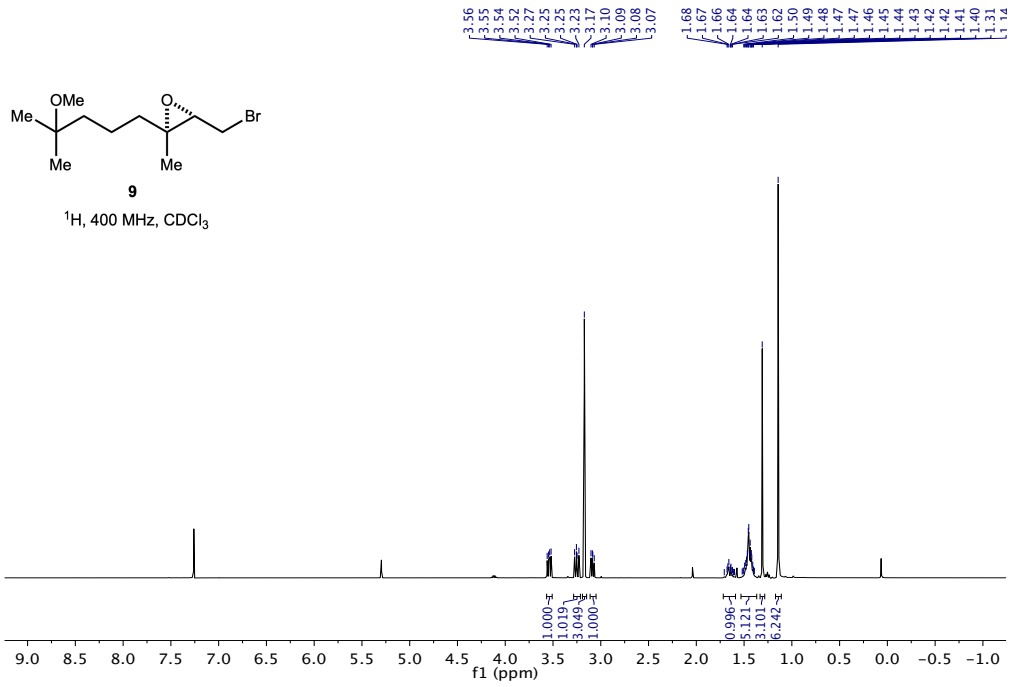
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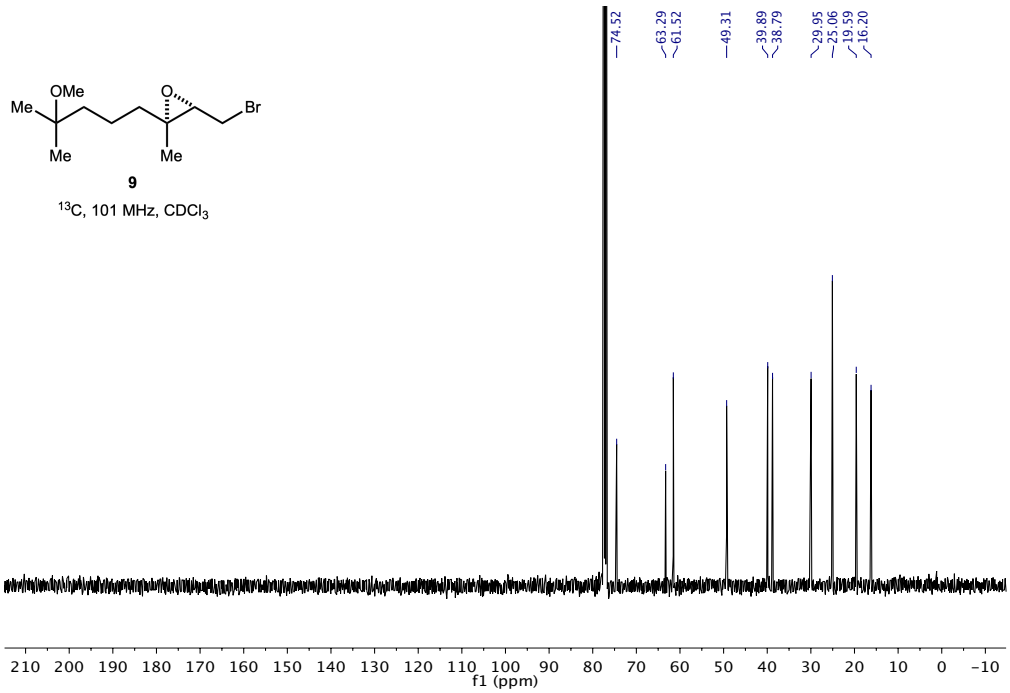
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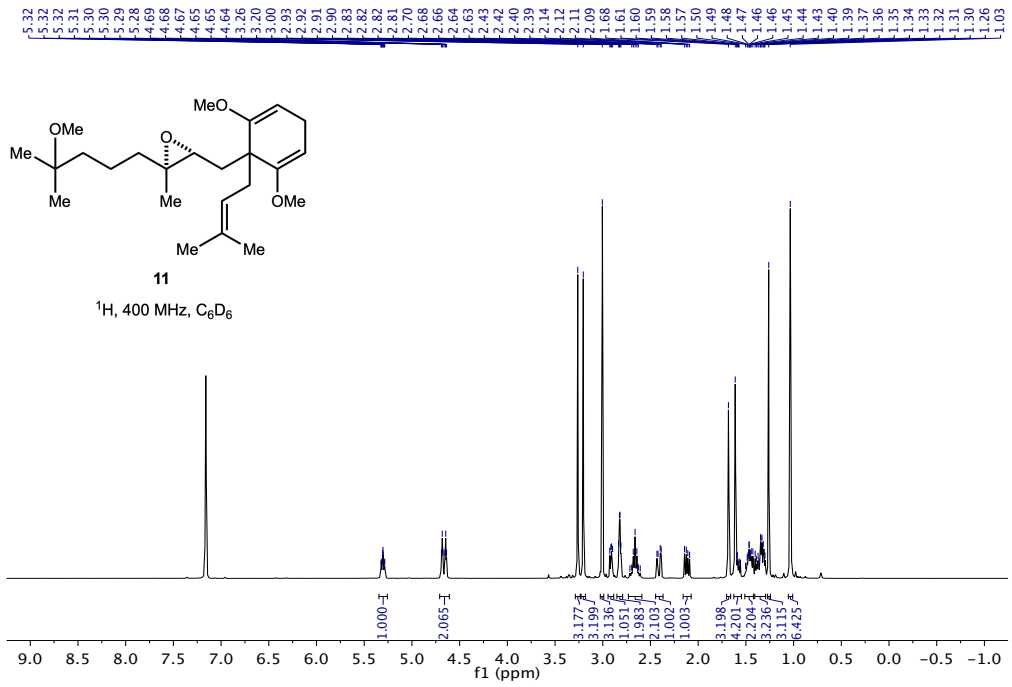
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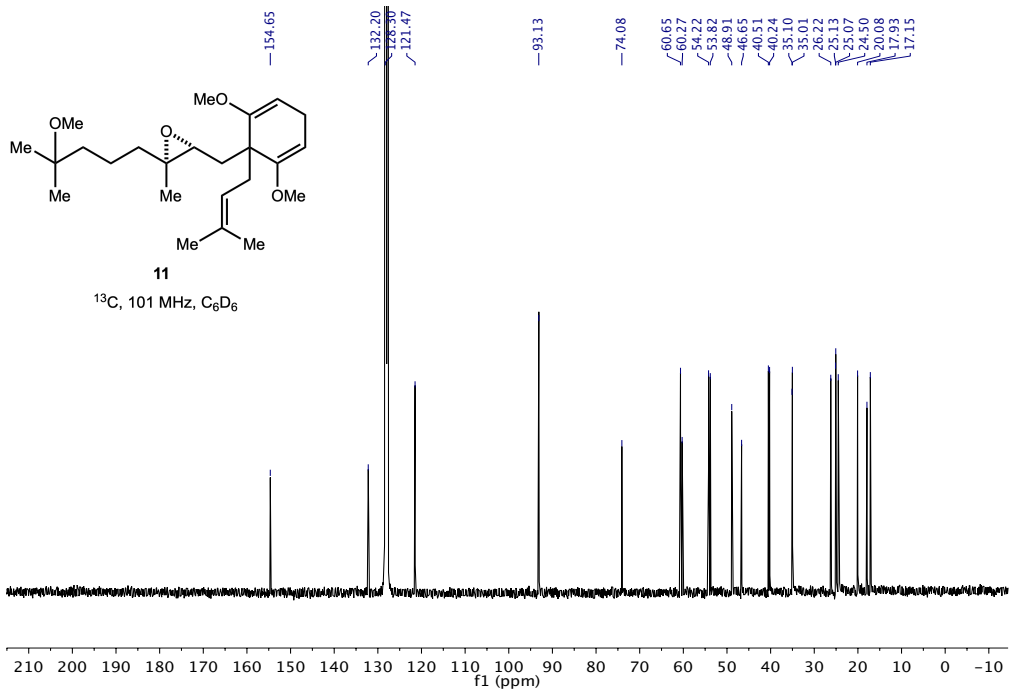
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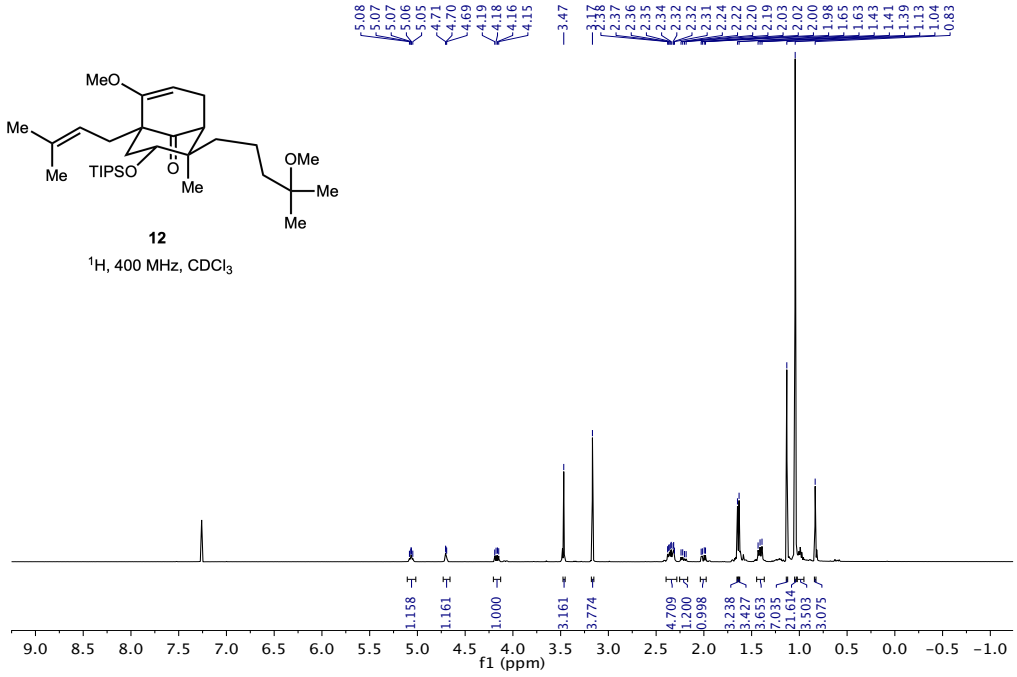
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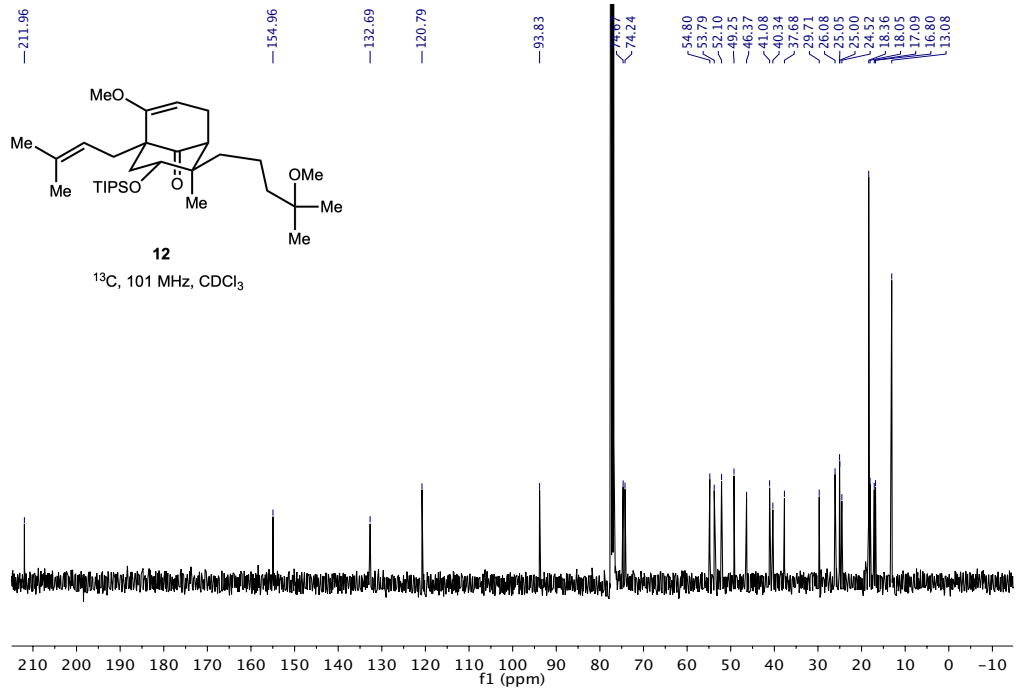
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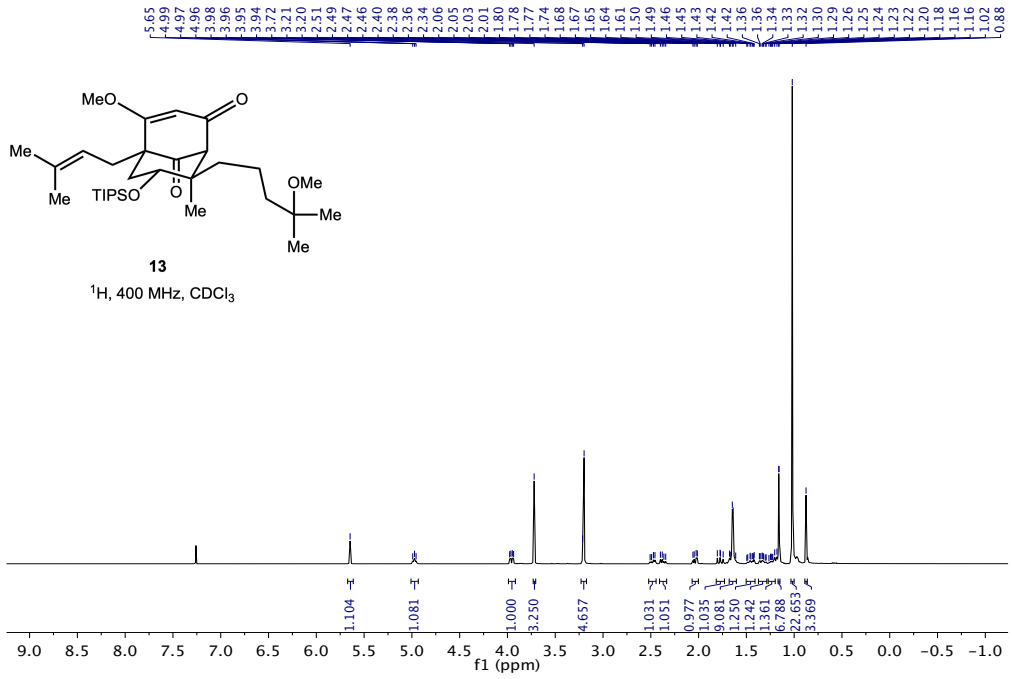
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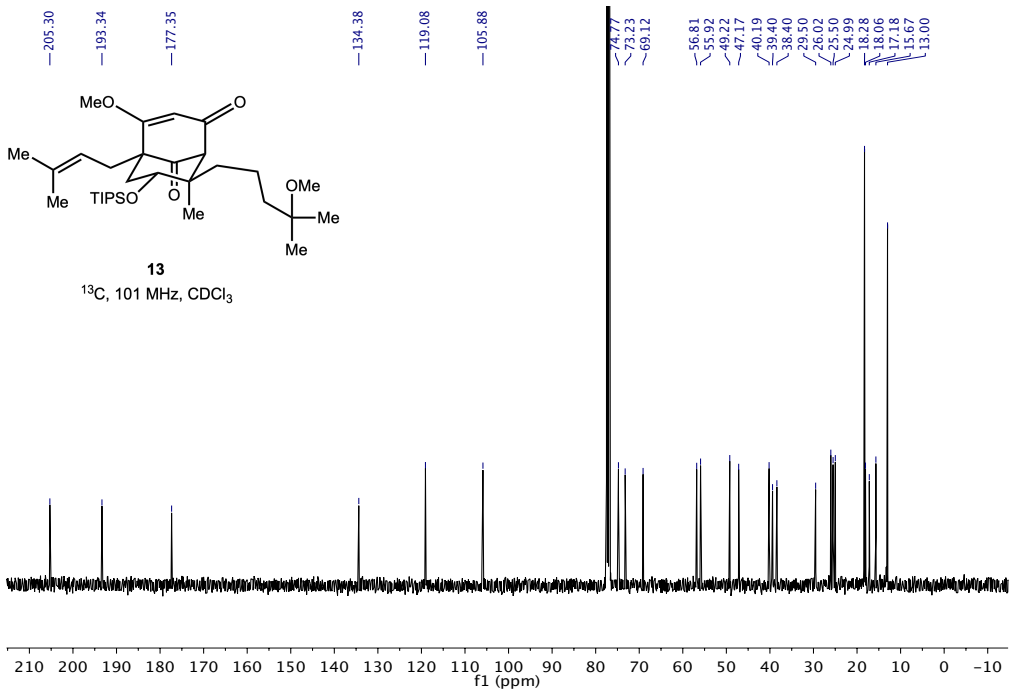
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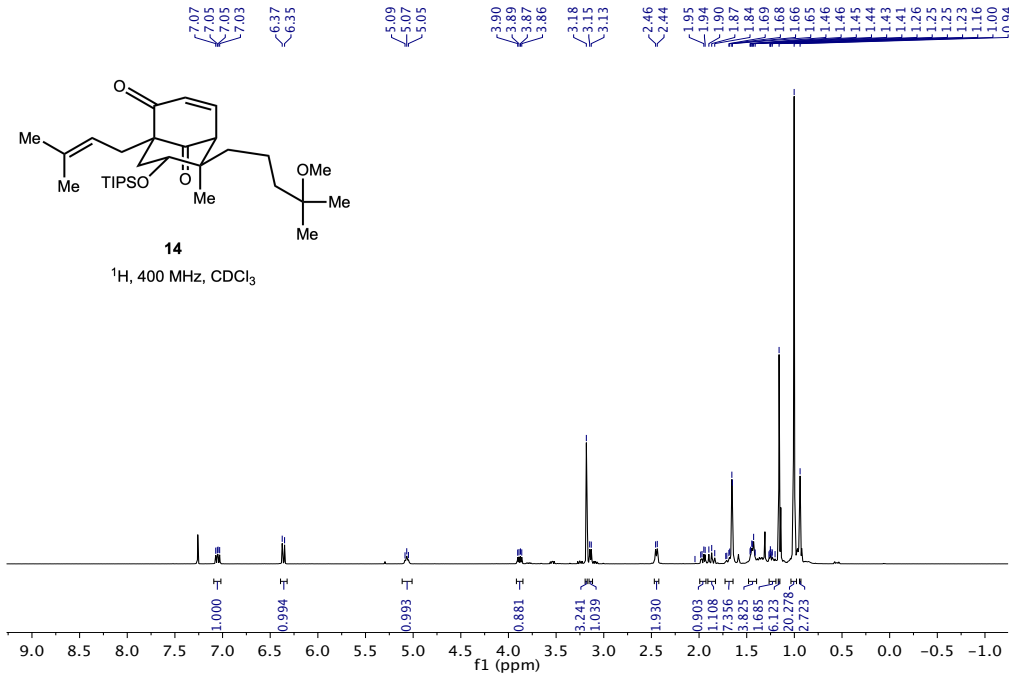
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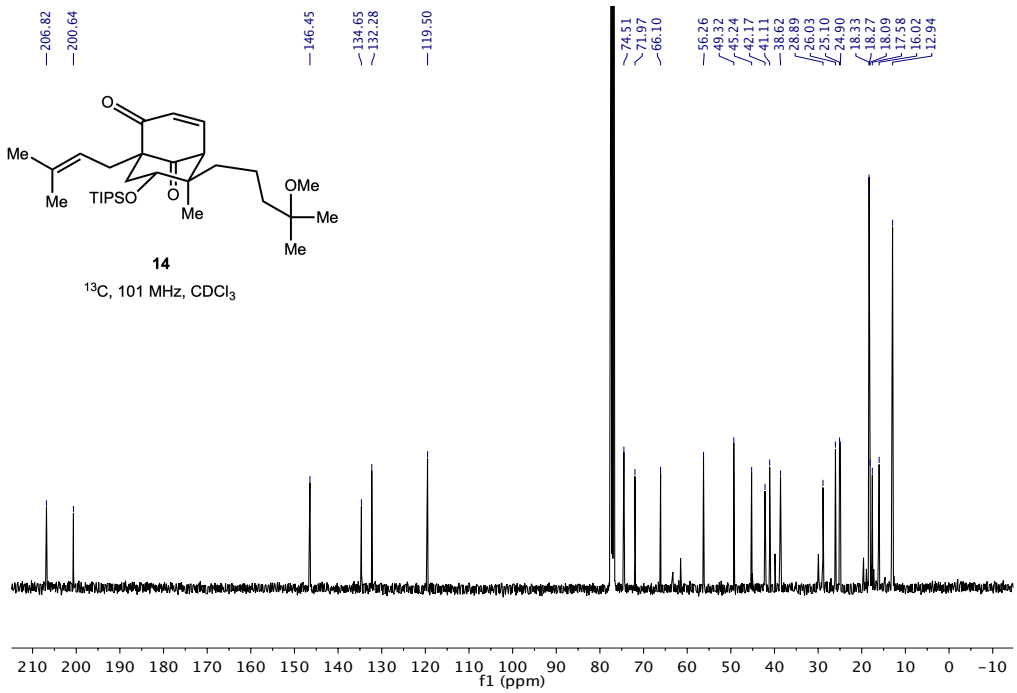
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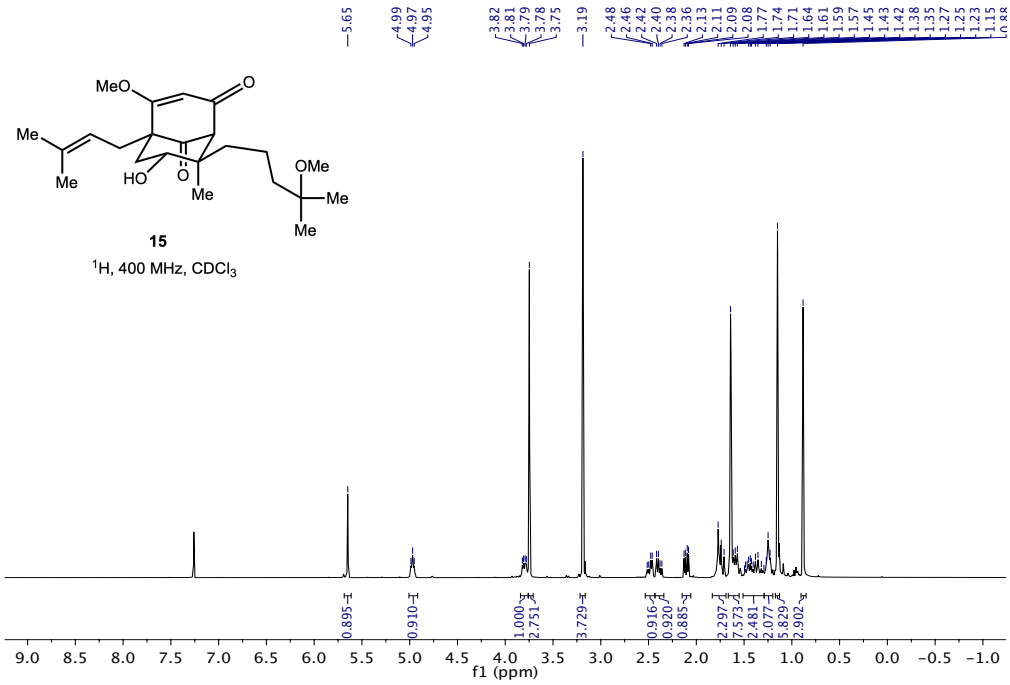
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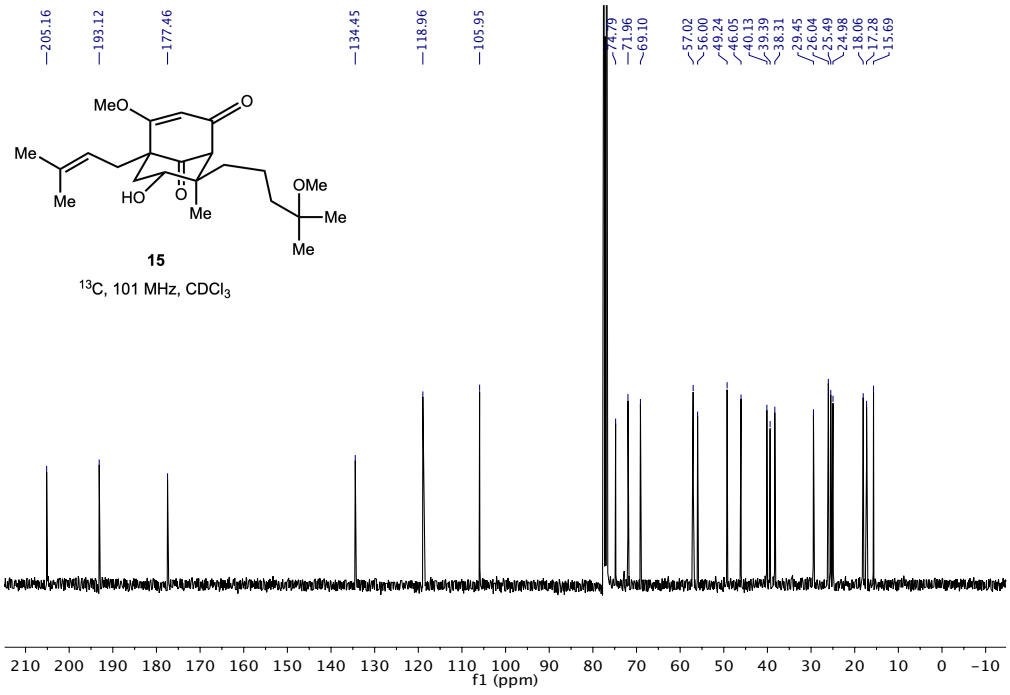
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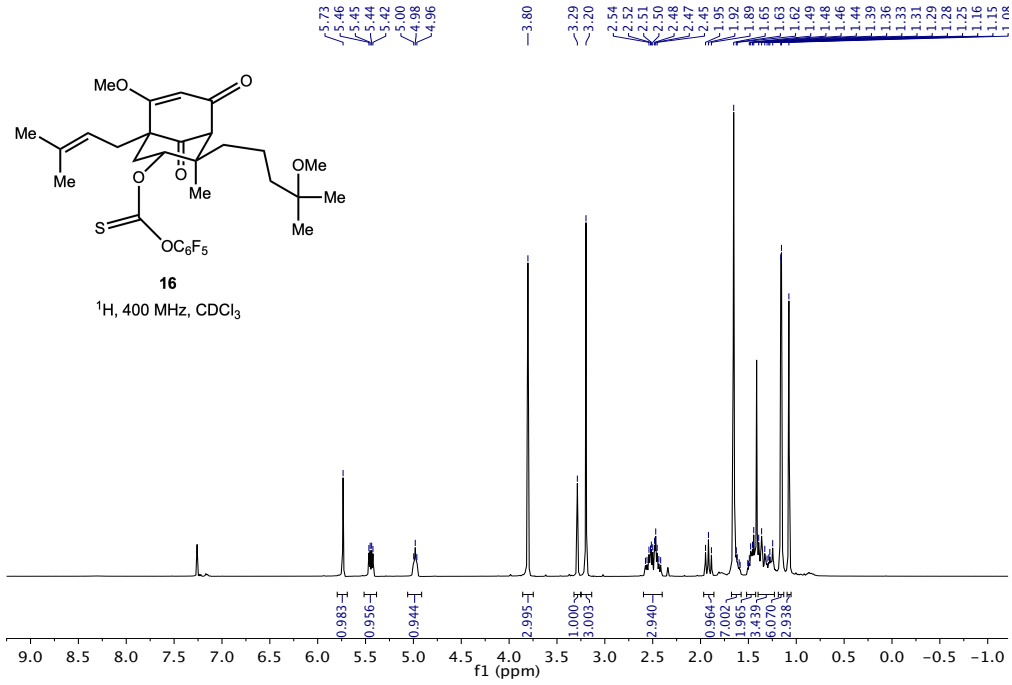
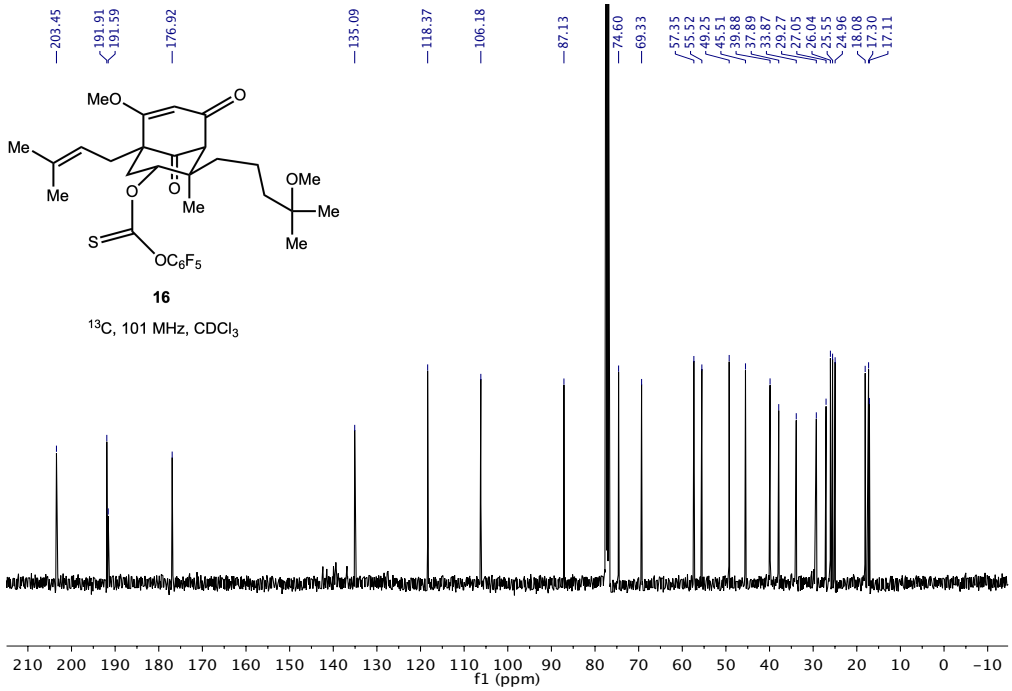
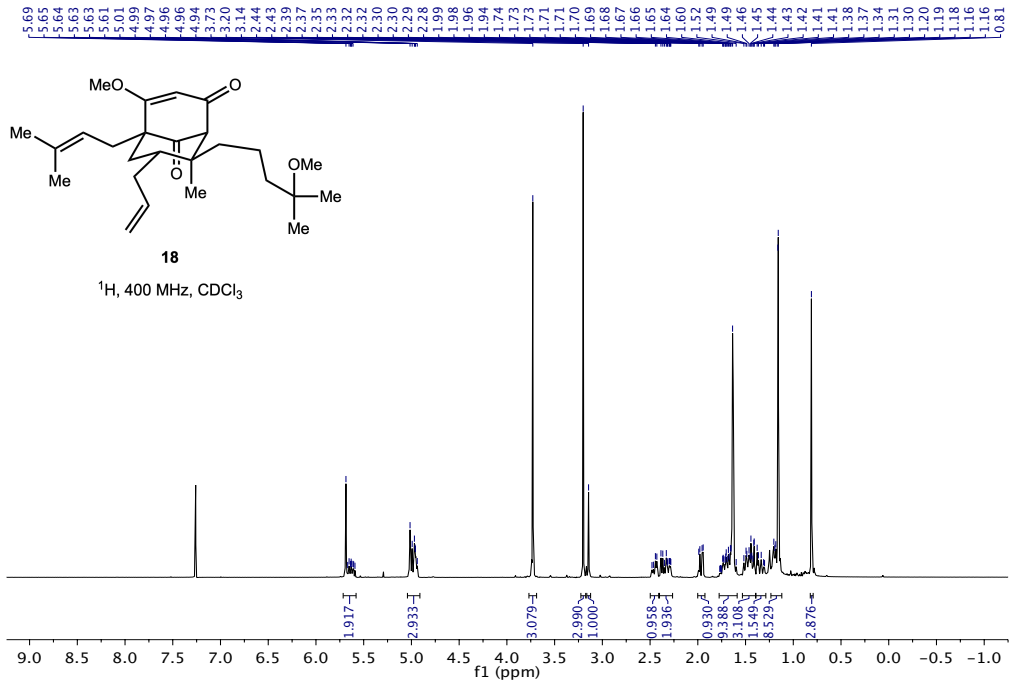
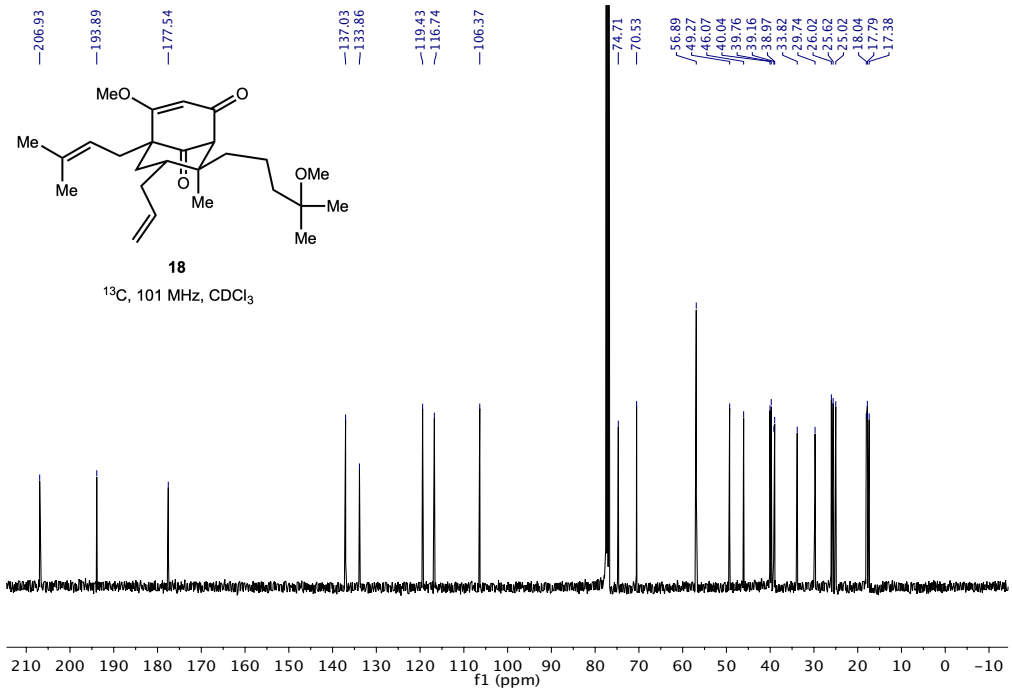
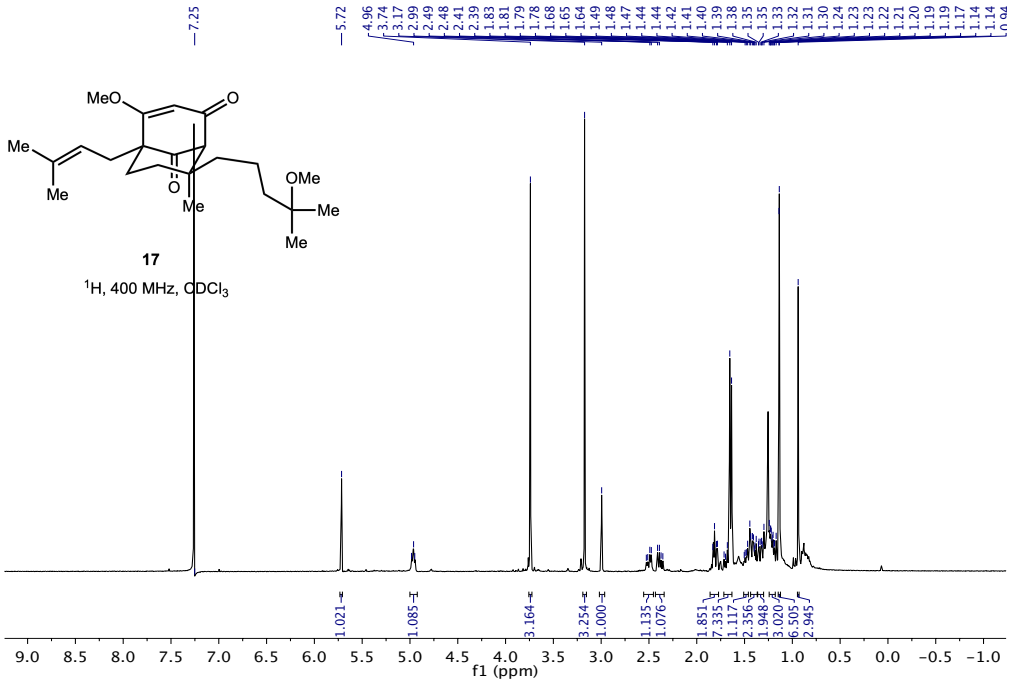
13C, 101 MHz, CDCl3
f1 (ppm)

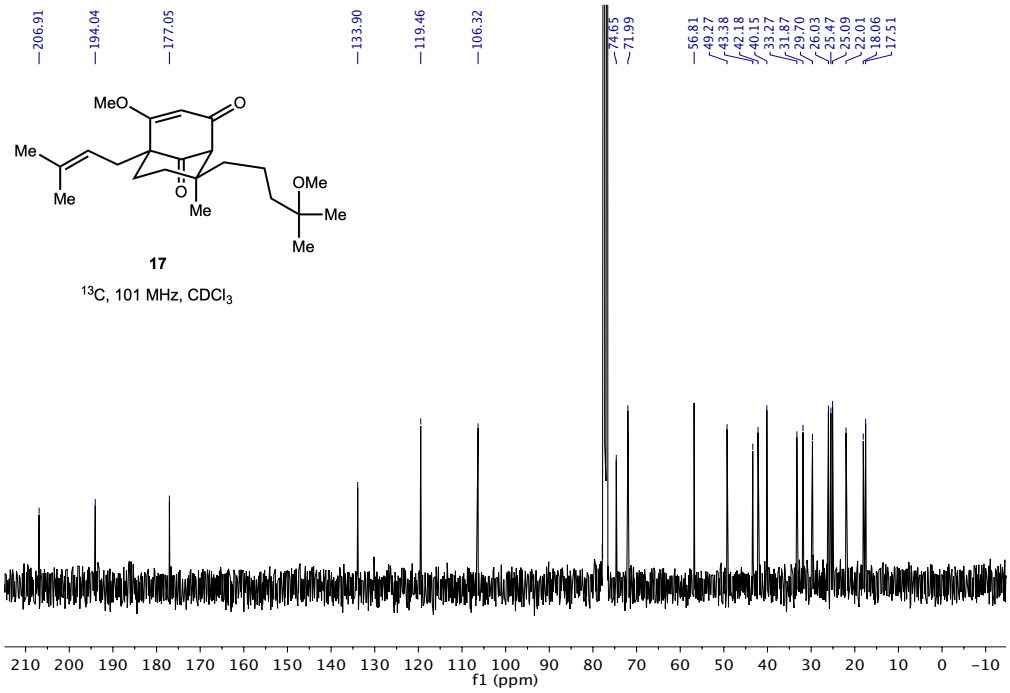

MeO
O
Me
Me
O
O
Me
OMe
Me
Me
S
OC6F5
16
1H, 400 MHz, CDCl3
f1 (ppm)

