# I. Stereoselective Construction of Polycyclic Architectures: Enantioselective Catalytic Transannular Ketone-Ene Reactions and an Enantioselective Total Synthesis of ( + )-Reserpine II. Synthesis of Chiral Bisthioureas for AnionAbstraction Catalysis 

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## I. Stereoselective Construction of Polycyclic Architectures:

## Enantioselective Catalytic Transannular Ketone-Ene Reactions and

 an Enantioselective Total Synthesis of (+)-Reserpine
## II. Synthesis of Chiral Bisthioureas for Anion-Abstraction Catalysis

A thesis presented
by

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to

The Department of Chemistry and Chemical Biology
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
in the subject of
Chemistry

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# I. Stereoselective Construction of Polycyclic Architectures: Enantioselective Catalytic Transannular Ketone-Ene Reactions and an Enantioselective Total Synthesis of (+)-Reserpine 

## II. Synthesis of Chiral Bisthioureas for Anion-Abstraction Catalysis


#### Abstract

The research presented herein explores three aspects of asymmetric catalysis: (1) the development of new catalytic enantioselective reactions, (2) the application of stereoselective catalysis to natural product total synthesis, and (3) the design and synthesis of new chiral catalysts.

In Chapter 1, an asymmetric transannular ene reaction of electronically unactivated ketones is reported. The transformation is catalyzed by a new chromium(III) tridentate Schiff-base catalyst and provides access to trans-decalinol frameworks in high diastereo- and enantioselectivity.

A convergent total synthesis of indole alkaloid (+)-reserpine is presented in Chapter 2. The synthesis uses two key catalytic asymmetric methods: an enantioselective kinetic resolution of terminal epoxides catalyzed by an oligomeric Co (salen) complex and a catalyst-controlled diastereoselective formal aza-Diels-Alder reaction catalyzed by a primary aminothiourea. These methods enabled an enantioselective synthesis of the classic target and addressed the historically problematic C3 stereocenter of the molecule.


Through the investigation of various synthetic routes we were able to access two unnatural diastereomers of methyl reserpate: 16-epi-(+)-methyl reserpate and 15,16-di-epi-(+)-methyl reserpate.

Chapter 3 describes the syntheses of rationally designed bisthioureas for anionabstraction catalysis. Recent mechanistic investigations have led to the identification of productive and nonproductive thiourea dimerization modes in the context of an asymmetric alkylation of $\alpha$-chloroethers. Based on this work, we synthesized covalently tethered thioureas that enforce proximity of the hydrogen bond donor moieties for cooperative electrophile activation while disfavoring nonproductive self-aggregation. Significant enhancements in reactivity are obtained with the bisthioureas relative to analogous monomeric thioureas in the model reaction.

## Table of Contents

Abstract ..... iii
Table of Contents ..... v
Acknowledgments ..... viii
Dedication ..... xii
List of Abbreviations ..... xiii
Chapter 1. Enantioselective Catalytic Transannular Ketone-Ene
Reactions
1.1. Introduction ..... 2
1.2. Catalytic Enantioselective Transannular Reactions ..... 2
1.2.1. Enantioselective Desymmetrization of Meso Epoxides ..... 3
1.2.2. Enantioselective Transannular Diels-Alder Reactions ..... 4
1.2.3. Asymmetric Transannular Aldol Reactions ..... 5
1.2.4. Enantioselective Transannular Claisen Rearrangements ..... 6
1.3. The Ketone-Ene Reaction ..... 7
1.4. Substrate Choice ..... 13
1.5. Results and Discussion ..... 15
1.5.1. Substrate Synthesis ..... 15
1.5.2. Catalyst Screen ..... 16
1.5.3. Chromium(III) Tridentate Schiff-Base Catalysts ..... 17
1.5.4. Catalyst Optimization Studies ..... 20
1.5.5. Substrate Scope ..... 24
1.5.6. Limitations ..... 27
1.6. Conclusions ..... 28
1.7. Experimental Section ..... 30
1.8. X-Ray Crystallographic Analysis of Benzoate S14 ..... 67
Chapter 2. Enantioselective Total Synthesis of (+)-Reserpine ..... 82
2.1. Introduction ..... 83
2.2. Previous Strategies to Obtain the Desired C3 Configuration ..... 84
2.2.1. The Woodward Approach: Conformational Biasing and
C3 Epimerization
2.2.2. The Stork Approach: Kinetic Cyclization of an Amino-Nitrile
2.2.3. The Kwon Approach: C3 Stereochemical Relay via a $6 \pi$-Electrocyclization
2.3. Previous Work towards the Synthesis of (+)-Reserpine in the Jacobsen Group
2.4. Remaining Challenges ..... 93
2.5. Improved Synthesis of Enone 19 ..... 94
2.6. Strategies for the Completion of the Reserpine Synthesis ..... 96
2.6.1. Attempted Closure of the E-Ring Via Enamine ..... 96
Alkylation
2.6.2. Radical Deoxygenation Attempts for Installing the C15 ..... 100
Stereogenic Center
2.6.3. Re-evaluation of an Enal Hydrogenation ..... 103
2.6.4. Hydrogenation of an Unprotected Indole Intermediate ..... 106
2.7. Completion of the Synthesis of ( + )-Reserpine ..... 109
2.8. Conclusions ..... 113
2.9. Experimental Section ..... 115
2.10. Spectroscopic Comparisons of Synthetic (+)-Reserpine and ..... 142Commercial (-)-Reserpine
2.11. X-Ray Crystallographic Analysis of 60 ..... 143
Chapter 3. Synthesis of Chiral Bisthiourea Catalysts ..... 160
3.1. Introduction ..... 161
3.2. Hydrogen Bond Donor-Assisted Anion-Abstraction ..... 161
3.3. Proposed Mechanistic Scenario ..... 163
3.4. Synthetic Strategies ..... 167
3.4.1. Strategy 1: Esterification of Two Functionalized Thiourea Monomers
3.4.2. Strategy 2: Late-Stage Installation of Thiourea B ..... 170
3.4.3. Strategy 3: Late-Stage Installation of Thiourea A ..... 172
3.4.4. Synthesis of Bisthiourea $\mathbf{8}$ ..... 173
3.5. Comparison of Bisthioureas $\mathbf{7}$ and $\mathbf{8}$ with Monomer $\mathbf{3}$ ..... 176
3.6. Conclusions and Outlook ..... 177
3.7. Experimental Section ..... 181

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for my parents,
Dayananda and Ranjani Rajapaksa

## List of Abbreviations

| $\AA$ | angstrom |
| :---: | :---: |
| Ac | acetyl |
| AcOH | acetic acid |
| Ad | 1-adamantyl |
| AIBN | azobisisobutyronitrile |
| APCI | atmospheric pressure chemical ionization |
| Ar | aryl |
| atm | atmosphere |
| Bn | benzyl |
| Boc | tert-butoxycarbonyl |
| brsm | based on recovered starting material |
| Bu | butyl |
| ${ }^{\circ} \mathrm{C}$ | degree Celsius |
| CAN | ceric ammonium nitrate |
| $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ | dichloromethane |
| conv. | conversion |
| cis | on the same side |
| $\delta$ | chemical shift in parts per million |
| D | dextrarotatory |
| D | Deuterium |
| DBU | 1,8-diazobicyclo[5.4.0]undec-7-ene |


| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| :---: | :---: |
| DIPEA | di-isopropylethylamine |
| DMAP | 4-N,N-dimethylaminopyridine |
| DMF | dimethylformamide |
| DMP | Dess-Martin Periodinane |
| DMSO | dimethyl sulfoxide |
| dr | diastereomeric ratio |
| $E$ | Ger., entgegen |
| EDC | (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) |
| ee | enantiomeric excess |
| ent- | enantiomeric |
| equiv | equivalents |
| ESI | electrospray ionization |
| Et | ethyl |
| $\mathrm{Et}_{2} \mathrm{O}$ | ethyl ether |
| $\mathrm{Et}_{3} \mathrm{~N}$ | triethylamine |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| FADA | formal aza-Diels-Alder |
| g | gram |
| GC | gas chromatography |
| h | hour |
| $\mathrm{H}_{2}$ | hydrogen |


| HF | hydrogen fluoride |
| :---: | :---: |
| HOBt | hydroxybenzotriazole |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectroscopy |
| Hz | Hertz |
| i | iso |
| IR | infrared |
| J | coupling constant |
| KH | potassium hydride |
| KHMDS | potassium hexamethyldisilazide |
| L | liter |
| L | levorotatory |
| LDA | lithium diisopropylamide |
| LHMDS | lithium hexamethyldisilazide |
| LRMS | low-resolution mass spectrometry |
| $m$ | meta |
| M | molar |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| min | minute |
| mol | mole |
| Ms | methanesulfonyl |


| MS | molecular sieves |
| :---: | :---: |
| $n$ | normal |
| N | normal |
| $\mathrm{NaBH}_{4}$ | sodium borohydride |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| o | ortho |
| $p$ | para |
| $\mathrm{Pd} / \mathrm{C}$ | palladium on carbon |
| Ph | phenyl |
| PMB | p-methoxybenzyl |
| ppm | parts per million |
| Pr | propyl |
| psi | pounds per square inch |
| $\mathrm{PtO}_{2}$ | platinum dioxide |
| quant. | quantitative |
| pyr | pyridine |
| $R$ | rectus |
| rac- | racemic |
| RSM | recovered starting material |
| rt | room temperature |
| s | second |


| S | sinister |
| :--- | :--- |
| SFC | supercritical fluid chromatography |
| $t$ | tertiary |
| TBAF | tetra-n-butylammonium fluoride |
| TBME | tert-butyl methyl ether |
| TBS | t-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | tetrahydrofuran |
| THF | thin-layer chromatography |
| TLC | 3,4,5-trimethoxylbenzoyl anhydride |
| TMB | trimethylsilyl |
| TMS | on opposite sides |
| trans | p-toluenesulfonyl |
| Ts | p-toluenesulfonic acid |
| P-TsOH | ultra-violet |
| UV | Gerammen |

## Chapter 1

# Enantioselective Catalytic Transannular Ketone-Ene Reactions ${ }^{1}$ 

[^0]
### 1.1. Introduction

Transannular chemical reactions are noteworthy for generating structurally and stereochemically rich products from relatively simple precursors in a single transformation. ${ }^{2}$ The first applications of chiral catalysts to promote transannular reactions were recently identified, and these methods will be discussed in the following section. Motivated by the power of ene-type reactions in organic synthesis, we became interested in extending the asymmetric catalytic transannular reaction concept to this important class of $\mathrm{C}-\mathrm{C}$ bond-forming reactions. ${ }^{3}$ In this chapter, we present the development of an enantioselective catalytic transannular ketone-ene reaction.

### 1.2. Catalytic Enantioselective Transannular Reactions

The use of chiral catalysts to achieve absolute stereocontrol in transannular reactions is an area of chemistry that has only recently received attention. As the following examples demonstrate, this powerful strategy provides access to challenging molecular architectures. Two of the examples further illustrate the elegance of the approach through the application of an asymmetric transannular reaction to a natural product total synthesis.

[^1]
### 1.2.1. Enantioselective Desymmetrization of Meso Epoxides ${ }^{4}$

During their investigations of base-promoted isomerizations of epoxides derived from medium-sized cyclic cis-olefins, Hodgson and coworkers identified a transannular bond forming process that proceeds with good enantioselectivity and high yields with a catalytic amount of chiral amine 5 (Scheme 1.1). In these transformations, a chiral lithium base effects an enantioselective $\alpha$-deprotonation of meso epoxides 1 and 3 , which is followed by a diastereoselective bond insertion across the ring to generate fused polycyclic products 2 and $\mathbf{4}$ in good yield and enantioselectivity. Although Hodgson only demonstrated the catalytic desymmetrization with two epoxides, it is noteworthy that similar levels of product enantioenrichment were obtained for $\mathbf{2}$ and $\mathbf{4}$ despite differences in substrate ring-size ( 8 vs. 9 ) and the bond participating in the insertion reaction ( $\mathrm{C}-\mathrm{H}$ vs. $\mathrm{N}-\mathrm{C}$ ).


Scheme 1.1. Enantioselective Desymmetrization of meso Epoxides

[^2]
### 1.2.2. Enantioselective Transannular Diels-Alder Reactions ${ }^{5}$

In 2007, Jacobsen and coworkers reported a highly enantioselective catalytic transannular Diels-Alder (TADA) reaction of macrocycles containing dienophiles and ( $E, E$ )-dienes. Oxazaboroldine Lewis acid 6 catalyzes this transformation and is remarkably tolerant to substrate modifications to the dienophile identity (enoate vs. enone) and ring-size (14-16) (Scheme 1.2). A range of macrocyclic substrates were found to undergo asymmetric TADA reactions to provide tricyclic products in good diastereo- and enantioselectivity.