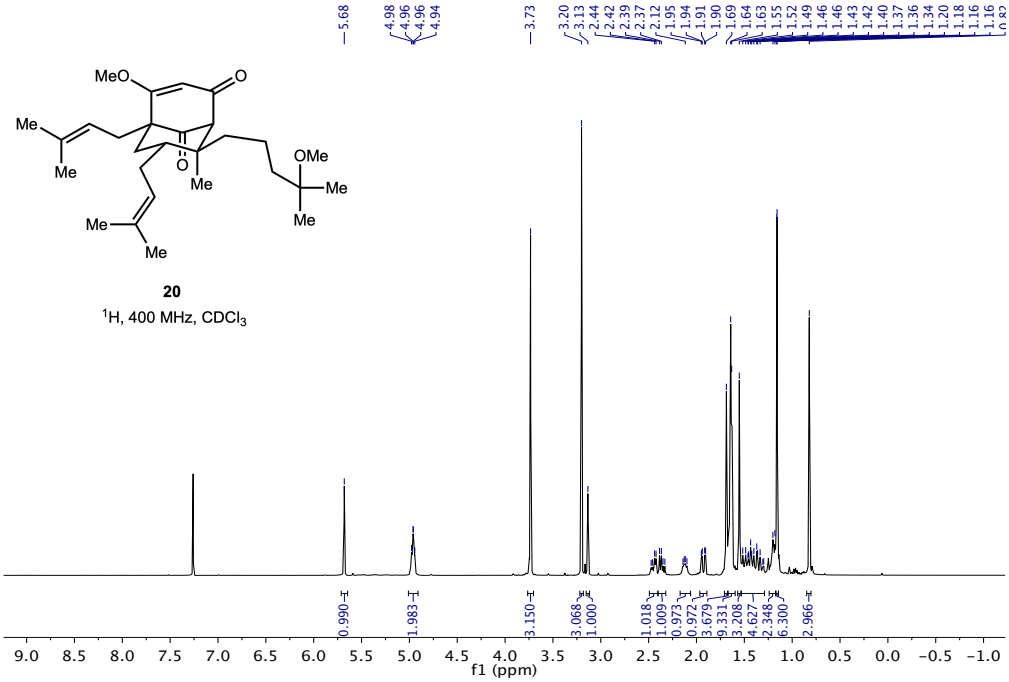

MeO
O
Me
Me
O
O
Me
OMe
Me
Me
S
OC6F5
16
13C, 101 MHz, CDCl3
f1 (ppm)

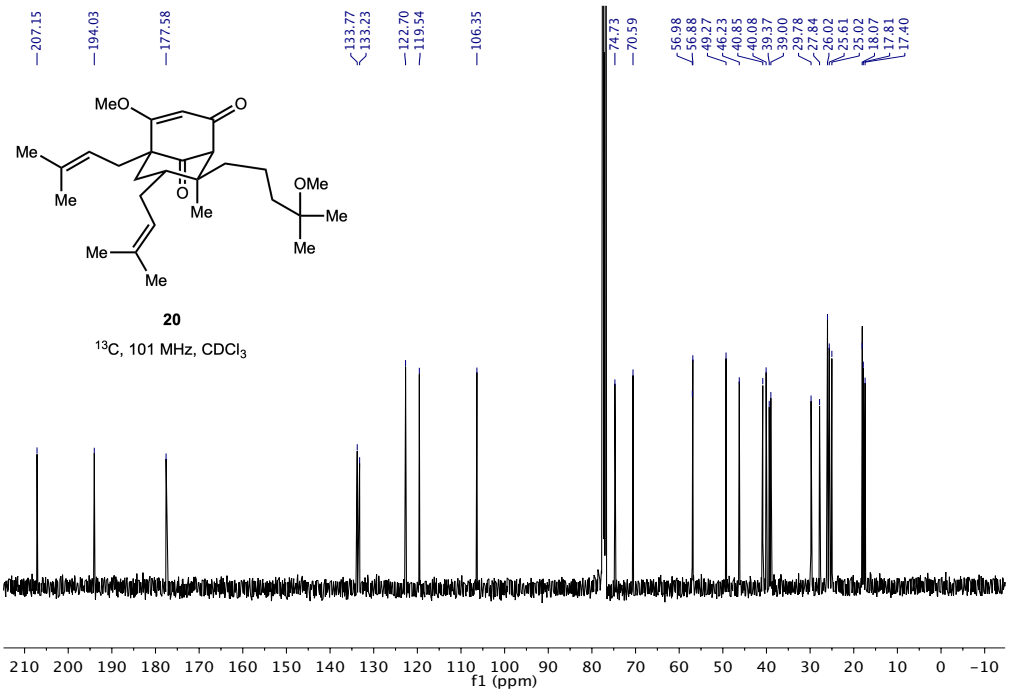

MeO
O
Me
Me
O
Me
OMe
Me
Me
18
1H, 400 MHz, CDCl3
f1 (ppm)

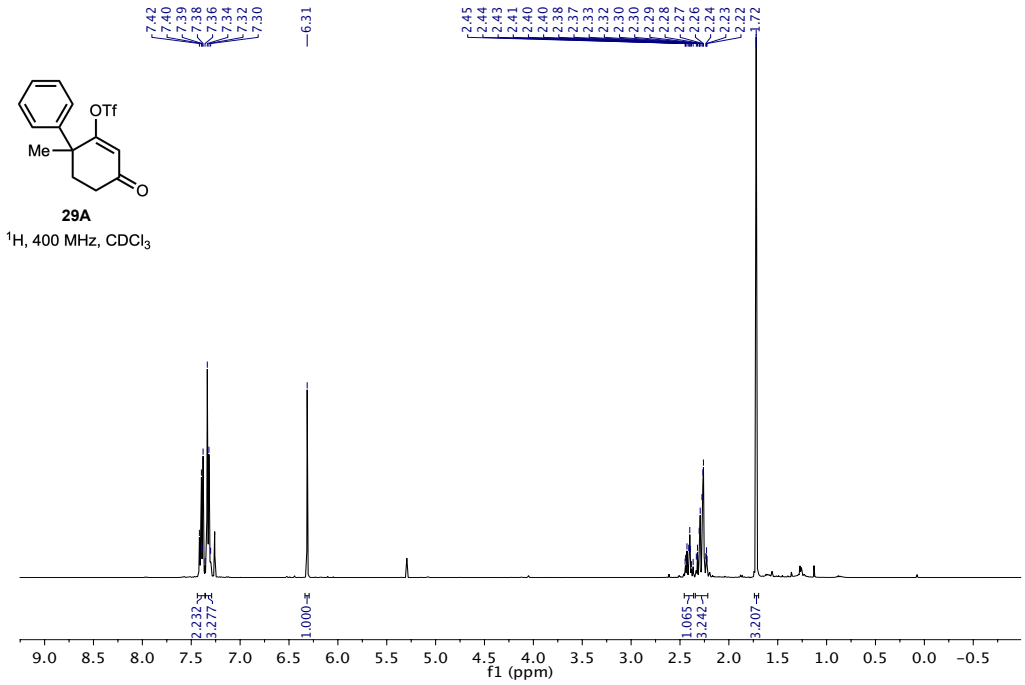

MeO
O
Me
Me
O
Me
OMe
Me
Me
18
13C, 101 MHz, CDCl3
f1 (ppm)

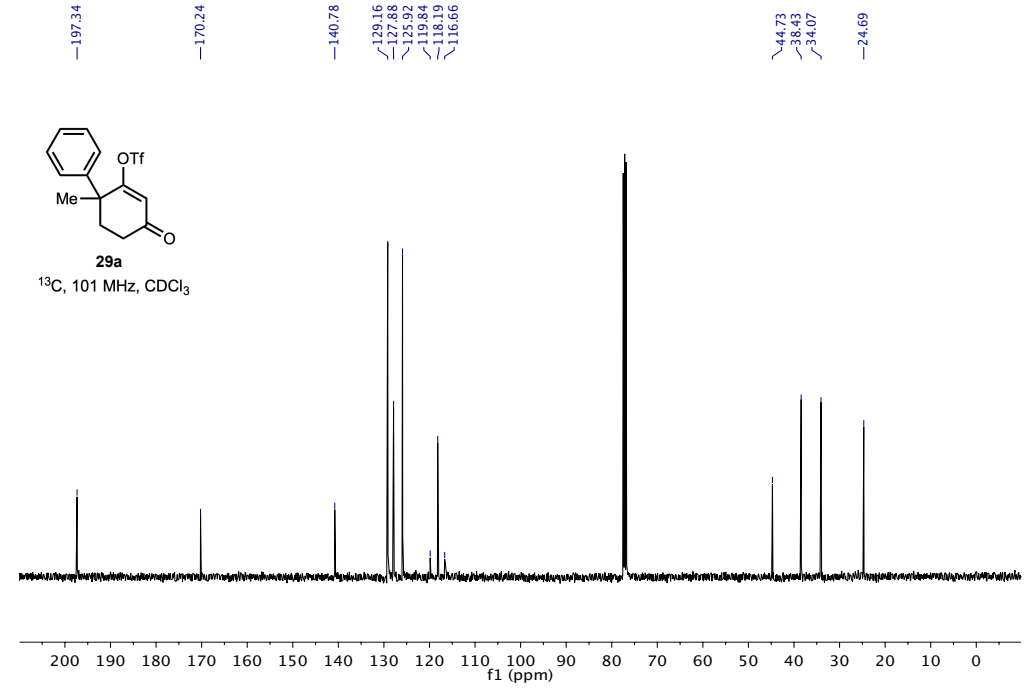

MeO
O
Me
Me
O
Me
OMe
Me
Me
17
1H, 400 MHz, CDCl3
f1 (ppm)

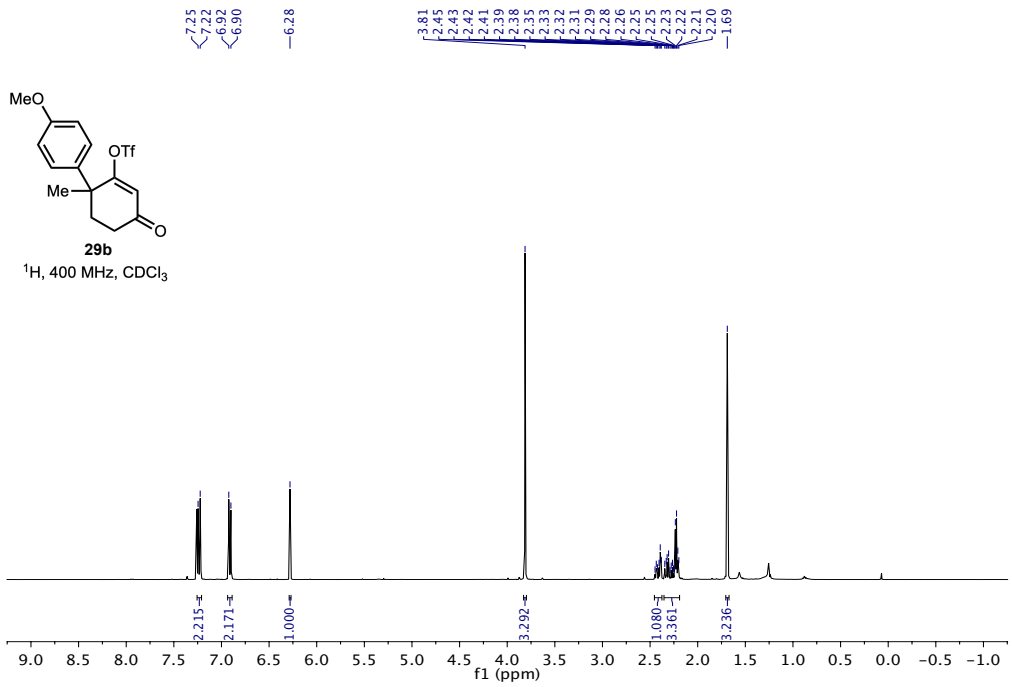

MeO
O
Me
Me
O
Me
OMe
Me
Me
17
13C, 101 MHz, CDCl3
f1 (ppm)

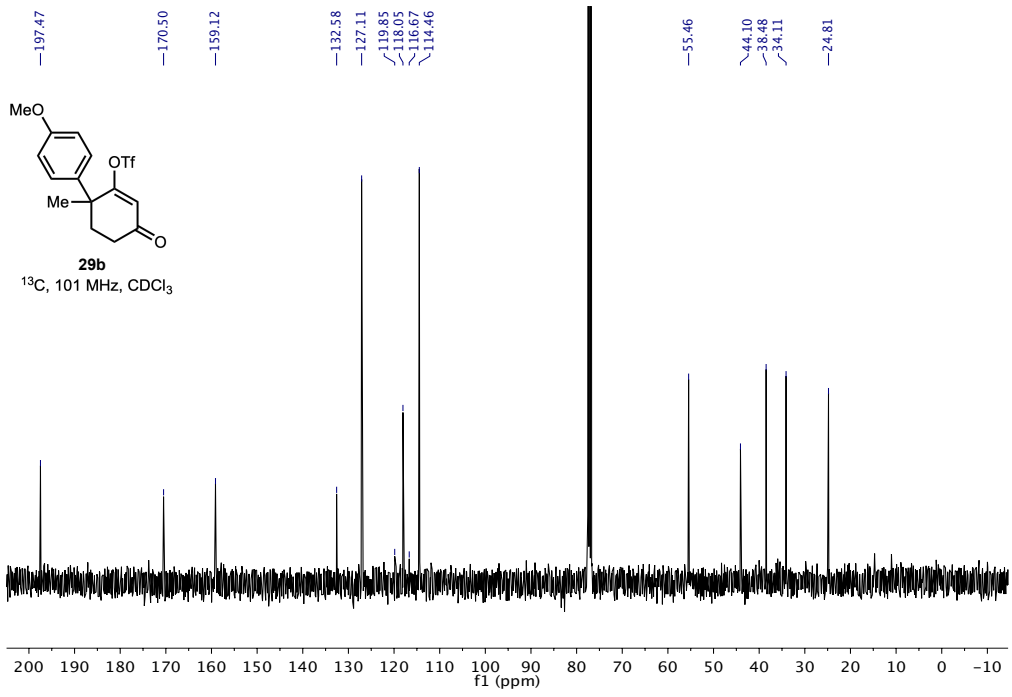

MeO
O
Me
Me
O
Me
OMe
Me
Me
Me
Me
20
1H, 400 MHz, CDCl3
5.68
4.98
4.96
4.96
4.94
3.73
3.20
3.13
2.44
2.42
2.39
2.37
2.12
1.95
1.94
1.91
1.90
1.69
1.64
1.63
1.55
1.52
1.49
1.46
1.46
1.43
1.42
1.40
1.37
1.36
1.34
1.20
1.18
1.16
1.16
0.990
1.983
3.150
3.068
1.000
1.018
1.009
0.973
0.972
3.679
9.331
3.208
4.627
2.348
6.300
2.966
f1 (ppm)

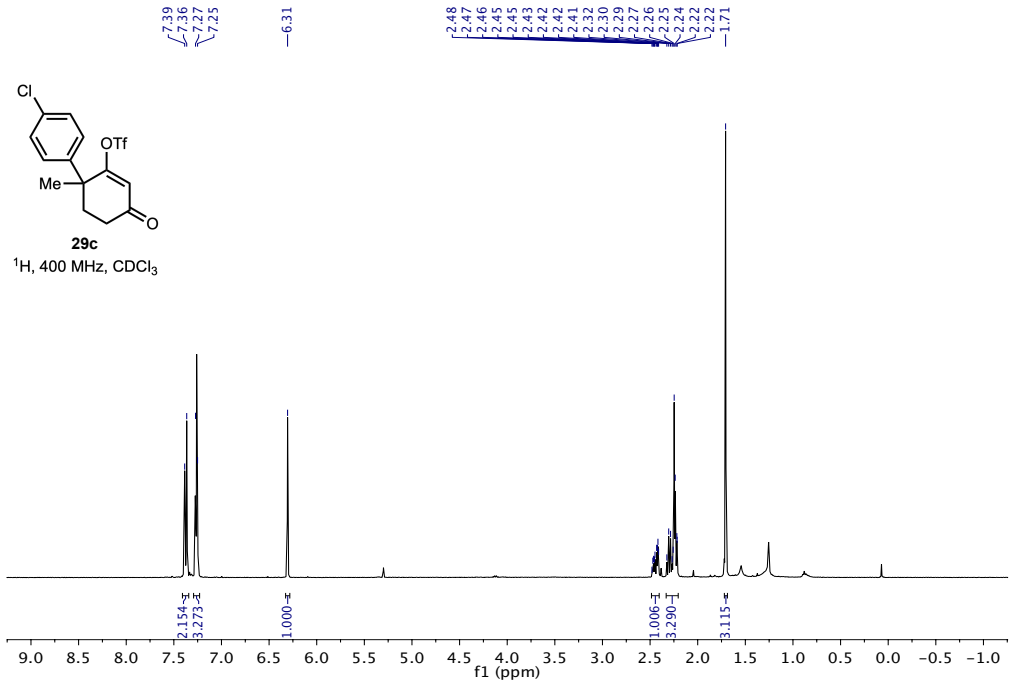

MeO
O
Me
Me
O
Me
OMe
Me
Me
Me
Me
20
13C, 101 MHz, CDCl3
207.15
194.03
177.58
133.77
133.23
122.70
119.54
106.35
74.73
70.59
56.98
56.88
49.27
46.23
40.85
40.08
39.37
39.00
29.78
27.84
26.02
25.61
25.02
18.07
17.81
17.40
f1 (ppm)

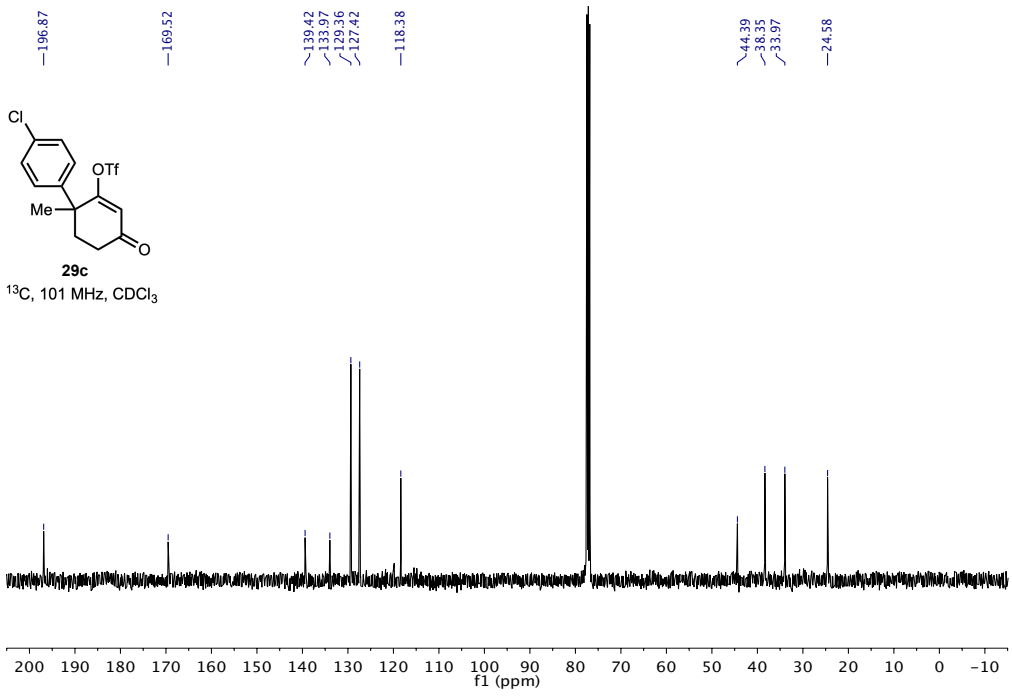

7.42
7.40
7.39
7.38
7.36
7.34
7.32
7.30
6.31
2.45
2.44
2.43
2.41
2.40
2.40
2.38
2.37
2.33
2.32
2.30
2.30
2.29
2.28
2.27
2.26
2.24
2.23
2.22
1.72
OTf
Me
O
29A
1H, 400 MHz, CDCl3
2.232
3.277
1.000
1.065
3.242
3.207
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

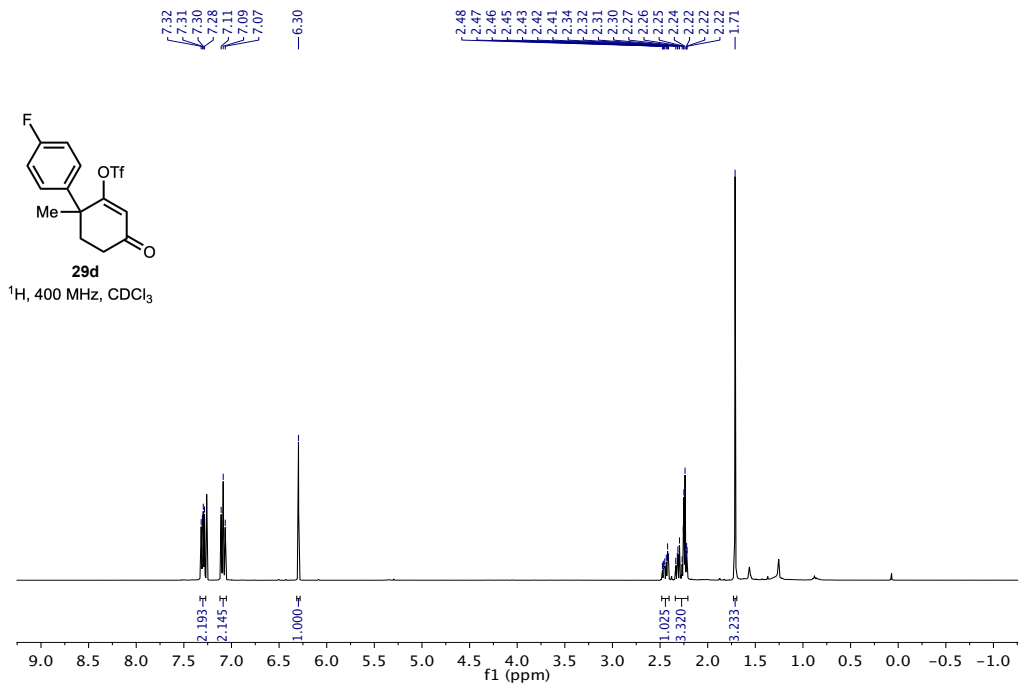

197.34
170.24
140.78
129.16
127.88
125.92
119.84
118.19
116.66
44.73
38.43
34.07
24.69
OTf
Me
O
29a
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

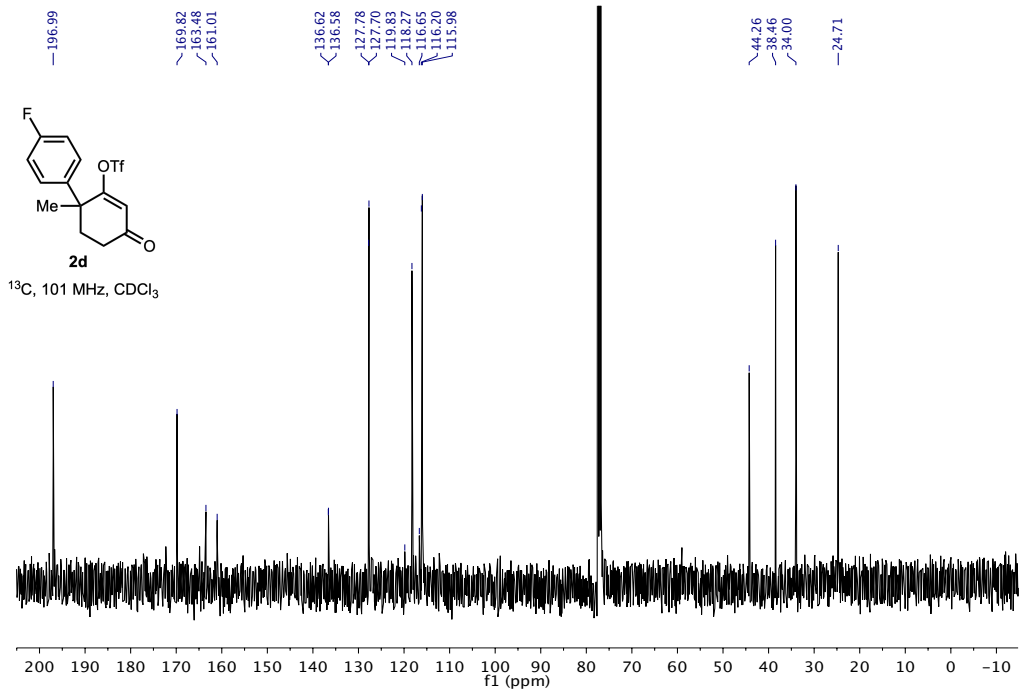

7.25
7.22
6.92
6.90
6.28
3.81
2.45
2.43
2.42
2.41
2.39
2.38
2.35
2.33
2.32
2.31
2.29
2.28
2.26
2.25
2.23
2.22
2.21
2.20
1.69
MeO
OTf
Me
O
29b
1H, 400 MHz, CDCl3
2.215
2.171
1.000
3.292
1.080
3.361
3.236
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

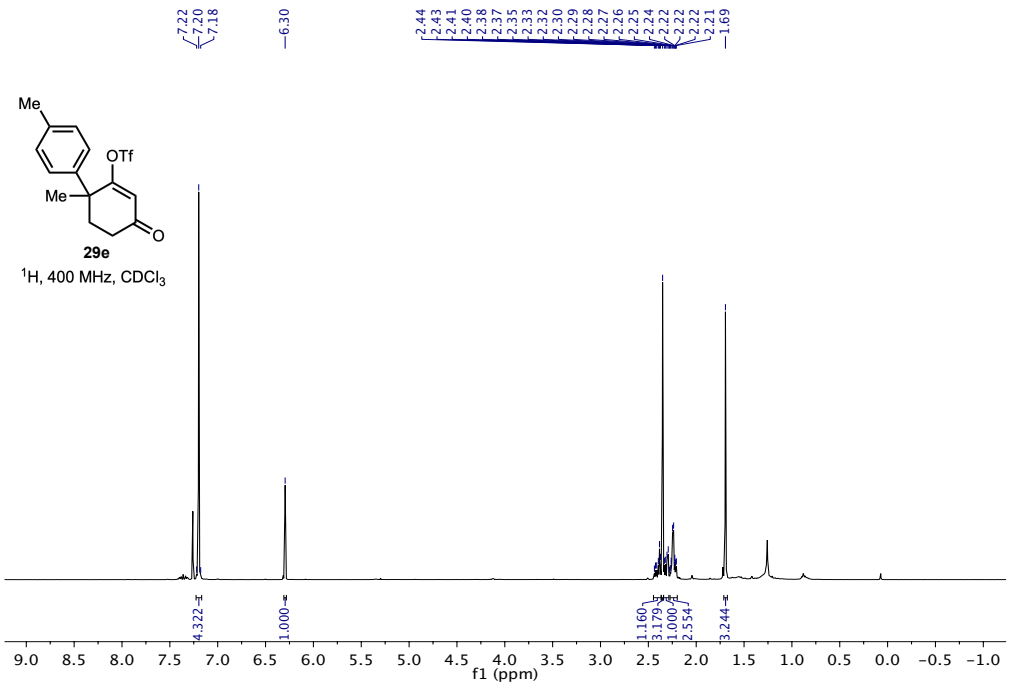

197.47
170.50
159.12
132.58
127.11
119.85
118.05
116.67
114.46
55.46
44.10
38.48
34.11
24.81
MeO
OTf
Me
O
29b
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

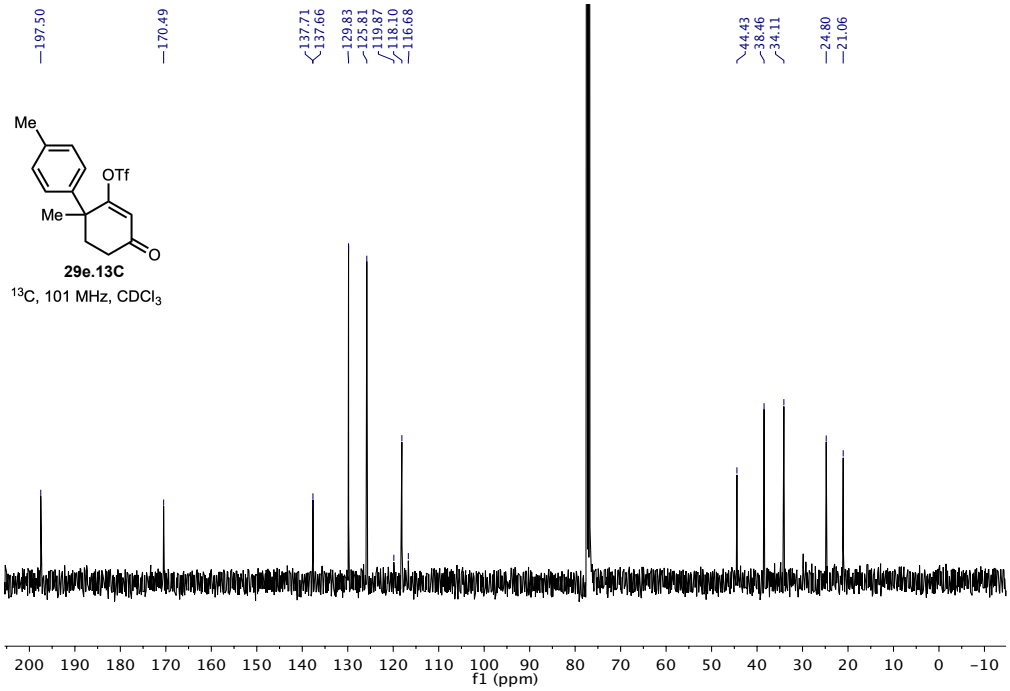

7.39
7.36
7.27
7.25
6.31
2.48
2.47
2.46
2.45
2.45
2.43
2.42
2.42
2.41
2.32
2.30
2.29
2.27
2.26
2.25
2.24
2.22
2.22
1.71
Cl
OTf
Me
O
29c
1H, 400 MHz, CDCl3
2.154
3.273
1.000
1.006
3.290
3.115
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

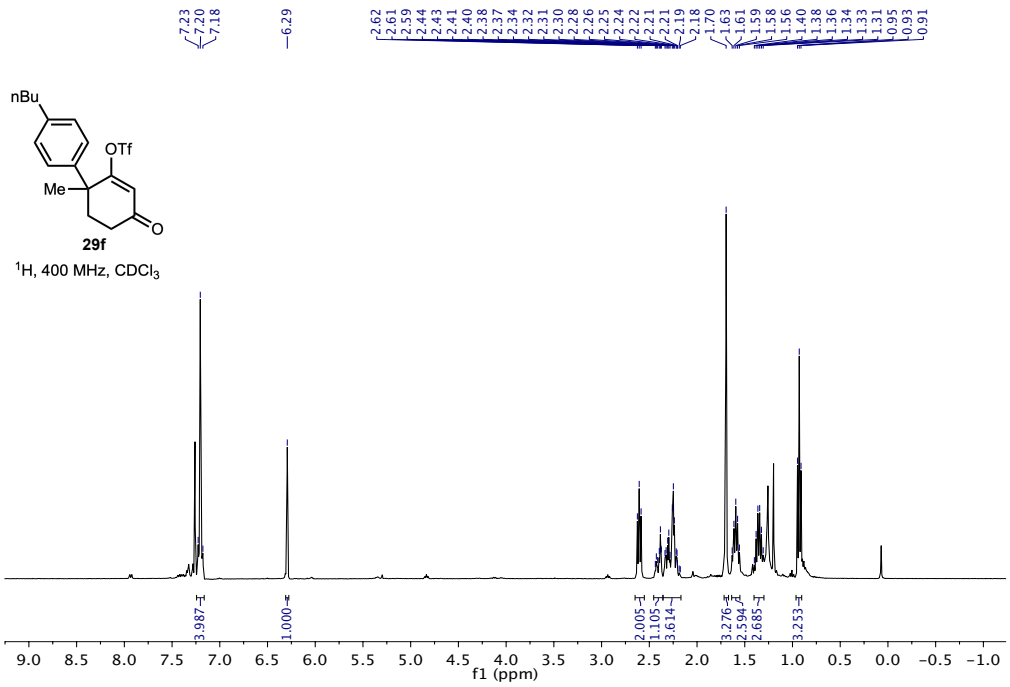

196.87
169.52
139.42
133.97
129.36
127.42
118.38
44.39
38.35
33.97
24.58
Cl
OTf
Me
O
29c
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

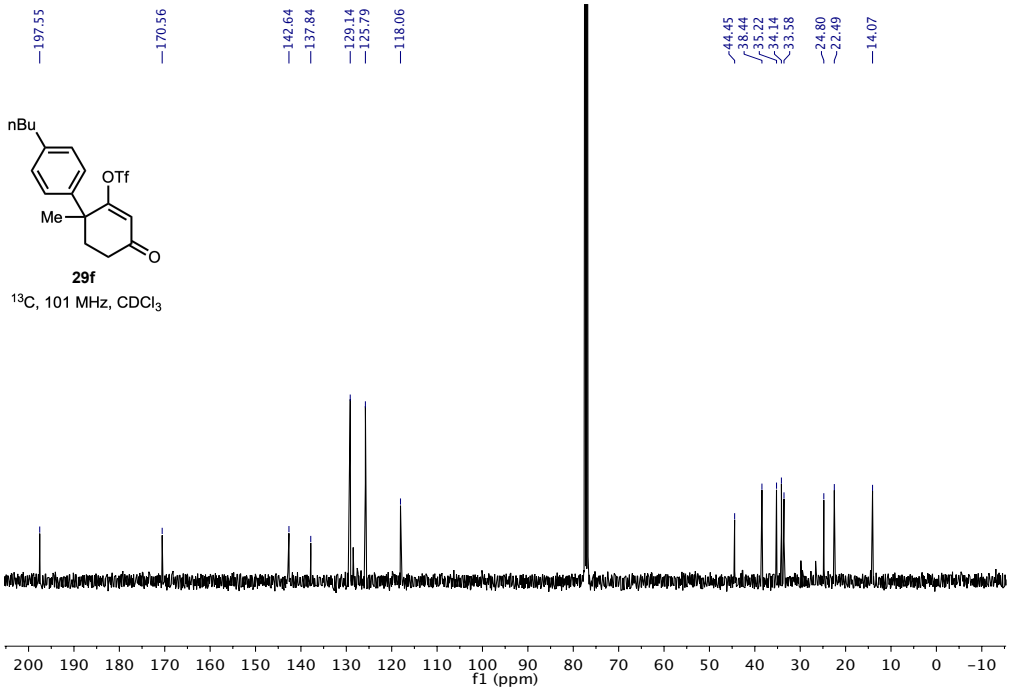

7.32
7.31
7.30
7.28
7.11
7.09
7.07
6.30
2.48
2.47
2.46
2.45
2.43
2.42
2.41
2.34
2.32
2.31
2.30
2.27
2.26
2.25
2.24
2.22
2.22
2.22
1.71
F
OTf
Me
O
29d
1H, 400 MHz, CDCl3
2.193
2.145
1.000
1.025
3.320
3.233
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

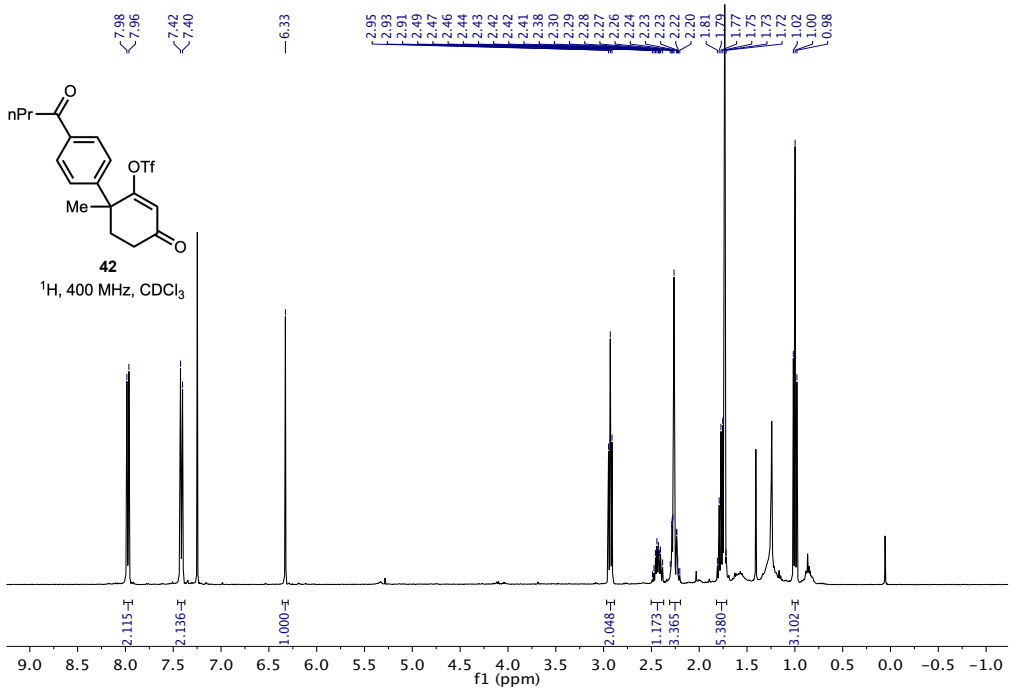

196.99
169.82
163.48
161.01
136.62
136.58
127.78
127.70
119.83
118.27
116.65
116.20
115.98
44.26
38.46
34.00
24.71
F
OTf
Me
O
2d
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

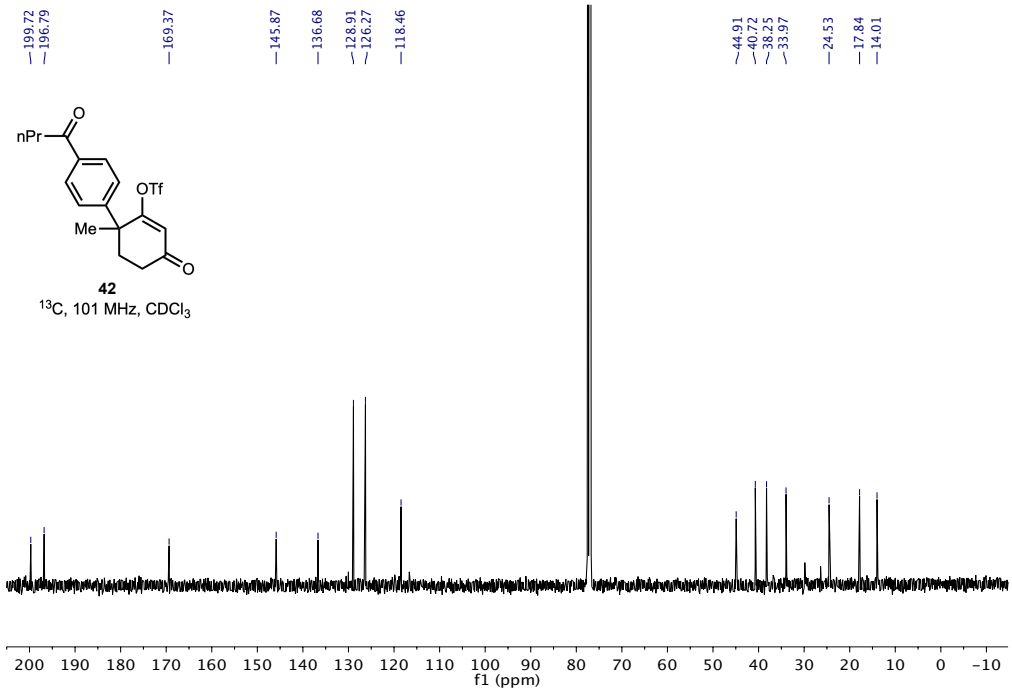

7.22
7.20
7.18
6.30
2.44
2.43
2.41
2.40
2.38
2.37
2.35
2.33
2.32
2.30
2.29
2.28
2.27
2.26
2.25
2.24
2.22
2.22
2.22
2.21
1.69
Me
OTf
Me
O
29e
1H, 400 MHz, CDCl3
4.322
1.000
1.160
3.179
1.000
2.554
3.244
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

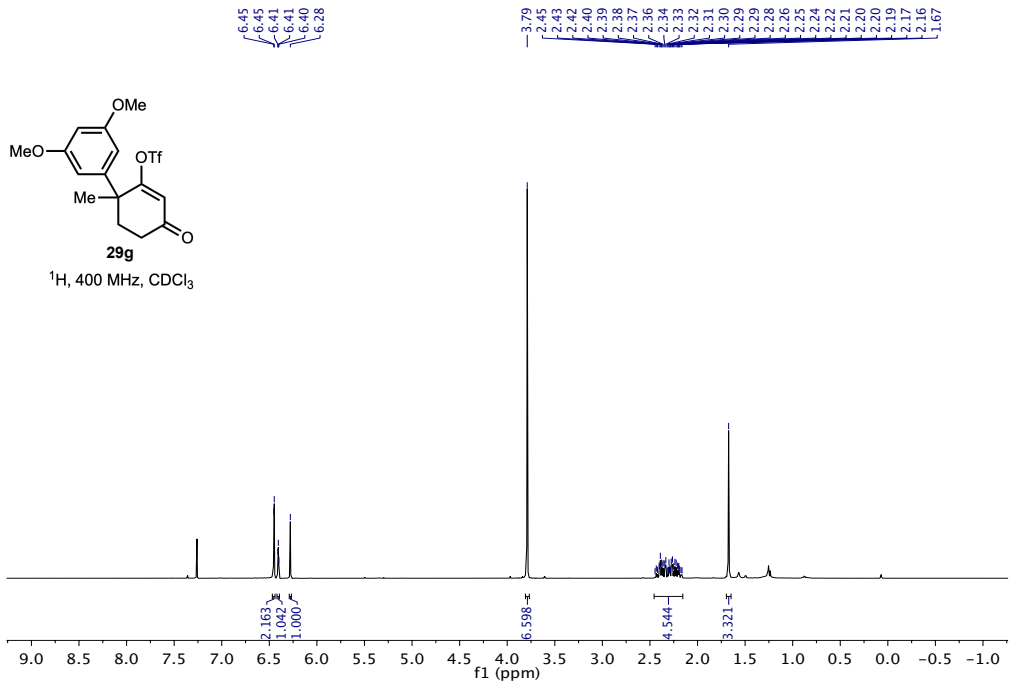

197.50
170.49
137.71
137.66
129.83
125.81
119.87
118.10
116.68
44.43
38.46
34.11
24.80
21.06
Me
OTf
Me
O
29e.13C
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

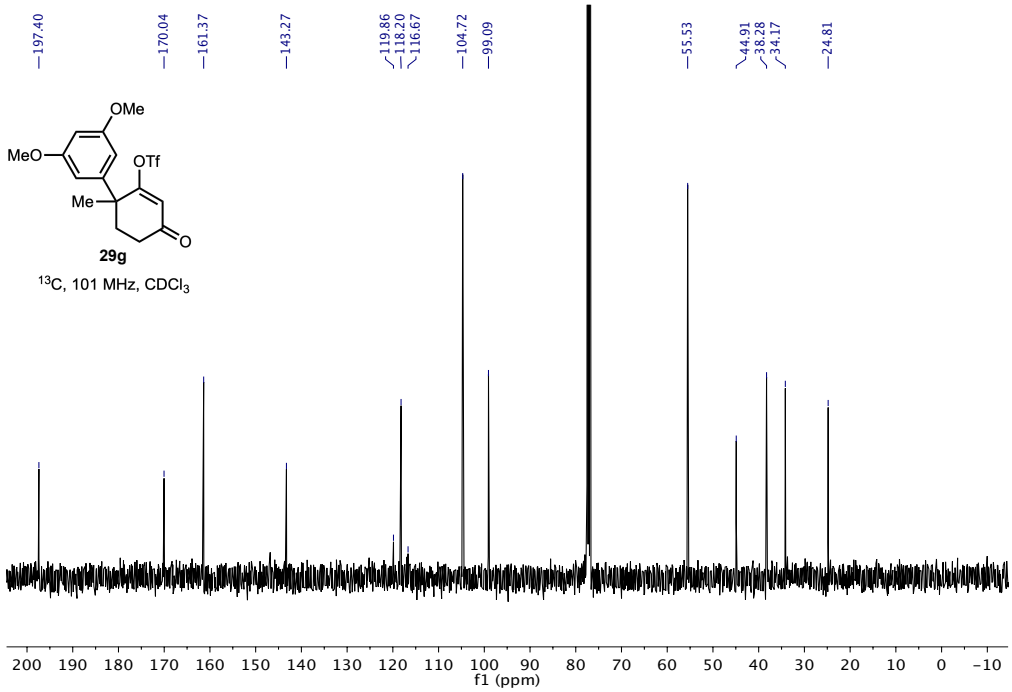

nBu
OTf
Me
O
29f
^{1}H, 400 MHz, $CDCl_3$
f1 (ppm)

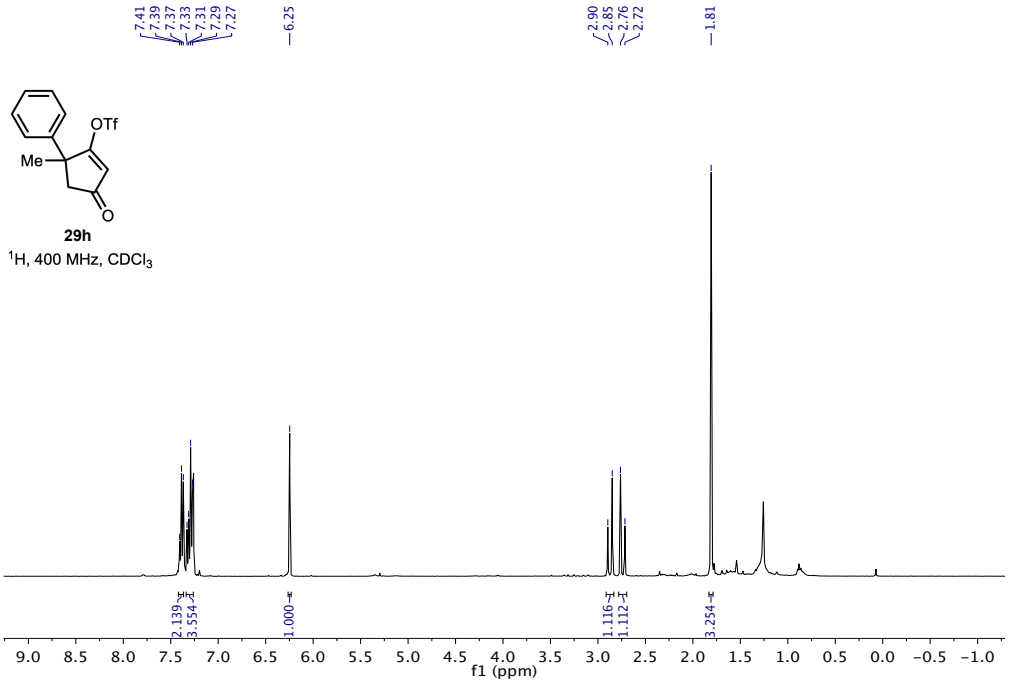

nBu
OTf
Me
O
29f
^{13}C, 101 MHz, $CDCl_3$
f1 (ppm)

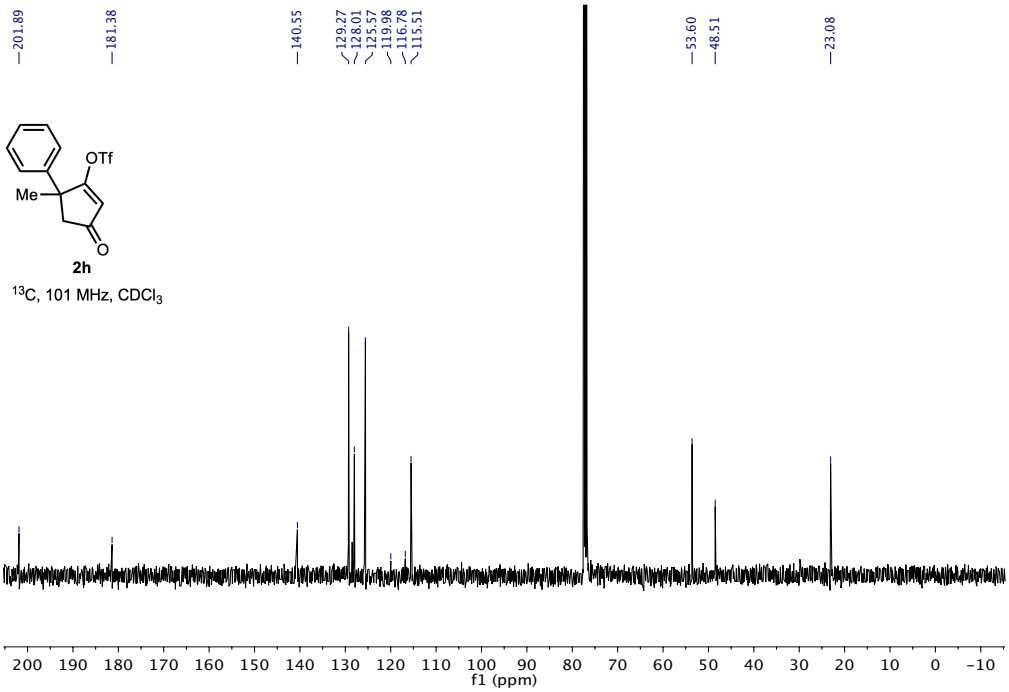

7.98
7.96
7.42
7.40
6.33
2.95
2.93
2.91
2.49
2.47
2.46
2.44
2.43
2.42
2.42
2.41
2.38
2.30
2.29
2.28
2.27
2.26
2.24
2.23
2.23
2.22
2.20
1.81
1.79
1.77
1.75
1.73
1.72
1.02
1.00
0.98
nPr
O
OTf
Me
O
42
1H, 400 MHz, CDCl3
2.115
2.136
1.000
2.048
1.173
3.365
5.380
3.102
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

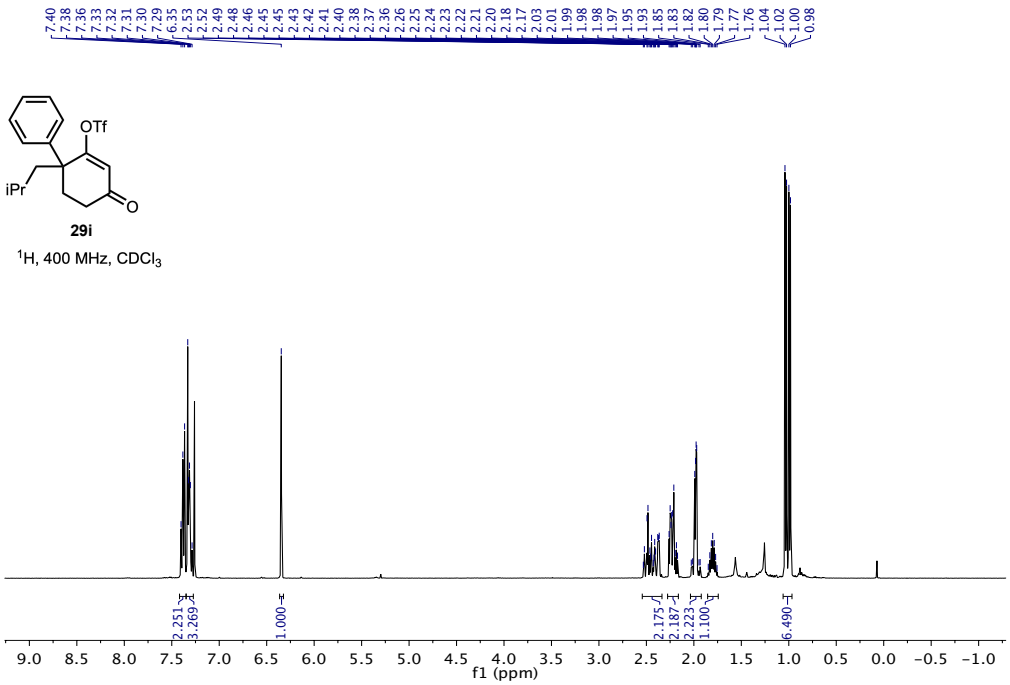

199.72
196.79
169.37
145.87
136.68
128.91
126.27
118.46
44.91
40.72
38.25
33.97
24.53
17.84
14.01
nPr
O
OTf
Me
O
42
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

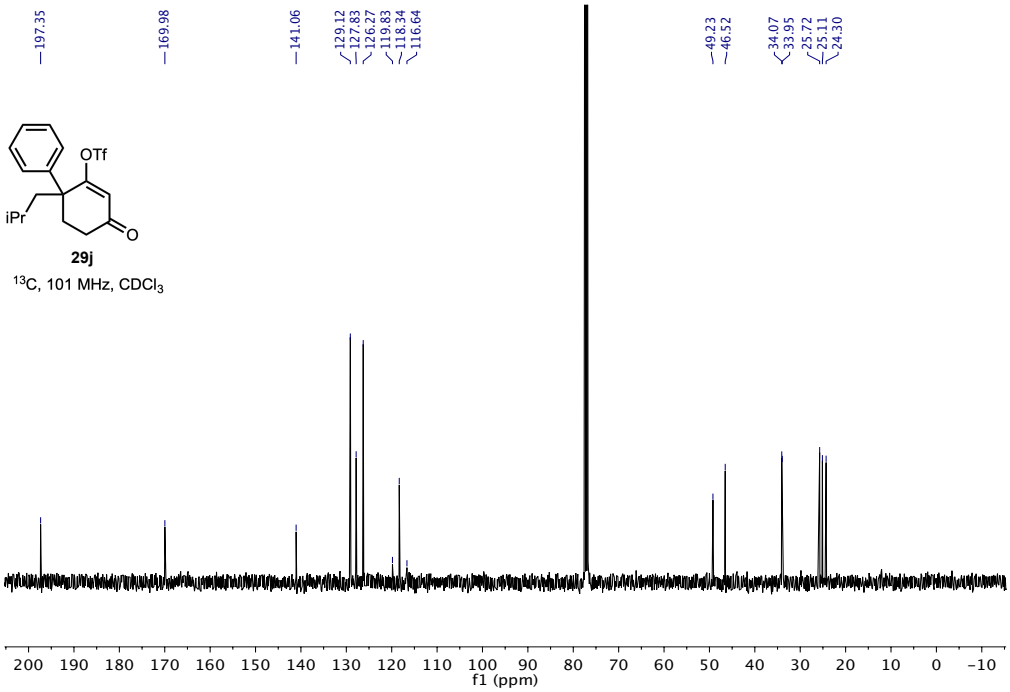

6.45
6.45
6.41
6.41
6.40
6.28
3.79
2.45
2.43
2.42
2.40
2.39
2.38
2.37
2.36
2.34
2.33
2.32
2.31
2.30
2.29
2.29
2.28
2.26
2.25
2.24
2.22
2.21
2.20
2.20
2.19
2.17
2.16
1.67
OMe
MeO
OTf
Me
O
29g
1H, 400 MHz, CDCl3
2.163
1.042
1.000
6.598
4.544
3.321
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

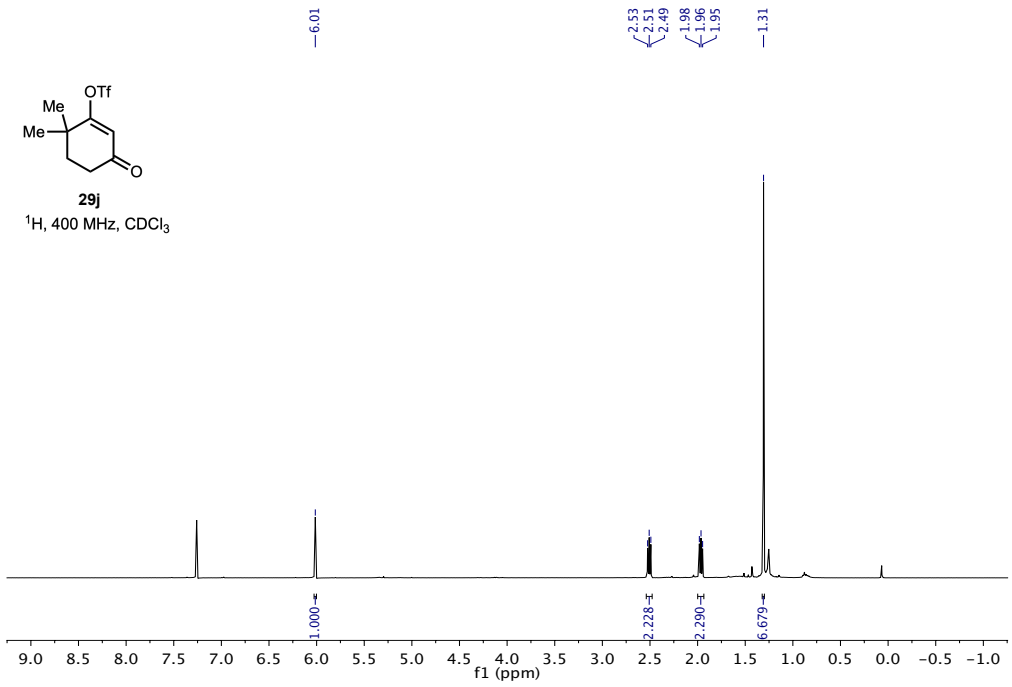

197.40
170.04
161.37
143.27
119.86
118.20
116.67
104.72
99.09
55.53
44.91
38.28
34.17
24.81
OMe
MeO
OTf
Me
O
29g
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

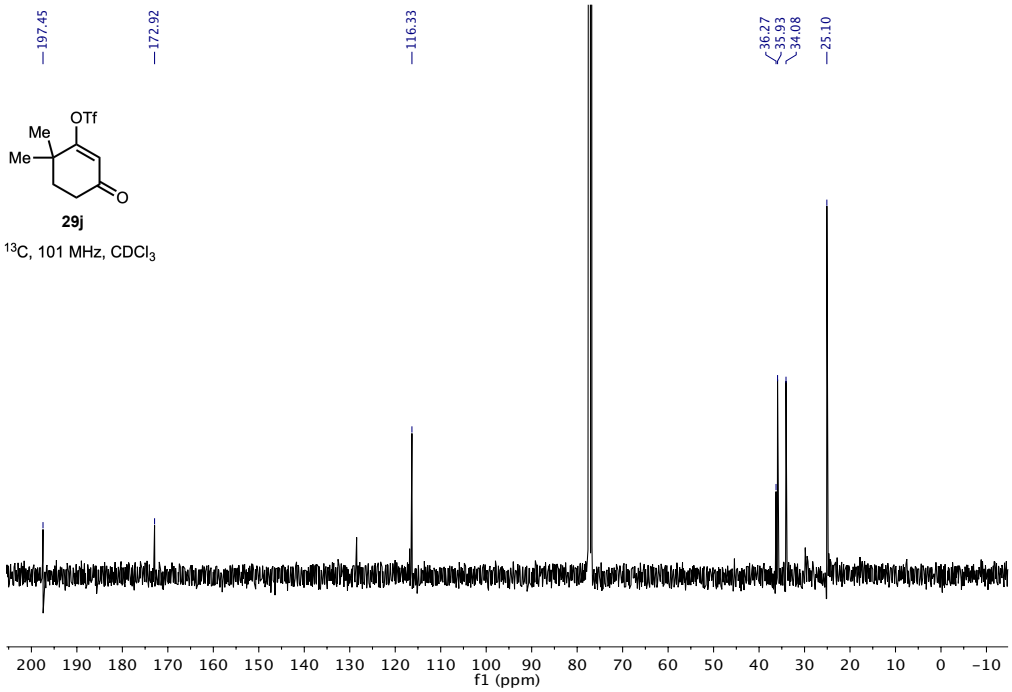

7.41
7.39
7.37
7.33
7.31
7.29
7.27
6.25
2.90
2.85
2.76
2.72
1.81
OTf
Me
O
29h
1H, 400 MHz, CDCl3
2.139
3.554
1.000
1.116
1.112
3.254
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

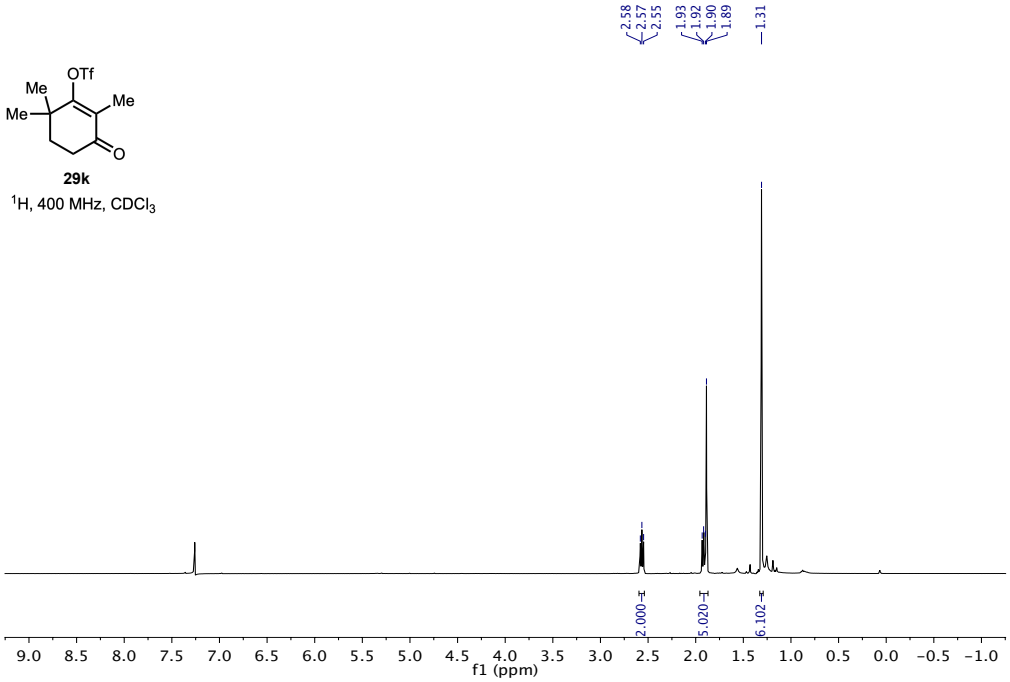

201.89
181.38
140.55
129.27
128.01
125.57
119.98
116.78
115.51
53.60
48.51
23.08
OTf
Me
O
2h
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

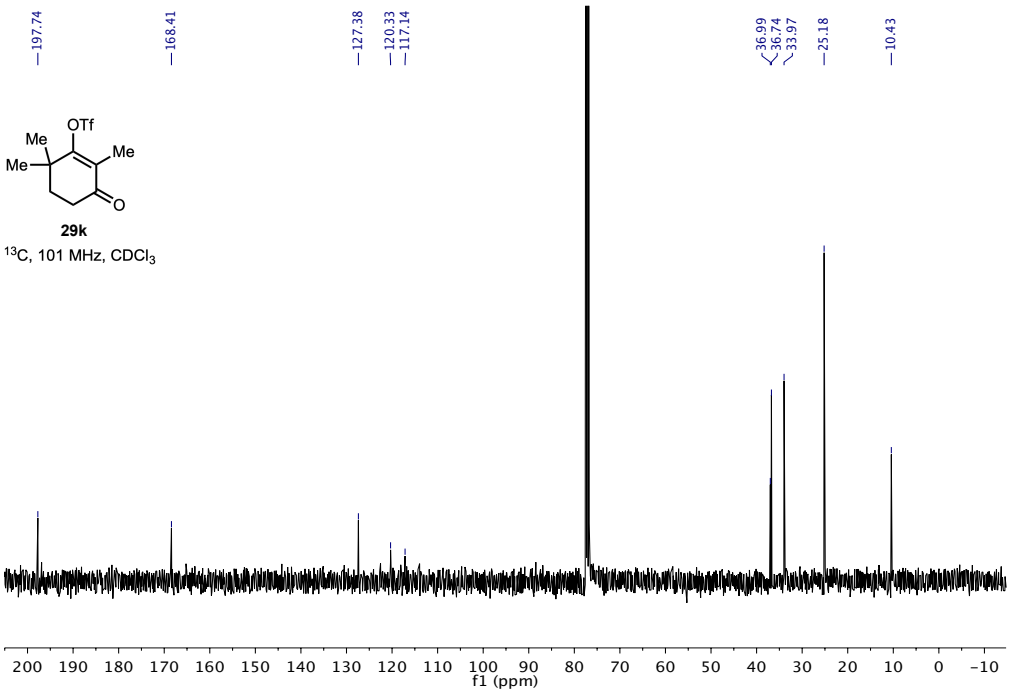

7.40
7.38
7.36
7.33
7.32
7.31
7.30
7.29
6.35
2.53
2.52
2.49
2.48
2.46
2.45
2.45
2.43
2.42
2.41
2.40
2.38
2.37
2.36
2.26
2.25
2.24
2.23
2.22
2.21
2.20
2.18
2.17
2.03
2.01
1.99
1.98
1.98
1.97
1.95
1.93
1.85
1.83
1.82
1.80
1.79
1.77
1.76
1.04
1.02
1.00
0.98
OTf
iPr
O
29i
1H, 400 MHz, CDCl3
2.251
3.269
1.000
2.175
2.187
2.223
1.100
6.490
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 0.0 -0.5 -1.0
f1 (ppm)

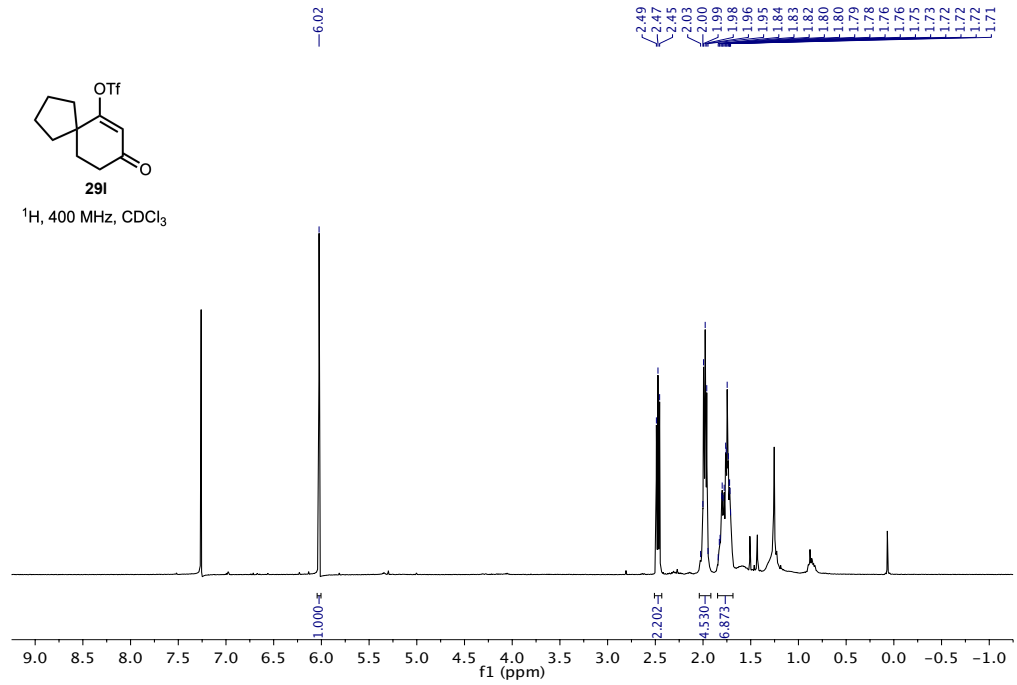

197.35
169.98
141.06
129.12
127.83
126.27
119.83
118.34
116.64
49.23
46.52
34.07
33.95
25.72
25.11
24.30
OTf
iPr
O
29j
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

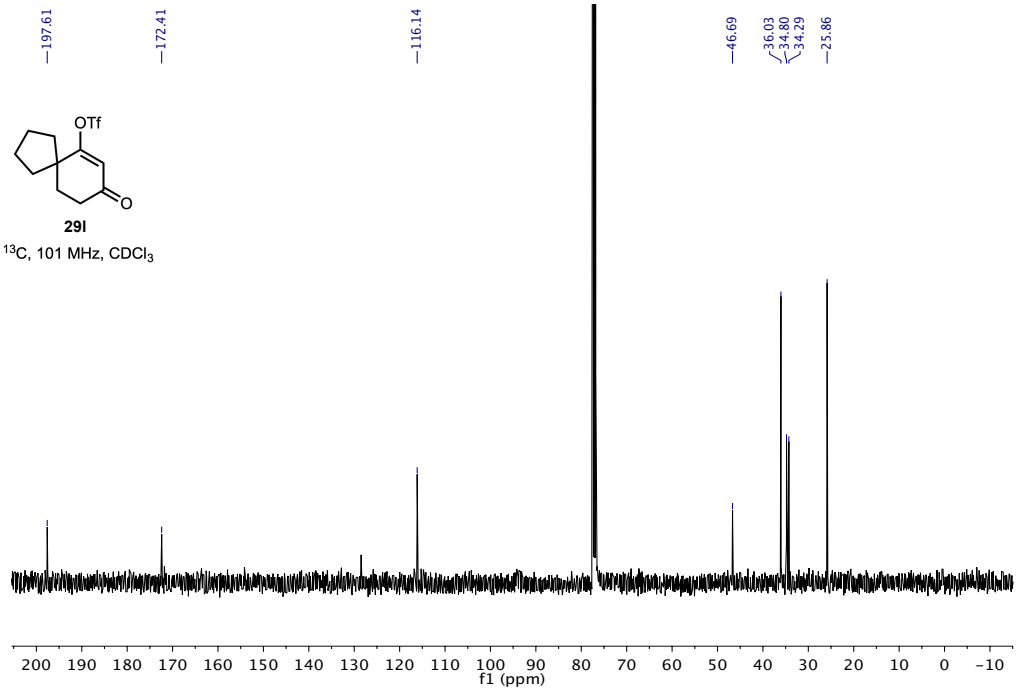

6.01
2.53
2.51
2.49
1.98
1.96
1.95
1.31
OTf
Me
Me
O
29j
1H, 400 MHz, CDCl3
1.000
2.228
2.290
6.679
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

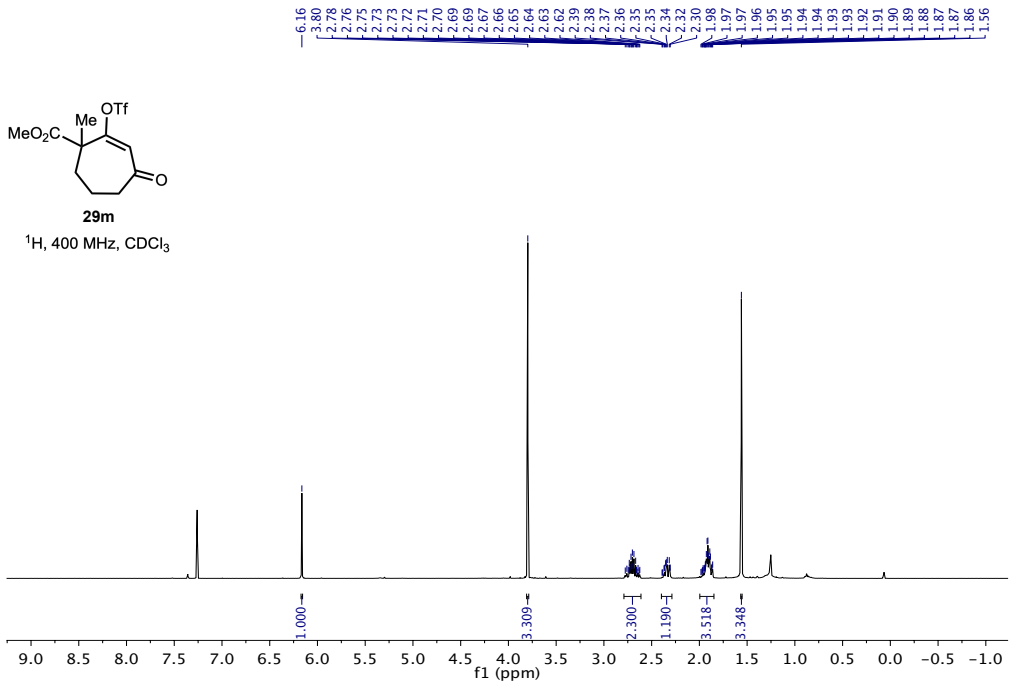

197.45
172.92
116.33
36.27
35.93
34.08
25.10
OTf
Me
Me
O
29j
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

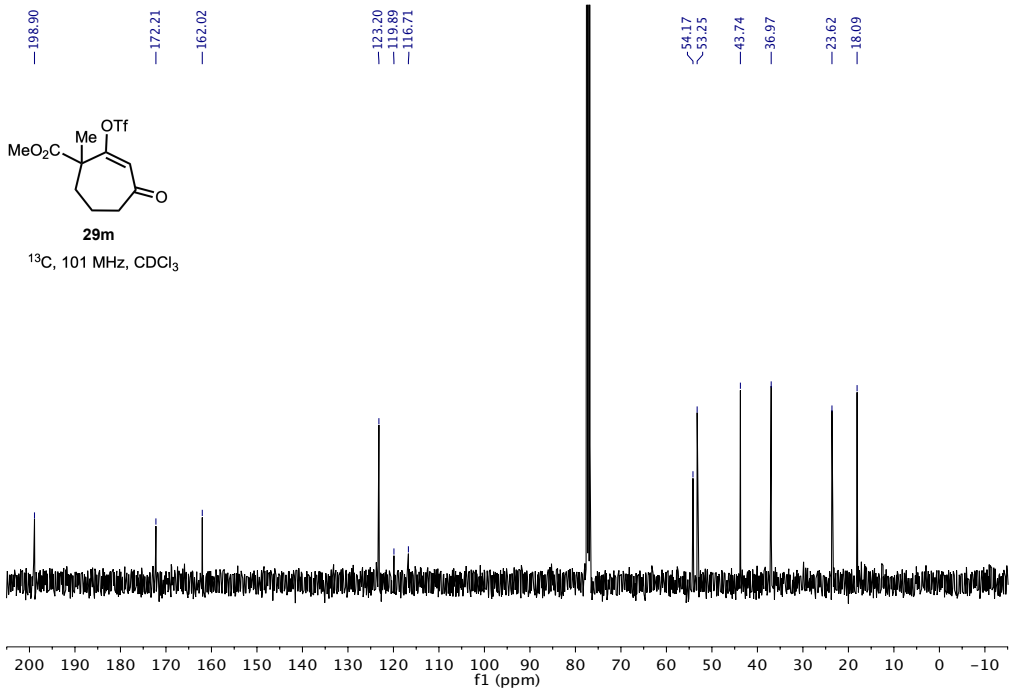

OTf
Me
Me
Me
O
29k
1H, 400 MHz, CDCl3
2.58
2.57
2.55
1.93
1.92
1.90
1.89
1.31
2.000
5.020
6.102
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

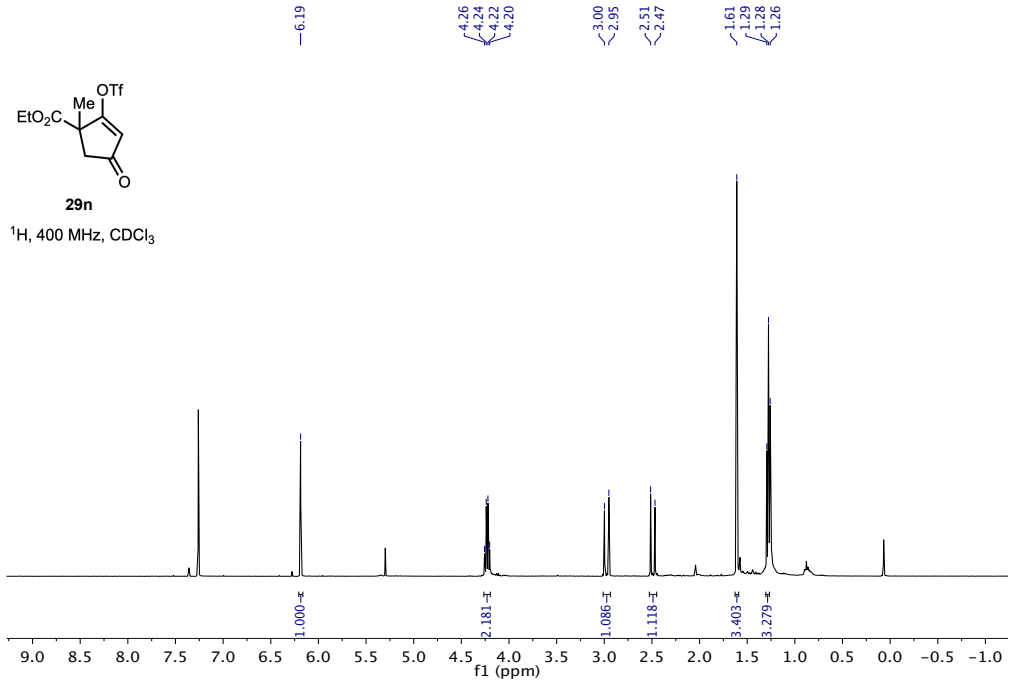

197.74
168.41
127.38
120.33
117.14
36.99
36.74
33.97
25.18
10.43
OTf
Me
Me
Me
O
29k
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

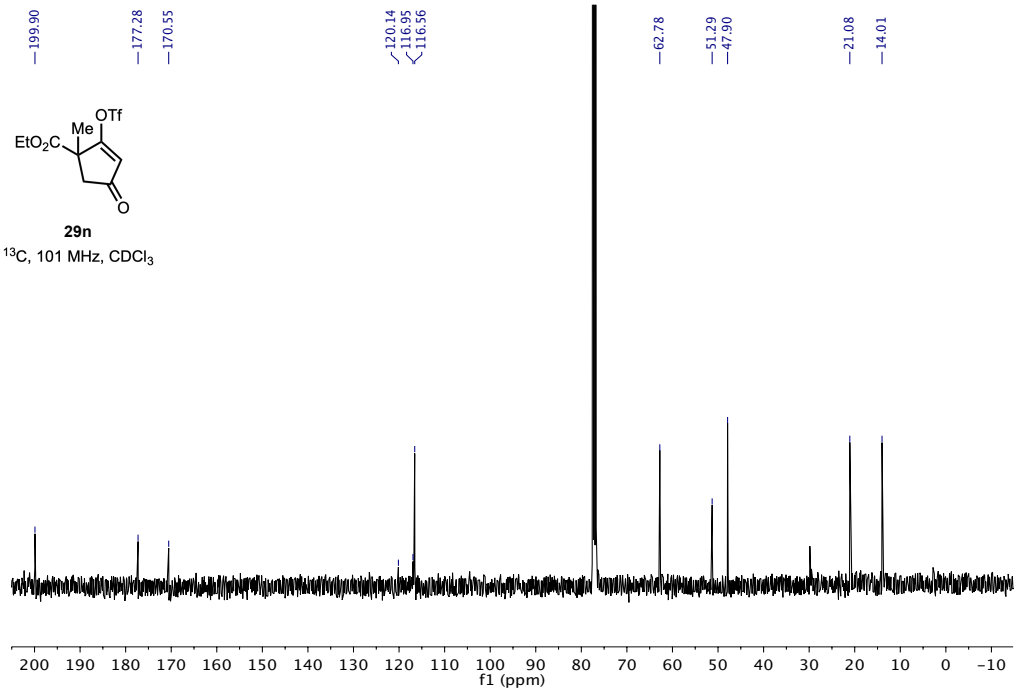

OTf
O
29l
1H, 400 MHz, CDCl3
6.02
2.49
2.47
2.45
2.03
2.00
1.99
1.98
1.96
1.95
1.84
1.83
1.82
1.80
1.80
1.79
1.78
1.76
1.76
1.75
1.73
1.72
1.72
1.72
1.72
1.71
1.000
2.202
4.530
6.873
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

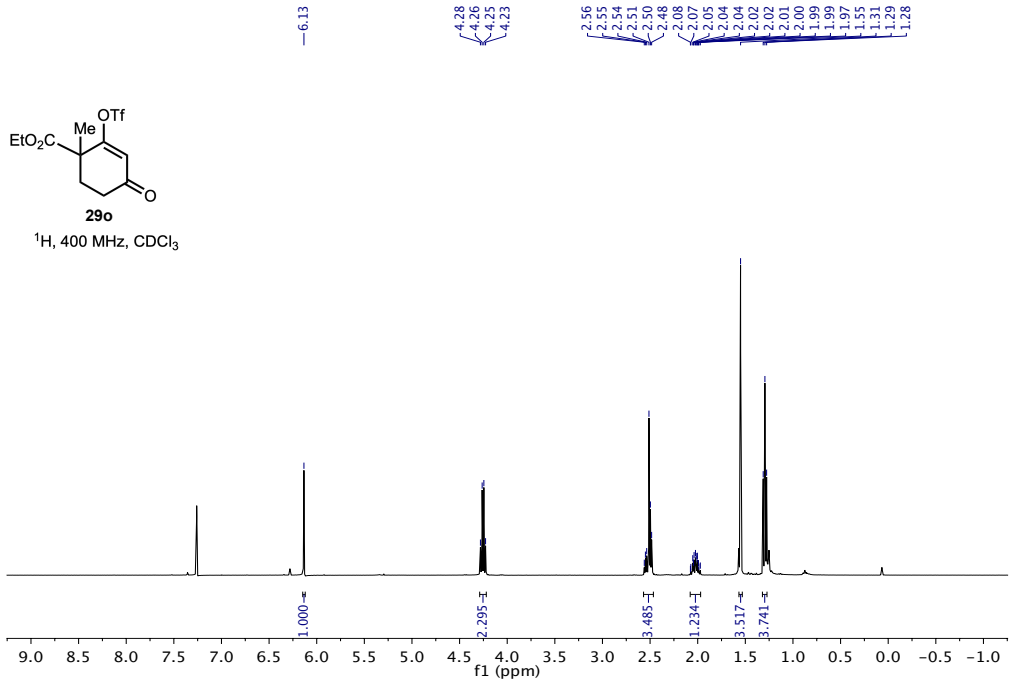

OTf
O
29l
13C, 101 MHz, CDCl3
197.61
172.41
116.14
46.69
36.03
34.80
34.29
25.86
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