$69 \%$
$>19: 1 \mathrm{dr}, 90 \%$ ee


78\% 5.9:1 dr, 90\% ee

$83 \%$
$4.2: 1 \mathrm{dr}, 88 \%$ ee


15\% 5.0:1 dr, 85\% ee

Scheme 1.2. Catalytic Asymmetric Transannular Diels-Alder (TADA) Reactions

The authors took advantage of the predictable selectivity of the oxazaborolidinecatalyzed TADA reaction in a total synthesis of bicyclic sesquiterpene natural product 11,12-diacetoxydrimane 10 (Scheme 1.3). The TADA reaction of 15 -membered cyclic silyl ether 7 afforded tricycle 8 in high efficiency and selectivity, and this single operation installed all four contiguous stereocenters of natural product. Importantly, executing the Diels-Alder reaction in a transannular context was found to be essential, as an analogous acyclic substrate did not undergo the corresponding intramolecular Diels-

[^3]Alder with catalyst 6, under thermal conditions, or even in the presence of a stronger Lewis acid. ${ }^{6}$


Scheme 1.3. Application of the Catalytic Asymmetric TADA to a Total Synthesis of 11,12-diacetoydrimane

### 1.2.3. Asymmetric Transannular Aldol Reactions ${ }^{7}$

List and coworkers reported an asymmetric transannular aldol reaction of medium-sized cyclic diketones that is catalyzed by 4-fluoro-proline derivative $\mathbf{1 1}$ (Scheme 1.4). ${ }^{8}$ Several 1,4-cyclooctanediones were found to undergo aldol cyclizations to provide cis-fused bicyclic alcohols in good yields and excellent enantioselectivities $(94-96 \%$ ee $)$. The synthetic utility of the method was illustrated through an enantioselective total synthesis of (+)-hirsutene (13), which uses an efficient and highly selective transannular aldolization of $\mathbf{1 2}$ as a key step.

[^4]

Scheme 1.4. Enantioselective Transannular Aldol Reactions

A striking feature of this chemistry is its sensitivity to deviations from the 1,4cyclooctanedione substrate framework (Figure 1.1). For example, products 14 and 15, which are obtained through transannular aldolizations of cyclononanediones have substantially diminished levels of enantioenrichment. Similarly, 16 and 17, derived from 10-membered cyclic diketones are obtained in low selectivities, with $\mathbf{1 7}$ being formed as a racemate. Finally, 1,4-cyclononanedione and 1,4-cyclodecanedione undergo transannular aldol condensations to afford achiral products 18 and 19.


14
$57 \%$
$82 \%$ ee


15
$82 \%$
$32 \%$ ee


16
22\%


17
$67 \%$
$0 \%$ ee


18
97\%


19
32\%

Figure 1.1. Transannular Aldolizations of 9- and 10-Membered Cyclic Diketones

### 1.2.4. Enantioselective Transannular Claisen Rearrangements ${ }^{9}$

Hiersemann and coworkers reported an asymmetric Claisen rearrangement of macrocyclic $O$-allyl- $\alpha$-ketoesters (21a-c) that is catalyzed by chiral copper salt 20 (Scheme 1.5). Unlike the previous examples, this transformation does not afford

[^5]polycyclic products but results in the synthesis of medium-sized cycloalkanes with vinyl and $\alpha$-ketoester substituents. The highly Lewis acidic copper bis(oxazoline) complex 20 promotes the arrangement of a series of $(E, E)$-macrocyclic allyl vinyl ethers to afford trans-substituted cycloalkanes in excellent enantioselectivity but with low to moderate diastereoselectivity.


Scheme 1.5. Hiersemann's Transannular Claisen-Rearrangement

### 1.3. The Ketone-Ene Reaction

These four examples demonstrate the efficiency of catalytic enantioselective transannular reactions in accessing challenging scaffolds. Inspired by this precedent, we became interested in developing a chiral catalyst for enantioselective transannular ketoneene reactions. The carbonyl-ene reaction is a valuable $\mathrm{C}-\mathrm{C}$ bond forming process that occurs between an enophile (a carbonyl) and an ene component (an olefin possessing an allylic hydrogen) to afford homoallylic alcohols and generate up to two new stereocenters (Scheme 1.6). ${ }^{10,11}$

[^6]

Scheme 1.6. The Carbonyl-Ene Reaction

This pericyclic reaction can be promoted under thermal or Lewis acidic conditions. Although a number of Lewis acid-catalyzed aldehyde-ene reactions have been reported, ${ }^{11}$ ketones are generally very poor reacting partners in Lewis acid-catalyzed processes. To date, enantioselective catalytic ketone-ene reactions have only been achieved with highly electrophilic ketones bearing strongly electron-withdrawing substituents. ${ }^{12,13}$ In 2000, Evans and coworkers reported the first catalytic enantioselective ketone-ene reaction. They demonstrated that C 2 -symmetric copper bis(oxazoline) complex 23 catalyzes ketone-ene reactions between 1,1-disubstituted olefins (used in 5-10-fold excess) and methyl pyruvate (24) in high yield and enantioselectivity (Scheme 1.7). ${ }^{12 \mathrm{a}}$

[^7]

Scheme 1.7. Evans's Enantioselective Copper Bis(oxazoline)-Catalyzed Ene Reactions of Methyl Pyruvate

Since this pioneering report, all subsequently reported enantioselective ketone-ene reactions have also employed $\alpha$-keto-carbonyl compounds, either due to the necessity for two-point binding of the substrate to the catalyst, or because of the enhanced electrophilicity of the ketone. Yang demonstrated that intramolecular ene reactions of $\alpha$ -keto-esters with internal olefins were catalyzed in high yield and selectivity by a related copper bis(oxazoline) complex (Scheme 1.8A). ${ }^{12 \mathrm{~b}}$ Strategies to expand the scope of either the ene or enophile component in asymmetric intermolecular ketone-ene reactions have centered on electronic activation. Mikami showed that a dicationic palladium complex prepared through an in situ counterion exchange of 26 catalyzes the intermolecular ene reaction of $\alpha$-ketoesters. ${ }^{12 c}$ With the introduction of the highly electron-withdrawing trifluoromethyl group, pyruvate 27 undergoes selective ene reactions with typically unreactive monosubstituted olefins (Scheme 1.8B). In a subsequent report, the same group demonstrated that the use of silyl enol ethers allowed the enophile scope to be expanded to $\alpha$-diketones. ${ }^{12 \mathrm{e}}$ In a particularly impressive example,
unsymmetrical diketone 28 is converted to 29 as a single regioisomer and in excellent enantioselectivity (Scheme 1.8C).
A) Intramolecular $\alpha$-Ketoester Ene Reactions



B) Trifluoropyruvate Ene Reactions

C) $\alpha$-Diketone Ene Reactions with Electron-Rich Olefins


29

Scheme 1.8. Lewis Acid-Catalyzed Enantioselective Ketone-Ene Reactions

Recently, Brønsted acid catalysts 30 and 31 have also been shown to catalyze enantioselective ketone-ene reactions (Scheme 1.9). However, both of these methods are limited to the highly reactive trifluoromethyl pyruvate 27. ${ }^{13}$


30, $\mathrm{Ar}^{2}=p-\mathrm{CH}_{3} \mathrm{OC}_{6} \mathrm{H}_{4}$
76\%, 96\% ee
Rueping et al. (Ref. 13b)


Scheme 1.9. Brønsted Acid Catalyzed Ketone-Ene Reactions

The Jacobsen group's work in the area of enantioselective hetero-ene reactions has involved the development of chiral Cr(III) tridentate Schiff-base complexes for interand intramolecular aldehyde-ene reactions (Scheme 1.10). ${ }^{14,15}$ The $\mathrm{Cr}(\mathrm{III})$-catalyzed intermolecular aldehyde-ene reaction occurs only with electron-rich olefins, and the intramolecular variant readily takes place with unactivated olefins. However, attempted extension of the developed aldehyde-ene methodologies to asymmetric inter- or intramolecular ketone-ene reactions of even highly activated trifluoromethyl ketones yielded unsatisfactory results (Scheme 1.11). ${ }^{14 \mathrm{c}, 15 \mathrm{~b}}$

[^8]

(B) Cr(III)-Catalyzed Intramolecular Aldehyde-Ene Reactions



Scheme 1.10. Cr(III)-Catalyzed Aldehyde-Ene Reactions



Scheme 1.11. Ketone-Ene Reactions with Cr(III) Tridentate Schiff-Base Catalysts

Although the scope of reported ketone-ene methodologies remains limited by the apparent necessity for an activated $\alpha$-dicarbonyl functionality, we envisioned that a transannular ketone-ene reaction may not require this feature. Given that the transannular disposition of reacting partners can confer a significant entropic advantage and corresponding reactivity enhancements, we considered the possibility of effecting
enantioselective transannular ene reactions of electronically unactivated ketones using chiral Schiff-base chromium(III) catalysts.

### 1.4. Substrate Choice

We were particularly interested in studying the transannular ketone-ene reaction of $(E)$-cyclodecenones, as the resulting products contain a decalinol framework that is prevalent in terpene natural products (Scheme 1.12). ${ }^{16}$ Furthermore, diastereoselective ketone-ene reactions of this substrate framework have been demonstrated. Yamamura reported thermal and Lewis acid-promoted transannular ketone-ene reactions of natural product preisocalamendiol 35 to afford dienol 36 in good yield (Scheme 1.13). ${ }^{17}$ The successful cyclization in the presence of $\mathrm{AlCl}_{3}$ under mild conditions suggested that chiral Lewis acid catalysts may be able to induce enantioselective transannular ketoneene reactions of cyclodecenone substrates. Additionally, the use of elevated temperatures $\left(180{ }^{\circ} \mathrm{C}\right)$ to effect the thermal ketone-ene reaction of preisocalamendiol is an indication that background cyclization of related substrates would likely not compete with a Lewis acid-catalyzed pathway.

[^9]





Scheme 1.12. Proposed Enantioselective Transannular Ketone-Ene Reaction and Selected Examples of Natural Products Featuring trans-Decalinol Frameworks


Scheme 1.13. Thermal and Lewis Acid-Promoted Transannular Ketone-Ene Reactions of Preisocalamendiol

We recognized that our efforts would need take into consideration the known temperature-dependent planar chirality of medium-sized cyclic $(E)$-olefin substrates. ${ }^{18}$ For efficient, enantioselective transannular ene reactions to be possible, the reaction must necessarily occur under conditions where interconversion of the enantiomeric conformers of the substrate takes place. In that context, Barriault has studied diastereoselective ene reactions of $(E)$-cyclodecenones in cascade oxy-Cope-ene transformations and has shown that those cyclic structures are configurationally flexible under the elevated temperatures of the thermal reaction $\left(140-220{ }^{\circ} \mathrm{C}\right)$ (Scheme 1.14). ${ }^{19}$ Additionally, the configurational

[^10]instability of some cyclic (E)-olefins, determined through racemization half-life measurements, suggests that elevated temperatures will not be required for conformer interconversion of cyclodecenones containing trisubstituted olefins (Figure 1.2). ${ }^{20}$


Scheme 1.14. Barriault's Tandem Oxy-Cope-Ene Reaction


10 s at it
 $10^{-4}$ s at it


3 d at $100{ }^{\circ} \mathrm{C} \quad 1.6 \mathrm{~h}$ at $0^{\circ} \mathrm{C}$

spontaneous

Figure 1.2. The Half-Life of Racemization for Medium-Sized Cyclic (E)-Olefins

### 1.5. Results and Discussion

### 1.5.1. Substrate Synthesis

Based on the prior studies on this substrate framework, we chose to study the transannular ketone-ene reaction of (E)-5-methyl-cyclodec-5-enone 39a, which was readily synthesized from cyclohexene oxide in four steps (Scheme 1.15). ${ }^{19 \mathrm{a}}$ A coppercatalyzed epoxide opening with isopropenyl magnesium bromide provided secondary alcohol 37 in quantitative yield. Under Swern oxidation conditions, the alcohol was converted to a $\beta, \gamma$-unsaturated ketone, which was reacted with vinylmagnsium bromide to

[^11]provide divinyl alcohol 38 in good yield and in >19:1 diastereomeric ratio. Treatment of 38 with potassium hydride and 18-crown-6 ether effected an anionic oxy-Cope rearrangement to provide 39a as a single olefin isomer. ${ }^{21}$ Cyclodecenone 39a can be stored neat at $-30{ }^{\circ} \mathrm{C}$ for at least three months without decomposition or isomerization. ${ }^{22}$


Scheme 1.15. Synthesis of Model Substrate (E)-5-methyl-cyclodec-5-enone 39a

### 1.5.2. Catalyst Screen

With the model substrate in hand, an evaluation of chiral metal(salen) and metal tridentate Schiff-base complexes, was conducted under conditions that afforded no observable background conversion of cyclodecenone 39a (Scheme 1.16). Of the Lewis acids evaluated, the chromium(III) tridentate Schiff-base complex 33, ${ }^{14 b, 23}$ was uniquely effective in promoting the desired transformation. The ketone-ene reaction catalyzed by 33 provided trans-decalinol 40a as a single regioisomer in $62 \%$ yield, $>19: 1 \mathrm{dr}$, and $79 \%$ ee. The high substrate conversion along with high product enantioenrichment confirmed that cyclodecenone 39a is configurationally dynamic under the reaction conditions.