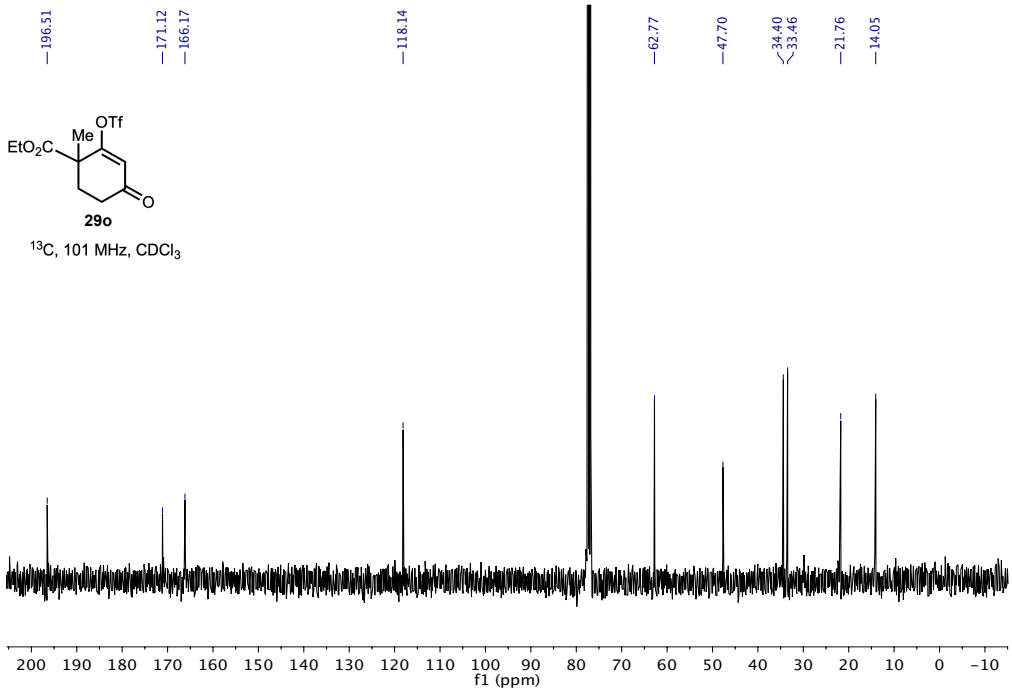

6.16
3.80
2.78
2.76
2.75
2.73
2.72
2.71
2.70
2.69
2.69
2.67
2.66
2.65
2.64
2.63
2.62
2.39
2.38
2.37
2.36
2.35
2.34
2.32
2.30
1.98
1.97
1.97
1.96
1.95
1.95
1.94
1.94
1.93
1.93
1.92
1.91
1.90
1.89
1.88
1.87
1.87
1.86
1.56
OTf
Me
MeO2C
O
29m
1H, 400 MHz, CDCl3
1.000
3.309
2.300
1.190
3.518
3.348
9.0 8.5 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 0.0 -0.5 -1.0
f1 (ppm)

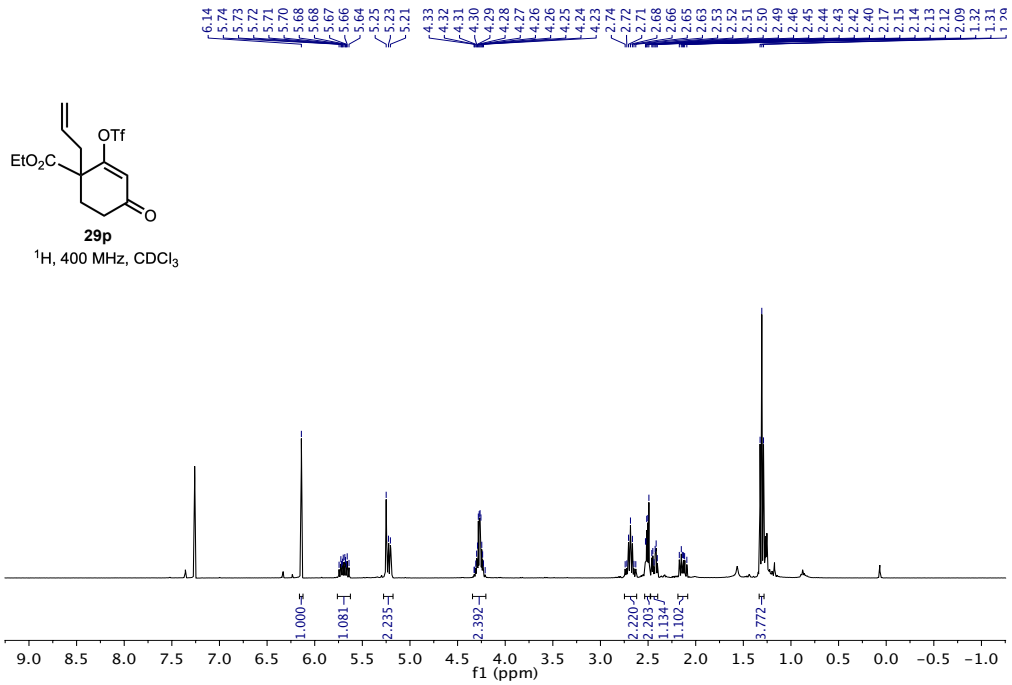

198.90
172.21
162.02
123.20
119.89
116.71
54.17
53.25
43.74
36.97
23.62
18.09
OTf
Me
MeO2C
O
29m
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

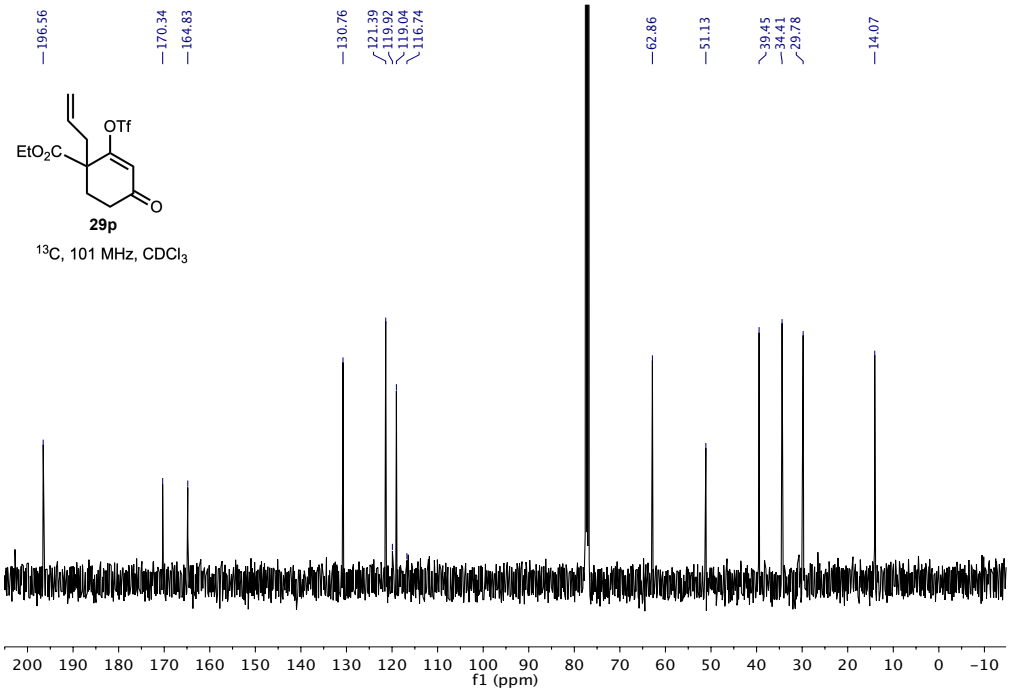

6.19
4.26
4.24
4.22
4.20
3.00
2.95
2.51
2.47
1.61
1.29
1.28
1.26
OTf
Me
EtO2C
O
29n
1H, 400 MHz, CDCl3
1.000
2.181
1.086
1.118
3.403
3.279
f1 (ppm)

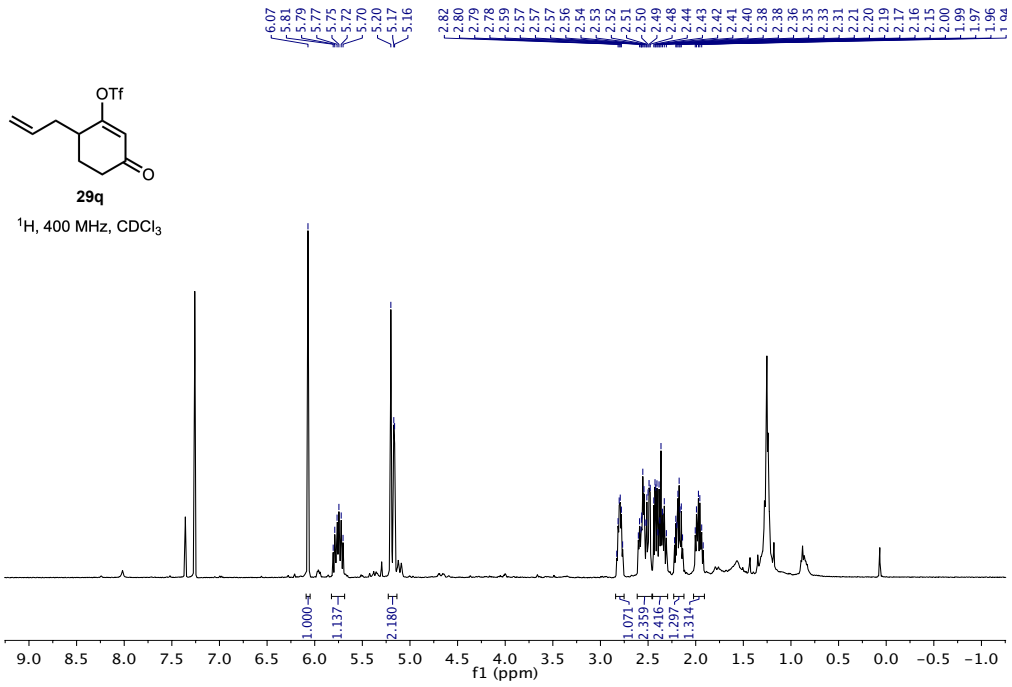

199.90
177.28
170.55
120.14
116.95
116.56
62.78
51.29
47.90
21.08
14.01
OTf
Me
EtO2C
O
29n
13C, 101 MHz, CDCl3
f1 (ppm)

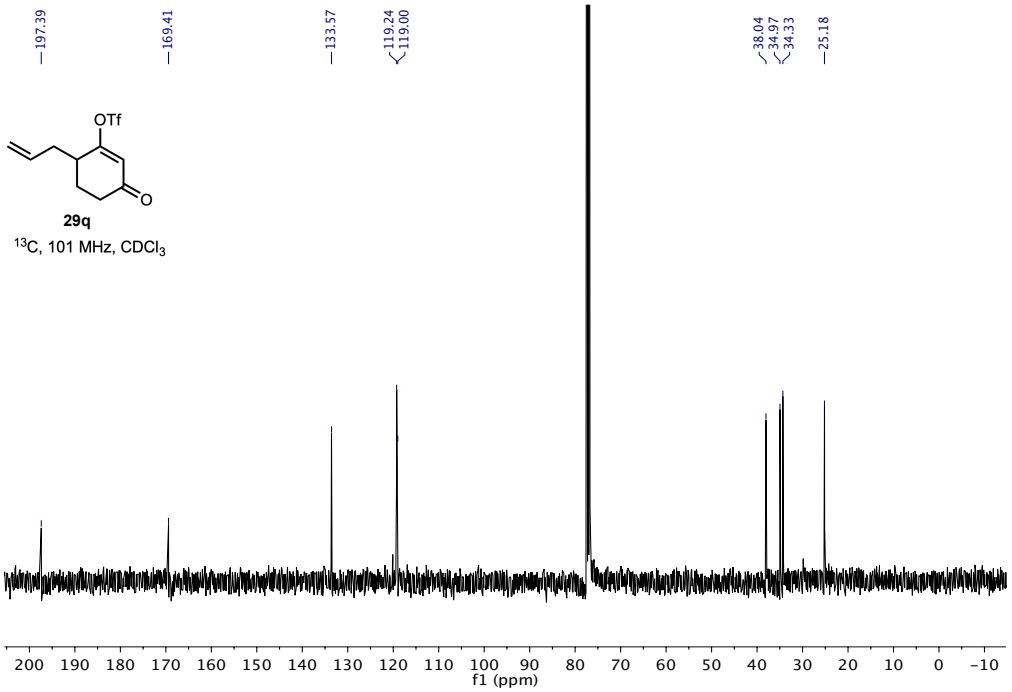

6.13
4.28
4.26
4.25
4.23
2.56
2.55
2.54
2.51
2.50
2.48
2.08
2.07
2.05
2.04
2.04
2.02
2.02
2.01
2.00
1.99
1.99
1.97
1.55
1.31
1.29
1.28
OTf
Me
EtO2C
O
29o
1H, 400 MHz, CDCl3
1.000
2.295
3.485
1.234
3.517
3.741
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

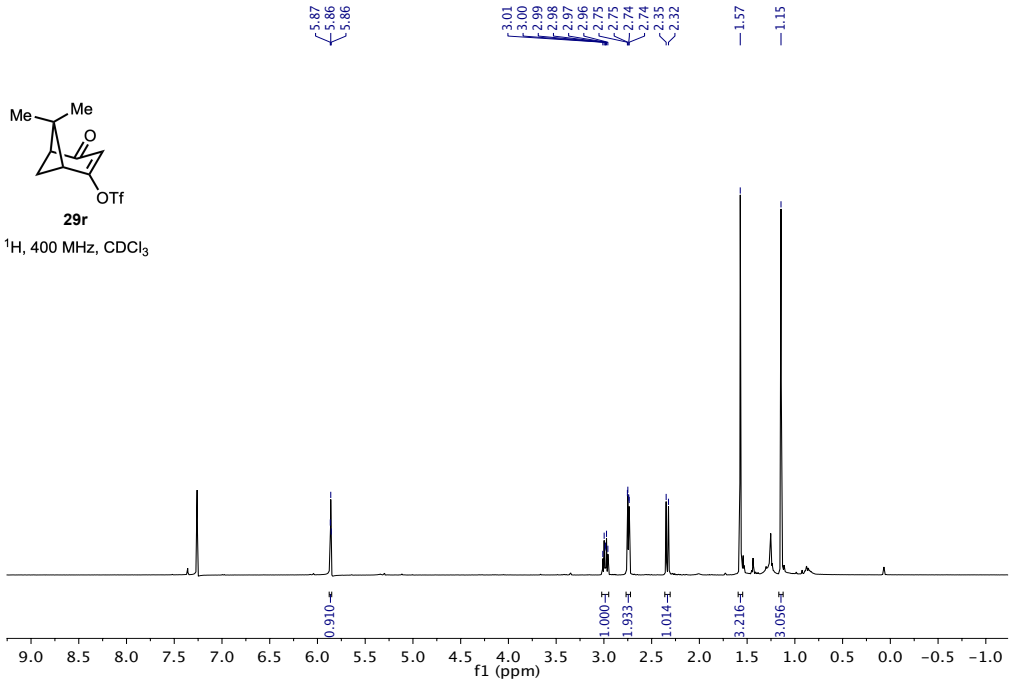

196.51
171.12
166.17
118.14
62.77
47.70
34.40
33.46
21.76
14.05
OTf
Me
EtO2C
O
29o
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

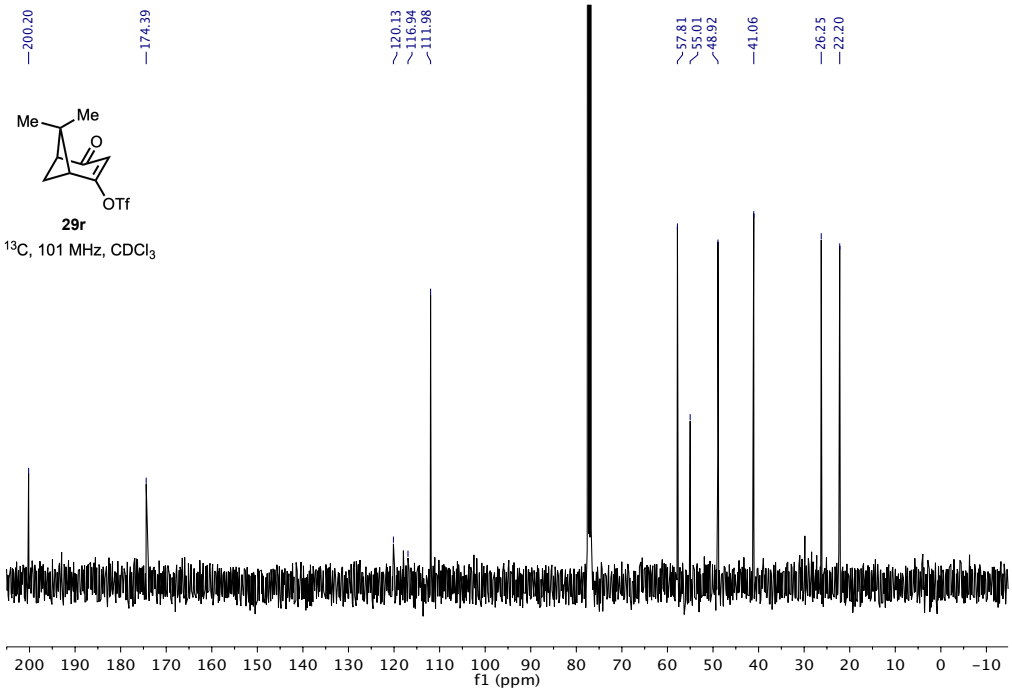

OTf
EtO2C
O
29p
1H, 400 MHz, CDCl3
f1 (ppm)

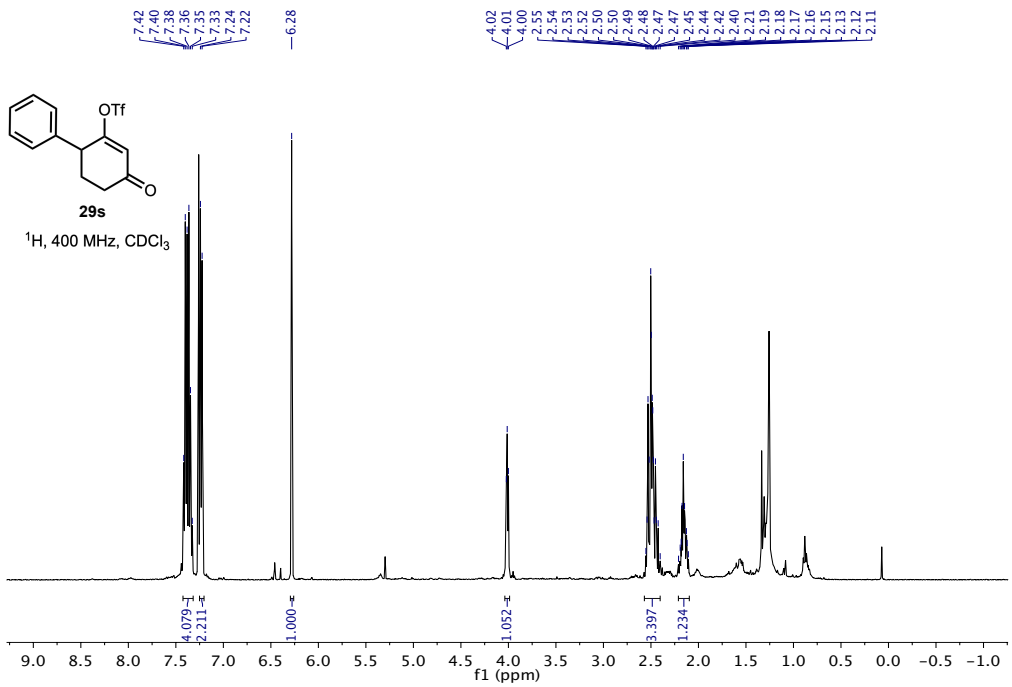

OTf
EtO2C
O
29p
13C, 101 MHz, CDCl3
f1 (ppm)

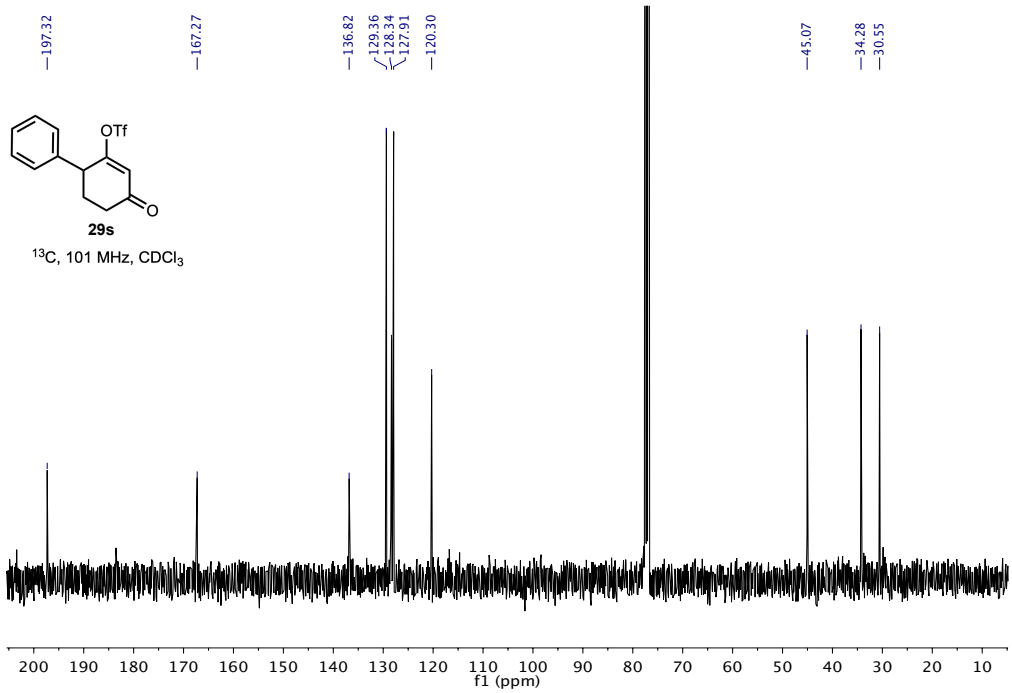

OTf
O
29q
^{1}H, 400 MHz, $CDCl_3$
6.07
5.81
5.79
5.77
5.75
5.72
5.70
5.20
5.17
5.16
2.82
2.80
2.79
2.78
2.59
2.57
2.57
2.57
2.56
2.54
2.53
2.52
2.51
2.50
2.49
2.48
2.44
2.43
2.42
2.41
2.40
2.38
2.38
2.36
2.35
2.33
2.31
2.21
2.20
2.19
2.17
2.16
2.15
2.00
1.99
1.97
1.96
1.000
1.137
2.180
1.071
2.359
2.416
1.297
1.314
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 0.0 −0.5 −1.0
f1 (ppm)

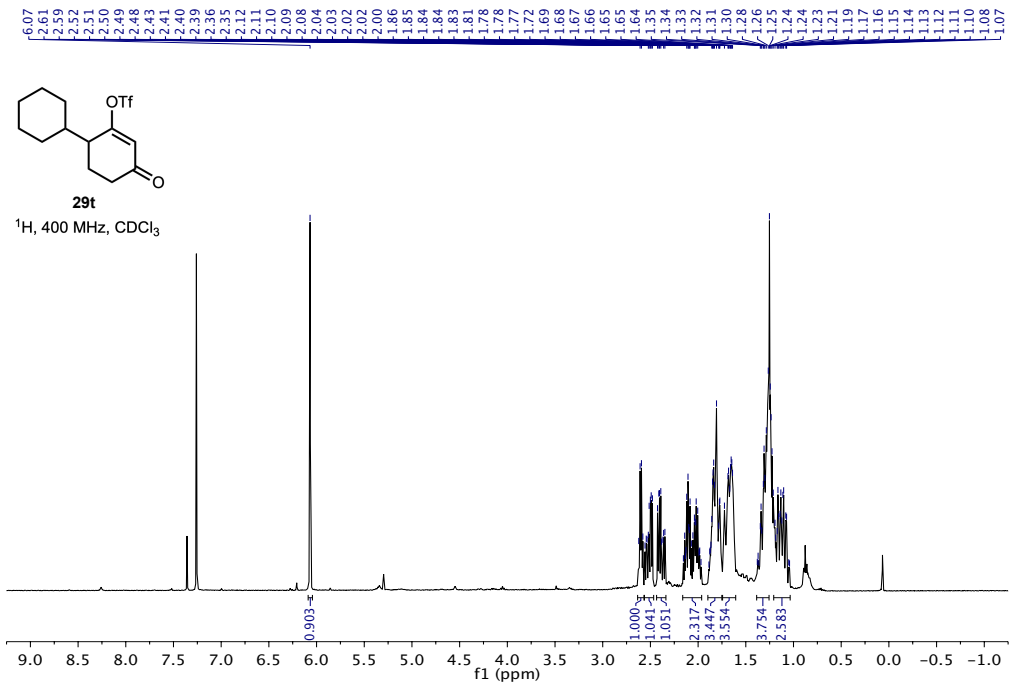

197.39
169.41
133.57
119.24
119.00
38.04
34.97
34.33
25.18
OTf
O
29q
^{13}C, 101 MHz, $CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

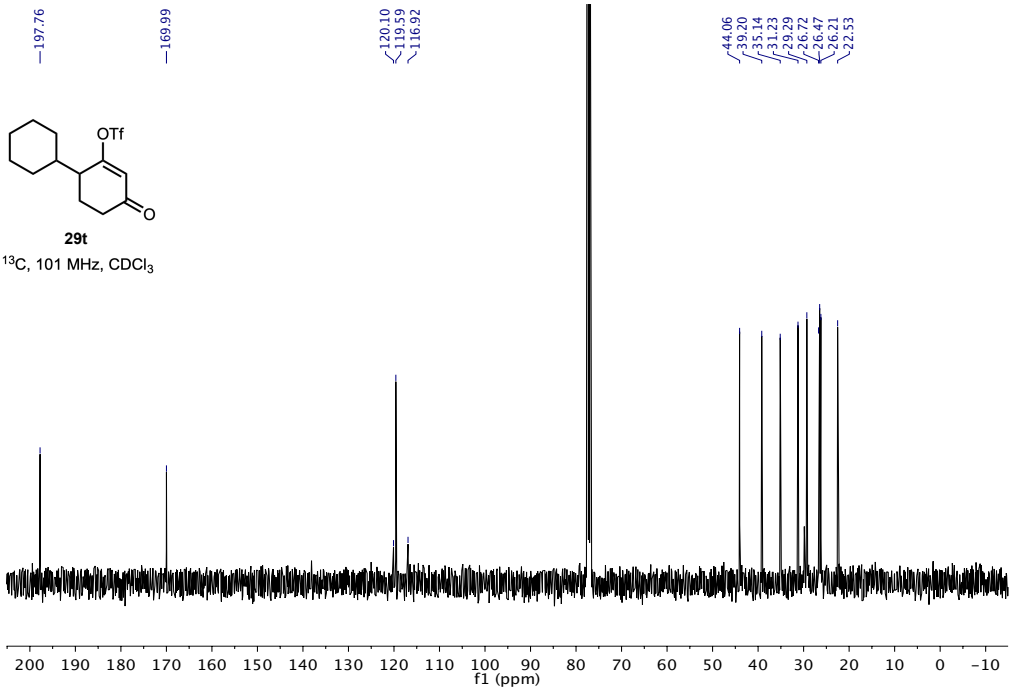

Me
Me
O
OTf
29r
^{1}H, 400 MHz, $CDCl_3$
5.87
5.86
5.86
3.01
3.00
2.99
2.98
2.97
2.96
2.75
2.75
2.74
2.74
2.35
2.32
1.57
1.15
0.910
1.000
1.933
1.014
3.216
3.056
f1 (ppm)

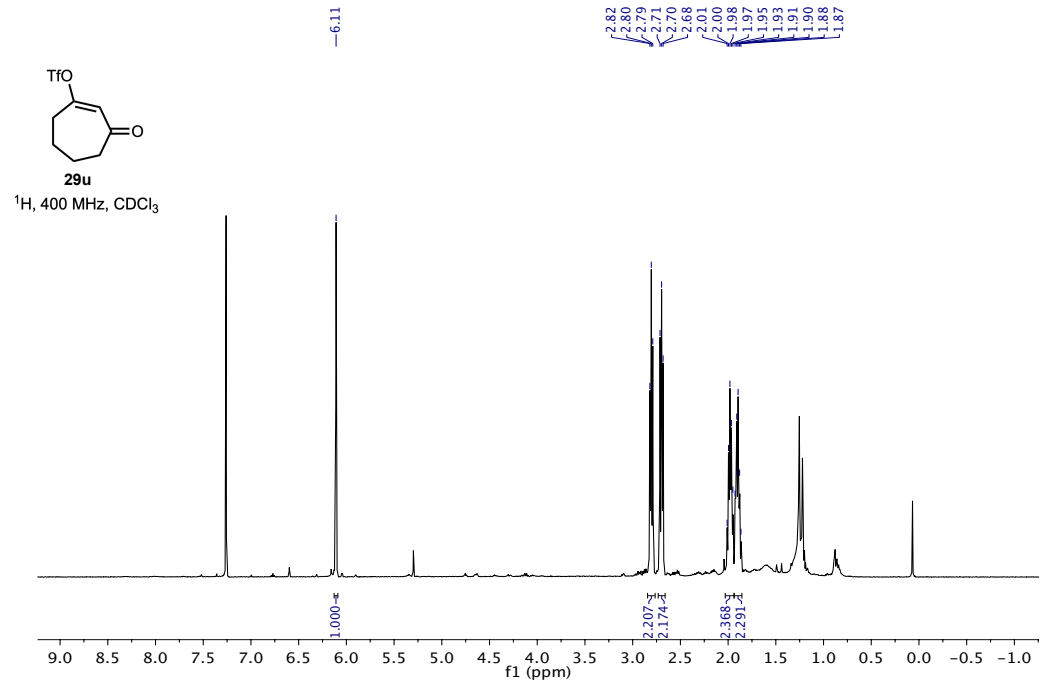

Me
Me
O
OTf
29r
^{13}C, 101 MHz, $CDCl_3$
200.20
174.39
120.13
116.94
111.98
57.81
55.01
48.92
41.06
26.25
22.20
f1 (ppm)

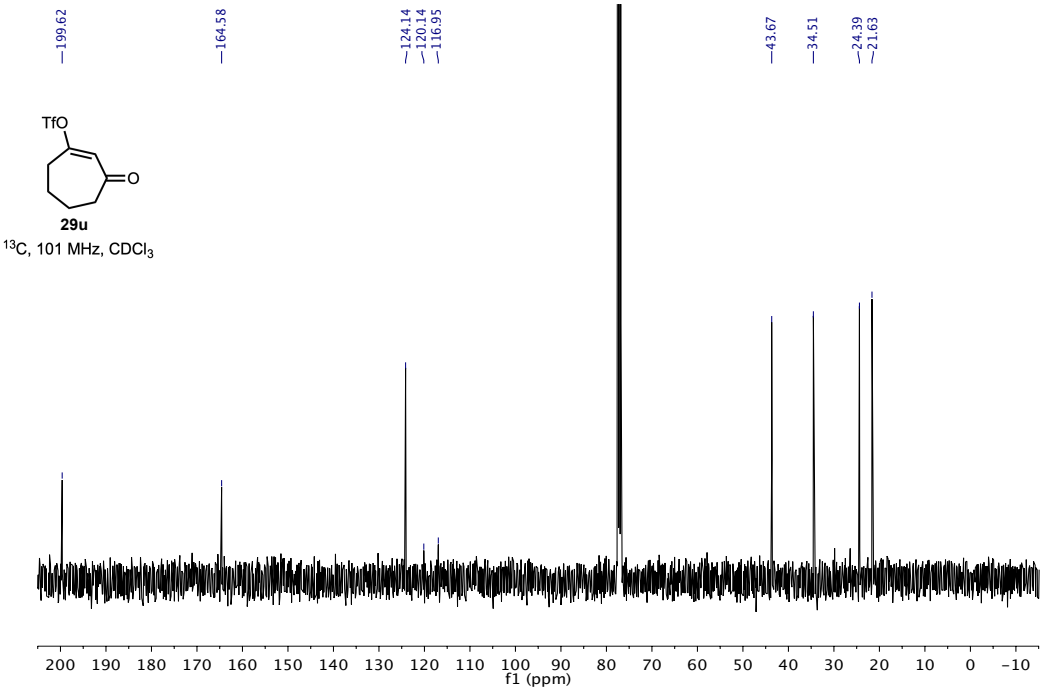

7.42
7.40
7.38
7.36
7.35
7.33
7.24
7.22
6.28
4.02
4.01
4.00
2.55
2.54
2.53
2.52
2.50
2.50
2.49
2.48
2.47
2.47
2.45
2.44
2.42
2.40
2.21
2.19
2.18
2.17
2.16
2.15
2.13
2.12
2.11
OTf
O
29s
1H, 400 MHz, CDCl3
4.079
2.211
1.000
1.052
3.397
1.234
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

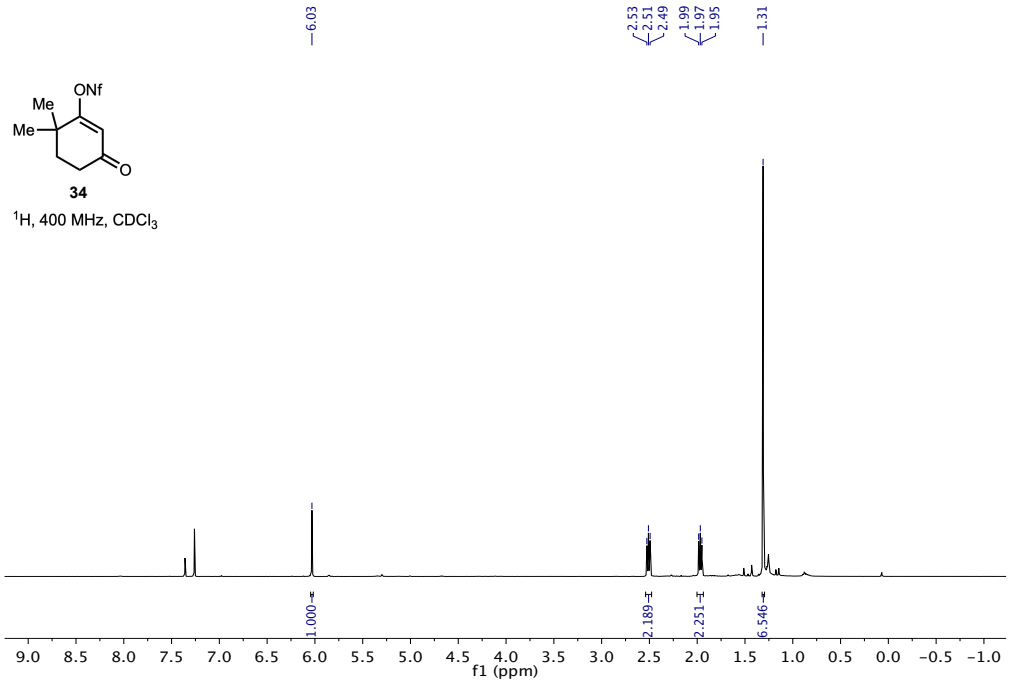

197.32
167.27
136.82
129.36
128.34
127.91
120.30
45.07
34.28
30.55
OTf
O
29s
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

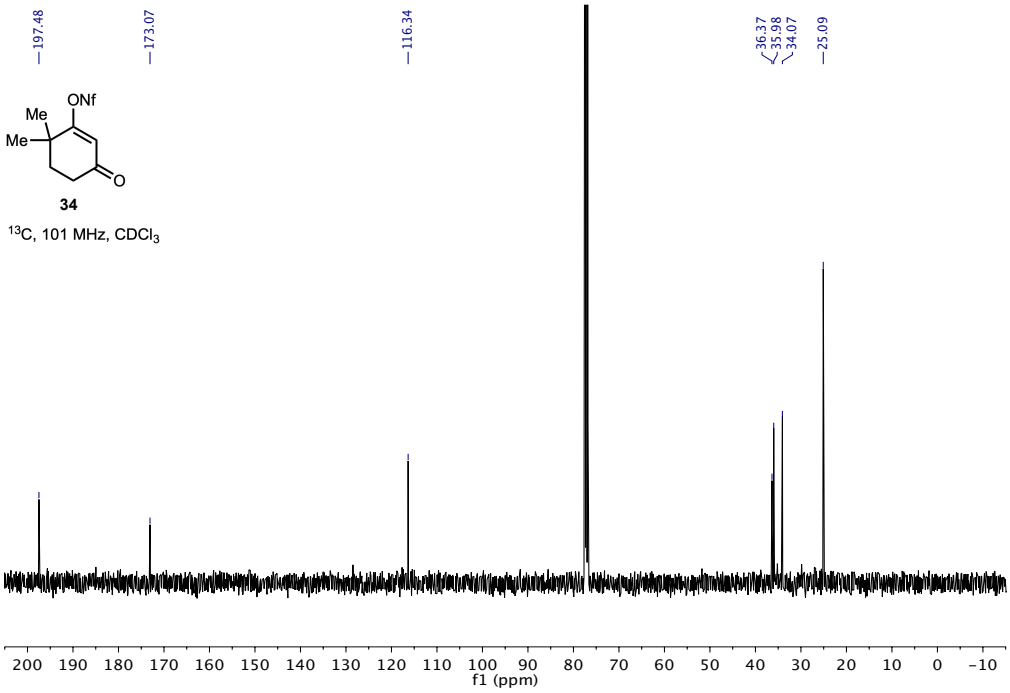

OTf
O
29t
1H, 400 MHz, CDCl3
f1 (ppm)

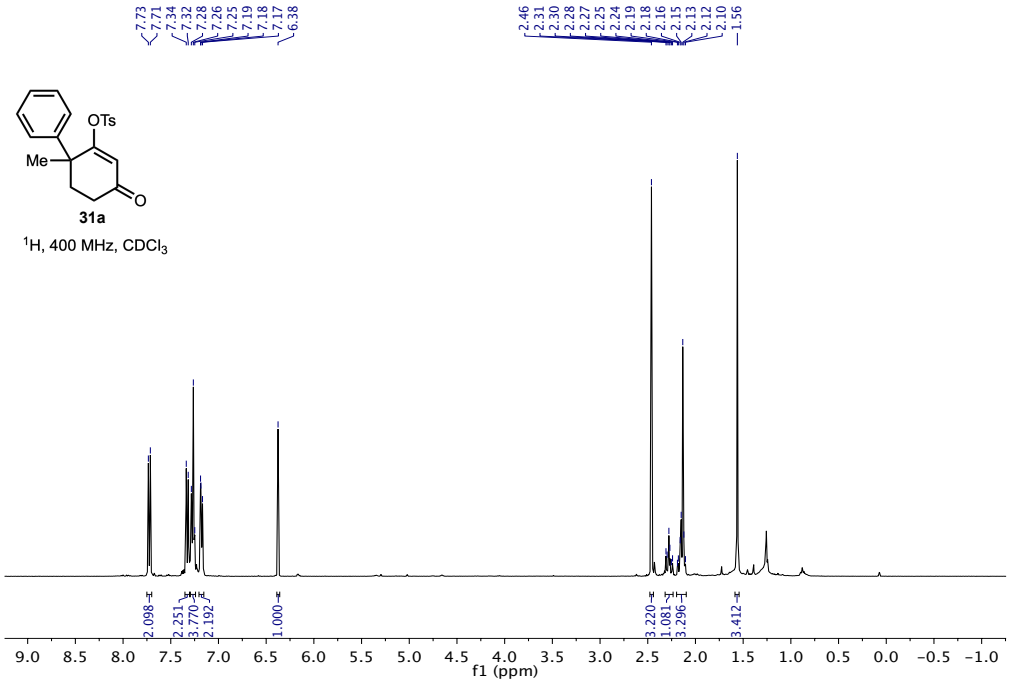

OTf
O
29t
13C, 101 MHz, CDCl3
f1 (ppm)

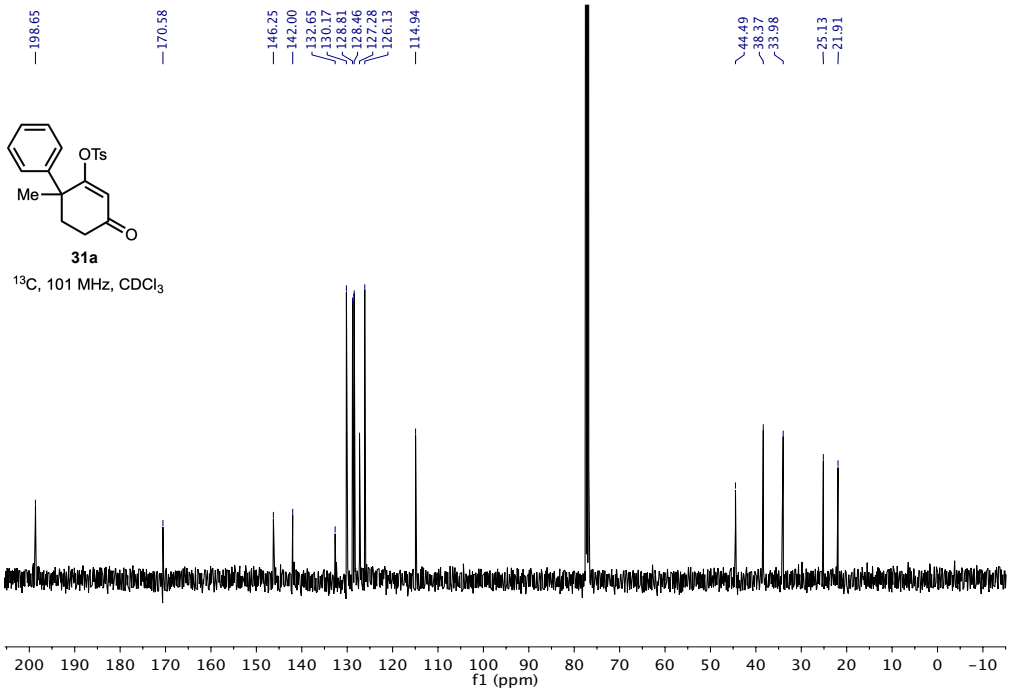

TfO
O
29u
^{1}H, 400 MHz, $CDCl_3$
6.11
2.82
2.80
2.79
2.71
2.70
2.68
2.01
2.00
1.98
1.97
1.95
1.93
1.91
1.90
1.88
1.87
1.000
2.207
2.174
2.368
2.291
f1 (ppm)