[^12]

$0 \%(14 \%)^{a}$

-2)
$0 \%(14 \%)^{a}$
${ }^{a}$ Yields and conversions (in parantheses) were deteremined by ${ }^{1} \mathrm{H}$ NMR analysis of crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. ${ }^{b} 39$ a was completely consumed, and afforded 40 as a single regioisomer and diastereomer, as deteremined by ${ }^{1} \mathrm{H}$ NMR analysis of the crude reaction mixture. Yield was determined by isolation. ${ }^{d}$ Determined by GC analysis using commercial chiral columns.

Scheme 1.16. Initial Screen of Chiral Lewis Acids

### 1.5.3. Chromium(III) Tridentate Schiff-Base Catalysts

Chromium(III) tridentate Schiff-base complexes were first developed for enantioselective hetero-Diels-Alder (HDA) reactions of aldehydes and monooxygenated dienes (Scheme 1.17A). ${ }^{24}$ Related complexes were subsequently shown to be effective for a number of other asymmetric pericyclic transformations involving aldehyde and

[^13]quinone substrates, including variants of the HDA reaction, ${ }^{25}$ aldehyde-ene reactions (Scheme 1.10), and quinone-Diels-Alder (QDA) cycloadditions (Scheme 1.17B). ${ }^{26}$ Mechanistic investigations have indicated that the catalysts activate carbonyl groups through single-point binding. ${ }^{14 \mathrm{c}}$
(A) Cr(III)-Catalyzed Enantioselective HDA Reactions

(B) Cr(III)-Catalyzed Enantioselective QDA Reactions


( $R, S$ )-41, $\mathrm{n}=1$
$(R, S)-42, \mathrm{n}=2$

| entry | catalyst | time | yield | ee | regioselectivity |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $(\boldsymbol{R}, \boldsymbol{S})-\mathbf{4 1}$ | 10 min | 86 | 96 | $12: 1$ |
| 2 | $(\boldsymbol{R}, \boldsymbol{S}) \mathbf{- 4 2}$ | 26 h | 82 | 39 | $3.3: 1$ |

Scheme 1.17. Enantioselective Cr(III)-Catalyzed HDA and QDA Reactions

The depictions of complexes 32-34 and 41-42 used in Schemes 1.10 and 1.17 summarize key structural data that has been gained about these catalysts (Scheme 1.18). X-ray crystallography data indicate that complex 34, derived from ortho-t-Bu-substituted salicylaldimine 43 , is a dimer in the solid state with the two $\mathrm{Cr}(\mathrm{III})$ centers bridged by oxygen atoms of the aminoindanol ligand. This class of dimeric catalysts will be referred to as Type II dimers for the remainder of the chapter. ${ }^{27}$ The optimal HDA catalyst (42)

[^14]displays an alternate dimerization mode (Type I), wherein a water molecule bridges the two Cr (III) centers. This complex is derived from ortho-(1-adamantyl)-substituted Schiffbase ligand 44. The bulky adamantyl group is thought to preclude formation of an aminoindanol bridged Type II dimer. Mechanistic studies carried out by former graduate student, Rebecca Ruck, provided evidence that the dimeric structures of $\mathbf{3 4}$ and 42 are maintained in solution and are relevant for catalysis of the aldehyde-ene and HDA reactions. ${ }^{28}$ Complex 41, which is also derived from tridentate Schiff base 44, is prepared under identical conditions to complex 42 except for an acidic workup. This catalyst was found to crystallize as a monomer. Evidence that solid structure data for $\mathbf{4 1}$ and $\mathbf{4 2}$ have reactivity implications is shown in Scheme 1.17B. Monomer 41 affords faster and more selective QDA reactions than dimeric catalyst 42 (entries $1-2$ ). The $\mathrm{Cr}(\mathrm{III})$ centers of all three of these complexes have octahedral geometry with water molecules occupying available coordination sites. A feature common to all methods that employ Cr (III) tridentate Schiff-base complexes is the requirement for desiccant (molecular sieves or BaO ). It is proposed that this additive sequesters a coordinated water molecule from the highly Lewis acidic Cr (III) center to provide a free coordination site for carbonyl activation.

[^15]
$(S, R)-43$


$(S, R)-34$
"Type II dimer"
( $R, S$ )-44


Scheme 1.18. Different Classes of $\mathrm{Cr}(\mathrm{III})$ Tridentate Schiff-Base Complexes

### 1.5.4. Catalyst Optimization Studies

Based on the results of our initial catalyst screen, we evaluated complexes 34, 41, and 42 as representative members of each $\mathrm{Cr}(\mathrm{III})$ tridentate Schiff-base crystal-type (Type II dimer, monomer, and Type I dimer, respectively) for the transannular ketoneene reaction of 39a (Table 1.1). In the presence of activated $4 \AA$ molecular sieves, all three catalyzed the desired reaction providing nearly complete conversion after 48 h . These catalysts afforded trans-decalinol 40a in moderate to good enantioselectivity and
all provided the same sense of enantioinduction. Unlike the QDA reaction, the transannular ketone-ene reaction does not show a pronounced selectivity difference with monomeric and dimeric catalysts 41 and 42 (entries 2 and 3). ${ }^{29}$

Table 1.1. Evaluation of Structurally Different $\mathrm{Cr}(\mathrm{III})$ Tridentate Schiff-Base Complexes

${ }^{\text {a }}$ Conversion was approximated as $100 *(40 a-39 a) /(40 a+39 a)$, based on ${ }^{1} \mathrm{H}$ NMR integration of the crude reaction mixture. Product diastereomeric ratio was determined to be $>19: 1$ based on ${ }^{1} \mathrm{H}$ NMR analysis of the crude reaction mixture. ${ }^{b}$ Determined by GC analysis using commercial chiral columns.

Further optimization studies were carried out on the two dimeric catalyst scaffolds. ${ }^{30}$ A series of catalysts containing variation at the para-position of the salicylaldehyde portion of the Schiff-base ligands was evaluated (Table 1.2). However, the effect of modifying this substituent on product enantioselectivity was minimal for both types of dimers.

[^16]Table 1.2 Variation of the Schiff-base para-Substituent

${ }^{\text {a }}$ Conversion was approximated as $100 \star(40 a-39 a) /(40 a+39 a)$, based on ${ }^{1} \mathrm{H}$ NMR integration of the crude reaction mixture. Product diastereomeric ratio was determined to be $>19: 1$ based on ${ }^{1} \mathrm{H}$ NMR analysis of the crude reaction mixture. ${ }^{b}$ Determined by GC analysis using commercial chiral columns.

The HDA reaction shows reactivity and selectivity dependence on the identity of the catalyst counterion. ${ }^{24 \mathrm{a}, \mathrm{c}}$ A counterion exchange on complex 42 from chloride to the noncoordinating $\mathrm{SbF}_{6}{ }^{-}$counterion induced rate accelerations and selectivity enhancements for some substrates. Hence, we broadly investigated the impact of modifying the counterion associated with catalyst 42 on the ketone-ene reaction. Pronounced effects were observed, with reactivity increasing steadily as the coordinating ability of the counterion decreased (Table 1.3). Catalysts 52 and 53, bearing $\mathrm{PF}_{6}{ }^{-}$and $\mathrm{SbF}_{6}{ }^{-}$counterions, respectively, promoted complete conversion within 24 h , albeit with diminished enantioselectivities as compared to the chloride complex (entries 6-7 vs. entry 1). ${ }^{31}$ Complexes bearing sulfonate counterions were somewhat less reactive, but induced significantly improved enantioselectivities (entries 3 and 4), with triflate complex 50 identified as the optimal catalyst of the series.
${ }^{31}$ The transannular ketone-ene reaction conducted with complex 53 afforded minor olefin byproducts ( $<10 \%$ ), an indication of diminished regioselectivity with this more Lewis acidic catalyst.

Table 1.3. Counterion Effects on Reactivity and Selectivity

${ }^{\text {a }}$ Determined by GC analysis of the crude reaction mixtures using dodecane as an internal standard. ${ }^{b}$ Determined by 1 H NMR analysis of the crude reaction mixtures. ${ }^{c}$ Determined by GC analysis using commercial chiral columns.

Analogous counterion exchanges were carried out on the optimal Type I and II chloride complexes 45 and 47 (identified from the experiments in Table 1.2) and monomer 41. Triflate 54 catalyzed a more selective ketone-ene reaction than the corresponding chloride complex, providing decalinol 40a in $87 \%$ ee. This enhancement in selectivity is in accord with the counterion effect observed between Type I chloride complex 42 and triflate 50. Enantioselectivity induced by triflate 55 was fairly similar to that of the corresponding Type II chloride complex ( $85 \%$ vs. $87 \%$ ee). In contrast, the triflate complex 56 provided the ketone-ene product with significantly lower enantioenrichment than the corresponding monomeric chloride complex ( $1 \%$ ee vs. $60 \%$ ee). Although these data are not conclusive about the structure of optimal catalyst 50, they empirically indicate that the catalyst preparation procedure is important. ${ }^{32}$

[^17]

(S,R)-45 (X=CI): 100\% conv, -67\% ee (S,R)-54 (X=OTf): $100 \%$ conv, $-87 \%$ ee

(S,R)-47 (X=CI): 100\% conv, -87\% ee (S,R)-55 (X=OTf): $100 \%$ conv, $-85 \%$ ee

(S,R)-41 (X=Cl): 100\% conv, -60\% ee (R,S)-56 (X=OTf): 100\% conv, 1\% ee

Scheme 1.19. Counterion Effects Based on the Chloride Complex Structure Type

### 1.55. Substrate Scope ${ }^{33}$

With complex 50 identified as the optimal catalyst, the substrate scope of the enantioselective transannular ketone-ene reaction was evaluated (Table 1.4). Full conversion of cyclodecenone 39a was achieved by extending the reaction time to 48 h , and product 40a was obtained in $81 \%$ yield and $93 \%$ ee (entry 1). The absolute stereochemistry of 40a was determined by X-ray crystallographic analysis of the corresponding para-Br-benzoate, and the assignments for the other products were made by analogy (Figure 1.3).

[^18]


Figure 1.3. ORTEP Diagram of the para-Br-benzoate of 40a Showing 50\% Probability Displacement

Gem-dimethyl-substituted trans-decalinols 40b and 40c, were accessed in high yield and enantioselectivity (entries 2 and 3), but the closely analogous product 40d was obtained in low yield and as a racemate (entry 4). Analysis of the chair-chair conformations of these substrates provides a plausible explanation (Figure 1.4). ${ }^{34}$ Only cyclodecenone 40d possesses a syn-pentane relationship between its methyl substituents, and the pseudo-axial methyl substituent at C 3 is also likely to interfere with complexation of the Lewis acidic catalyst. With these substitution effects in mind, we probed more highly functionalized substrates (Table 1.4, entries 5 and 6). The acid-sensitive acetal 40e and unconjugated diene 40 f both proved to be effective substrates, affording the corresponding ene products in high enantioselectivities and good yields. Additionally, ether 57 and cyclononenone 59 underwent enantioselective ketone-ene reactions to afford the corresponding bicyclic alcohol products, although in diminished yields and enantioselectivities.

[^19]Table 1.4. Substrate Scope of the $\mathrm{Cr}(\mathrm{III})$-Catalyzed Ketone-Ene
(\%)
${ }^{\text {a }}$ Reactions were performed on a 0.2 mmol scale with $5 \mathrm{~mol} \%$ catalyst 50 ( $10 \mathrm{~mol} \%$ based on Cr ) and in the presence of powdered $4 \AA$ molecular sieves at rt in anhydrous toluene ([substrate] = 4 M ). Unless otherwise noted, reactions showed complete conversion after 48 h and the bicyclic alcohol product was obtained as a single regioisomer. ${ }^{b}$ Isolated yield of the ketone-ene products following purification by flash chromatography. ${ }^{c}$ Determined by
${ }^{1}$ H NMR analysis of the crude reaction mixtures. ${ }^{d}$ Determined by GC analysis using commercial chiral columns. ${ }^{e}$ Combined yield of 40 d and an inseparable regioisomeric product. ${ }^{f}$ Reaction time was 24 h .


Figure 1.4. Rationale for the Low Observed Reactivity of 39d Relative to 39b and 39c

Tetrasubstituted alkene $\mathbf{6 1}$ proved much less reactive than trisubstituted olefins 39a-f under the catalytic conditions, undergoing only $19 \%$ conversion after 24 h at $50{ }^{\circ} \mathrm{C}$. The transannular ketone-ene reaction afforded trans-decalinol 62, bearing a quaternary stereocenter, in $12 \%$ yield and $73 \%$ ee (Scheme 1.20). Cyclodecenone (+)-61 was recovered in $69 \%$ yield and in $10 \%$ ee, confirming that this substrate undergoes racemization slowly under the catalytic conditions, and that complex $\mathbf{5 0}$ induced a measurable kinetic resolution. ${ }^{35}$


Scheme 1.20. Kinetic Resolution of Planar Chiral Cyclodecenone 61

### 1.56. Limitations

Acyclic ketones $\mathbf{6 3}$ and $\mathbf{6 4}$ did not undergo intramolecular ene reactions under the optimized conditions or at $50{ }^{\circ} \mathrm{C}$ (Scheme 1.21 ). These results may be an indication that the reactivity enhancements conferred to transannular substrates are essential for $\mathrm{Cr}(\mathrm{III})$ catalyzed ketone-ene reaction. However, attempted ketone-ene reactions of a number of

[^20]other cyclic substrates were unsuccessful as well. For example, (Z)-5-methyl-cyclodecenone (65), the olefin isomer of model substrate 39a did not afford any of the predicted cis-fused decalinol. (E)-Cyclodecenones 66 and 67, which differ from 39a in the relative positions of the ene and enophile components in the ring, and were predicted to afford [3.5.0]-bicyclic alcohols, were also unreactive. Finally, 11-membered cyclic keto-olefin 68 did not afford the corresponding ketone-ene product. The sensitivity of the reaction to perturbations in ring-size is similar to that of List's transannular aldol reaction. ${ }^{7}$ These data suggest that the transannular strategy, which properly aligned the two reactive components of model substrate 39a for the ene reaction, might have the opposite effect with many of these other medium-sized cyclic substrates, prohibiting the desired reaction from taking place.





Scheme 1.21. Unsuccessful Substrates

### 1.6. Conclusions

In conclusion, we have demonstrated that chiral chromium(III) tridentate Schiffbase complex 50 catalyzes transannular ketone-ene reactions of $(E)$-cyclodecenones in
high diastereo- and enantioselectivity to access trans-decalinols. The dramatic counterion effects observed in the ketone-ene reaction are intriguing and are not well understood at this time. Structural elucidation of complex 50 may provide an understanding of the role the triflate counterion has in defining the chiral environment of the catalyst.

Significantly, the transannular strategy provides entropic activation for the ketone-ene reaction and allows electronically unactivated ketones to be engaged as substrates in a chiral Lewis acid-catalyzed process. This finding is in line with previous observations regarding the $\mathrm{Cr}(\mathrm{III})$-catalyzed aldehyde-ene reactions: intermolecular reactions occurs only with activated electron-rich olefins whereas the entropically activated intramolecular variant tolerates unactivated olefins. This trend suggests that other typically inert functional groups may undergo transannular reactions with appropriate electronic tuning of the reaction partner.

### 1.7. Experimental Section

## A. General Information

Unless otherwise noted, all reactions were performed under a positive pressure of anhydrous nitrogen or argon in flame- or oven-dried glassware. Moisture- and airsensitive reagents were dispensed using oven-dried stainless steel syringes or cannulae and were introduced to reaction flasks through rubber septa. Reactions conducted below ambient temperature were cooled by external baths (dry ice/acetone for $-78{ }^{\circ} \mathrm{C}$ and ice/water for $0^{\circ} \mathrm{C}$ ). Reactions conducted above ambient temperature were heated by an oil bath.

Analytical thin layer chromatography (TLC) was performed on glass plates precoated with silica $60 \mathrm{~F}_{254}(0.25 \mathrm{~mm})$ or on aluminum sheets pre-coated with neutral aluminum oxide $60 \mathrm{~F}_{254}(0.2 \mathrm{~mm})$. Visualization was carried out by exposure to a UVlamp (short wave 254 nm , long wave 365 nm ), and by heating after staining the plate with a ceric ammonium molybdate, potassium permanganate, or phosphomolybdic acid solution. Extraction and chromatography solvents were reagent or HPLC grade and were used without further purification. Flash column chromatography was carried out over silica gel ( $60 \AA, 230-400 \mathrm{mesh})$ from EM Science, Davisil ${ }^{\mathrm{TM}}$ (Grade 643, $150 \AA, 200-$ 425 mesh) from Aldrich, or activated neutral aluminum oxide (Brockman I standard grade, $58 \AA, 150$ mesh) from Aldrich. Flash column chromatography was conducted on a Biotage Isolera automated chromatography system.

Materials. Commercial reagents and solvents were used with the following exceptions: tetrahydrofuran, diethyl ether, toluene, and dichloromethane employed as reaction solvents were dried by passage through columns of activated alumina. Triethylamine was distilled from calcium hydride at 760 torr prior to use. Chloroform-d was treated with and stored over anhydrous potassium carbonate prior to use. Powdered $4 \AA$ MS were purchased from Sigma-Aldrich, activated by heating in a commercial microwave oven, and stored in a vial sealed with parafilm in a desiccator. 4,4-dimethylcyclohexanone was prepared according to the reported procedure. ${ }^{36}$ Intermediates S10, $\mathbf{S 1 1}$ and S12 were prepared according to reported procedures. ${ }^{37,38,39}$

Instrumentation. Proton nuclear magnetic resonance ( ${ }^{1} \mathrm{H}$ NMR) spectra and carbon nuclear magnetic resonance $\left({ }^{13} \mathrm{C}\right.$ NMR) spectra were recorded on a Varian Mercury-400 (400MHz), Inova-500 (500MHz), or an Inova-600 $(600 \mathrm{MHz})$ spectrometer at $23{ }^{\circ} \mathrm{C}$, unless otherwise noted. Chemical shifts for protons are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent $\left(\mathrm{CHCl}_{3}: 7.26 \mathrm{ppm}\right)$. Chemical shifts for carbons are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane and are referenced to the NMR solvent $\left(\mathrm{CDCl}_{3}: 77.16 \mathrm{ppm}\right)$. Data are represented as follows: chemical shift, multiplicity $(\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{m}=$ multiplet, $\mathrm{br}=$ broad), integration, and coupling constant $(J)$ in Hertz (Hz). Infrared (IR) spectroscopy was performed on the neat compounds on a Brucker Tensor 27 FT-IR

[^21]Spectrometer using OPUS software. Data are represented as follows: frequency of absorption $\left(\mathrm{cm}^{-1}\right)$, intensity of absorption ( $\mathrm{s}=$ strong, $\mathrm{m}=$ medium, $\mathrm{w}=$ weak $)$. Mass spectra were obtained on an Agilent 1200 series 6120 Quadrupole LC/MS. Optical rotation data were collected using a $1-\mathrm{mL}$ cell using a 0.5 dm path length on a Jasco P2000 polarimeter and are reported as $[\alpha]_{\mathrm{D}}{ }^{23}$ (concentration in grams $/ 100 \mathrm{~mL}$ solvent). Reported rotations are the average of 3-5 measurements per sample.

## B. Catalyst Preparation and Characterization


( $R, S$ )-42


Chromium(III) Chloride Complex (S,R)-42
Catalyst (S,R)-42 was prepared according to the published procedure. ${ }^{24 \mathrm{c}}$
$(S, R)-42$

## General Procedure A - Counteranion Exchange

A flame-dried 50 mL round-bottom flask equipped with a stir bar and septum was wrapped with aluminum foil and charged with a silver salt bearing the desired counterion ( $0.0924 \mathrm{mmol}, 0.95$ equiv). To this flask was added complex $42(50 \mathrm{mg}, 0.097 \mathrm{mmol}, 1$ equiv). To the flask, under an atmosphere of argon, was added TBME ( 16.2 mL ). The reaction mixture was stirred at room temperature for 3 h , after which the contents were filtered through Celite ${ }^{\circledR}$. The pad of Celite ${ }^{\circledR}$ was rinsed with an additional portion of

TBME ( 16.2 mL ). The filtrate was concentrated to afford the desired complex, which was used without further purification.


Chromium(III) Tosylate Complex (S,R)-49
Following General procedure A , the counterion exchange was performed with (S,R)-42 (100 mg, $0.19 \mathrm{mmol}, 1$ equiv) and $\mathrm{AgOTs}(50.5 \mathrm{mg}, 0.18 \mathrm{mmol}, 0.95$ equiv) to provide catalyst (S,R)-49 as a brown powder (84\%). FTIR (neat, $\mathrm{cm}^{-1}$ ) 3198 (br m) 2902 (m) 1616 (s) 1538 (m) 1434 (m) 1307 (w) 1229 (s) 1169 (m) 1078 (m) 1010 (m) 945 (w) 812 (m) 744 (s).


Chromium(III) Triflate Complex ( $\boldsymbol{R}, \mathbf{S}$ )-50
Following General Procedure A, the counterion exchange was performed with ( $\boldsymbol{R}, \mathbf{S} \mathbf{)} \mathbf{- 4 2}(200 \mathrm{mg}, 0.39 \mathrm{mmol}, 1$ equiv) and $\operatorname{AgOTf}$ ( $95 \mathrm{mg}, 0.37 \mathrm{mmol}, 0.95$ equiv) to provide catalyst ( $\boldsymbol{R}, \mathbf{S}$ )-50 as a brown powder ( $244 \mathrm{mg}, 98 \%$ ). FTIR (neat, $\mathrm{cm}^{-1}$ ) 3271 (br w) 2902 (m) 2845 (w) 1614 (m) 1538 (m) 1453 (w) 1294 (m) 1227 (s) 1170 (s) 1026 (s) 980 (w) 811 (w) 746 (s).


## Chromium(III) Triflimide Complex ( $\boldsymbol{R}, \mathbf{S}$ )-51

Following General Procedure A, the counterion exchange was performed with ( $\boldsymbol{R}, \mathbf{S}$ )-42 $(50 \mathrm{mg}, 0.097 \mathrm{mmol}, 1$ equiv) and $\mathrm{AgNTf}_{2}(35.9 \mathrm{mg}, 0.0924 \mathrm{mmol}, 0.95$ equiv) to provide
catalyst ( $\boldsymbol{R}, \mathbf{S}$ )-51 as a brown powder ( $62.3 \mathrm{mg}, 83 \%$ ). FTIR (neat, $\mathrm{cm}^{-1}$ ) $3538(\mathrm{br} w) 2905$ (w) 2850 (w) 1614 (m) 1541 (m) 1431 (w) 1349 (m) 1298 (m) 1227 (m) 1188 (s) 1135 (m) 1057 (s) 981 (m) 748 (m).
 Chromium(III) Hexafluorophosphate Complex ( $\boldsymbol{R}, \boldsymbol{S}$ )-52

Following General Procedure A, the counterion exchange was performed with $(\boldsymbol{R}, \boldsymbol{S})-\mathbf{4 2}(50 \mathrm{mg}, 0.097 \mathrm{mmol}, 1$ equiv $)$ and $\mathrm{AgPF}_{6}$ ( $23.4 \mathrm{mg}, 0.0924 \mathrm{mmol}, 0.95$ equiv) to provide catalyst (R,S)-52 as a brown powder ( $50.3 \mathrm{mg}, 82 \%$ ). FTIR (neat, $\mathrm{cm}^{-1}$ ) 3532 (br w) 2901 (m) 2848 (w) 1614 (m) 1538 (m) 1431 (w) 1300 (w) 1228 (m) 1151 (m) 1054 (m) 839 (s) 749 (m).