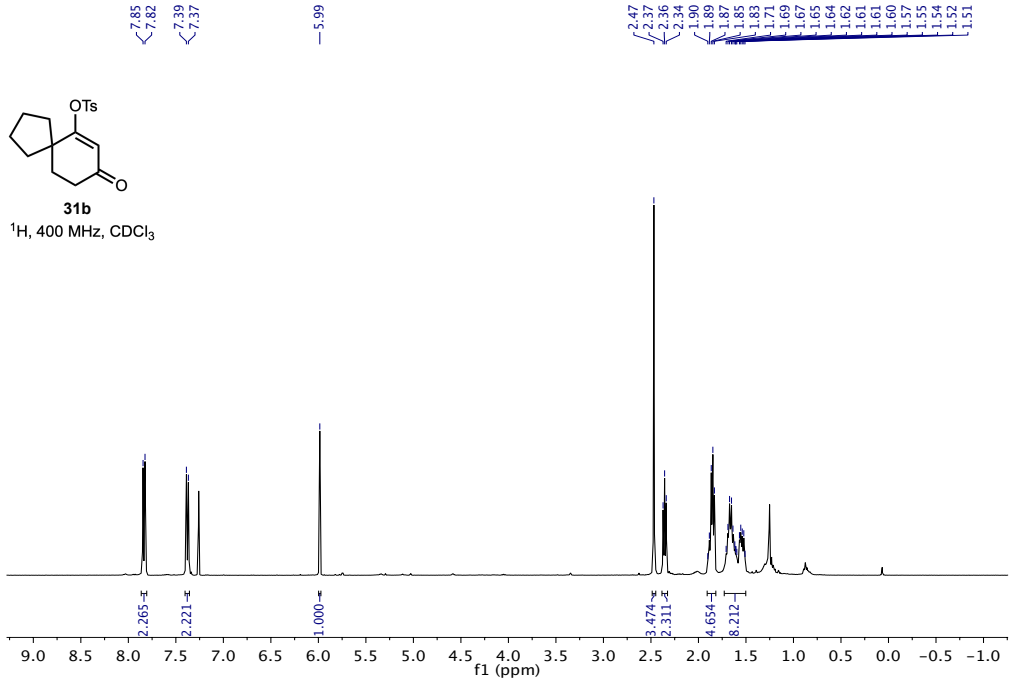

TfO
O
29u
^{13}C, 101 MHz, $CDCl_3$
199.62
164.58
124.14
120.14
116.95
43.67
34.51
24.39
21.63
f1 (ppm)

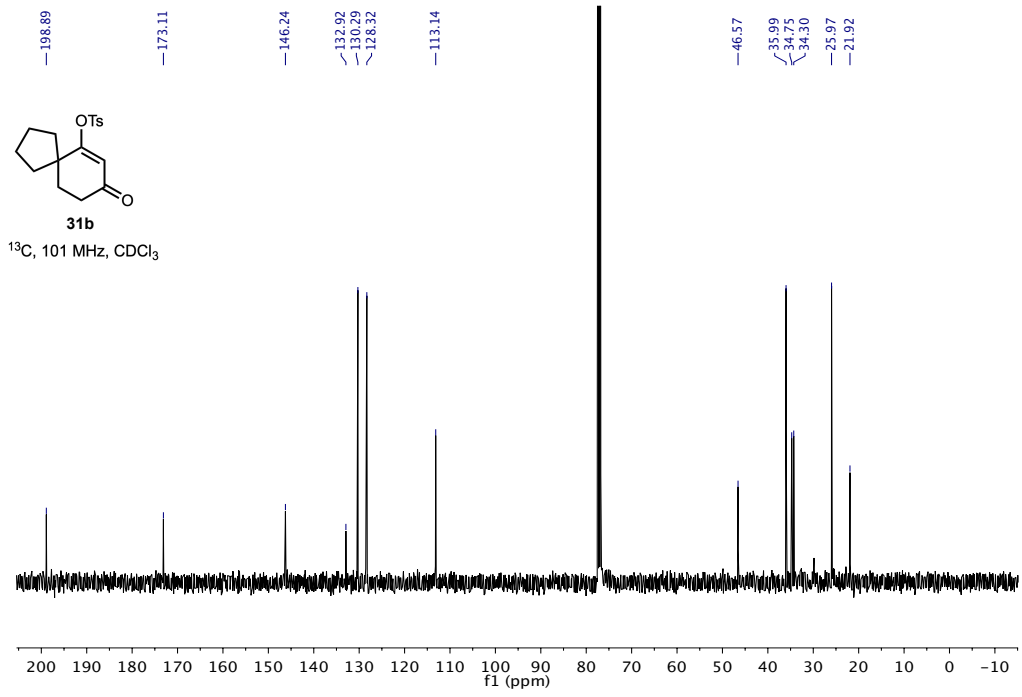

6.03
2.53
2.51
2.49
1.99
1.97
1.95
1.31
ONf
Me
Me
O
34
1H, 400 MHz, CDCl3
1.000
2.189
2.251
6.546
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

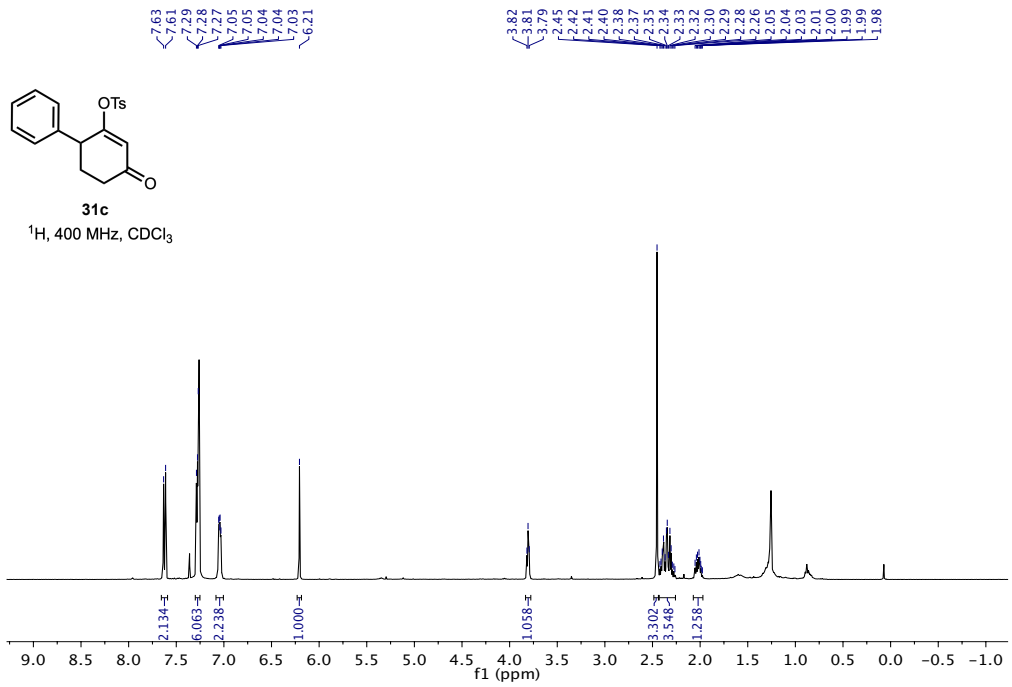

197.48
173.07
116.34
36.37
35.98
34.07
25.09
ONf
Me
Me
O
34
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

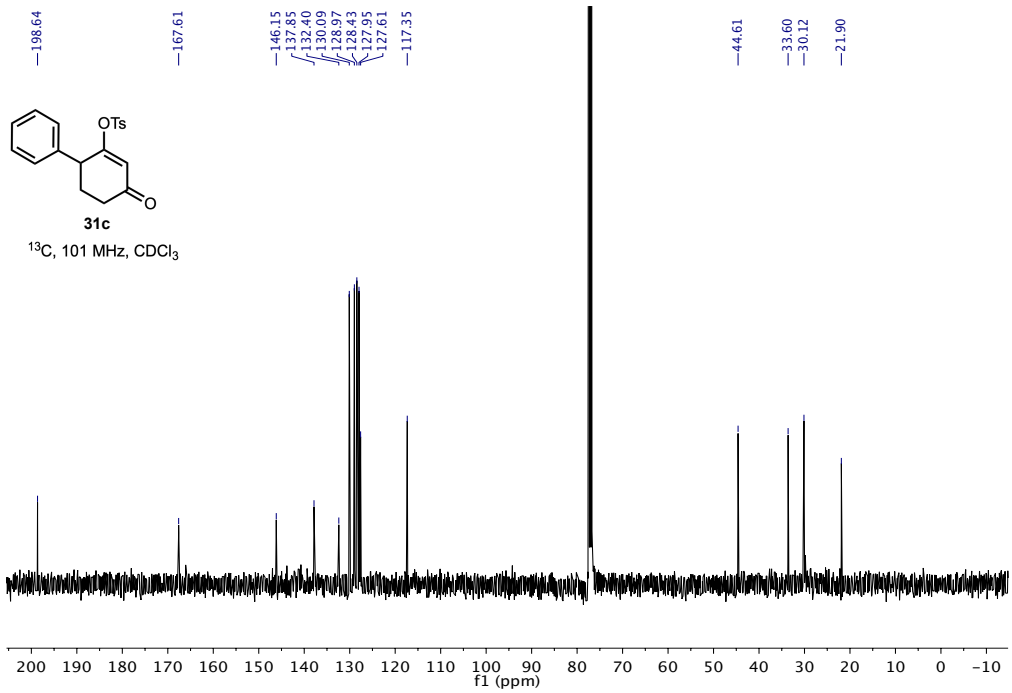

7.73
7.71
7.34
7.32
7.28
7.26
7.25
7.19
7.18
7.17
6.38
2.46
2.31
2.30
2.28
2.27
2.25
2.24
2.19
2.18
2.16
2.15
2.13
2.12
2.10
1.56
OTs
Me
O
31a
1H, 400 MHz, CDCl3
2.098
2.251
3.770
2.192
1.000
3.220
1.081
3.296
3.412
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

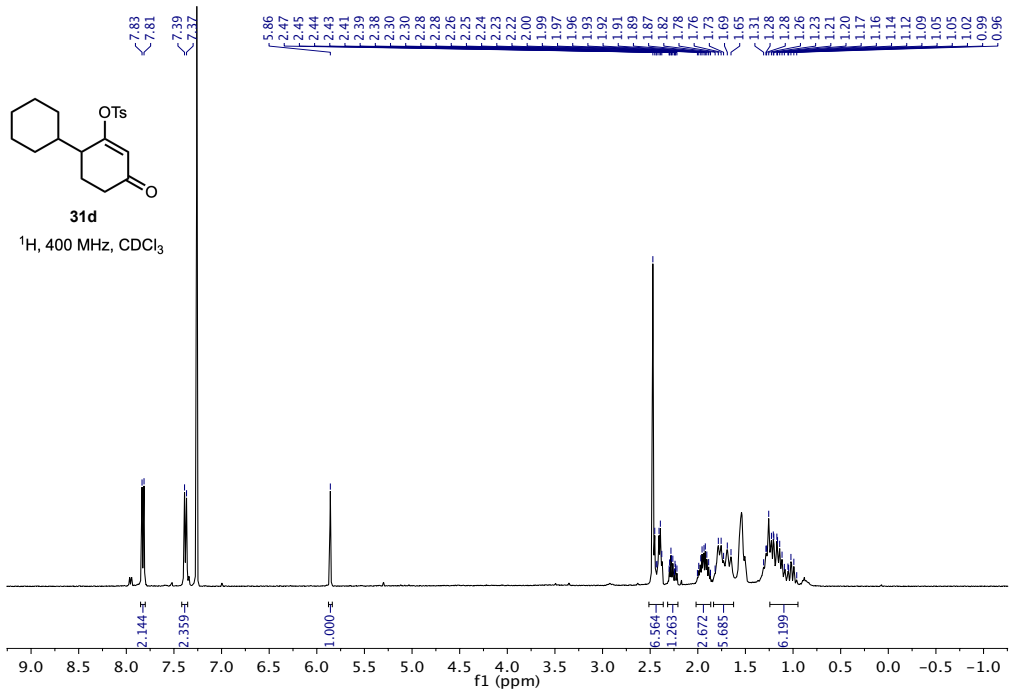

198.65
170.58
146.25
142.00
132.65
130.17
128.81
128.46
127.28
126.13
114.94
44.49
38.37
33.98
25.13
21.91
OTs
Me
O
31a
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

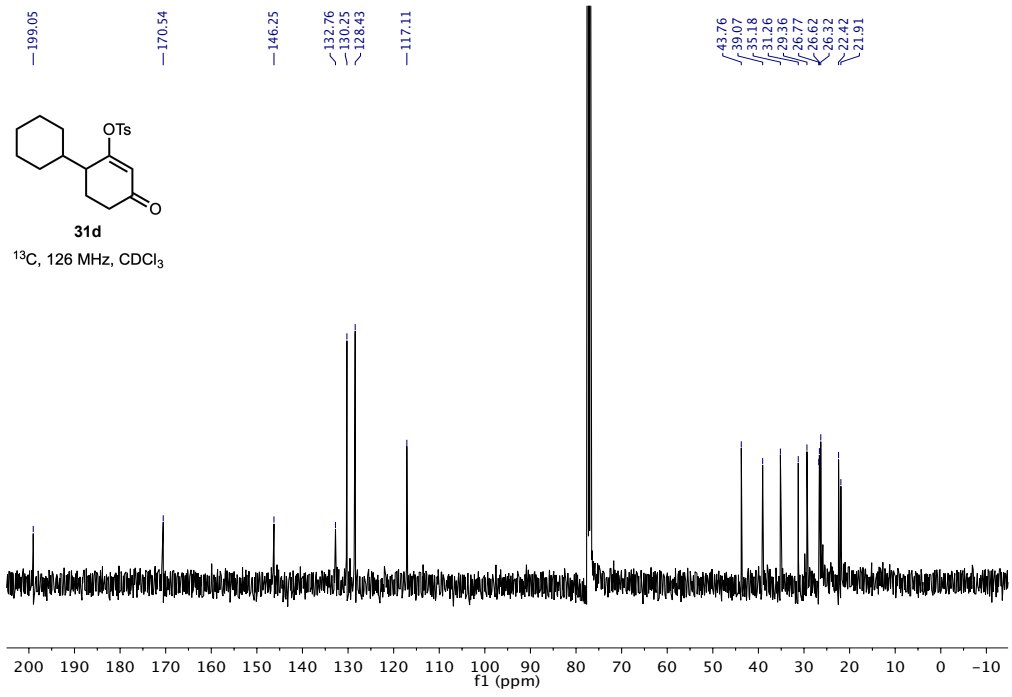

7.85
7.82
7.39
7.37
5.99
2.47
2.37
2.36
2.34
1.90
1.89
1.87
1.85
1.83
1.71
1.69
1.67
1.65
1.64
1.62
1.61
1.61
1.60
1.57
1.55
1.54
1.52
1.51
OTs
O
31b
1H, 400 MHz, CDCl3
2.265
2.221
1.000
3.474
2.311
4.654
8.212
f1 (ppm)

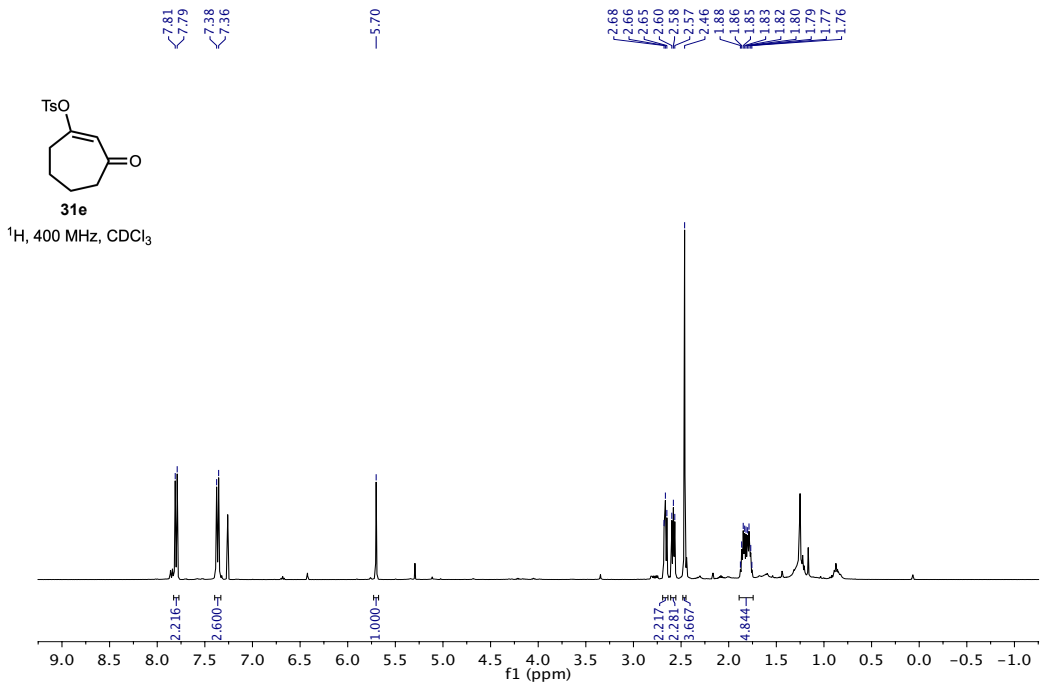

198.89
173.11
146.24
132.92
130.29
128.32
113.14
46.57
35.99
34.75
34.30
25.97
21.92
OTs
O
31b
13C, 101 MHz, CDCl3
f1 (ppm)

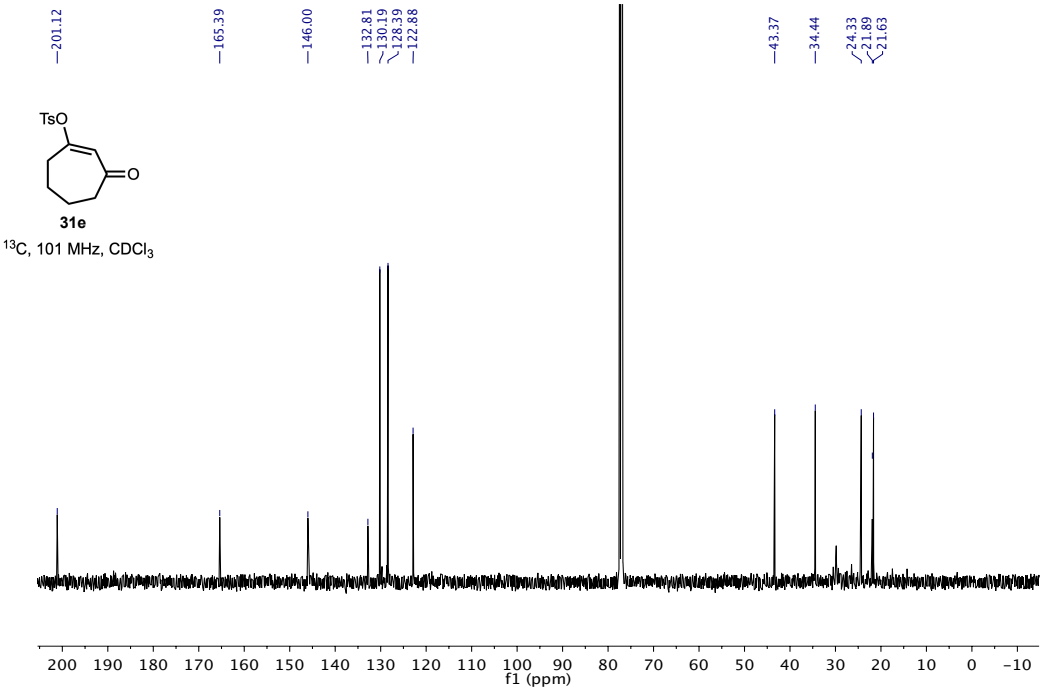

7.63
7.61
7.29
7.28
7.27
7.05
7.05
7.04
7.04
7.03
6.21
3.82
3.81
3.79
2.45
2.42
2.41
2.40
2.38
2.37
2.35
2.34
2.33
2.32
2.30
2.29
2.28
2.26
2.05
2.04
2.03
2.01
2.00
1.99
1.99
1.98
OTs
O
31c
1H, 400 MHz, CDCl3
2.134
6.063
2.238
1.000
1.058
3.302
3.548
1.258
f1 (ppm)

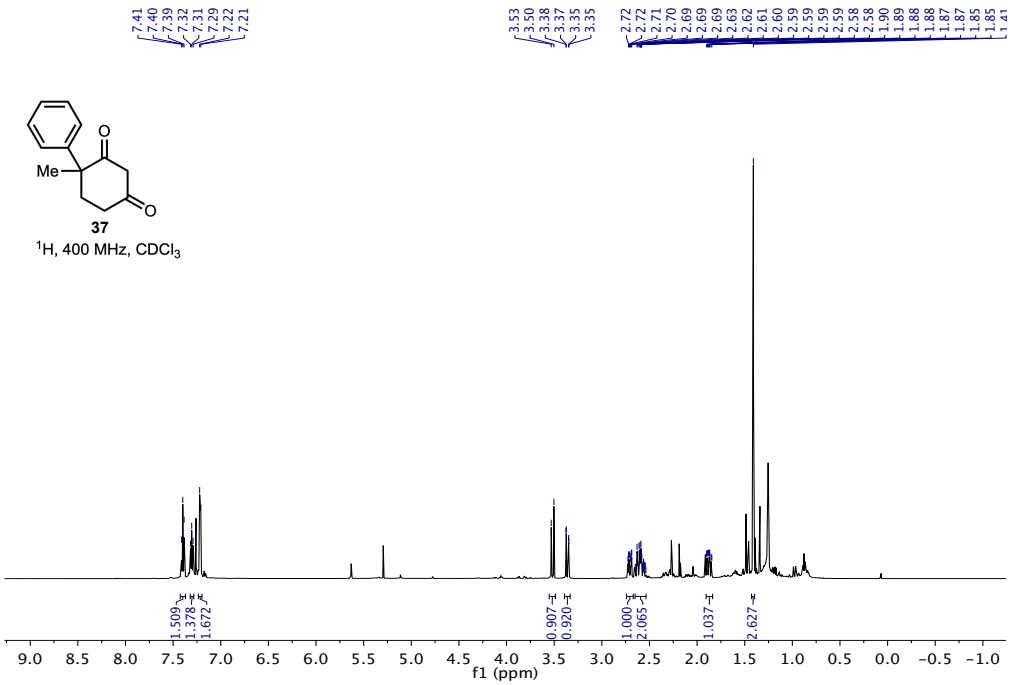

198.64
167.61
146.15
137.85
132.40
130.09
128.97
128.43
127.95
127.61
117.35
44.61
33.60
30.12
21.90
OTs
O
31c
13C, 101 MHz, CDCl3
f1 (ppm)

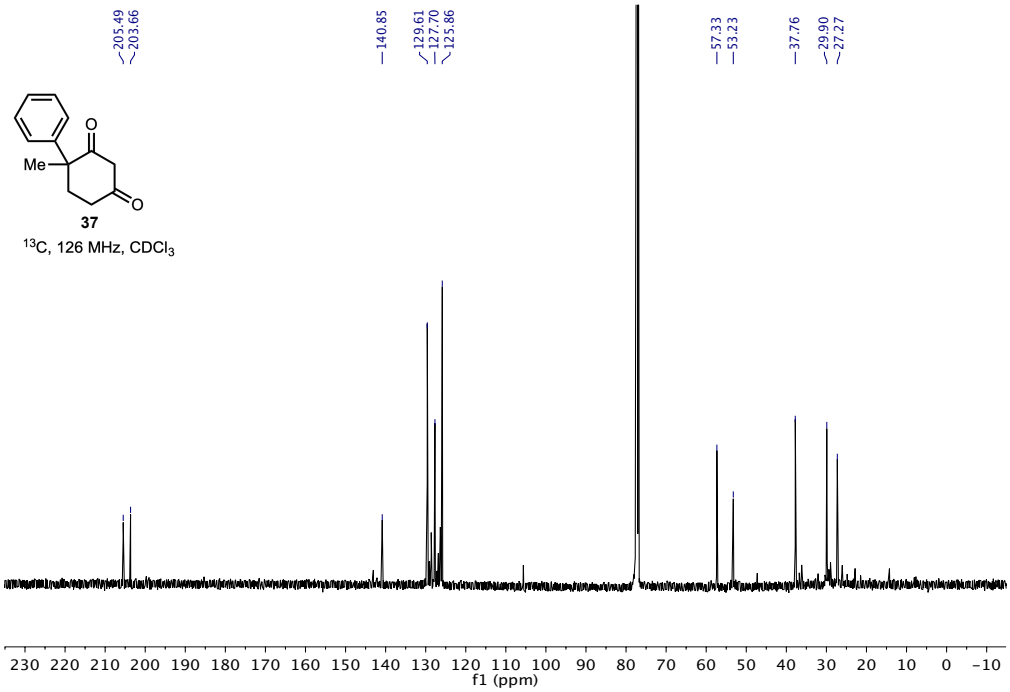

OTs
O
31d
^{1}H, 400 MHz, $CDCl_3$
f1 (ppm)

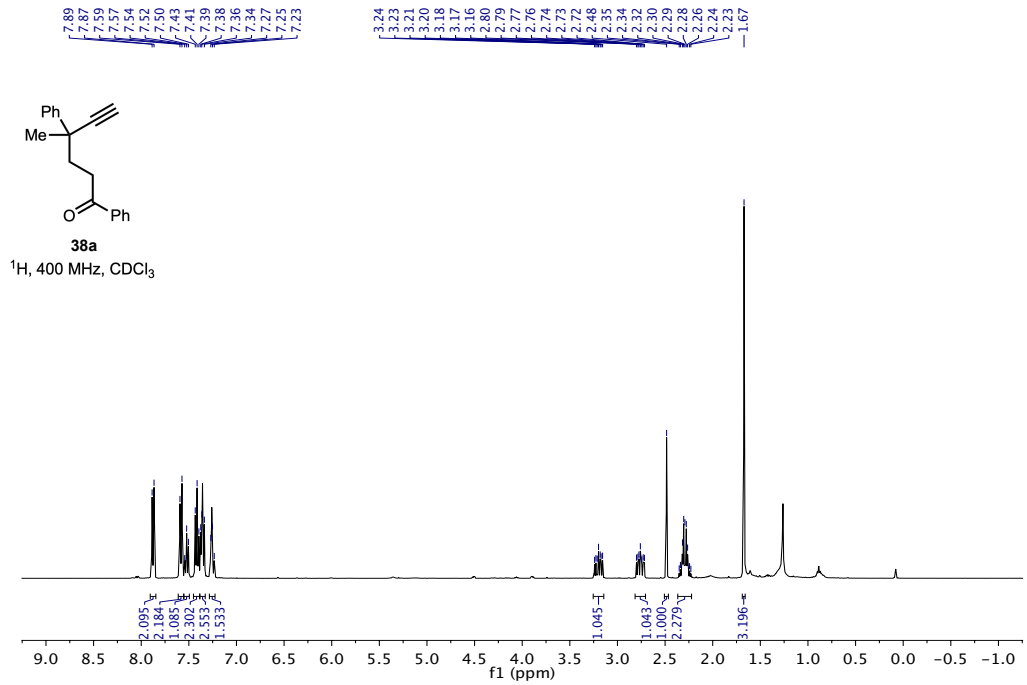

OTs
O
31d
^{13}C, 126 MHz, $CDCl_3$
f1 (ppm)

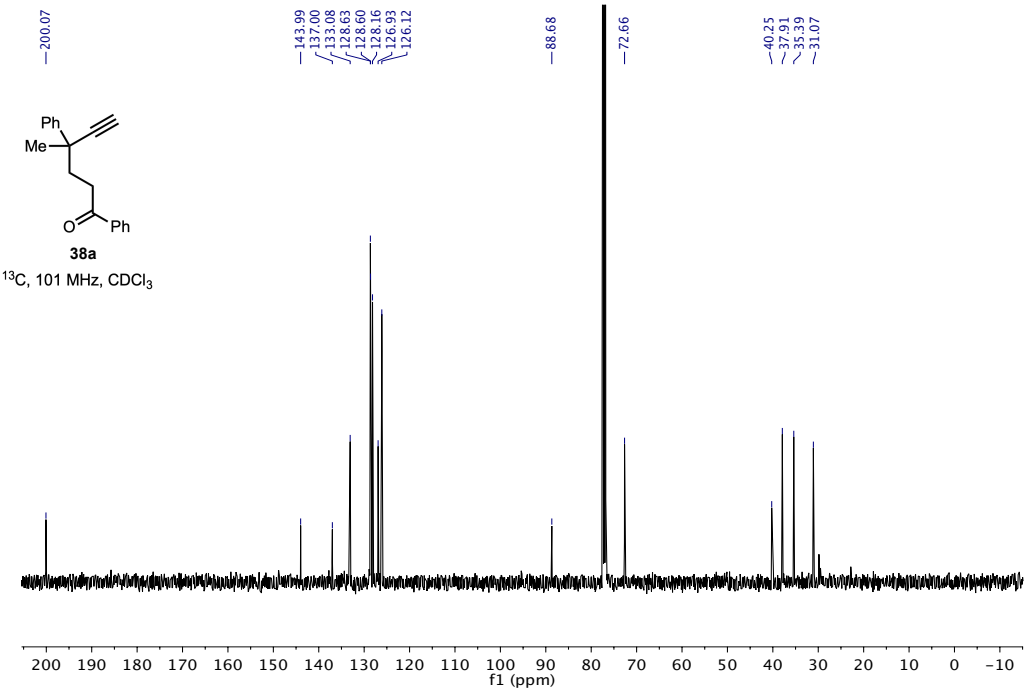

7.81
7.79
7.38
7.36
5.70
2.68
2.66
2.65
2.60
2.58
2.57
2.46
1.88
1.86
1.85
1.83
1.82
1.80
1.79
1.77
1.76
TsO
O
31e
1H, 400 MHz, CDCl3
2.216
2.600
1.000
2.217
2.281
3.667
4.844
f1 (ppm)

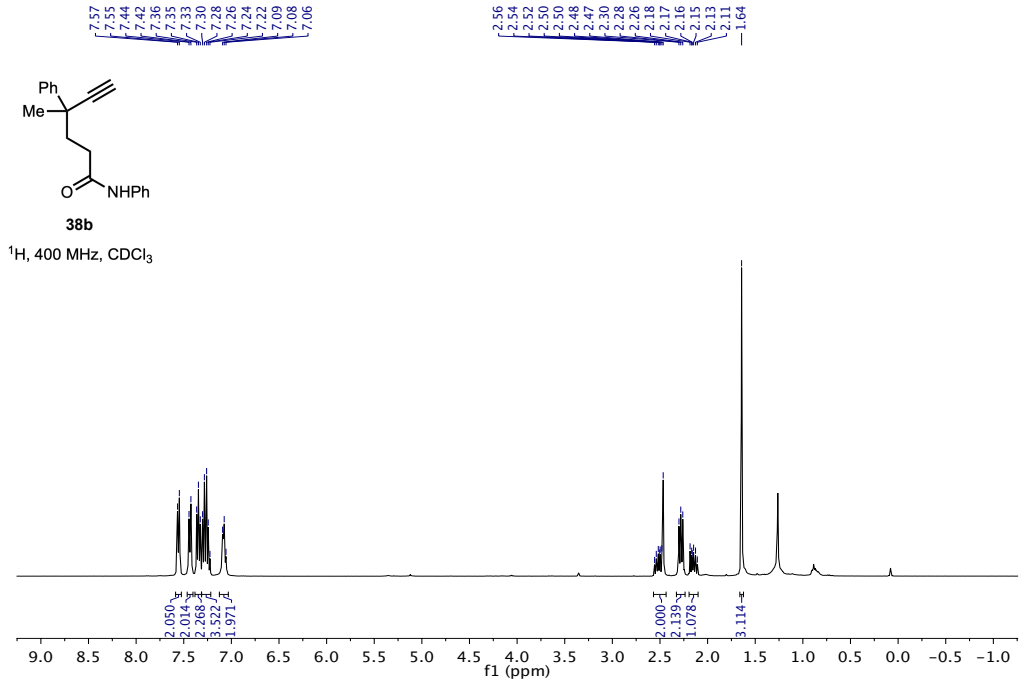

201.12
165.39
146.00
132.81
130.19
128.39
122.88
43.37
34.44
24.33
21.89
21.63
TsO
O
31e
13C, 101 MHz, CDCl3
f1 (ppm)

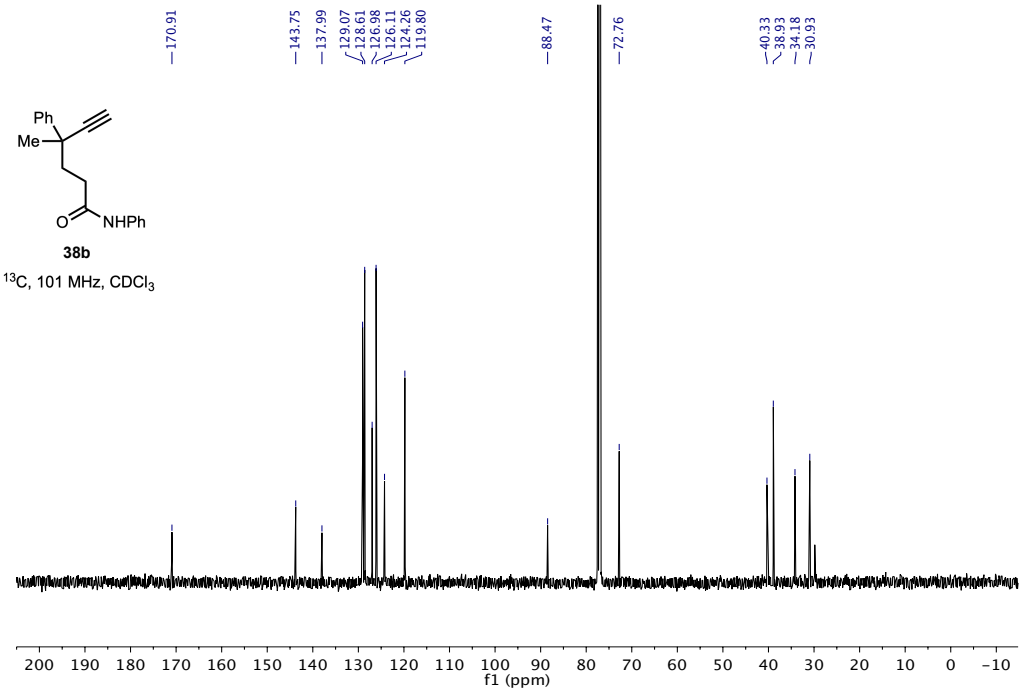

7.41
7.40
7.39
7.32
7.31
7.29
7.22
7.21
3.53
3.50
3.38
3.37
3.35
3.35
2.72
2.72
2.71
2.70
2.69
2.69
2.69
2.63
2.62
2.61
2.60
2.59
2.59
2.59
2.59
2.58
2.58
1.90
1.89
1.88
1.88
1.87
1.87
1.85
1.85
1.41
Me
O
O
37
1H, 400 MHz, CDCl3
1.509
1.378
1.672
0.907
0.920
1.000
2.065
1.037
2.627
9.0 8.5 8.0 7.5 7.0 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 0.0 -0.5 -1.0
f1 (ppm)

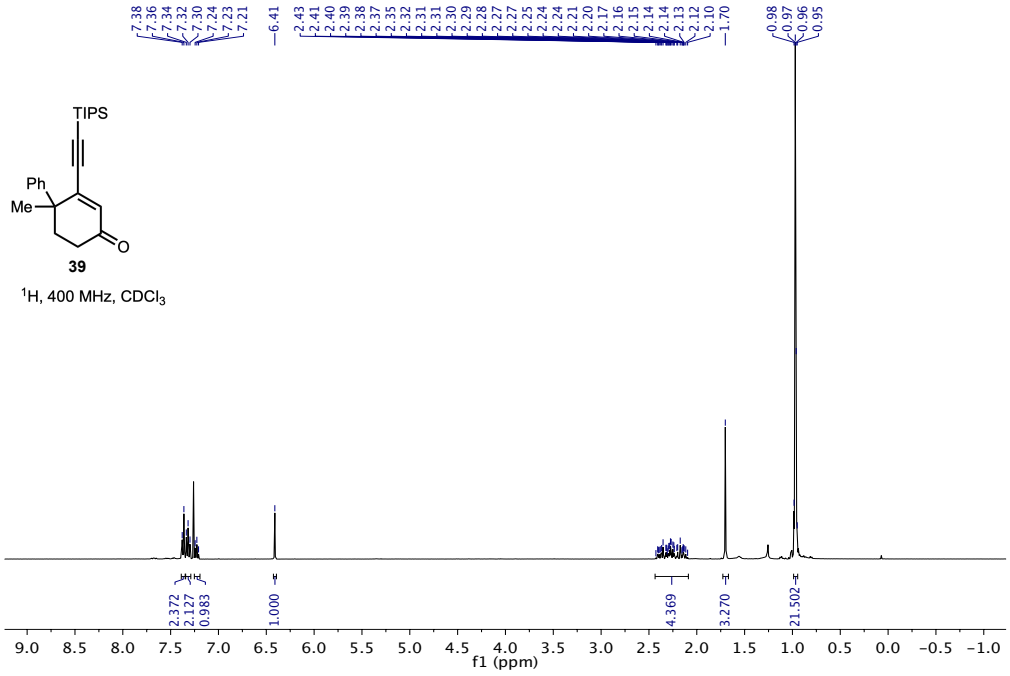

205.49
203.66
140.85
129.61
127.70
125.86
57.33
53.23
37.76
29.90
27.27
Me
O
O
37
13C, 126 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

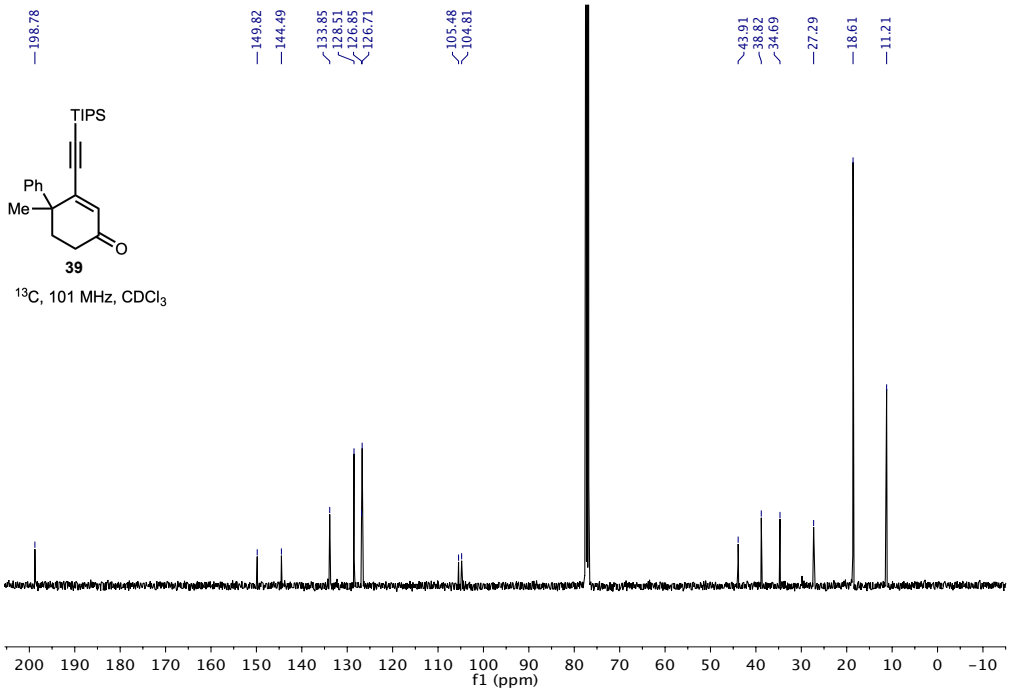

Ph
Me
O
Ph
38a
1H, 400 MHz, CDCl3
f1 (ppm)