Chromium(III) Hexafluoroantimonate Complex ( $\boldsymbol{R}, \boldsymbol{S}$ )-53
Following General Procedure A, the counterion exchange was performed with ( $\boldsymbol{R}, \boldsymbol{S}$ )-42 ( $50 \mathrm{mg}, 0.097 \mathrm{mmol}, 1$ equiv) and $\mathrm{AgSbF} 6(31.8 \mathrm{mg}, 0.0924 \mathrm{mmol}, 0.95$ equiv) to provide catalyst 53 as a brown powder ( $67.4 \mathrm{mg}, 96 \%$ ). This complex has previously been characterized. ${ }^{24 \mathrm{c}}$

## C. Substrate Syntheses

General Synthetic Scheme for Transannular Ketone-Ene Substrates 39a, 39c, 39d, and 59


General Procedure B - Cu-catalyzed addition of Grignard reagents to meso epoxides ${ }^{40}$ A flame-dried 3 L round-bottom flask under $\mathrm{N}_{2}$ was charged with $\mathrm{CuI}(2.9 \mathrm{~g}, 15.3 \mathrm{mmol}$, 0.15 equiv) and THF ( 1 L ) and cooled to $-30{ }^{\circ} \mathrm{C}$ (dry ice/acetone). To this suspension was added a solution of Grignard in THF ( $150 \mathrm{mmol}, 1.5$ equiv) over a period of 30 m . After another 10 m at $-30^{\circ} \mathrm{C}$, meso epoxide ( $100 \mathrm{mmol}, 1$ equiv) was added dropwise, neat, over 10 m , and the reaction mixture was allowed to gradually warm to room temperature overnight. The dark reaction mixture was cooled to $0^{\circ} \mathrm{C}$ and quenched by slow addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(200 \mathrm{~mL})$. The contents were diluted with DI $\mathrm{H}_{2} \mathrm{O}(200 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 500 \mathrm{~mL})$. The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The residue was re-dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to afford crude alcohol that, unless otherwise noted, was carried on to the next reaction without further purification.

$( \pm)-(1 \mathrm{~S}, 2 \mathrm{R})$-2-(prop-1-en-2-yl)cyclohexanol (37) ${ }^{41}$

37

[^22]This compound was prepared according to General Procedure B, with cyclohexene oxide $(9.8 \mathrm{~g}, 100 \mathrm{mmol}, 1$ equiv) and isopropenylmagnesium bromide ( 0.5 M in $\mathrm{THF}, 300 \mathrm{~mL}$, $150 \mathrm{mmol}, 1.5$ equiv). The known alcohol 37 was obtained as a yellow oil ( 12.7 g ) that was carried forward to the following reactions without further purification.


## ( $\pm$ )-(1S,2R)-2-(3-methylbut-2-en-2-yl)cyclohexanol (S1c)

This compound was synthesized according to General Procedure B, with cyclohexene oxide ( $600 \mathrm{mg}, 6.11 \mathrm{mmol}, 1$ equiv) and (3-methylbut-2-en-2yl)magnesium bromide ( $0.25 \mathrm{M}, 30 \mathrm{~mL}, 1.5$ equiv). The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $50 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford S 1 c $(698 \mathrm{mg}, 4.15 \mathrm{mmol}, 68 \%)$ as a clear oil. $\mathrm{R} f=0.2$ ( $50 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $) ;{ }^{1} \mathrm{H}$ NMR ( 500 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 3.43(\mathrm{td}, J=9.84,4.58 \mathrm{~Hz}, 1 \mathrm{H}) 2.45(\mathrm{ddd}, J=11.79,9.96,3.89 \mathrm{~Hz}, 1$ H) 2.02-2.09 (m, 1 H) 1.75-1.82(m, 1 H) $1.73(\mathrm{~s}, 3 \mathrm{H}) 1.71(\mathrm{~s}, 3 \mathrm{H}) 1.64-1.70(\mathrm{~m}, 2$ H) $1.58(\mathrm{~s}, 3 \mathrm{H}) 1.44-1.52(\mathrm{~m}, 1 \mathrm{H}) 1.18-1.39(\mathrm{~m}, 4 \mathrm{H}) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 128.7, 127.6, 71.2, 49.1, 34.3, 29.3, 26.0, 25.1, 21.4, 20.4, 13.1; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3417 (br m) 2929 (s) 2857 (m) 1449 (m) 1375 (w) 1272 (w) 1162 (w) 1146 (w) 1060 (s) $1010(\mathrm{~m}) 962(\mathrm{~m}) 852(\mathrm{~m}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{11} \mathrm{H}_{19}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}: 151.1$; found: 151.1.


## ( $\pm$ )-(1S,2R)-2-(prop-1-en-2-yl)cyclopentanol (S8)

This compound was prepared according to General Procedure B with s8 cyclopentene oxide ( $8.4 \mathrm{~g}, 100 \mathrm{mmol}, 1$ equiv) and isopropenylmagnesium bromide ( 0.5 M in THF, $300 \mathrm{~mL}, 1.5$ equiv). The crude product was obtained as a yellow oil (8.6 g) and was carried forward to the following reaction without further purification.

General Procedure $\mathbf{C}-$ Swern oxidation to generate $\beta-\gamma$ unsaturated ketone intermediates

An oven-dried 250 mL round-bottom flask under argon was charged with a stir bar, $\mathrm{CH}_{2} \mathrm{Cl}_{2}(39 \mathrm{~mL})$, and oxalyl chloride ( $3.5 \mathrm{~mL}, 40.9 \mathrm{mmol}, 1.2$ equiv) and cooled to -78 ${ }^{\circ} \mathrm{C}$. To this solution was added dropwise a solution of DMSO $(6.0 \mathrm{~mL}, 85.2 \mathrm{mmol}, 2.5$ equiv) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(39 \mathrm{~mL})$. After the mixture was stirred for 5 m , a solution of alcohol (34.1 mmol, 1.0 equiv) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(30+2 \times 5 \mathrm{~mL}$ rinses) was added dropwise. The reaction mixture was stirred 1 h at $-78{ }^{\circ} \mathrm{C}$, at which point it was quenched by addition of $\mathrm{NEt}_{3}$ ( $23.8 \mathrm{~mL}, 170 \mathrm{mmol}, 5.0$ equiv) and immediately warmed to room temperature. The contents were diluted with DI $\mathrm{H}_{2} \mathrm{O}(50 \mathrm{~mL})$ and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 50 \mathrm{~mL})$. The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. To remove amine salts, the crude residue was twice suspended in $5 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes, filtered, and concentrated to isolate the $\beta-\gamma$ unsaturated ketone. This product was carried forward without further purification. ${ }^{42}$

General Procedure D - Grignard addition to $\beta$ - $\gamma$ enone intermediates
A flame-dried 500 mL round-bottom flask was charged with a stir bar, $\beta-\gamma$ unsaturated ketone ( $14.5 \mathrm{mmol}, 1$ equiv) and THF ( 145 mL ) and cooled to $0^{\circ} \mathrm{C}$. A solution of Grignard reagent in THF ( $17.4 \mathrm{mmol}, 1.2$ equiv) was added dropwise under argon. The reaction was allowed to warm to room temperature overnight and was then quenched by slow addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(50 \mathrm{~mL})$. The crude mixture was diluted with

[^23]DI $\mathrm{H}_{2} \mathrm{O}(50 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{x} 100 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by flash column chromatography to afford the divinyl alcohol.

General Procedure E - Cerium trichloride mediated Grignard addition to $\beta-\gamma$ enones ${ }^{43}$ A flame-dried 100 mL round-bottom flask was charged with anhydrous cerium trichloride ( $2.1 \mathrm{~g}, 8.5 \mathrm{mmol}, 2.5$ equiv) and THF ( 17 mL ), and the resultant suspension was stirred for 2 h at room temperature. The flask was cooled to $-78{ }^{\circ} \mathrm{C}$, and $t$ butyllithium ( 1.7 M in pentane) was added dropwise until the suspension took on a persistent faint pink color ( $\sim 5$ drops). The flask was brought to room temperature, and $\beta$ $\gamma$ unsaturated ketone ( $3.4 \mathrm{mmol}, 1.0$ equiv) was added as a solution in THF $(10 \mathrm{~mL}+2 \mathrm{x}$ 3.5 mL rinses). The suspension was stirred under $\mathrm{N}_{2}$ at room temperature for an additional 2 h . The flask was cooled to $-78^{\circ} \mathrm{C}$ and the reaction mixture was stirred at this temperature for 8 h , at which point saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$ was added $(20 \mathrm{~mL})$ and the flask was brought to room temperature. The resultant emulsion was treated with 1 N $\mathrm{HCl}(10 \mathrm{~mL})$ and was extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 20 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to afford the crude product which was purified by flash column chromatography to afford the desired divinyl alcohol.


[^24]Procedure C to afford known ketone 2a as a dark orange oil $(4.2 \mathrm{~g})$. This product was carried forward without further purification.


38

## $( \pm)-(1 S, 2 R)$-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (38) ${ }^{19}$

According to General Procedure D, crude ketone S2a ( $2.0 \mathrm{~g}, 14.5 \mathrm{mmol}$ ) was reacted with vinylmagnesium bromide (1.0 M in THF, $17.4 \mathrm{~mL}, 17.4 \mathrm{mmol}$, 1.2 equiv) to afford the crude addition product in $20: 1 \mathrm{dr}$ in favor of the title compound. The crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $6 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford the divinyl alcohol $38(1.32 \mathrm{~g}, 7.9 \mathrm{mmol}, 55 \%$ yield) as a pale yellow oil. $\mathrm{R} f=0.34\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm}$ 5.87 (ddd, $J=17.17,10.76,1.37 \mathrm{~Hz}, 1 \mathrm{H}) 5.11-5.23(\mathrm{~m}, 1 \mathrm{H}) 4.92-5.02(\mathrm{~m}, 1 \mathrm{H}) 4.81$ $4.89(\mathrm{~m}, 1 \mathrm{H}) 4.73(\mathrm{~d}, J=0.92 \mathrm{~Hz}, 1 \mathrm{H}) 2.04(\mathrm{dd}, J=12.59,3.43 \mathrm{~Hz}, 1 \mathrm{H}) 1.74(\mathrm{~s}, 3 \mathrm{H})$ $1.71-1.80(\mathrm{~m}, 2 \mathrm{H}) 1.58-1.71(\mathrm{~m}, 2 \mathrm{H}) 1.49-1.57(\mathrm{~m}, 1 \mathrm{H}) 1.39-1.49(\mathrm{~m}, 2 \mathrm{H}) 1.21-$ $1.30(\mathrm{~m}, 1 \mathrm{H}),{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 148.4,146.5,111.8,110.7,72.8,52.5$, 38.1, 27.4, 26.2, 25.7, 21.3; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3551 (m), 3482 (br m), 3082 (w), 2933 ( s ), 2856 (m), 2671 (w), 1638 (m), 1447 (m), 1373 (m), 1285 (m), 1197 (w), 1077 (m), 997 (m), 971 ( s$), 916$ ( s$), 856(\mathrm{~m}), 838(\mathrm{~m}), 666(\mathrm{~m}), 611(\mathrm{~m}) . \mathrm{MS}$ (APCI) m/z calc'd for $\mathrm{C}_{11} \mathrm{H}_{17}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 149.1; found: 149.1.

( $\pm$ )-(1S,2R)-2-(3-methylbut-2-en-2-yl)-1-vinylcyclohexanol (S3c)
Alcohol S1c ( $650 \mathrm{mg}, 3.9 \mathrm{mmol}, 1$ equiv) was oxidized according to General Procedure C to afford ketone S2c, which was carried forward without purification. According to General Procedure E, ketone S2c was reacted with
vinylmagnesium bromide ( 1.0 M in THF, $9.6 \mathrm{~mL}, 9.6 \mathrm{mmol}, 2.5$ equiv) to afford the crude addition product in $>19: 1 \mathrm{dr}$ in favor of the title compound. The crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $25 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford S3c as a clear oil (518 mg, $2.7 \mathrm{mmol}, 68 \%$ yield over 2 steps). $\mathrm{R} f=0.37(10 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.86(\mathrm{dd}, J=17.40,10.99 \mathrm{~Hz}, 1 \mathrm{H})$ 5.12 (dd, $J=16.94,1.37 \mathrm{~Hz}, 1 \mathrm{H}) 4.91(\mathrm{dd}, J=10.99,1.37 \mathrm{~Hz}, 1 \mathrm{H}) 2.55(\mathrm{dd}, J=12.59,2.98$ Hz, 1 H ) 1.84-1.97(m, 1 H) 1.75-1.83(m, 1 H) 1.66-1.74 (m, 1 H$) 1.64$ (br. s., 3 H ) $1.62(\mathrm{~s}, 6 \mathrm{H}) 1.51-1.61(\mathrm{~m}, 3 \mathrm{H}) 1.18-1.39(\mathrm{~m}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 148.4, 146.5, 111.8, 110.7, 72.8, 52.5, 38.1, 27.4, 26.2, 25.7, 21.3; FTIR (neat, $\mathrm{cm}^{-}$ ${ }^{1}$ ) 3491 (br m) 3084 (w) 2929 (s) 2959 (m) 1640 (w) 1447 (s) 1413 (m) (1375 (m) 1268 (m) 1244 (m) 1164 (m) 1150 (m) 1056 (w) 992 (m) 963 (s) 916 (s) 859 (w) 816 (m) 668 (m). MS (APCI) m/z calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}: 177.2$; found: 177.2.

( $\pm$ )-(1S,2R)-1-(2-methylprop-1-enyl)-2-(prop-1-en-2-yl)cyclohexanol (S3d) According to General Procedure D, crude ketone S2a (1.0 g, $7.2 \mathrm{mmol}, 1$ equiv) was reacted with 2-methyl-1-propenylmagnesium bromide ( 0.5 M in THF, $17.4 \mathrm{~mL}, 17.4 \mathrm{mmol}, 1.2$ equiv) to afford the crude addition product in $6: 1 \mathrm{dr}$ in favor of the title compound. The crude product was purified by flash column chromatography (Davisil ${ }^{\circledR}$, Biotage, 0 to $25 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes ) to afford $\mathbf{S 3 d}(452 \mathrm{mg}, 2.3$ $\mathrm{mmol}, 32 \%$ yield $)$ as a pale yellow oil. $\mathrm{Rf}=0.75\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.19(\mathrm{~s}, 1 \mathrm{H}) 4.88(\mathrm{~s}, 1 \mathrm{H}) 4.78(\mathrm{~s}, 1 \mathrm{H}) 2.06(\mathrm{dd}, \mathrm{J}=12.36,2.75$ $\mathrm{Hz}, 1 \mathrm{H}) 1.88(\mathrm{~d}, \mathrm{~J}=14.19 \mathrm{~Hz}, 1 \mathrm{H}) 1.83(\mathrm{~s}, 3 \mathrm{H}) 1.81(\mathrm{~s}, 3 \mathrm{H}) 1.69-1.78(\mathrm{~m}, 3 \mathrm{H}) 1.67(\mathrm{~s}$, $3 \mathrm{H}) 1.35-1.63(\mathrm{~m}, 4 \mathrm{H}) 1.23(\mathrm{qt}, \mathrm{J}=13.58,3.20 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ )
$\delta$ ppm 149.2, 132.49, 132.46, 112.2, 73.5, 53.5, 38.5, 27.8 (2 С) 26.3, 25.7, 21.6, 18.8;
FTIR (neat, $\mathrm{cm}^{-1}$ ) 3559 (m) 3502 (br m) 2078 (w) 2930 (s) 2855 (s) 1667 (m) 1637 (m) 1447 (s) 1375 (m) 1323 (w) 1286 (m) 1212 (w) 1179 (w) 1069 (m) 978 (s) 949 (m) 895
(s) $863(\mathrm{~m}) 734(\mathrm{~m}) . \mathrm{MS}(\mathrm{ESI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 177.1638; found: 177.1637.

s9
(土)-(1S,2R)-2-(prop-1-en-2-yl)-1-vinylcyclopentanol (S9)
Alcohol S8 (1.0g, $7.9 \mathrm{mmol}, 1$ equiv) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(80 \mathrm{~mL})$ in a 200 mL round-bottom flask. Dess-Martin periodinane ( $4.0 \mathrm{~g}, 9.4 \mathrm{mmol}, 1.2$ equiv) was added as a solid in one portion. The reaction was stirred at room temperature under $\mathrm{N}_{2}$ for 1 h , at which point the contents of the flask were poured into a 1 L Erlenmeyer flask containing a large stir bar and $\mathrm{Et}_{2} \mathrm{O}(80 \mathrm{~mL})$. A $10 \%$ aqueous sodium thiosulfate solution $(80 \mathrm{~mL})$ and saturated aqueous $\mathrm{NaHCO}_{3}(80 \mathrm{~mL})$ were added to the flask, and the contents were vigorously stirred for 1 h . The organic layer was separated and the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 50 \mathrm{~mL})$. The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude ketone was taken forward without purification.

According to General Procedure D, the intermediate ketone was reacted with vinylmagnesium bromide ( 1.0 M in THF, $9.5 \mathrm{~mL}, 9.5 \mathrm{mmol}, 1.2$ equiv) to afford the crude addition product in 9:1 dr in favor of the title compound. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $25 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford divinyl alcohol S9 as a yellow oil (497 mg, $3.2 \mathrm{mmol}, 41 \%$ over 2 steps). Characterization data match reported values. ${ }^{20 \mathrm{~d}}$

## General Procedure F - Anionic oxy-Cope rearrangement

A flame-dried 250 mL round-bottom flask was charged with $\mathrm{KH}(866 \mathrm{mg}, 21.7 \mathrm{mmol}$, 2.4 equiv), 18-crown-6 ( $6.8 \mathrm{~g}, 25.7 \mathrm{mmol}, 2.8$ equiv), and THF $(150 \mathrm{~mL})$ and cooled to 0 ${ }^{\circ} \mathrm{C}$ under an atmosphere of argon. A solution of divinyl alcohol ( $9.0 \mathrm{mmol}, 1$ equiv) in THF ( $30 \mathrm{~mL}+10 \mathrm{~mL}$ rinse) was added dropwise via cannula. The reaction was stirred at $0{ }^{\circ} \mathrm{C}$ for 30 m , after which it was warmed to room temperature. Once the reaction was determined to be complete by TLC analysis, the flask was cooled to $0{ }^{\circ} \mathrm{C}$ and quenched by slow addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(10 \mathrm{~mL})$. The reaction was further diluted with 100 mL DI $\mathrm{H}_{2} \mathrm{O}$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 100 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by flash column chromatography to afford the keto-olefin.
 (E)-5-methylcyclodec-5-enone (39a) ${ }^{33 \mathrm{~b}}$

According to General Procedure F, divinyl alcohol 38 ( $1.5 \mathrm{~g}, 9.0 \mathrm{mmol}, 1$ equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford cyclodecenone $39 \mathrm{a}(978 \mathrm{mg}, 5.9 \mathrm{mmol}, 65 \%$ yield). The product is a clear oil at room temperature and freezes to a white solid upon storage at $5{ }^{\circ} \mathrm{C}$. $\mathrm{R} f=0.26$ ( $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes, CAM); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, 23{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.17$ ( t , $J=7.10 \mathrm{~Hz}, 1 \mathrm{H}) 1.47(\mathrm{~s}, 3 \mathrm{H}) 1.12-2.81(\mathrm{~m}, 14 \mathrm{H}) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz},-20^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.18(\mathrm{dd}, J=10.07,3.20 \mathrm{~Hz}, 1 \mathrm{H}) 2.64(\mathrm{dd}, J=16.25,9.84 \mathrm{~Hz}, 1 \mathrm{H}) 2.25-2.47(\mathrm{~m}$, $3 \mathrm{H}) 2.17(\mathrm{dd}, J=12.36,5.95 \mathrm{~Hz}, 1 \mathrm{H}) 1.97-2.12(\mathrm{~m}, 3 \mathrm{H}) 1.52-1.89(\mathrm{~m}, 5 \mathrm{H}) 1.46(\mathrm{~s}, 3$ H) $1.20-1.40(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 209.6,137.9,126.8,45.3$, 43.4, 41.4, 29.0, 28.6, 26.0, 22.5, 16.0; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3392 (w), 2922 (s), 2852 (m),

2678 (w), 1703 (s), 1443 (s), 1425 (s), 1359 (m), 1181 (w), 1096 (s), 1017 (w), 924 (m), $859(\mathrm{~m}), 809(\mathrm{~m}), 774(\mathrm{~m}), 733(\mathrm{w}) . \mathrm{MS}(\mathrm{ESI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{11} \mathrm{H}_{19} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 167.1430; found: 167.1425 .


## (E)-4,4,5-trimethylcyclodec-5-enone (39c)

According to General Procedure F, divinyl alcohol S3c ( $388 \mathrm{mg}, 2.0 \mathrm{mmol}$, 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $50 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes and $\mathrm{SiO}_{2}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford cyclodecenone 39 c ( $294 \mathrm{mg}, 0.1 .5 \mathrm{mmol}, 76 \%$ yield) as a pale yellow oil. ${ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz}, 23^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right.$ ) $\delta \mathrm{ppm} 5.24(\mathrm{td}, J=7.33,0.92 \mathrm{~Hz}, 1 \mathrm{H}) 2.18-2.81$ (m, 4 H$) 2.09$ (br. s., 3 H ) $1.48-1.97$ (m, 5 H) $1.45(\mathrm{~s}, 3 \mathrm{H}) 1.07(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{1} \mathrm{H}$ NMR ( $\left.500 \mathrm{MHz},-40{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.19(\mathrm{~d}$, $J=10.74 \mathrm{~Hz}, 1 \mathrm{H}) 2.57(\mathrm{dd}, J=16.36,10.01 \mathrm{~Hz}, 1 \mathrm{H}) 2.49(\mathrm{t}, J=13.70 \mathrm{~Hz}, 1 \mathrm{H}) 2.26-2.38$ (m, 2 H) 2.06-2.17(m, 1 H) 1.95-2.05 (m, 1 H) $1.90(\mathrm{dd}, J=14.89,4.64 \mathrm{~Hz}, 1 \mathrm{H}) 1.66-$ $1.82(\mathrm{~m}, 2 \mathrm{H}) 1.51-1.63(\mathrm{~m}, 1 \mathrm{H}) 1.39(\mathrm{~s}, 3 \mathrm{H}) 1.23-1.35(\mathrm{~m}, 2 \mathrm{H}) 1.06(\mathrm{~s}, 3 \mathrm{H}) 0.97(\mathrm{~s}$, $3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz},-40{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 210.2,143.0,124.4,45.8,39.3,39.1$, 39.0, 29.3, 28.6, 28.0, 24.8, 22.1, 13.6; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2921 (m) 1705 (s) 1446 (m) 1370 (m) 1355 (m) 1179 (w) 1132 (s) 1080 (w) 1064 (w) 1040 (m) 1000 (w) 910 (m) 853 (m) $807(\mathrm{~m}) 733(\mathrm{~m})$; MS (ESI) $\mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 177.1638; found: 177.1642.

(E)-3,3,5-trimethylcyclodec-5-enone (39d)

According to General Procedure F, divinyl alcohol S3d (200 mg, 1.03 mmol , 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $5 \%$
$\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford cyclodecenone $39 \mathrm{~d}(120 \mathrm{mg}, 0.61 \mathrm{mmol}, 61 \%$ yield) as a white crystalline solid. $\mathrm{Rf}=0.4$ ( $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes ); ${ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz},-40{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta$ ppm 5.20 (t, $J=6.80 \mathrm{~Hz}, 1 \mathrm{H}) 2.60(\mathrm{dd}, J=16.36,10.50 \mathrm{~Hz}, 1 \mathrm{H}) 2.40(\mathrm{~d}, J=14.65 \mathrm{~Hz}, 1 \mathrm{H})$ 2.27 (dd, $J=16.36,9.03 \mathrm{~Hz}, 1 \mathrm{H}) 1.95-2.03$ (m, 3 H$) 1.92(\mathrm{~d}, \mathrm{~J}=14.65 \mathrm{~Hz}, 1 \mathrm{H}) 1.85$ (d, $J=12.21 \mathrm{~Hz}, 1 \mathrm{H}) 1.68-1.78(\mathrm{~m}, 2 \mathrm{H}) 1.55(\mathrm{~s}, 3 \mathrm{H}) 1.45-1.57(\mathrm{~m}, 1 \mathrm{H}) 1.36(\mathrm{~s}, 3 \mathrm{H})$ $1.24-1.33(\mathrm{~m}, 1 \mathrm{H}) 0.91(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm}$ 209.9, 138.6, 129.0, 54.1, 53.0, 46.4, 43.3, 34.8, 28.5 (2C), 27.1, 22.2, 18.8; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2952 (s) 2925 (m) 1703 (s) 1447 (m) 1365 (m) 1286 (w) 1152 (m) 1109 (m) 1057 (m) 979 (m) $890(\mathrm{w}) 793(\mathrm{~m}) 735(\mathrm{~m}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{23} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 195.2$; found: 195.2.