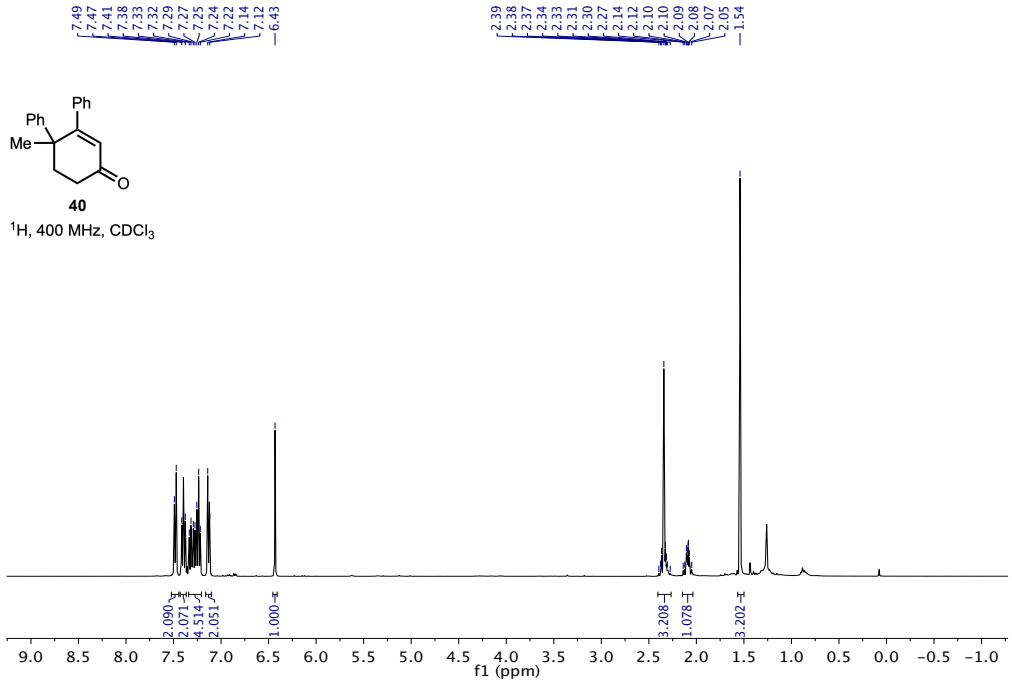

Ph
Me
O
Ph
38a
13C, 101 MHz, CDCl3
f1 (ppm)

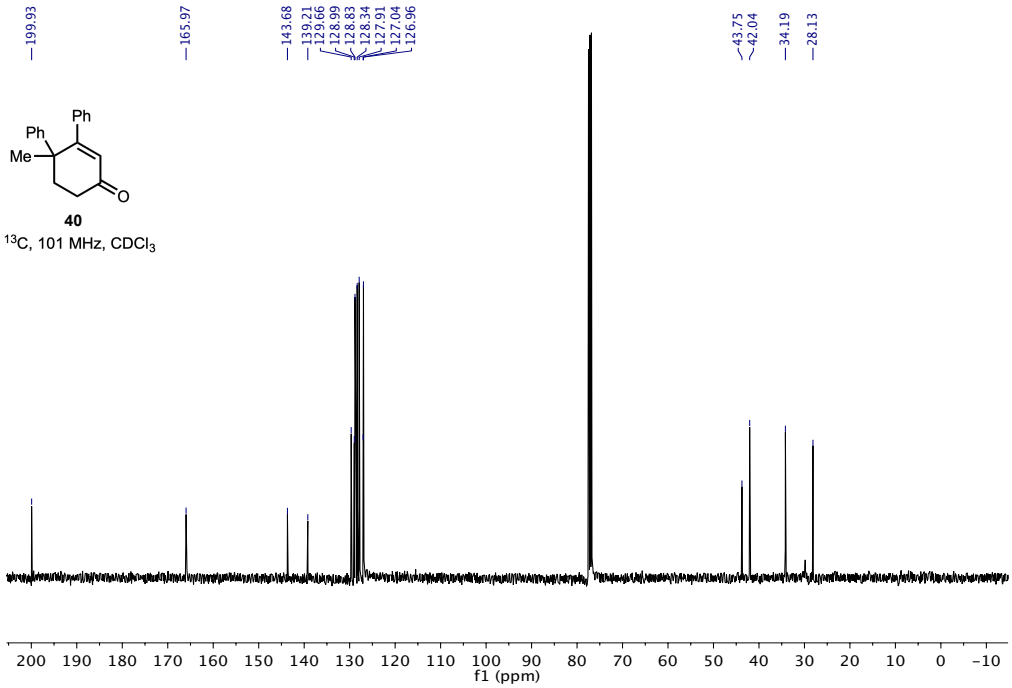

7.57
7.55
7.44
7.42
7.36
7.35
7.33
7.30
7.28
7.26
7.24
7.22
7.09
7.08
7.06
2.56
2.54
2.52
2.50
2.50
2.48
2.47
2.30
2.28
2.26
2.18
2.17
2.16
2.15
2.13
2.11
1.64
Ph
Me
O
NHPh
38b
1H, 400 MHz, CDCl3
2.050
2.014
2.268
3.522
1.971
2.000
2.139
1.078
3.114
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

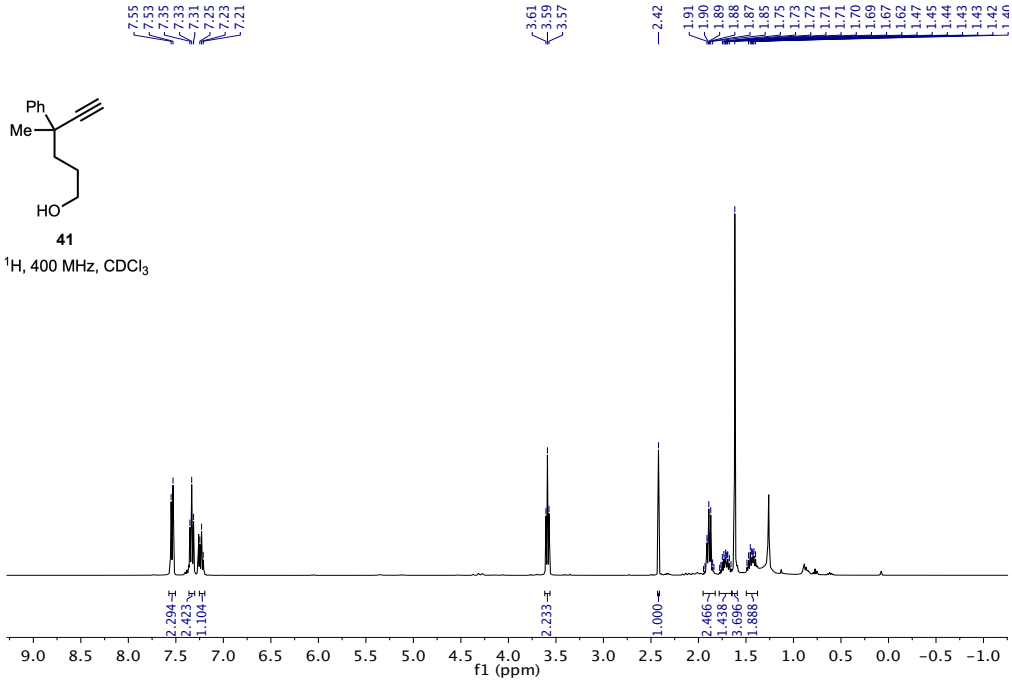

170.91
143.75
137.99
129.07
128.61
126.98
126.11
124.26
119.80
88.47
72.76
40.33
38.93
34.18
30.93
Ph
Me
O
NHPh
38b
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

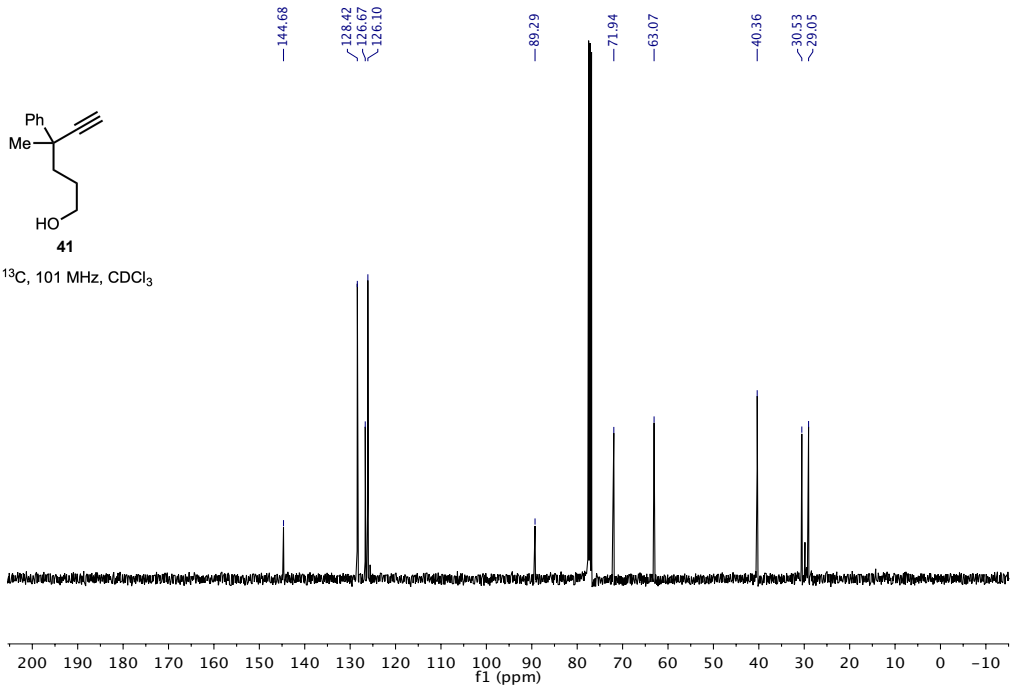

TIPS
Ph
Me
O
39
^{1}H, 400 MHz, $CDCl_3$
7.38
7.36
7.34
7.32
7.30
7.24
7.23
7.21
6.41
2.43
2.41
2.40
2.39
2.38
2.37
2.35
2.32
2.31
2.31
2.30
2.29
2.28
2.27
2.27
2.25
2.24
2.24
2.21
2.20
2.17
2.16
2.15
2.14
2.14
2.13
2.12
2.10
1.70
0.98
0.97
0.96
0.95
2.372
2.127
0.983
1.000
4.369
3.270
21.502
f1 (ppm)

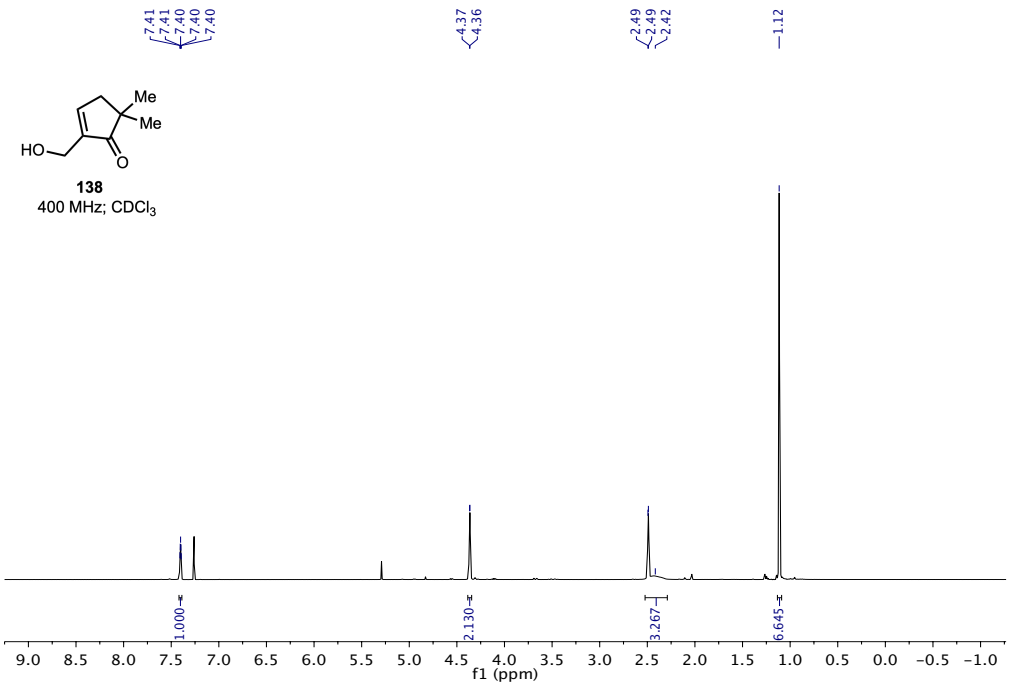

TIPS
Ph
Me
O
39
^{13}C, 101 MHz, $CDCl_3$
198.78
149.82
144.49
133.85
128.51
126.85
126.71
105.48
104.81
43.91
38.82
34.69
27.29
18.61
11.21
f1 (ppm)


7.49
7.47
7.41
7.38
7.33
7.32
7.29
7.27
7.25
7.24
7.22
7.14
7.12
6.43
2.39
2.38
2.37
2.34
2.33
2.31
2.30
2.27
2.14
2.12
2.10
2.10
2.09
2.08
2.07
2.05
1.54
Ph
Ph
Me
O
40
1H, 400 MHz, CDCl3
2.090
2.071
4.514
2.051
1.000
3.208
1.078
3.202
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 0.0 -0.5 -1.0
f1 (ppm)

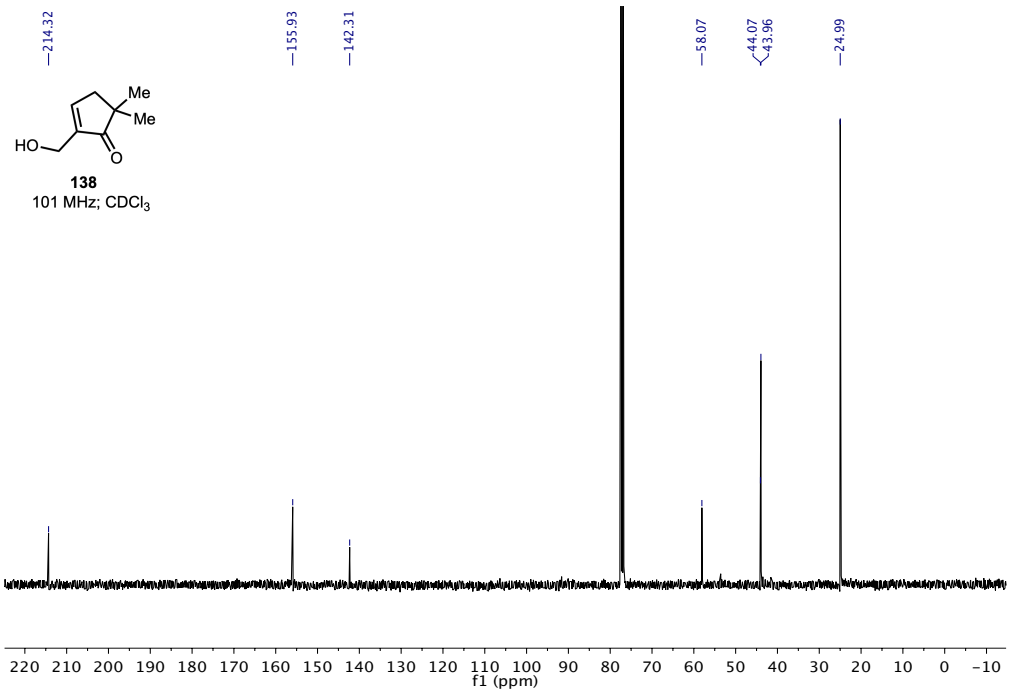

199.93
165.97
143.68
139.21
129.66
128.99
128.83
128.34
127.91
127.04
126.96
43.75
42.04
34.19
28.13
Ph
Ph
Me
O
40
13C, 101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
Me
HO
41
1H, 400 MHz, CDCl3
7.55
7.53
7.35
7.33
7.31
7.25
7.23
7.21
3.61
3.59
3.57
2.42
1.91
1.90
1.89
1.88
1.87
1.85
1.75
1.73
1.72
1.71
1.71
1.70
1.69
1.67
1.62
1.47
1.45
1.44
1.43
1.43
1.42
2.294
2.423
1.104
2.233
1.000
2.466
1.438
3.696
1.888
f1 (ppm)

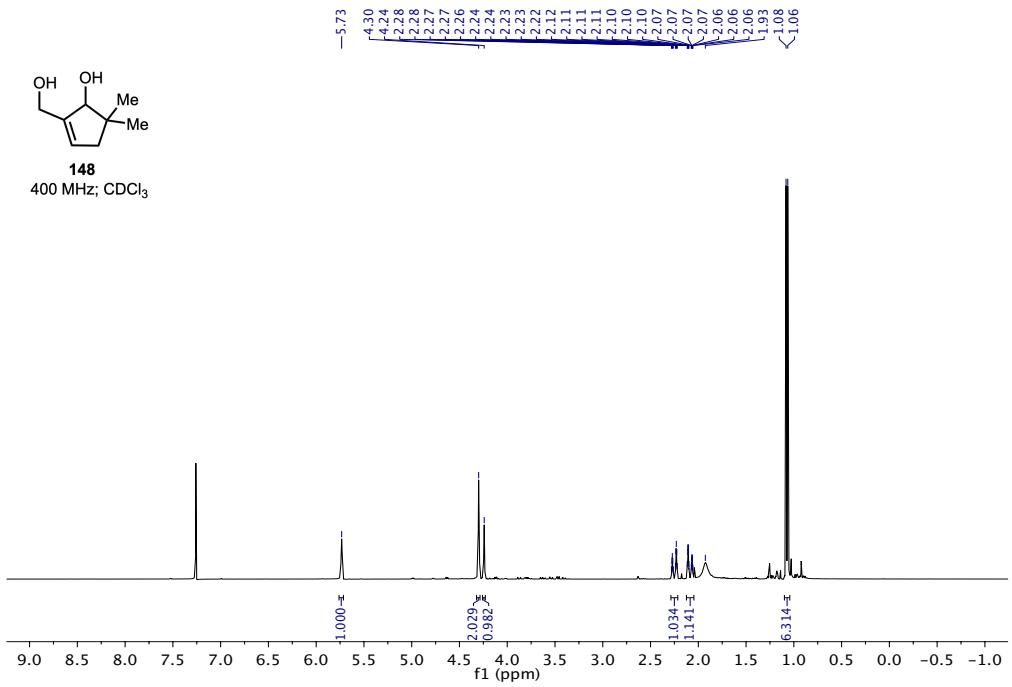

Ph
Me
HO
41
13C, 101 MHz, CDCl3
144.68
128.42
126.67
126.10
89.29
71.94
63.07
40.36
30.53
29.05
f1 (ppm)

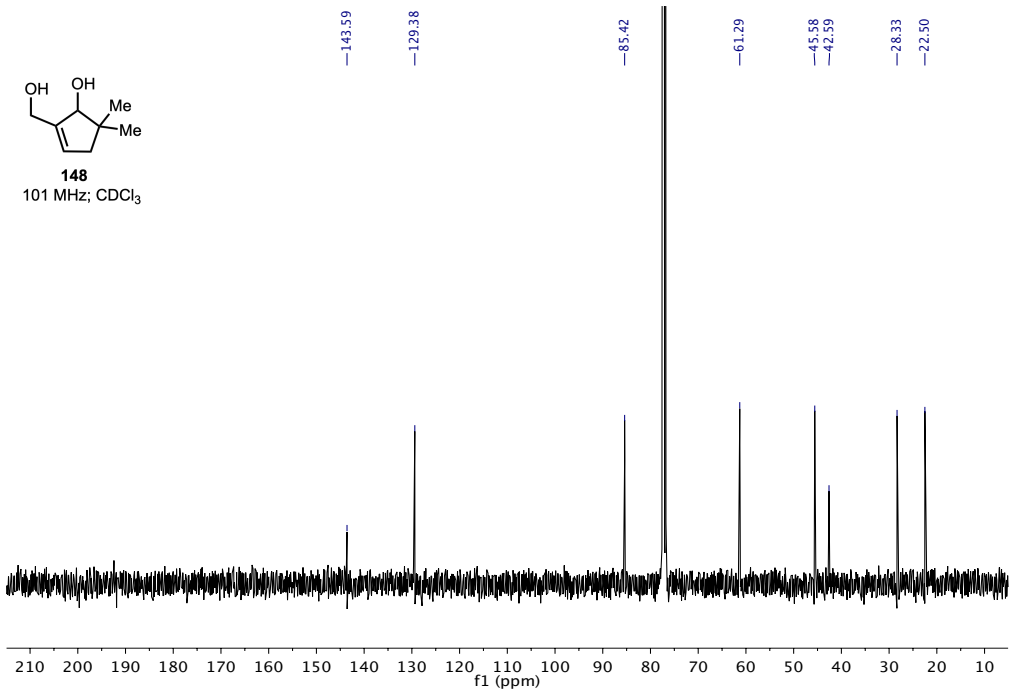


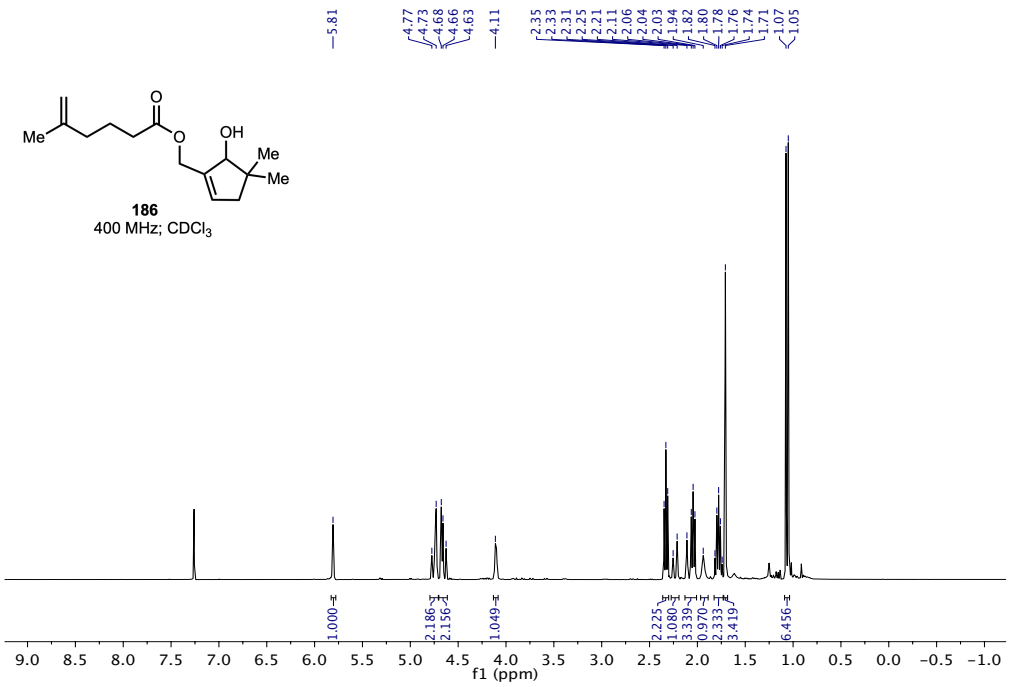
138
400 MHz; $CDCl_3$

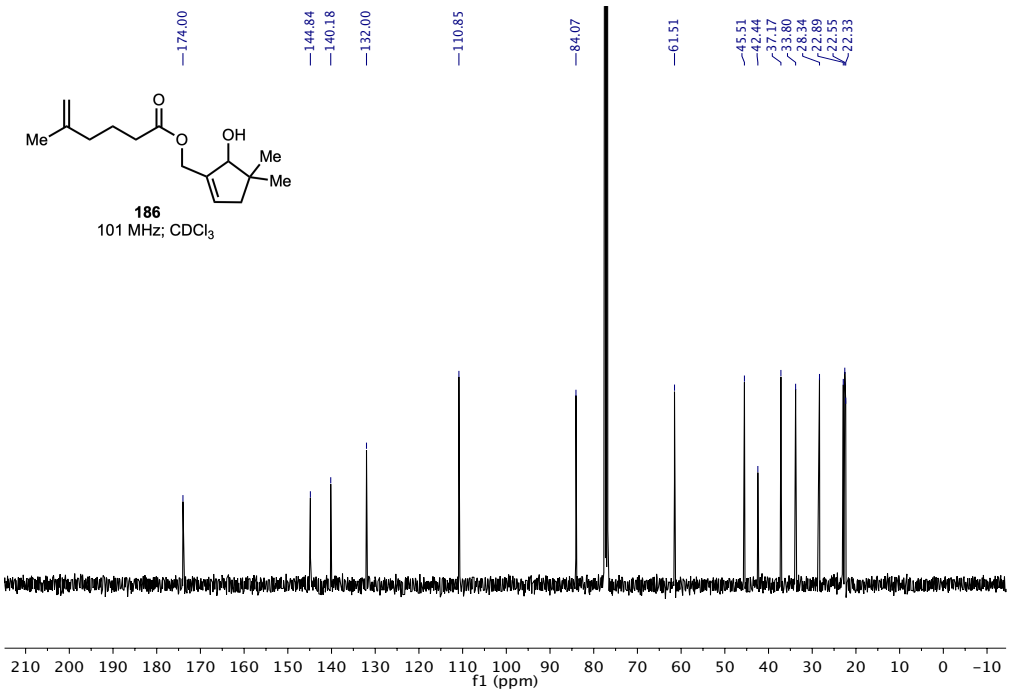


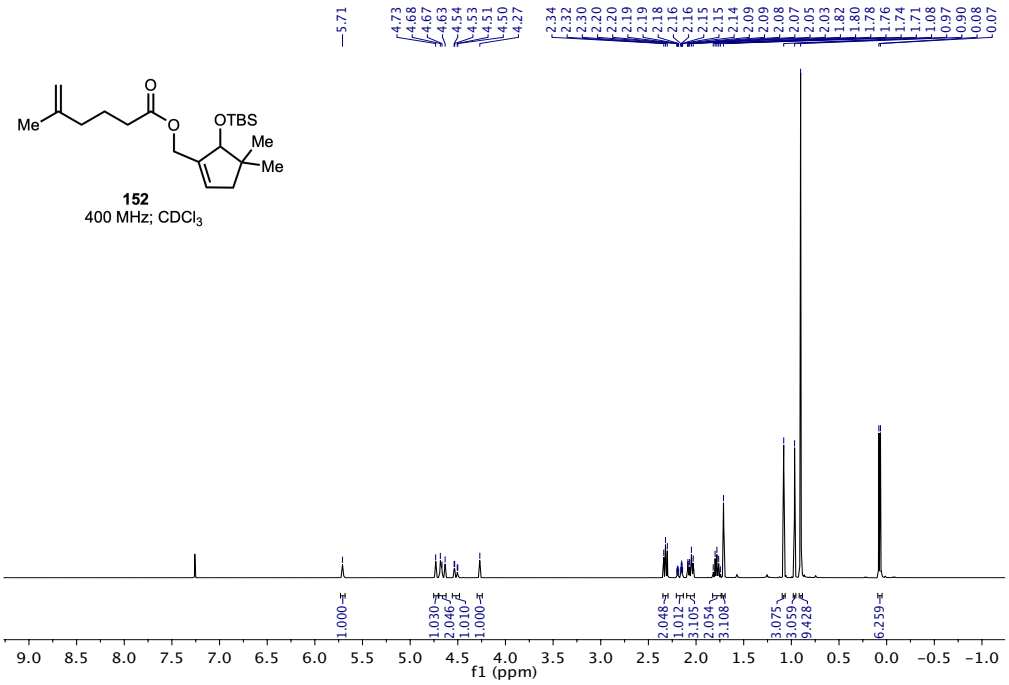
138
101 MHz; $CDCl_3$

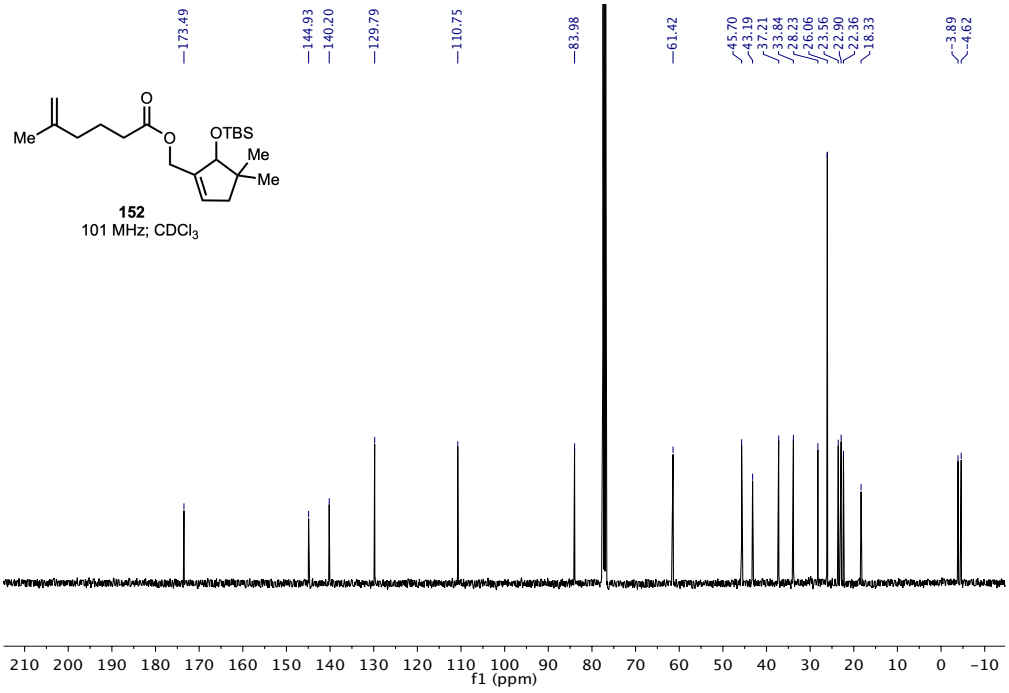

OH
OH
Me
Me
148
400 MHz; CDCl3
5.73
4.30
4.24
2.28
2.28
2.27
2.27
2.26
2.24
2.24
2.23
2.23
2.22
2.12
2.11
2.11
2.11
2.10
2.10
2.10
2.07
2.07
2.07
2.07
2.06
2.06
2.06
1.93
1.08
1.06
1.000
2.029
0.982
1.034
1.141
6.314
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

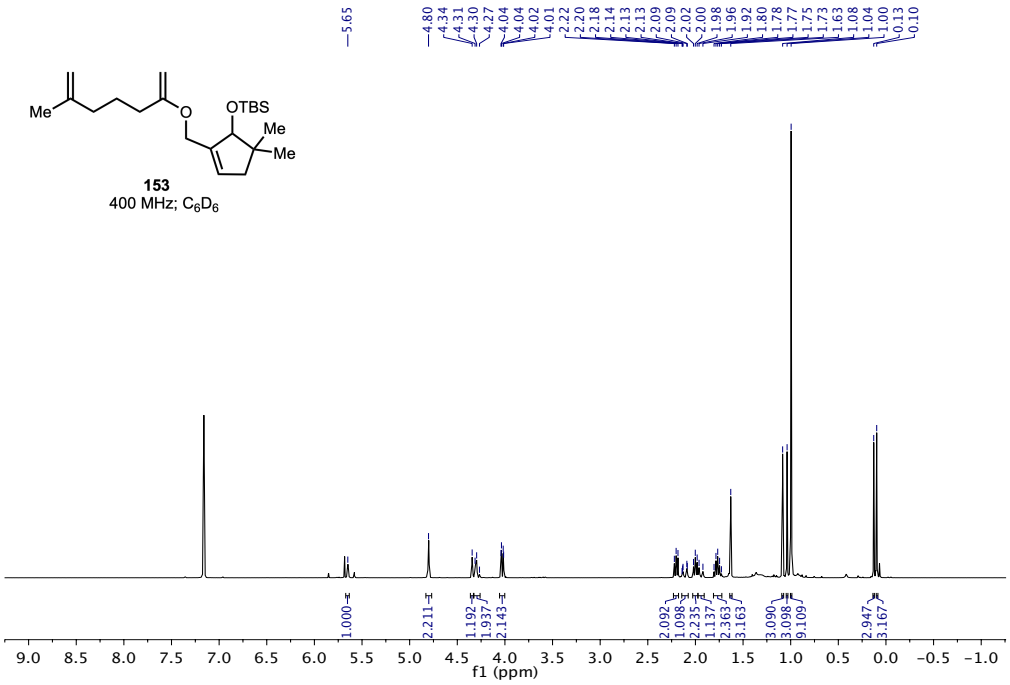

OH
OH
Me
Me
148
101 MHz; CDCl3
143.59
129.38
85.42
61.29
45.58
42.59
28.33
22.50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

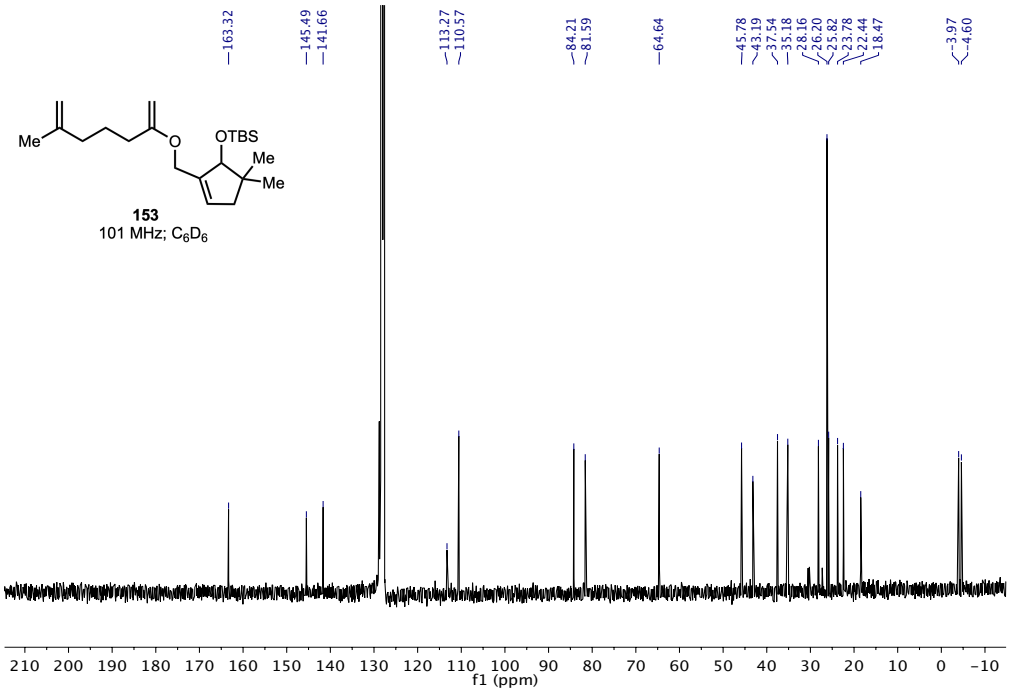

5.81
4.77
4.73
4.68
4.66
4.63
4.11
2.35
2.33
2.31
2.25
2.21
2.11
2.06
2.04
2.03
1.94
1.82
1.80
1.78
1.76
1.74
1.71
1.07
1.05
Me
O
O
OH
Me
Me
186
400 MHz; CDCl3
1.000
2.186
2.156
1.049
2.225
1.080
3.339
0.970
2.333
3.419
6.456
f1 (ppm)

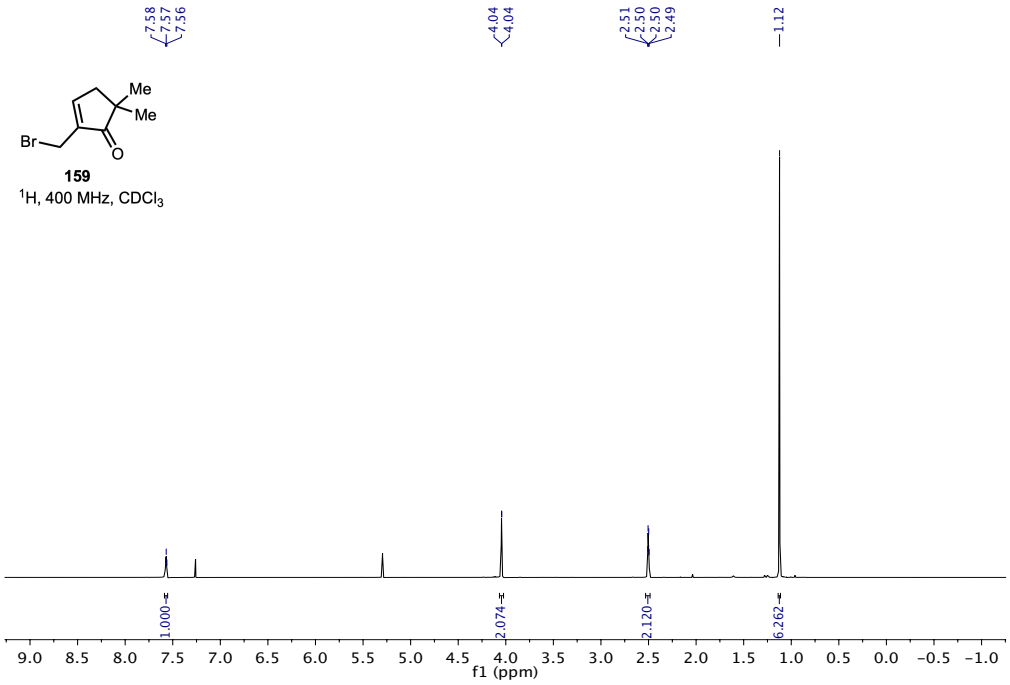

174.00
144.84
140.18
132.00
110.85
84.07
61.51
45.51
42.44
37.17
33.80
28.34
22.89
22.55
22.33
Me
O
O
OH
Me
Me
186
101 MHz; CDCl3
f1 (ppm)


Me
O
O
OTBS
Me
Me
152
400 MHz; CDCl3
5.71
4.73
4.68
4.67
4.63
4.54
4.53
4.51
4.50
4.27
2.34
2.32
2.30
2.20
2.20
2.19
2.19
2.18
2.16
2.16
2.15
2.15
2.14
2.09
2.09
2.08
2.07
2.05
2.03
1.82
1.80
1.78
1.76
1.74
1.71
1.08
0.97
0.90
0.08
0.07
1.000
1.030
2.046
1.010
1.000
2.048
1.012
3.105
2.054
3.108
3.075
3.059
9.428
6.259
f1 (ppm)

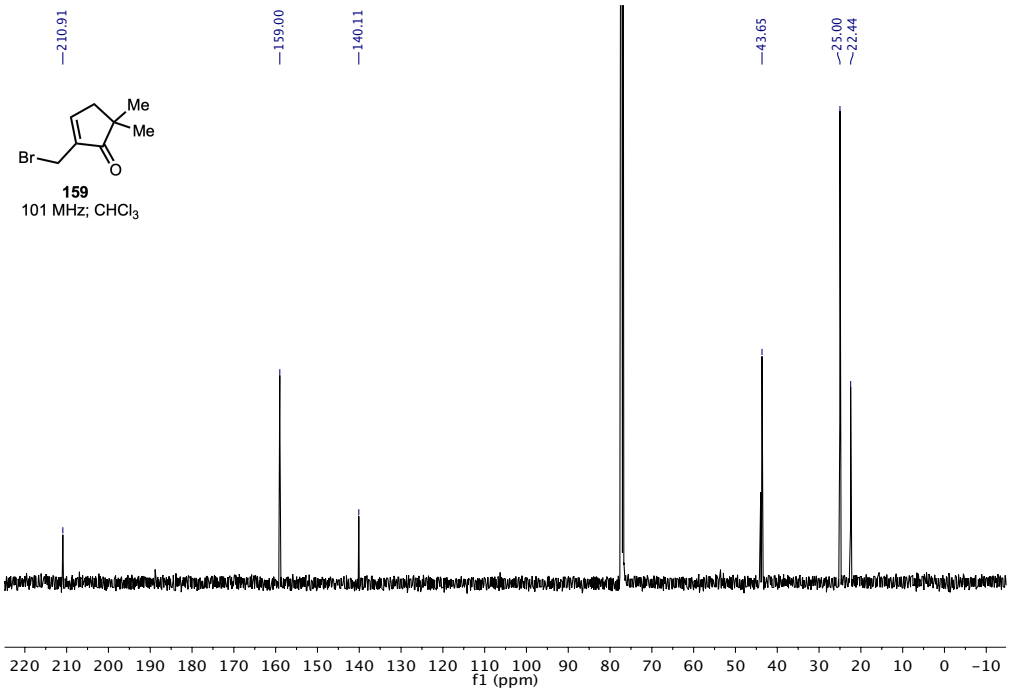

Me
O
O
OTBS
Me
Me
152
101 MHz; CDCl3
173.49
144.93
140.20
129.79
110.75
83.98
61.42
45.70
43.19
37.21
33.84
28.23
26.06
23.56
22.90
22.36
18.33
-3.89
-4.62
f1 (ppm)


Me
O
OTBS
Me
Me
153
400 MHz; C6D6
5.65
4.80
4.34
4.31
4.30
4.27
4.04
4.04
4.02
4.01
2.22
2.20
2.18
2.14
2.13
2.13
2.09
2.09
2.02
2.00
1.98
1.96
1.92
1.80
1.78
1.77
1.75
1.73
1.63
1.08
1.04
1.00
0.13
0.10
1.000
2.211
1.192
1.937
2.143
2.092
1.098
2.235
1.137
2.363
3.163
3.090
3.098
9.109
2.947
3.167
f1 (ppm)