59

## (E)-5-methylcyclonon-5-enone (59)

According to General Procedure F, divinyl alcohol S9 (200 mg, $1.32 \mathrm{mmol}, 1$ equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $5 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford cyclononenone $59(83 \mathrm{mg}, 0.54 \mathrm{mmol}, 42 \%$ yield) as a pale yellow solid. Characterization data match reported values. ${ }^{20 d}$

## Scheme for the Synthesis of Transannular Ketone-Ene Substrate 39b




[^25]A thick-walled vial was charged with a stir bar, 4,4-dimethyl cyclohexanone ( $252 \mathrm{mg}, 2.0$ $\mathrm{mmol}, 1$ equiv), and $\left[\left(t-\mathrm{Bu}_{3} \mathrm{P}\right) \mathrm{PdBr}\right]_{2}(19 \mathrm{mg}, 0.025 \mathrm{mmol}, 1.25 \mathrm{~mol} \%)$ and sealed with a pressure septum cap. Under a positive pressure of $\mathrm{N}_{2}$, toluene ( 4 mL ) was added followed by a solution of LHMDS ( 1.0 M in toluene, $5 \mathrm{~mL}, 5 \mathrm{mmol}, 2.5$ equiv). The resultant suspension was stirred for 5 m at room temperature, after which 2-bromopropene ( $262 \mu \mathrm{~L}$, $3.0 \mathrm{mmol}, 1.5$ equiv) was added in a single portion. The $\mathrm{N}_{2}$ inlet was removed, and the vial was immersed in a $80{ }^{\circ} \mathrm{C}$ oil bath and stirred at this temperature for 24 h . The vial was cooled to room temperature and the contents were poured into $\mathrm{Et}_{2} \mathrm{O}(10 \mathrm{~mL})$ and washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(5 \mathrm{~mL})$ and DI water $(5 \mathrm{~mL})$. The organic layer was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $40 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford $\mathbf{S 2 b}(146 \mathrm{mg}, 0.88 \mathrm{mmol}, 44 \%$ yield) as a clear oil. $\mathrm{R} f=0.45$ (20\% $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $) ;{ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 4.90-4.97(\mathrm{~m}, 1 \mathrm{H}) 4.72(\mathrm{dt}$, $J=1.76,0.88 \mathrm{~Hz}, 1 \mathrm{H}) 3.15(\mathrm{dd}, J=13.33,5.42 \mathrm{~Hz}, 1 \mathrm{H}) 2.44-2.55(\mathrm{~m}, 1 \mathrm{H}) 2.29$ (ddd, $J=14.64,4.69,2.90 \mathrm{~Hz}, 1 \mathrm{H}) 1.79(\mathrm{t}, J=13.47,1 \mathrm{H}) 1.61-1.76(\mathrm{~m}, 3 \mathrm{H}) 1.72(\mathrm{~s}, 3 \mathrm{H}) 1.23$ (s, 3 H ) $1.05(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 211.3,143.5,113.1,54.1,44.8$, 39.7, 38.5, 31.6, 30.7, 24.4, 21.2; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2955 (m), 2925 (m), 2865 (m), 1712 (s), 1649 (w), 1462 (m), 1446 (m), 1308 (w), 1153 (m), 1099 (m), 1009 (w), 890 (s), 828 (w), $732(\mathrm{w}) ; \mathrm{MS}(\mathrm{ESI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{11} \mathrm{H}_{19} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 167.1430; found: 167.1422.

$( \pm)$-(1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S3b)
According to General Procedure E, ketone S2b (267.3 mg, $1.6 \mathrm{mmol}, 1.0$ equiv) was reacted with vinylmagnesium bromide ( 1.0 M in THF, $4.0 \mathrm{~mL}, 4.0 \mathrm{mmol}, 2.5$ equiv) to afford the crude addition product in $4.6: 1 \mathrm{dr}$ in favor of the title compound. The
crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $5 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford $\mathbf{S 3 b}(114 \mathrm{mg}, 0.58 \mathrm{mmol}, 36 \%$ yield) as a pale yellow oil. $\mathrm{R} f=0.59\left(5 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.90(\mathrm{dd}$, $J=17.09,10.74 \mathrm{~Hz}, 1 \mathrm{H}) 5.19$ (dd, $J=17.09,0.98 \mathrm{~Hz}, 1 \mathrm{H}) 4.99$ (dd, $J=10.74,0.98 \mathrm{~Hz}, 1$ H) $4.90(\mathrm{t}, J=1.47 \mathrm{~Hz}, 1 \mathrm{H}) 4.75(\mathrm{~s}, 1 \mathrm{H}) 2.23(\mathrm{dd}, J=13.67,3.42 \mathrm{~Hz}, 1 \mathrm{H}) 1.75(\mathrm{~s}, 3 \mathrm{H})$ $1.58-1.72(\mathrm{~m}, 4 \mathrm{H}) 1.48(\mathrm{dt}, J=12.94,3.05 \mathrm{~Hz}, 1 \mathrm{H}) 1.19$ (ddd, $J=12.21,5.37,2.44 \mathrm{~Hz}, 1$ H) 1.12 (dt, $J=13.18,2.93 \mathrm{~Hz}, 1 \mathrm{H}) 0.96(\mathrm{~s}, 3 \mathrm{H}) 0.94(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 100 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 147.9,146.2,111.8,110.9,72.3,47.8,40.0,34.1,33.7,33.0,30.2,25.7$, 23.9; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3553 (m), 3482 (br m), 3083 (m), 2951 (s), 2865 (m), 1638 (m), 1449 (m), 1365 (m), 1283 (m), 1099 (m), $992(\mathrm{~m}), 962(\mathrm{~s}), 917(\mathrm{~s}), 897(\mathrm{~s}), 668(\mathrm{~m})$; MS (ESI) $\mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 177.1638; found: 177.1639.


1 equiv) underwent an anionic oxy-Cope rearrangement. The crude product was purified by flash column chromatography (Davisil $\circledR$, Biotage, 0 to $7 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford cyclodecenone $\mathbf{3 9 b}$ ( $55 \mathrm{mg}, 0.28 \mathrm{mmol}, 50 \%$ yield) as a white crystalline solid. $\mathrm{R} f=0.24\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, 23{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.30(\mathrm{t}$, $J=7.33 \mathrm{~Hz}, 1 \mathrm{H}$ ) $1.51-3.09(\mathrm{~m}, 12 \mathrm{H}) 1.41$ (s, 3 H ) 0.97 (br. s., 6 H ); ${ }^{1} \mathrm{H}$ NMR ( 500 MHz , $\left.-40{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.30(\mathrm{~d}, \mathrm{~J}=11.87 \mathrm{~Hz}, 1 \mathrm{H}) 2.85(\mathrm{dd}, \mathrm{J}=16.65,10.20 \mathrm{~Hz}, 1 \mathrm{H}) 2.23-$ 2.35 (m, 2 H) 2.16 (dd, $J=12.13,6.20 \mathrm{~Hz}, 1 \mathrm{H}) 2.03-2.13$ (m, 2 H$) 1.99$ (dd, $J=14.07$, $12.26 \mathrm{~Hz}, 1 \mathrm{H}) 1.76-1.90(\mathrm{~m}, 2 \mathrm{H}) 1.60-1.72(\mathrm{~m}, 2 \mathrm{H}) 1.41(\mathrm{~s}, 3 \mathrm{H}) 1.19(\mathrm{t}, J=12.39 \mathrm{~Hz}$, $1 \mathrm{H}) 1.00(\mathrm{~s}, 3 \mathrm{H}) 0.91(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\left.-40{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 210.0$, $138.6,123.4,43.4,41.5,40.7,40.0,34.3,34.2,33.1,26.4,24.3,16.0 ;$ FTIR (neat, $\mathrm{cm}^{-1}$ )

2951 (m) 2928 (m) 2868 (w) 1707 (s) 1472 (w) 1443 (m) 1426 (m) 1386 (m) 1363 (m) 1173 (w) 1108 (s) 910 (w) 839 (w) $740(w)$. MS (ESI) m/z calc'd for $\mathrm{C}_{13} \mathrm{H}_{23} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 195.1743; found: 195.1739.

Schemes for the Synthesis of Transannular Ketone-Ene Substrates 39e and 39f



$( \pm)(7 \mathrm{R}, 8 \mathrm{~S})$-7-(prop-1-en-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (S1e)
sie An oven-dried 50 mL round-bottom flask fitted with a Dean-Stark trap and reflux condenser was charged with $\mathbf{S 1 0}$ ( $1.4 \mathrm{~g}, 5.2 \mathrm{mmol}, 1$ equiv), ethylene glycol (294 $\mu \mathrm{L}, 5.2 \mathrm{mmol}$, 1 equiv), benzene $(10.4 \mathrm{~mL})$ and $\mathrm{pTsOH} \cdot \mathrm{H}_{2} \mathrm{O}(15 \mathrm{mg}$, cat. $)$. The side arm of the Dean-Stark trap was filled with benzene ( 10 mL ), and the flask was immersed in a $80^{\circ} \mathrm{C}$ oil bath under $\mathrm{N}_{2}$ overnight. The contents of the flask were concentrated to afford the crude acetal an orange oil that was carried forward without purification.

An oven-dried 50 mL round-bottom flask was charged with the intermediate silyl ether and THF ( 5 mL ) and cooled to $0^{\circ} \mathrm{C}$. To this was added a solution of TBAF (1.0M
in THF, $10.4 \mathrm{~mL}, 10.4 \mathrm{mmol}, 2$ equiv). The ice bath was removed and the reaction was stirred at room temperature for 48 h . The reaction was quenched with DI water and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 20 to $100 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford $\mathrm{Sie}(681 \mathrm{mg}, 3.44$ $\mathrm{mmol}, 66 \%$ yield, 2 steps) as a pale yellow oil. $\mathrm{R} f=0.28\left(50 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, CAM$) ;{ }^{1} \mathrm{H}$ NMR (500 MHz, $\mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 4.93$ (s, 1 H ) $4.91(\mathrm{~s}, 1 \mathrm{H}) 3.90-4.00(\mathrm{~m}, 4 \mathrm{H}) 3.44$ $3.55(\mathrm{~m}, 1 \mathrm{H}) 2.33$ (ddd, $J=13.18,9.77,3.91 \mathrm{~Hz}, 1 \mathrm{H}) 1.98-2.09(\mathrm{~m}, 1 \mathrm{H}) 1.83$ (d, $J=1.95 \mathrm{~Hz}, 1 \mathrm{H}) 1.78(\mathrm{dt}, J=9.40,2.87 \mathrm{~Hz}, 1 \mathrm{H}) 1.71(\mathrm{~s}, 3 \mathrm{H}) 1.67-1.73(\mathrm{~m}, 1 \mathrm{H}) 1.58-$ $1.67(\mathrm{~m}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 145.32,113.97,108.42,69.90,64.59$, 64.55, 51.26, 37.98, 33.23, 31.03, 18.93; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3454 (br m), 3073 (w), 2946 (m), 2881 (m), 1646 (w), 1361 (m), 1142 (m), 1142 (m), 1088 (s), 1022 (s), 947 (m), 924 (s); MS (ESI) $m / z$ calc'd for $\mathrm{C}_{11} \mathrm{H}_{19} \mathrm{O}_{3}[\mathrm{M}+\mathrm{H}]^{+}: 199.1329$, found: 199.1338.

( $\pm$ )-(7R,8S)-7-(prop-1-en-2-yl)-8-vinyl-1,4-dioxaspiro[4.5]decan-8-ol (S3e)

Alcohol S1e ( $681 \mathrm{mg}, 3.4 \mathrm{mmol}, 1.0$ equiv) was oxidized according to General Procedure $\mathbf{C}$ to afford the corresponding $\beta$, $\gamma$-unsaturated ketone S2e that was carried forward without further purification.