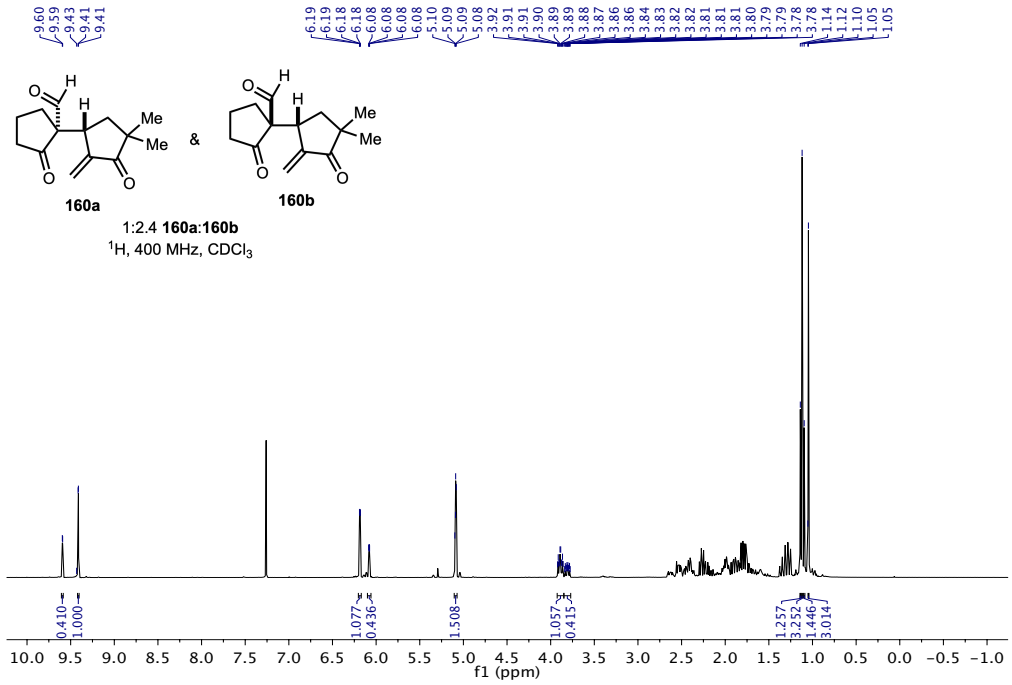

Me
O
OTBS
Me
Me
153
101 MHz; C6D6
163.32
145.49
141.66
113.27
110.57
84.21
81.59
64.64
45.78
43.19
37.54
35.18
28.16
26.20
25.82
23.78
22.44
18.47
-3.97
-4.60
f1 (ppm)

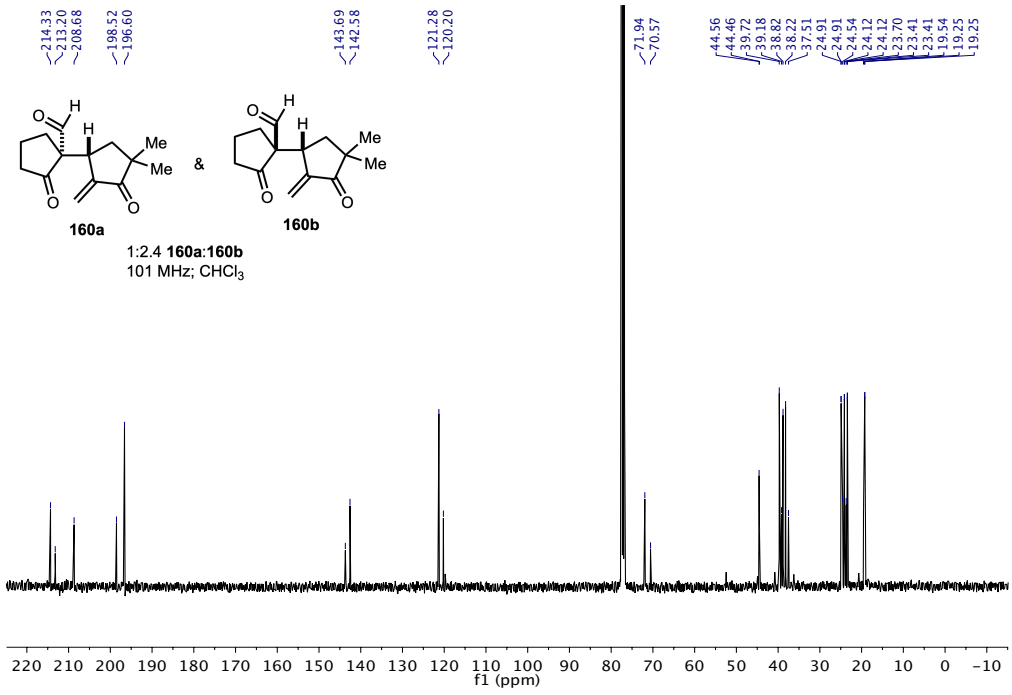


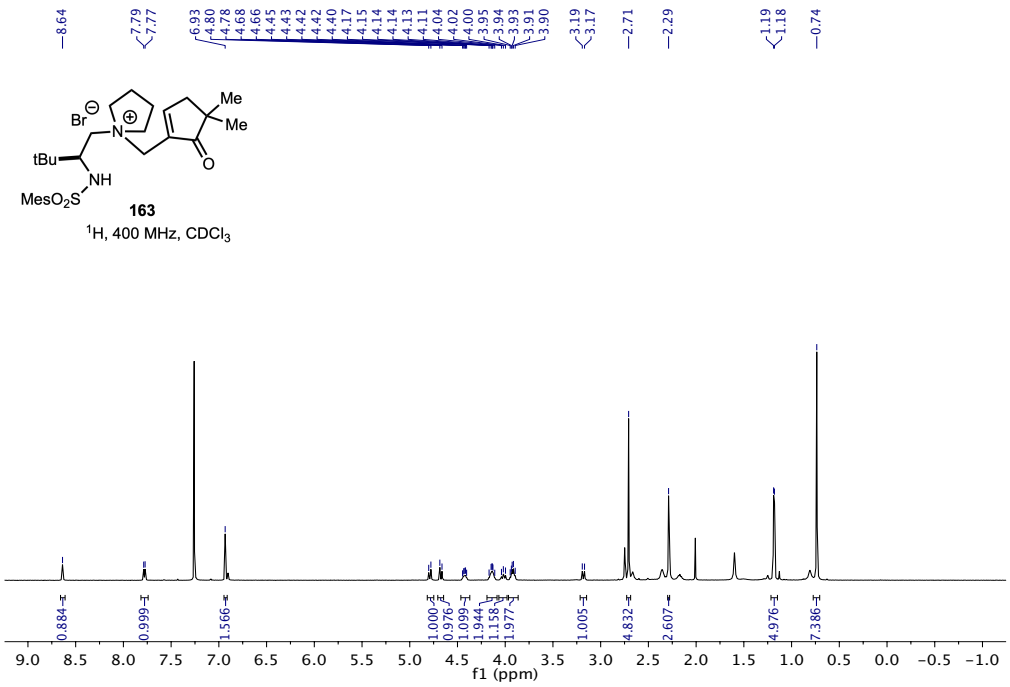
159
^{1}H, 400 MHz, $CDCl_3$

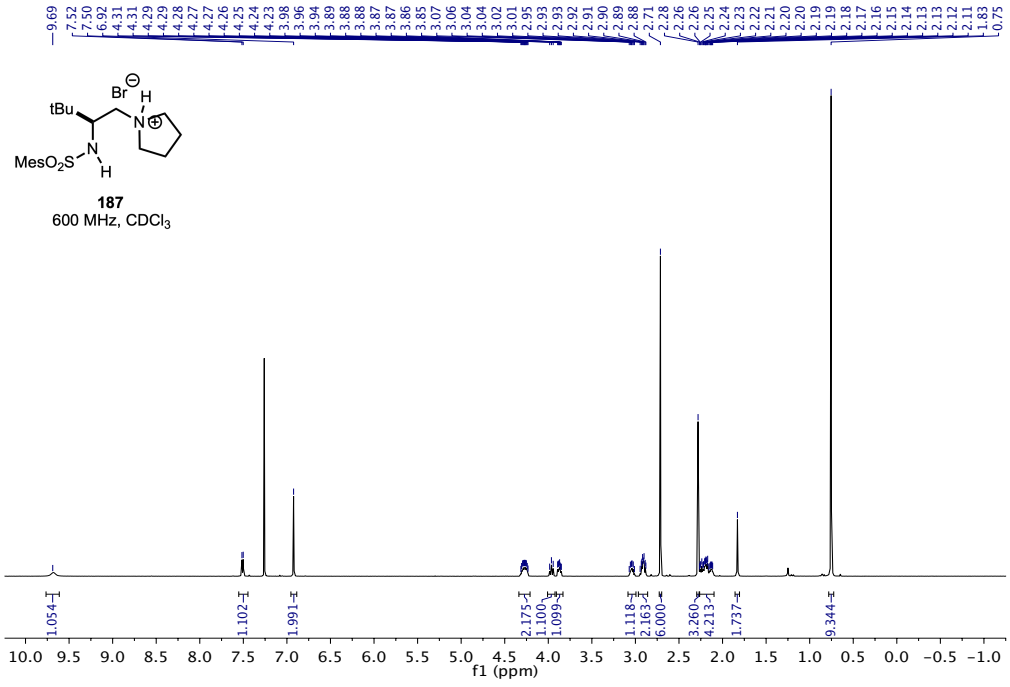


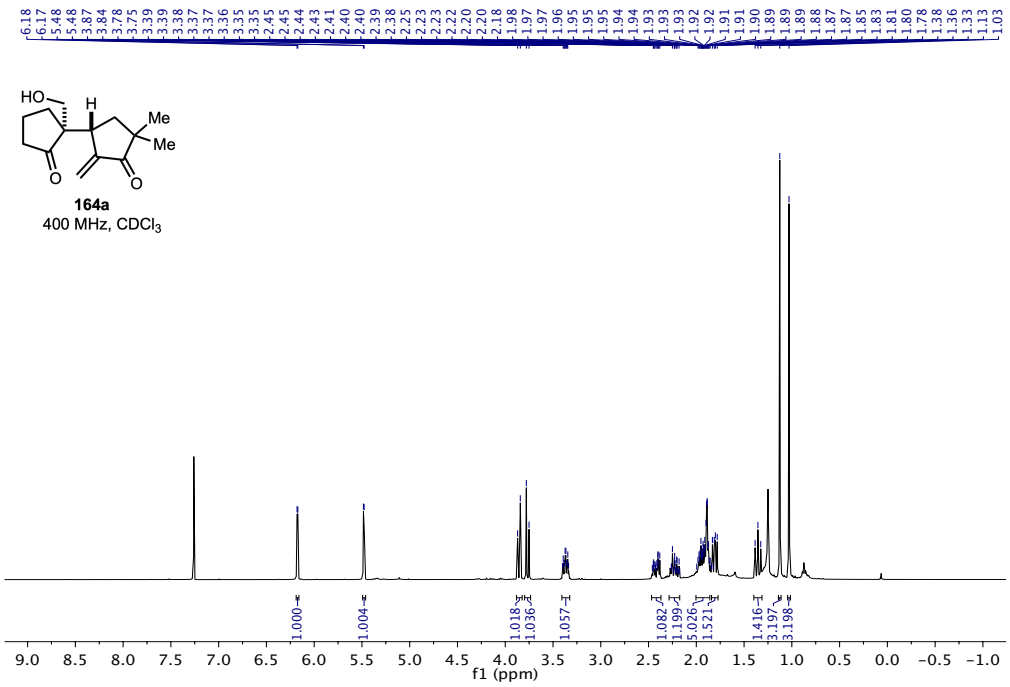
159
101 MHz; $CHCl_3$

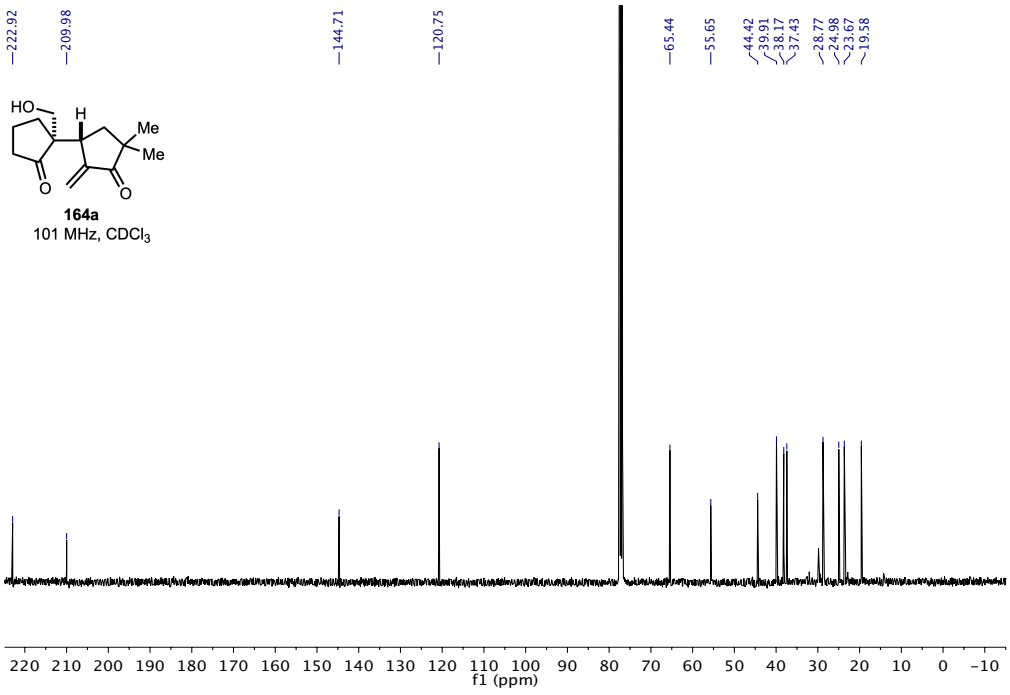

160a
&
160b
1:2.4 160a:160b
1H, 400 MHz, CDCl3
f1 (ppm)

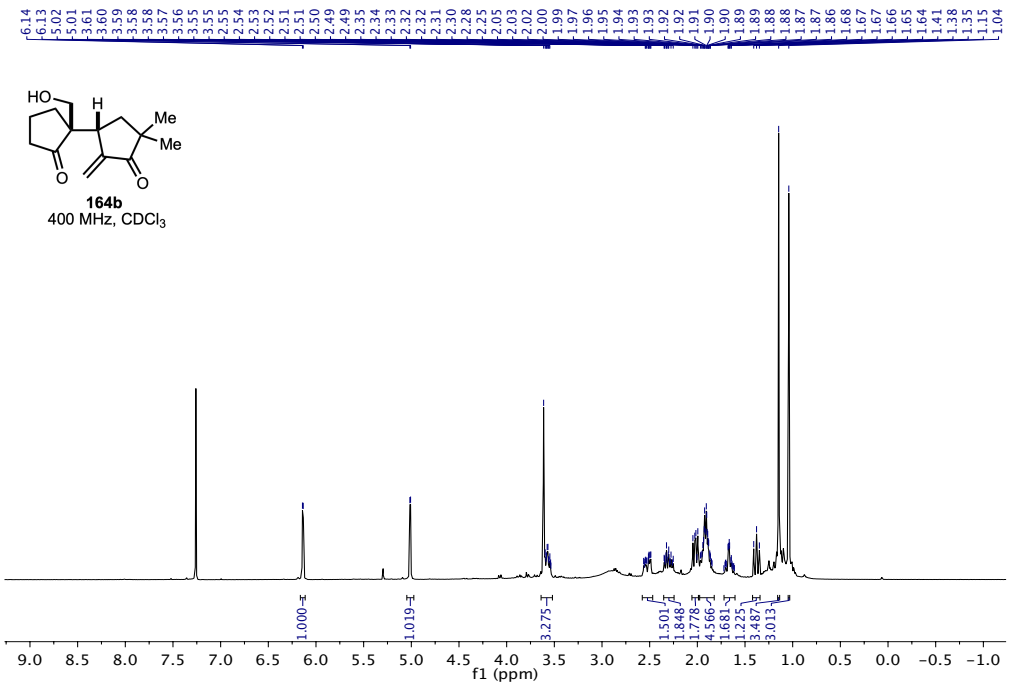

160a
&
160b
1:2.4 160a:160b
101 MHz; CHCl3
f1 (ppm)

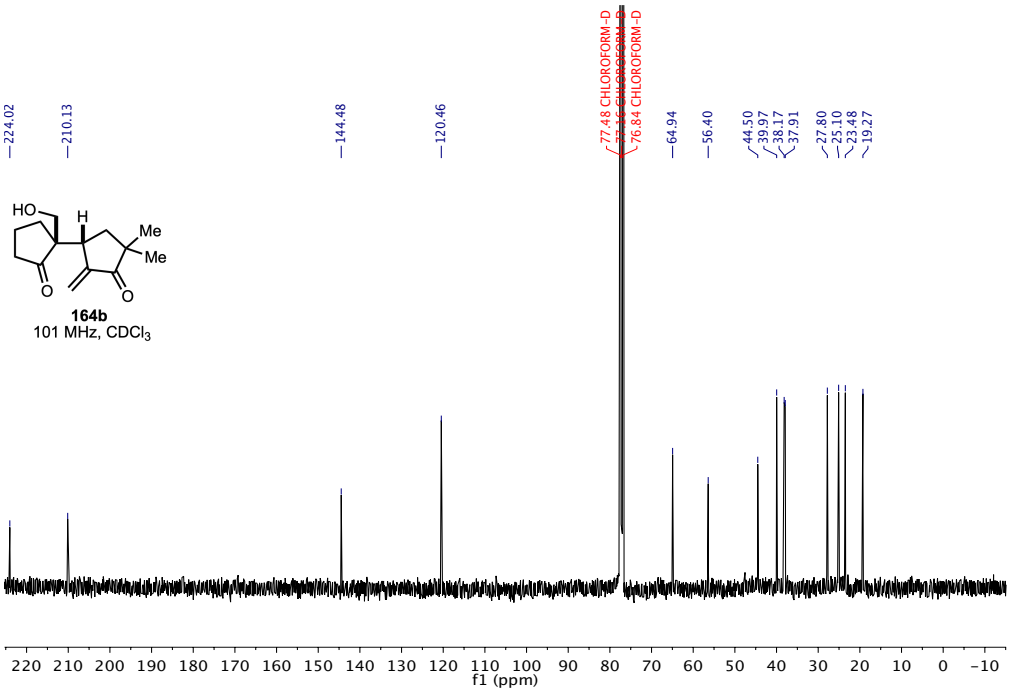

8.64
7.79
7.77
6.93
4.80
4.78
4.68
4.66
4.45
4.43
4.42
4.42
4.40
4.17
4.15
4.14
4.14
4.13
4.11
4.04
4.02
4.00
3.95
3.94
3.93
3.91
3.90
3.19
3.17
2.71
2.29
1.19
1.18
0.74
Br
Me
Me
tBu
NH
MesO2S
O
163
1H, 400 MHz, CDCl3
0.884
0.999
1.566
1.000
0.976
1.099
1.944
1.158
1.977
1.005
4.832
2.607
4.976
7.386
f1 (ppm)

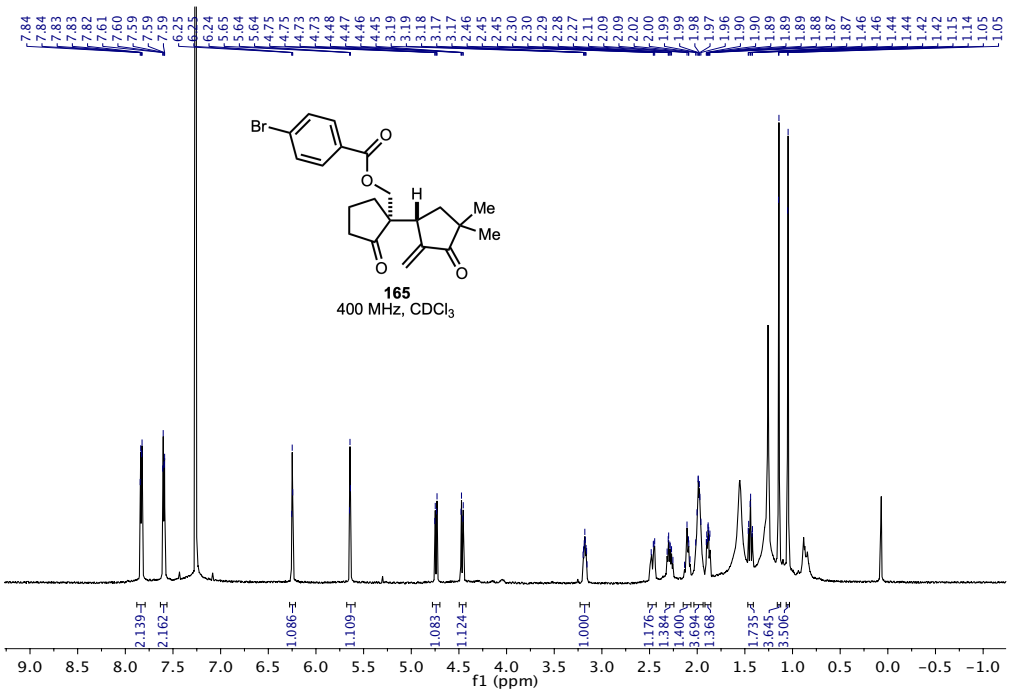

9.69
7.52
7.50
6.92
4.31
4.31
4.29
4.29
4.28
4.27
4.27
4.26
4.25
4.24
4.23
3.98
3.96
3.94
3.89
3.88
3.88
3.87
3.87
3.86
3.85
3.07
3.06
3.04
3.04
3.02
3.01
2.95
2.93
2.93
2.92
2.91
2.90
2.89
2.88
2.71
2.28
2.26
2.26
2.25
2.24
2.23
2.22
2.21
2.20
2.20
2.19
2.19
2.18
2.17
2.16
2.15
2.14
2.13
2.13
2.12
2.11
1.83
0.75
Br
H
tBu
N
MesO2S
N
H
187
600 MHz, CDCl3
1.054
1.102
1.991
2.175
1.100
1.099
1.118
2.163
6.000
3.260
4.213
1.737
9.344
f1 (ppm)

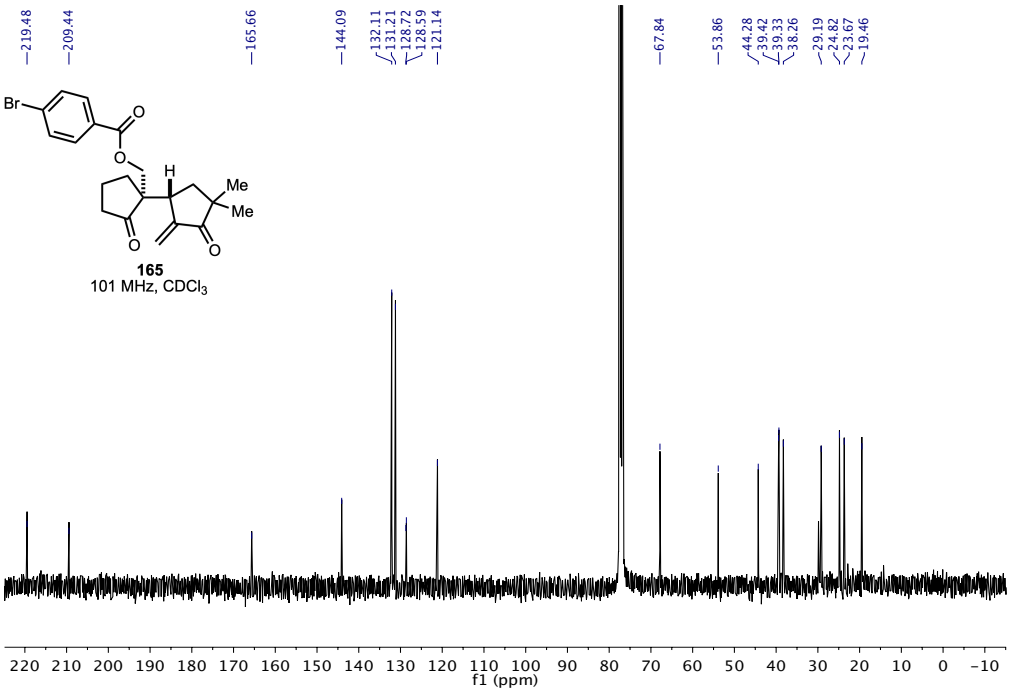

HO
H
Me
Me
O
O
164a
400 MHz, CDCl3
1.000
1.004
1.018
1.036
1.057
1.082
1.199
5.026
1.521
1.416
3.197
3.198
f1 (ppm)

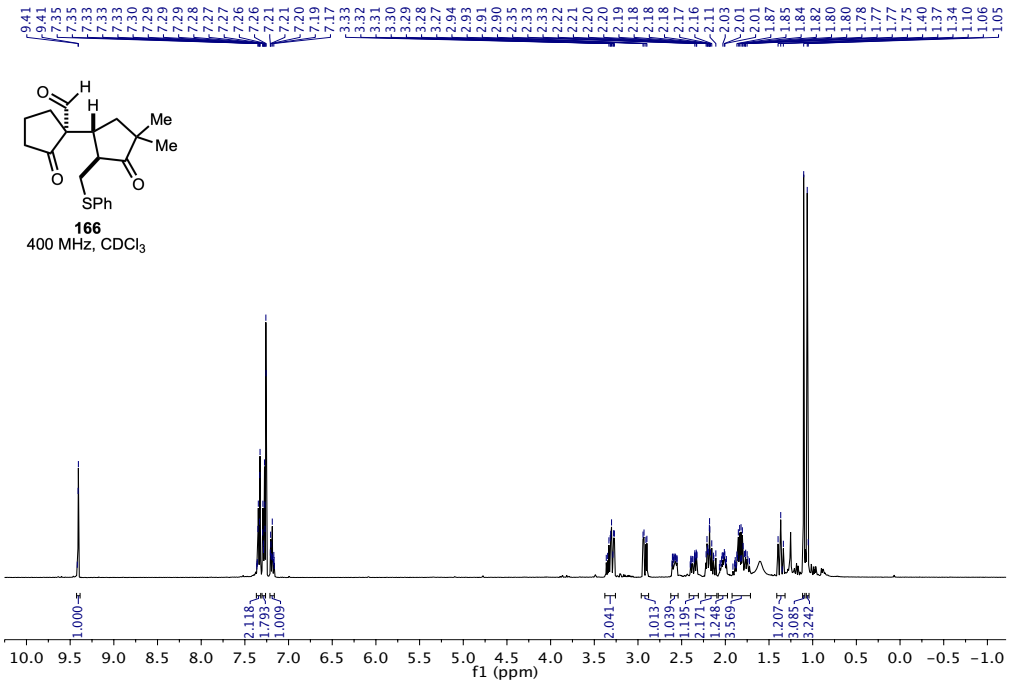

222.92
209.98
144.71
120.75
65.44
55.65
44.42
39.91
38.17
37.43
28.77
24.98
23.67
19.58
HO
H
Me
Me
O
O
164a
101 MHz, CDCl3
f1 (ppm)

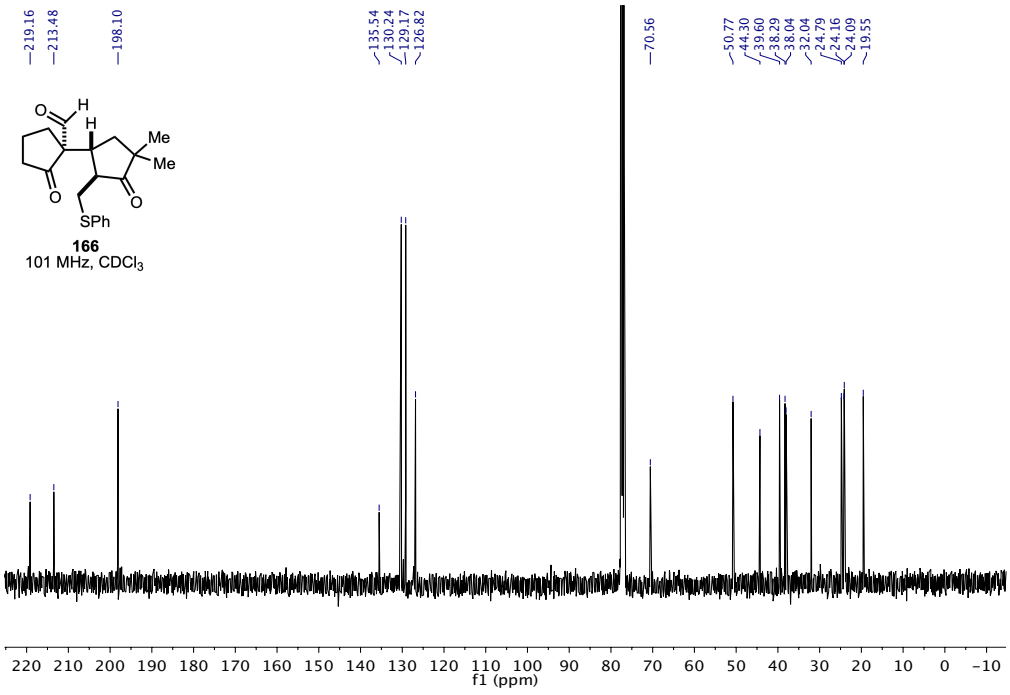

HO
H
Me
Me
O
O
164b
400 MHz, CDCl3
f1 (ppm)

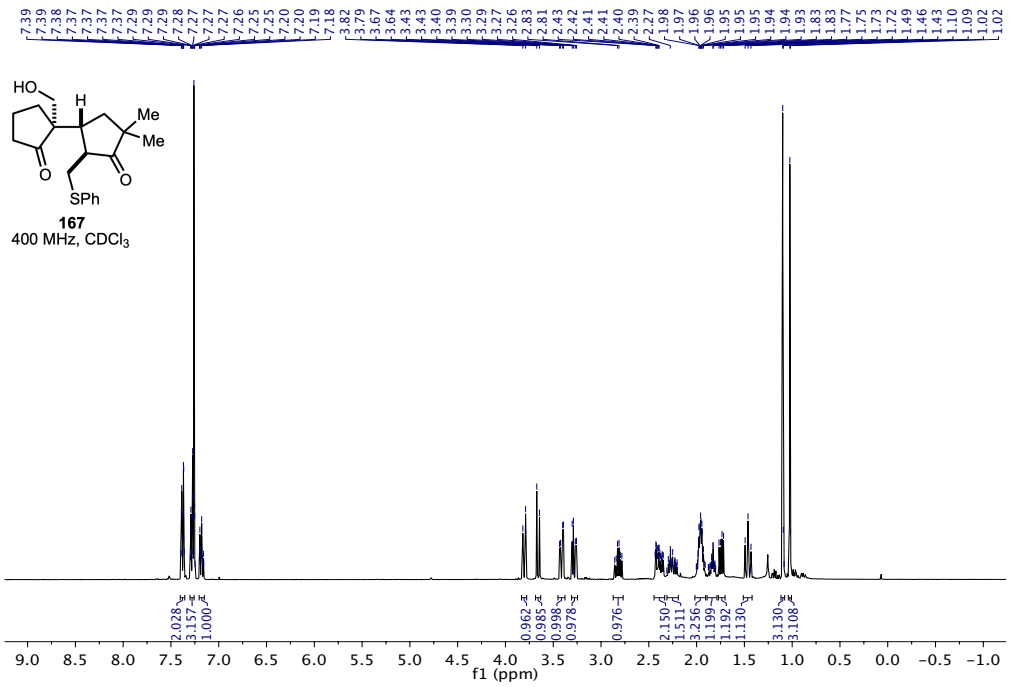

HO
H
Me
Me
O
O
164b
101 MHz, CDCl3
77.48 CHLOROFORM-D
76.84 CHLOROFORM-D
f1 (ppm)

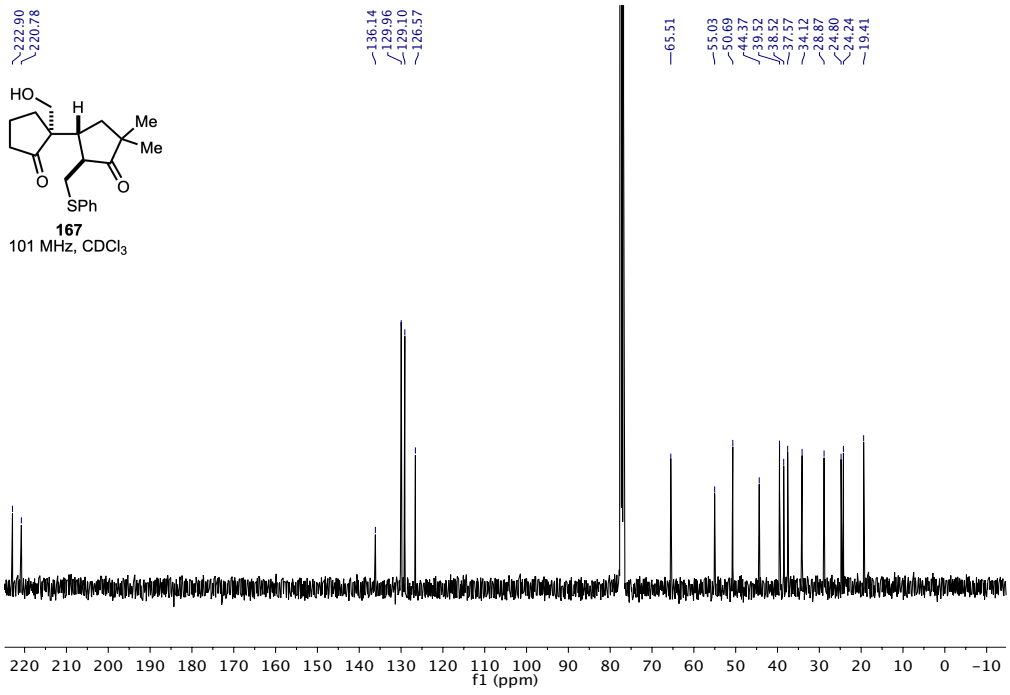

Br
O
O
H
Me
Me
O
O
165
400 MHz, CDCl3
f1 (ppm)

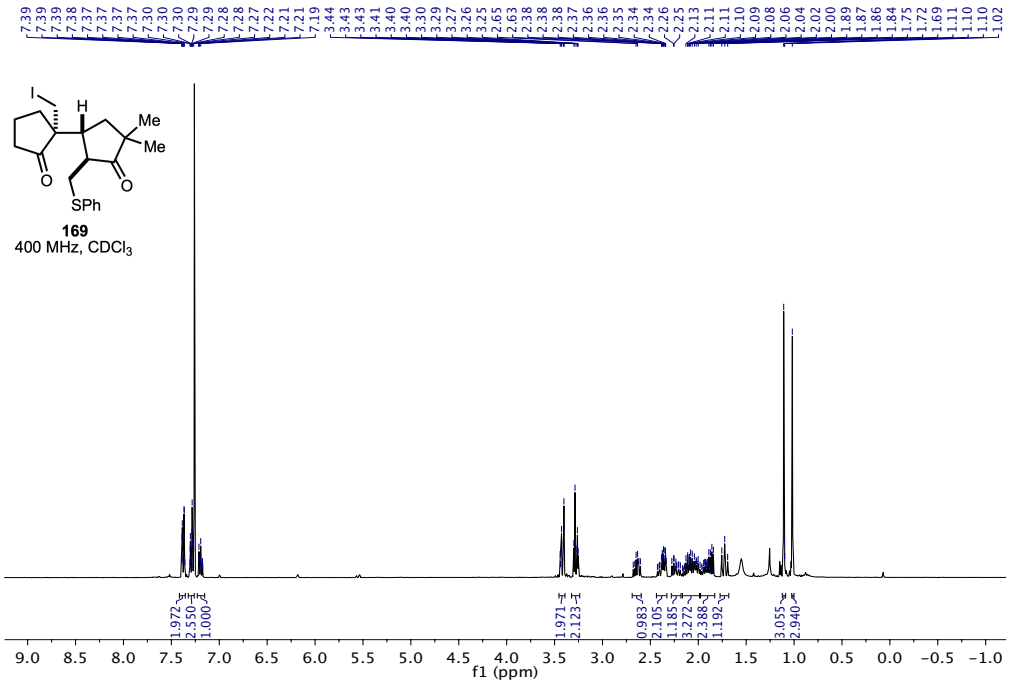

219.48
209.44
165.66
144.09
132.11
131.21
128.72
128.59
121.14
67.84
53.86
44.28
39.42
39.33
38.26
29.19
24.82
23.67
19.46
Br
O
O
H
Me
Me
O
O
165
101 MHz, CDCl3
f1 (ppm)

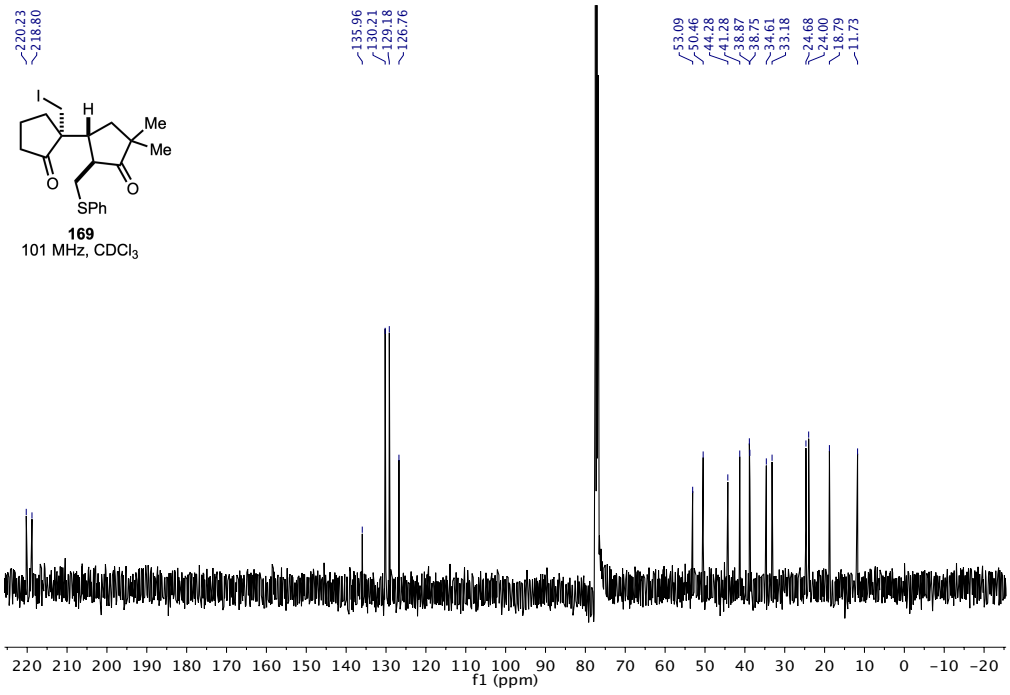

9.41 9.41 7.35 7.35 7.33 7.33 7.30 7.29 7.29 7.28 7.27 7.27 7.26 7.26 7.21 7.21 7.20 7.19 7.17 3.33 3.32 3.31 3.30 3.29 3.28 3.27 2.94 2.93 2.91 2.90 2.35 2.33 2.33 2.22 2.21 2.20 2.20 2.19 2.18 2.18 2.18 2.17 2.16 2.11 2.03 2.01 2.01 1.87 1.85 1.84 1.82 1.80 1.80 1.78 1.77 1.77 1.75 1.40 1.37 1.34 1.10 1.06 1.05
O
H
H
Me
Me
O
O
SPh
166
400 MHz, CDCl3
1.000
2.118
1.793
1.009
2.041
1.013
1.039
1.195
2.171
1.248
3.569
1.207
3.085
3.242
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 0.0 -0.5 -1.0
f1 (ppm)

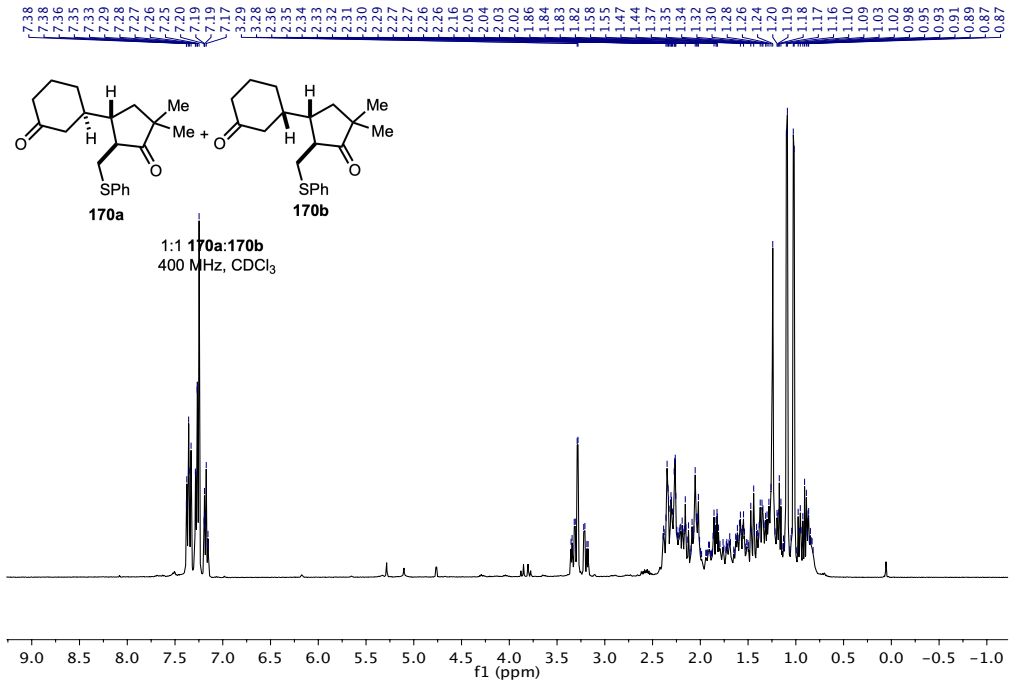

219.16
213.48
198.10
135.54
130.24
129.17
126.82
70.56
50.77
44.30
39.60
38.29
38.04
32.04
24.79
24.16
24.09
19.55
O
H
H
Me
Me
O
O
SPh
166
101 MHz, CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

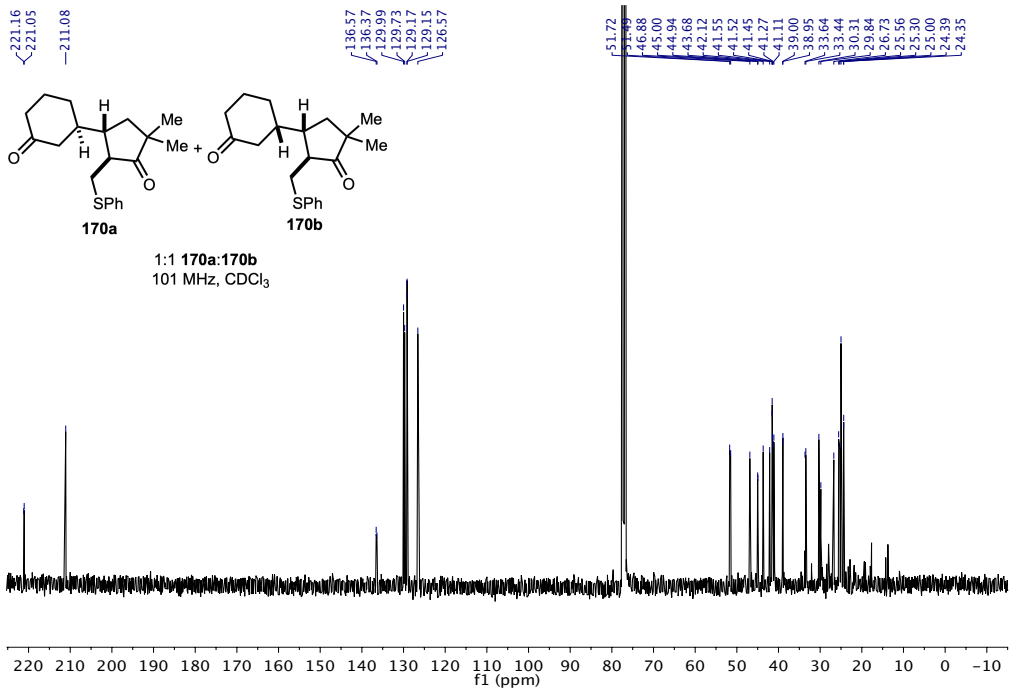

HO
H
Me
Me
O
O
SPh
167
400 MHz, CDCl3
f1 (ppm)

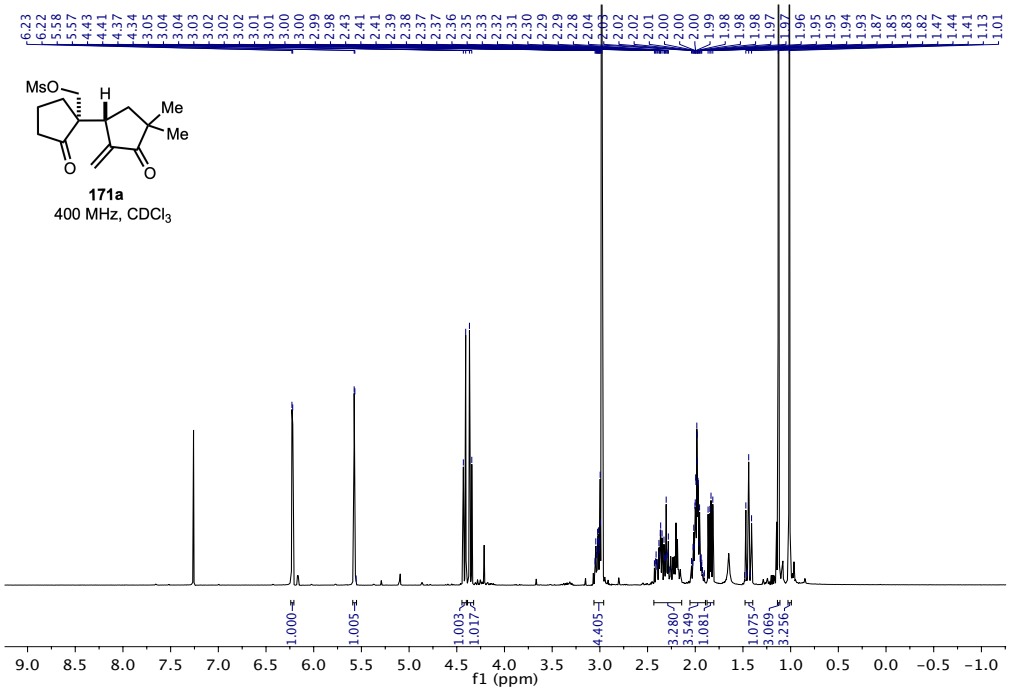

HO
H
Me
Me
O
O
SPh
167
101 MHz, CDCl3
f1 (ppm)

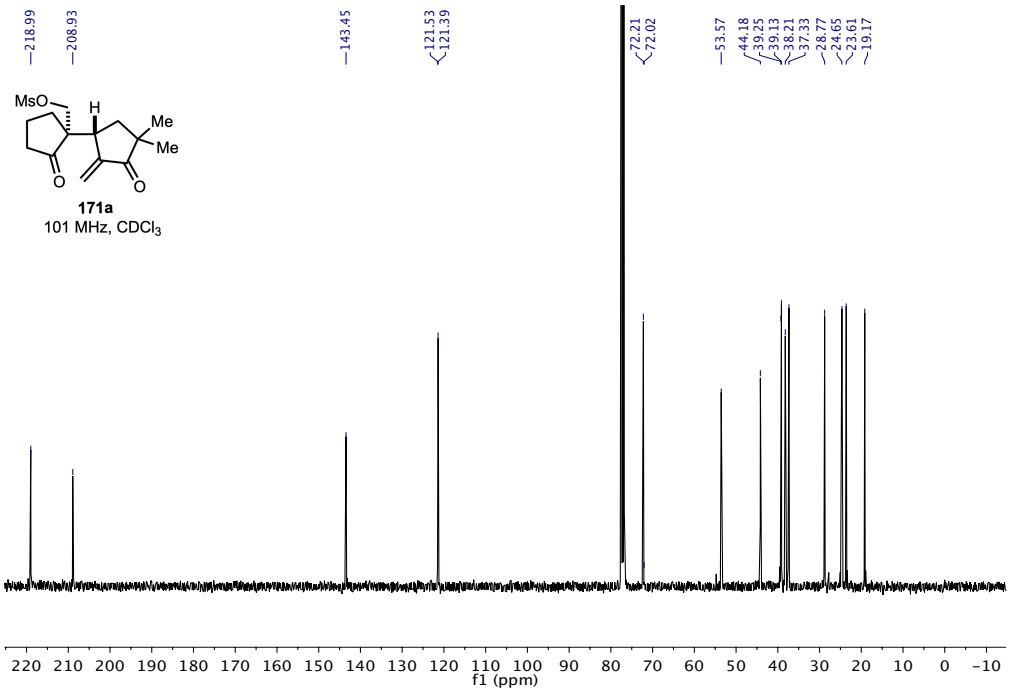

I
H
Me
Me
O
O
SPh
169
400 MHz, CDCl3
f1 (ppm)

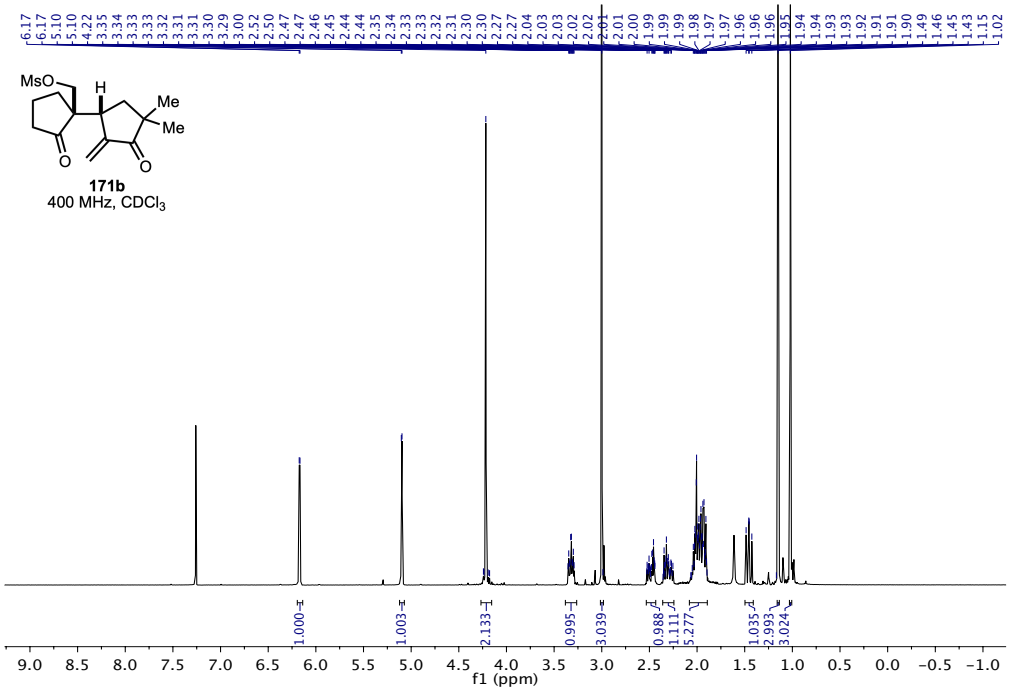

I
H
Me
Me
O
O
SPh
169
101 MHz, CDCl3
f1 (ppm)

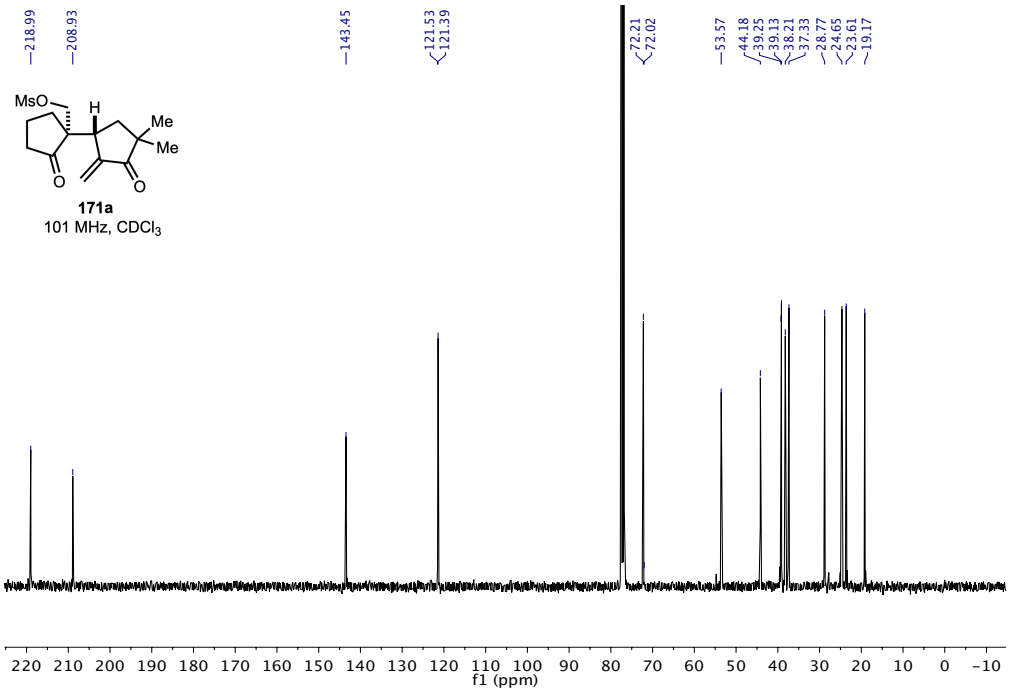

170a
170b
1:1 170a:170b
400 MHz, CDCl3
f1 (ppm)

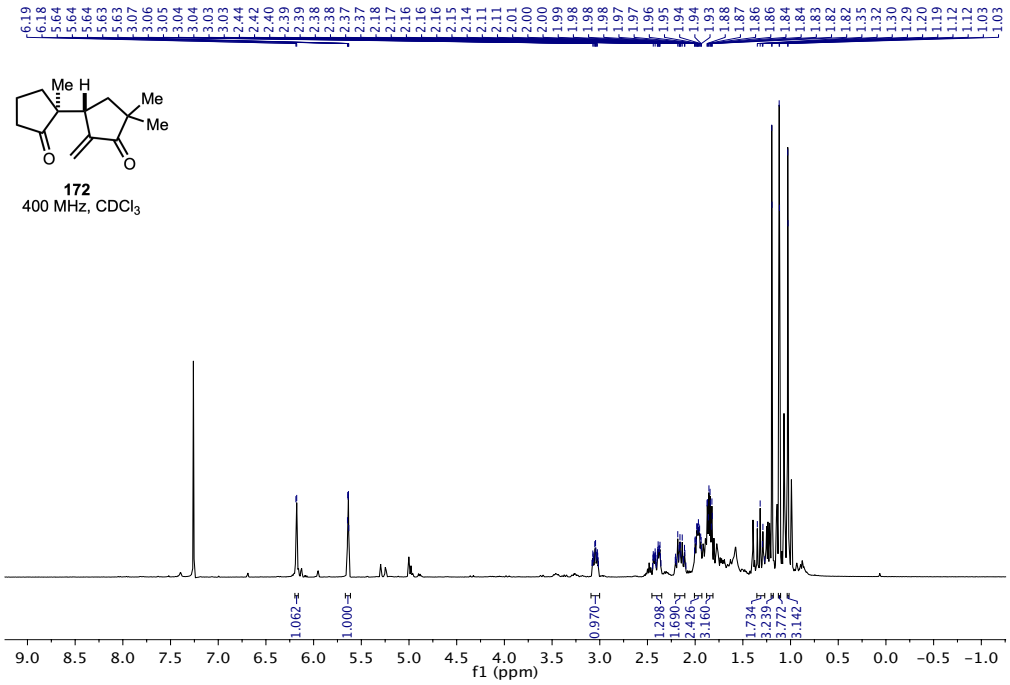

170a
170b
1:1 170a:170b
101 MHz, CDCl3
f1 (ppm)

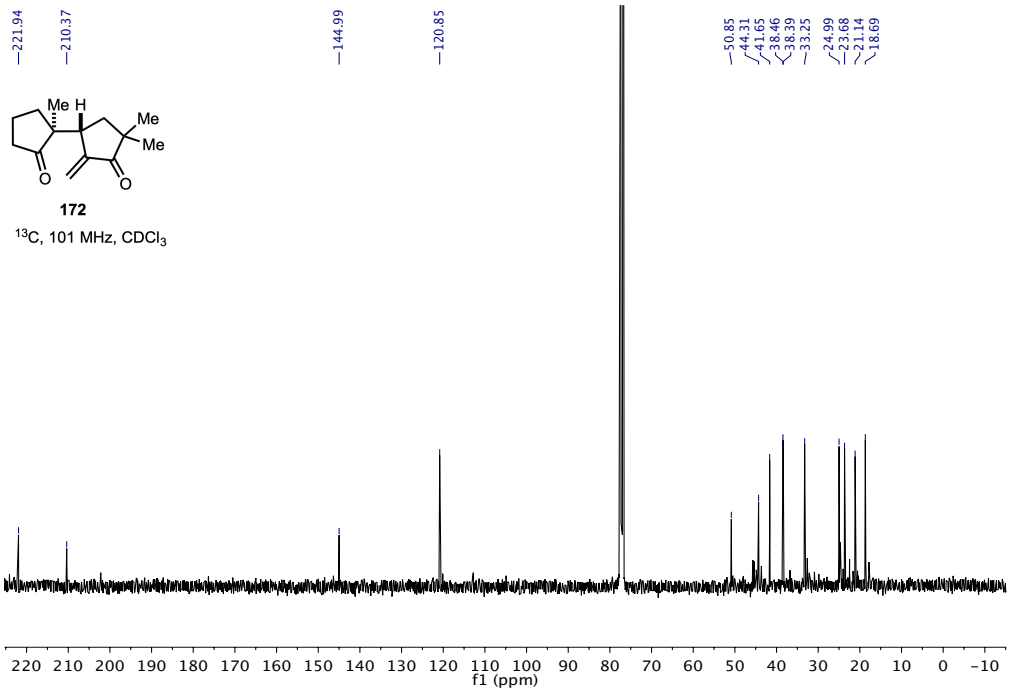

MsO
H
Me
Me
O
O
171a
400 MHz, CDCl3
f1 (ppm)

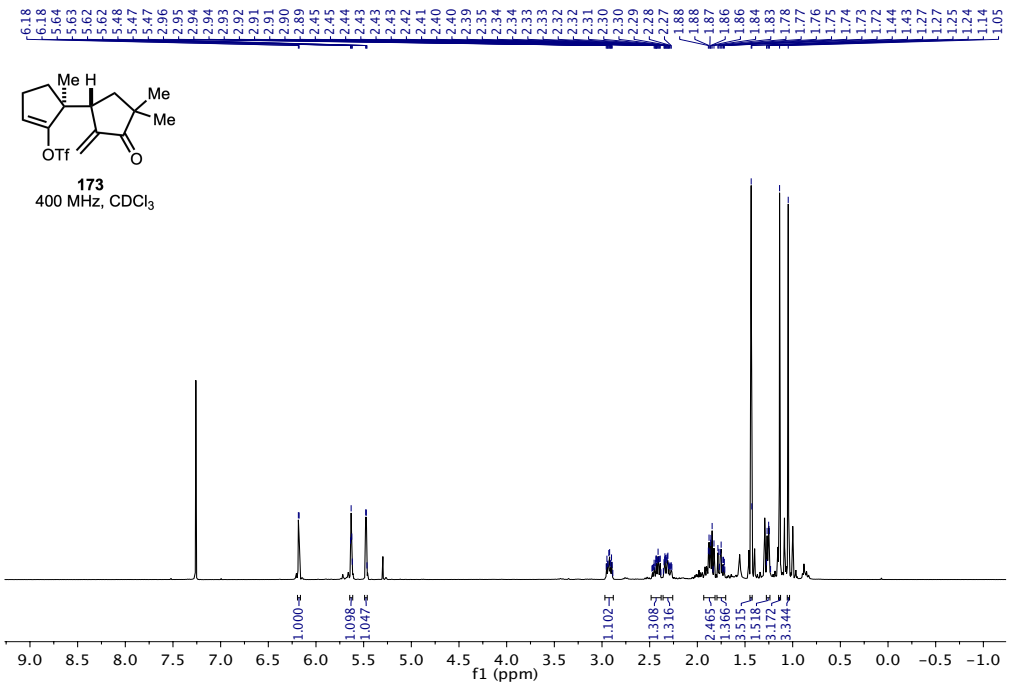

MsO
H
Me
Me
O
O
171a
101 MHz, CDCl3
f1 (ppm)

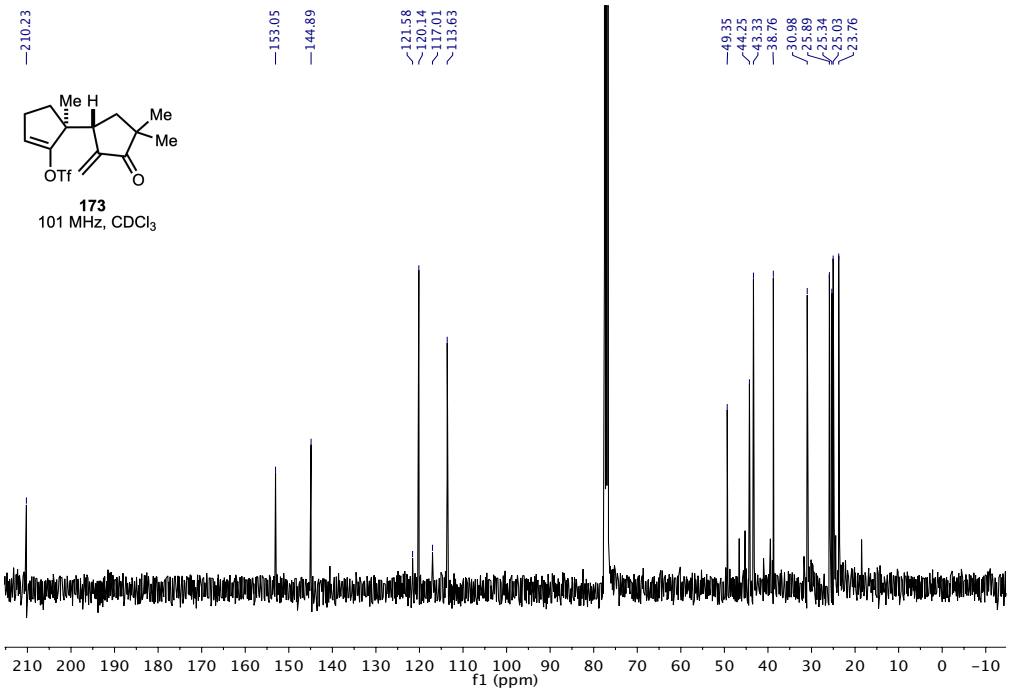

MsO
H
Me
Me
O
O
171b
400 MHz, CDCl3
f1 (ppm)

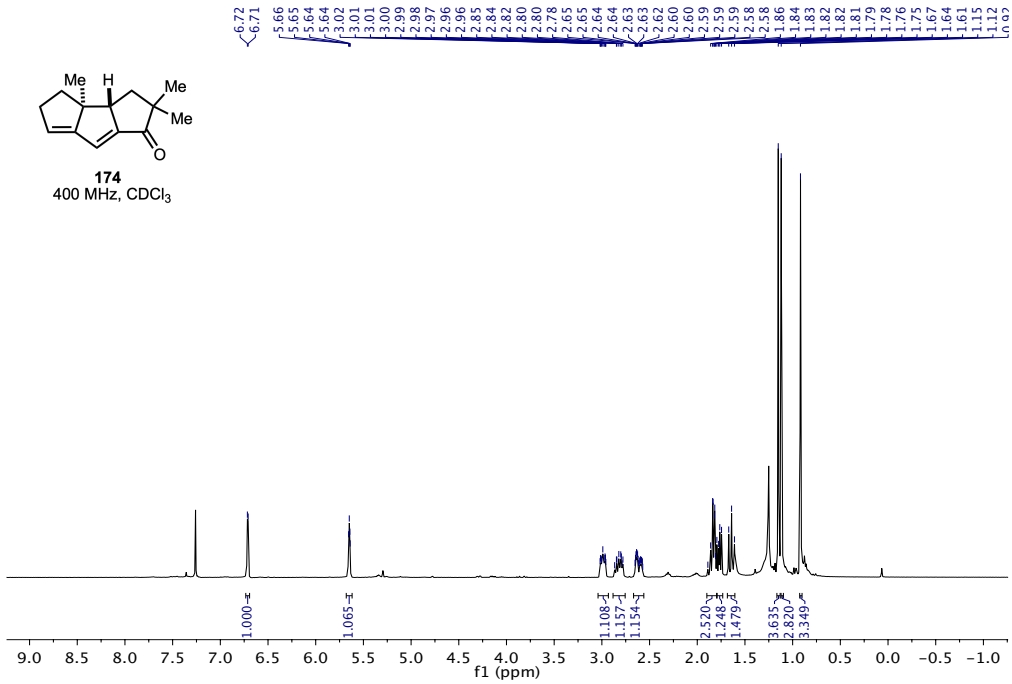

MsO
H
Me
Me
O
O
171a
101 MHz, CDCl3
f1 (ppm)

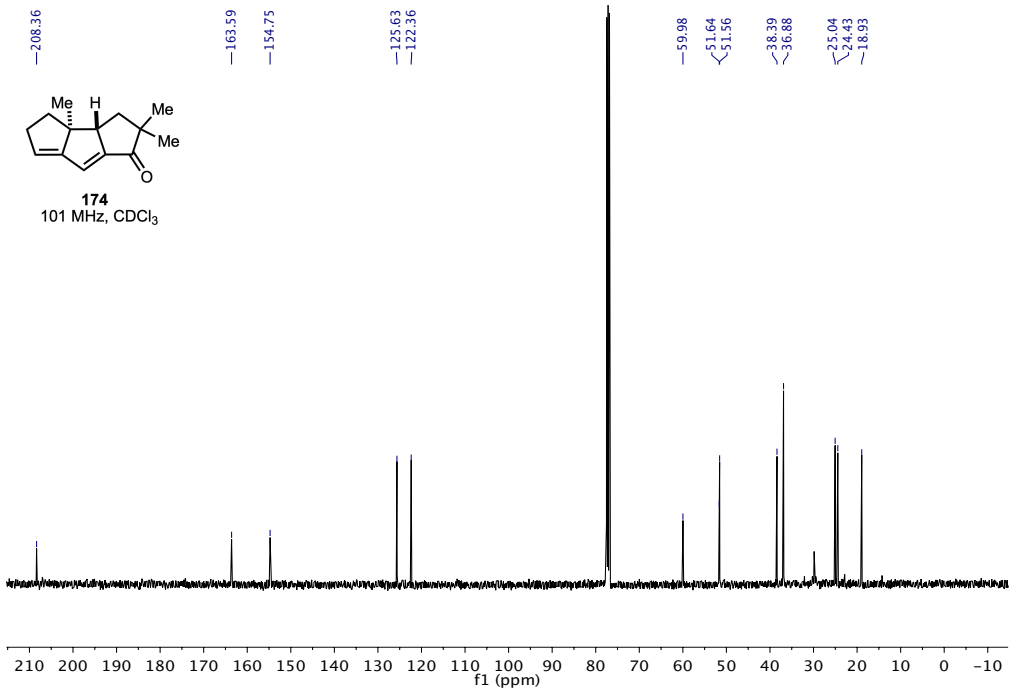

Me H
Me
Me
O
O
172
400 MHz, CDCl3
f1 (ppm)

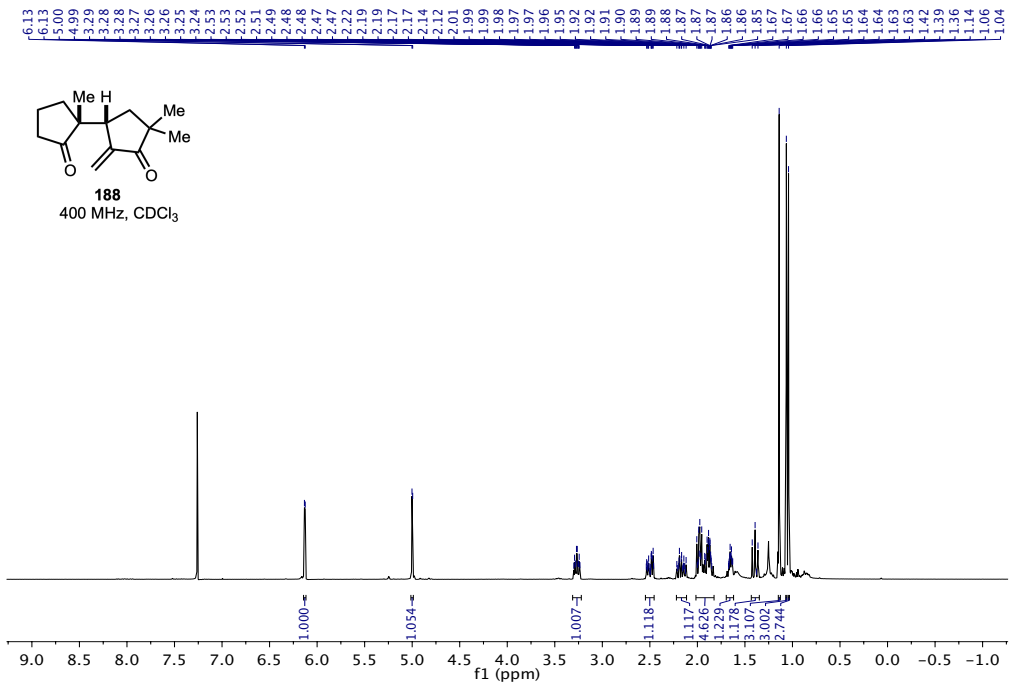

Me H
Me
Me
O
O
172
13C, 101 MHz, CDCl3
f1 (ppm)

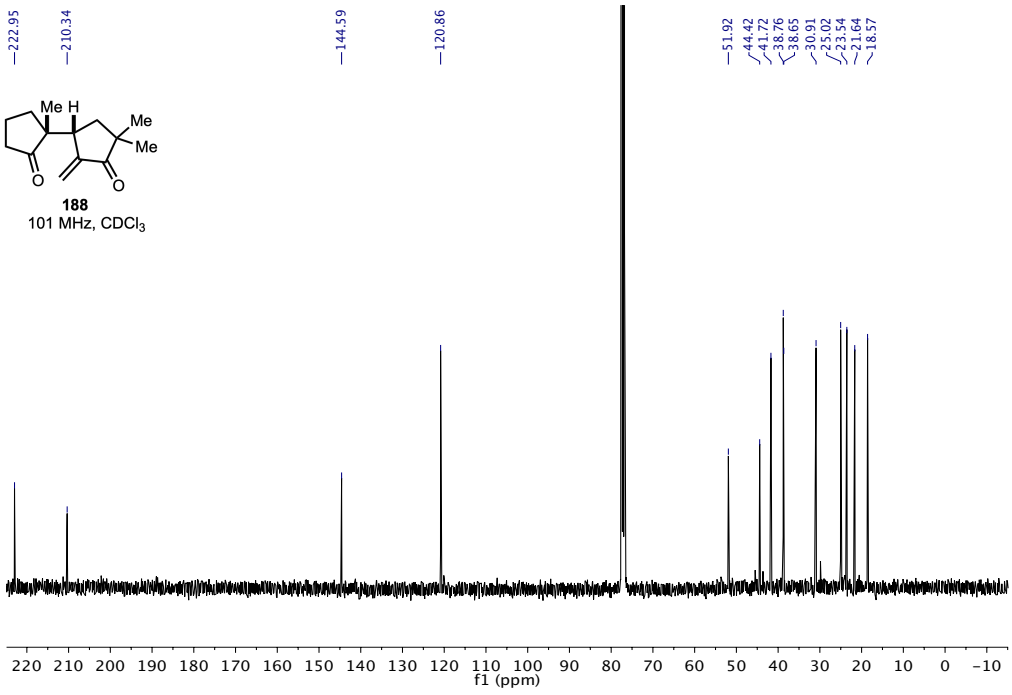

Me H
Me
Me
OTf
O
173
400 MHz, CDCl3
f1 (ppm)

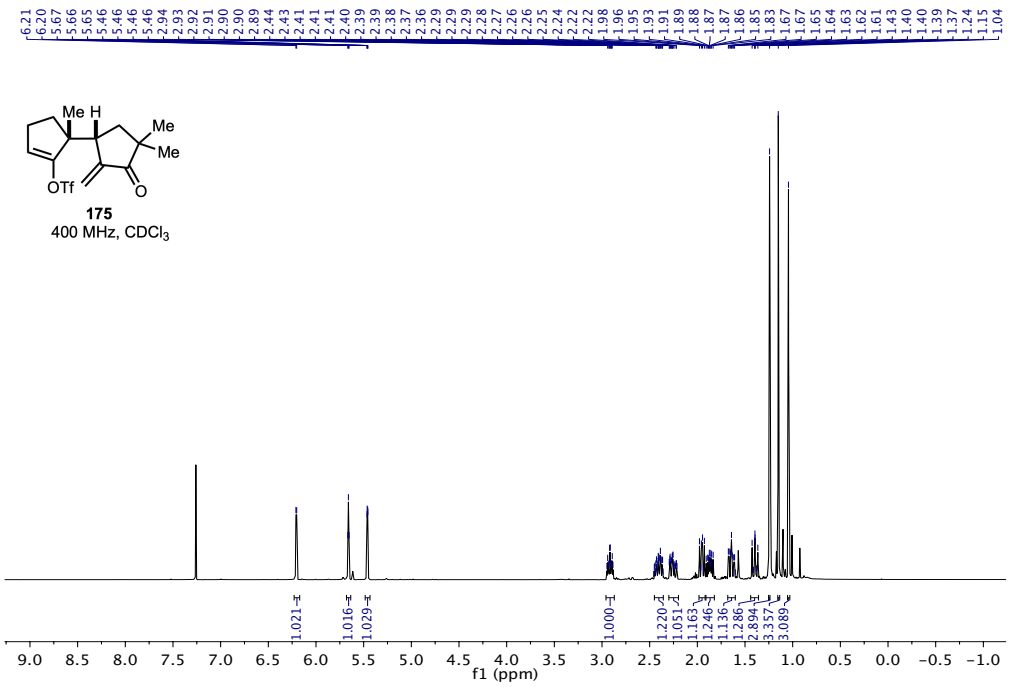

Me H
Me
Me
OTf
O
173
101 MHz, CDCl3
f1 (ppm)

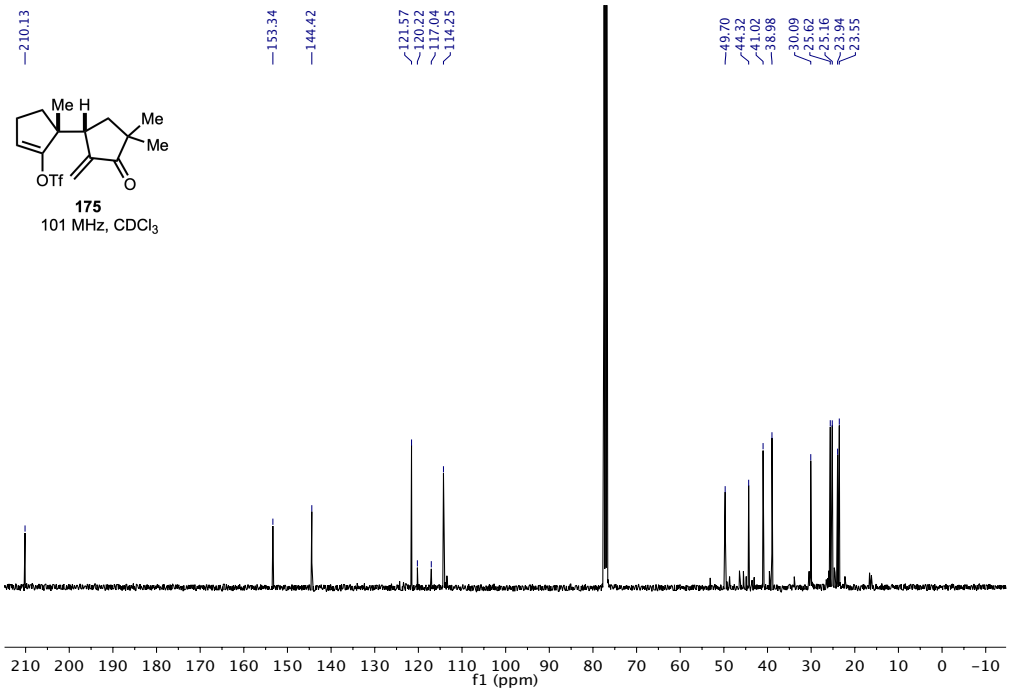

Me
H
Me
Me
O
174
400 MHz, CDCl3
f1 (ppm)

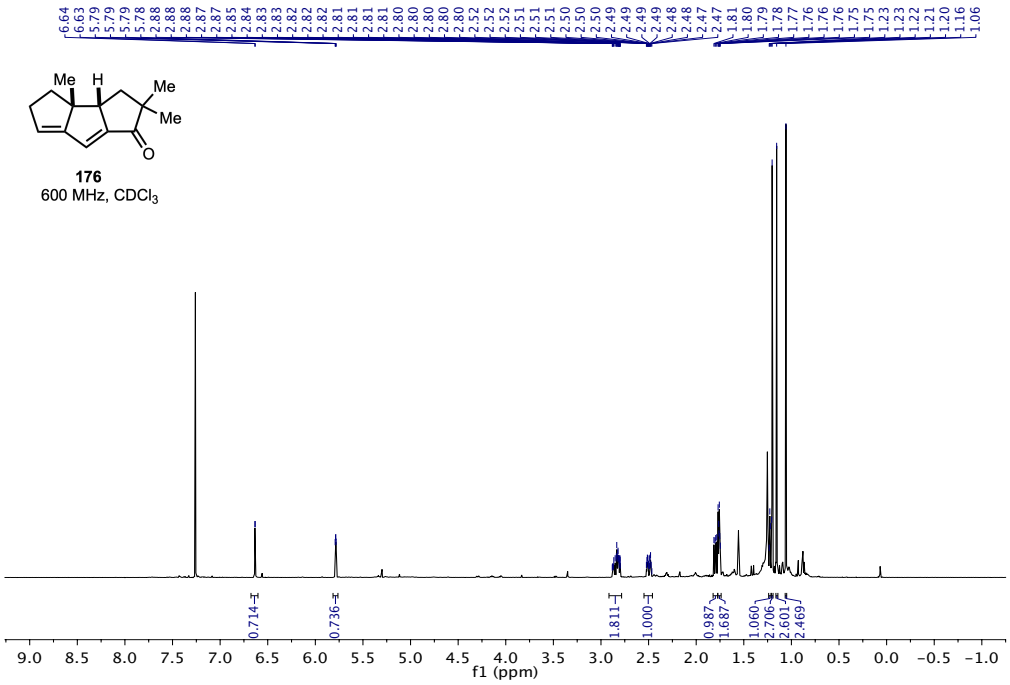

Me
H
Me
Me
O
174
101 MHz, CDCl3
f1 (ppm)

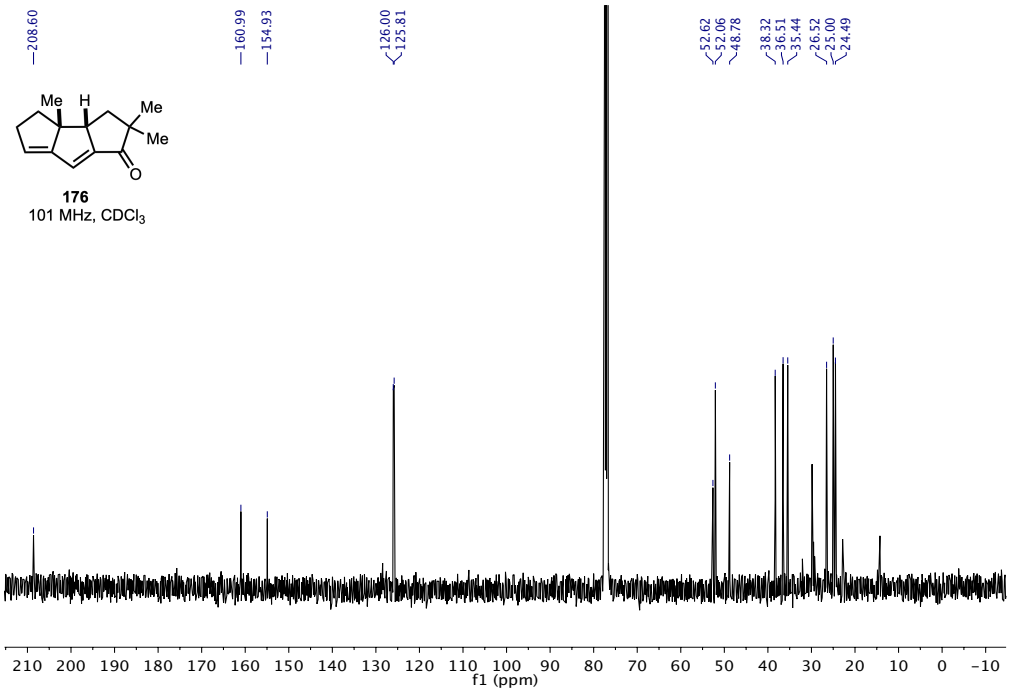

Me H
Me
Me
O
O
188
400 MHz, CDCl3
f1 (ppm)


Me H
Me
Me
O
O
188
101 MHz, CDCl3
f1 (ppm)


Me H
Me
Me
OTf
O
175
400 MHz, CDCl3
f1 (ppm)


Me H
Me
Me
OTf
O
175
101 MHz, CDCl3
f1 (ppm)


Me
H
Me
Me
O
176
600 MHz, CDCl3
f1 (ppm)


Me
H
Me
Me
O
176
101 MHz, CDCl3
f1 (ppm)