According to General Procedure E, crude ketone S2e (267.3 mg, $1.6 \mathrm{mmol}, 1.0$ equiv) was reacted with vinylmagnesium bromide ( 1.0 M in $\mathrm{THF}, 8.4 \mathrm{~mL}, 8.4 \mathrm{mmol}, 2.5$ equiv) to afford the crude addition product as a yellow oil and in 9.7:1 dr in favor of the title compound. The crude residue was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$,

Biotage, 0 to $40 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes ) to afford $\mathbf{S 3 e}(441 \mathrm{mg}, 2.0 \mathrm{mmol}, 57 \%$ yield over 2 steps) as a clear oil. $\mathrm{R} f=0.54(50 \% \mathrm{Et2O} /$ hexanes, CAM$) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm $5.88(\mathrm{dd}, J=17.17,10.76 \mathrm{~Hz}, 1 \mathrm{H}) 5.20(\mathrm{~d}, J=17.40 \mathrm{~Hz}, 1 \mathrm{H}) 5.01(\mathrm{~d}, J=10.53 \mathrm{~Hz}, 1$ H) $4.91(\mathrm{~d}, J=1.37 \mathrm{~Hz}, 1 \mathrm{H}) 4.74(\mathrm{~s}, 1 \mathrm{H}) 3.80-4.11(\mathrm{~m}, 4 \mathrm{H}) 2.44(\mathrm{dd}, J=13.74,3.66 \mathrm{~Hz}$, 1 H) $2.06(\mathrm{t}, J=13.28 \mathrm{~Hz}, 1 \mathrm{H}) 1.96(\mathrm{td}, J=13.39,4.35 \mathrm{~Hz}, 1 \mathrm{H}) 1.70-1.85(\mathrm{~m}, 2 \mathrm{H}) 1.74$ $(\mathrm{s}, 3 \mathrm{H}) 1.61-1.68(\mathrm{~m}, 1 \mathrm{H}) 1.55-1.60(\mathrm{~m}, 1 \mathrm{H}) 1.51(\mathrm{dt}, \mathrm{J}=12.82,2.98 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 146.81,145.41,112.44,111.50,109.08,72.03,64.39$, $49.60,35.80,35.60,30.03,25.58,25.55$; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3483 (br w), 2965 (m), 2883 (w), 1683 (w), 1438 (w), 1343 (m), 1272 (m), 1211 (w), 1180 (m), 1101 (s), 1037 (m), 992 (s), 953 (s), 917 (s), 733 (s). MS (ESI) m/z calc'd for $\mathrm{C}_{13} \mathrm{H}_{19} \mathrm{O}_{2}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 207.1380, found: 207.1377; calc'd for $\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{NaO}_{3}[\mathrm{M}+\mathrm{Na}]^{+}$247.1305, found 247.1313.

General Procedure G - Palladium-Catalyzed oxy-Cope Rearrangement A flame-dried 50 mL round-bottom flask was charged with a stir bar, divinyl alcohol ( $1.79 \mathrm{mmol}, 1$ equiv), and $\operatorname{THF}(17.9 \mathrm{~mL})$. To the resultant solution was added $\left(\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{CN}\right)_{2} \mathrm{PdCl}_{2}(69 \mathrm{mg}, 0.18 \mathrm{mmol}, 0.1$ equiv) as a solid. The flask was capped with a plastic stopper and was stirred at room temperature overnight. The reaction mixture was concentrated to afford the crude product, which was purified by flash column chromatography.

(E)-12-methyl-1,4-dioxaspiro[4.9]tetradec-12-en-8-one (39e)

According to General Procedure G, divinyl alcohol S3e (401 mg, 1.79 mmol, 1 equiv), underwent the palladium-catalyzed oxy-Cope
rearrangement. The crude product, an orange solid, was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $50 \% \mathrm{EtOAc} /$ hexanes $)$ to afford $39 \mathrm{e}(234 \mathrm{mg}, 1.04$ $\mathrm{mmol}, 58 \%$ yield) as a white crystalline solid. $\mathrm{R} f=0.24$ ( $20 \%$ EtOAc/hexanes, CAM) $;{ }^{1} \mathrm{H}$ NMR (500 MHz, $\left.\mathrm{CDCl}_{3}, 23{ }^{\circ} \mathrm{C}\right) \delta \mathrm{ppm} 5.29(\mathrm{t}, \mathrm{J}=6.87 \mathrm{~Hz}, 2 \mathrm{H}) 3.84-4.02(\mathrm{~m}, 4 \mathrm{H}) 3.04$ (br. s., 1 H ) $1.49-2.55(\mathrm{~m}, 11 \mathrm{H}) 1.44(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3},-40^{\circ} \mathrm{C}$ ) $\delta$ ppm 5.26 (d, $J=11.23 \mathrm{~Hz}, 1 \mathrm{H}) 3.84-4.05(\mathrm{~m}, 4 \mathrm{H}) 3.03(\mathrm{dd}, J=17.09,10.25 \mathrm{~Hz}, 1 \mathrm{H})$ 1.97-2.47 (m, 8 H) 1.81 (td, $J=12.21,3.40 \mathrm{~Hz}, 1 \mathrm{H}) 1.65$ (d, $J=10.25 \mathrm{~Hz}, 1 \mathrm{H}) 1.51$ $1.61(\mathrm{~m}, 1 \mathrm{H}) 1.41(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C} \operatorname{NMR}\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}, 23{ }^{\circ} \mathrm{C}\right) \delta \mathrm{ppm}$ 208.66, 139.99, $121.42,109.78,64.33,42.86,40.97,39.00,37.84,31.10,25.17,15.79 ;$ FTIR (neat, $\mathrm{cm}^{-1}$ ) 2936 (M), 2904 (m) 2882 (m), 1696 (s), 1428 (m), 1363 (m), 1261 (m), 1173 (w), 1107 (s), 1033 (s), 983 (m), 915 (s), 888 (s), 673 (w). MS (ESI) m/z calc'd for $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{O}_{3}$ $[\mathrm{M}+\mathrm{H}]^{+}: 225.1485$, found: 225.1499; calc'd for $\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{NaO}_{3}[\mathrm{M}+\mathrm{Na}]^{+} 247.1305$, found 247.1319.

$\pm$ )-tert-butyldimethyl((1R,2S)-4-methylene-2-(prop-1-en-2yl)cyclohexyloxy)silane (S4f)

To an oven-dried 25 mL round-bottom flask containing a stir bar and methyltriphenylphosphonium bromide ( $845 \mathrm{mg}, 2.25 \mathrm{mmol}, 1.5$ equiv) was added $\mathrm{Et}_{2} \mathrm{O}$ $(10 \mathrm{~mL})$ under nitrogen. The white suspension was cooled to $0^{\circ} \mathrm{C}$, and after 5 m at this temperature, $\mathrm{KOt}-\mathrm{Bu}(236 \mathrm{mg}, 2.1 \mathrm{mmol}, 1.4$ equiv) was added as a solid, portion-wise (roughly thirds) over 10 m , resulting in the formation of a bright yellow suspension. After stirring the reaction mixture at $0^{\circ} \mathrm{C}$ for an additional 30 m , a solution of ketone $\mathbf{S 1 0}$ (402 $\mathrm{mg}, 1.5 \mathrm{mmol}, 1$ equiv $)$ in $\mathrm{Et}_{2} \mathrm{O}(2 \mathrm{~mL}+2 \times 1 \mathrm{~mL}$ rinses to complete the transfer) was
added dropwise. The reaction mixture was stirred under nitrogen allowing the temperature to gradually reach room temperature. After 16 h , the pale orange reaction mixture was quenched by addition of saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(5 \mathrm{~mL})$. The reaction mixture was diluted with $\mathrm{H}_{2} \mathrm{O}(15 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{x} 10 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to provide a yellow solid which was purified by flash column chromatography (silica gel, Biotage, 0 to $4 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to provide the desired silyl ether S4f as a clear oil ( $385 \mathrm{mg}, 1.44 \mathrm{mmol}, 96 \%$ yield) $\mathrm{R} f=0.9\left(5 \% \mathrm{Et}_{2} \mathrm{O}\right.$ in hexanes $)$ ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.78(\mathrm{~d}, J=5.37 \mathrm{~Hz}, 1 \mathrm{H}), 4.78(\mathrm{~d}, J=5.37 \mathrm{~Hz}, 1 \mathrm{H})$, $4.64(\mathrm{~d}, J=6.35 \mathrm{~Hz}, 1 \mathrm{H}), 4.64(\mathrm{~d}, J=6.35 \mathrm{~Hz}, 1 \mathrm{H}), 3.63(\mathrm{td}, J=9.16,4.15 \mathrm{~Hz}, 1 \mathrm{H}) 2.29$ (dt, $J=14.16,3.90 \mathrm{~Hz}, 1 \mathrm{H}) 2.22(\mathrm{dd}, J=8.79,1.95 \mathrm{~Hz}, 1 \mathrm{H}) 2.00-2.14(\mathrm{~m}, 3 \mathrm{H}) 1.95(\mathrm{dq}$, $J=12.57,3.95 \mathrm{~Hz}, 1 \mathrm{H}) 1.71(\mathrm{~s}, 3 \mathrm{H}) 1.33-1.45(\mathrm{~m}, 1 \mathrm{H}) 0.85(\mathrm{~s}, 9 \mathrm{H}) 0.03(\mathrm{~s}, 3 \mathrm{H}) 0.01$ (s, 3 H ) ; ${ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 147.72, 147.22, 111.69, 108.05, 72.98, $54.23,38.44,36.33,32.76,25.96$ (3 C), 20.98, 18.23, -3.85, -4.70; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2937 (m), 2857 (m), 1650 (w), 1462 (w), 1362 (w), 1255 (m), 1101 (s), 1055 (w), 1006 (w), $886(\mathrm{~s}), 834(\mathrm{~s}), 773(\mathrm{~s}), 670(\mathrm{~m})$; MS (ESI) $m / z$ calc'd for $\mathrm{C}_{16} \mathrm{H}_{31} \mathrm{OSi}[\mathrm{M}+\mathrm{H}]^{+}$: 267.2139, found: 267.2140; calc'd for $\mathrm{C}_{16} \mathrm{H}_{30} \mathrm{KO}[\mathrm{M}+\mathrm{K}]^{+} 305.1698$, found 305.1699.


## (土)-(1S,2R)-4-methylene-2-(prop-1-en-2-yl)cyclohexanol (S1f)

An oven-dried 25 mL round-bottom flask under nitrogen was charged with a s1f stir bar, S4f ( $755.1 \mathrm{mg}, 2.83 \mathrm{mmol}, 1$ equiv), and $\mathrm{Et}_{2} \mathrm{O}(2.8 \mathrm{~mL})$, in that order. The resultant solution was cooled to $0^{\circ} \mathrm{C}$, and after stirring for 5 m at this temperature, TBAF ( $5.7 \mathrm{~mL}, 1 \mathrm{M}$ solution in THF, 5.7 mmol , 2.0 equiv) was added dropwise. The flask was
brought to room temperature and the reaction mixture was stirred for 48 h , at which point it was returned to $0{ }^{\circ} \mathrm{C}$ and quenched by the addition of DI $\mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL})$. The mixture was diluted with $\mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 10 \mathrm{~mL})$. The combined organics were diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to provide the crude product as an orange oil, which was purified by flash column chromatography (silica, Biotage, 0 to $40 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes ) to provide S1f as a clear oil ( $412 \mathrm{mg}, 2.7 \mathrm{mmol}$, $96 \%$ yield $) \mathrm{R} f=0.12\left(20 \% \mathrm{Et}_{2} \mathrm{O}\right.$ in hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 4.89 (quin, $J=1.60 \mathrm{~Hz}, 1 \mathrm{H}) 4.84(\mathrm{~s}, 1 \mathrm{H}) 4.64-4.67$ (m, 1 H) 4.63 (d, $J=1.37 \mathrm{~Hz}, 1$ H) $3.55(\mathrm{td}, J=10.07,4.12 \mathrm{~Hz}, 1 \mathrm{H}) 2.26-2.33(\mathrm{~m}, 1 \mathrm{H}) 2.19-2.24(\mathrm{~m}, 1 \mathrm{H}) 1.97-2.14$ (m, 5H) $1.70(\mathrm{~s}, 3 \mathrm{H}) 1.27-1.37(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm}$ 146.82, $145.86,113.40,108.66,70.37,55.03,37.93,34.63,32.73,18.99$; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3404 (br, m), 3073 (w), 2938 (m), 1647 (m), 1439 (m), 1253 (w), 1067 (s), 1043 (m), 1021 (m), 888 (s), 834 (w), 654 (s). MS (ESI) $m / z$ calc'd for $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 153.1274$, found: 153.1273; calc'd for $\mathrm{C}_{10} \mathrm{H}_{16} \mathrm{NaO}[\mathrm{M}+\mathrm{Na}]^{+}$175.1093, found 175.1101.


## ( $\pm$ )-(1S,2R)-4-methylene-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S3f)

Alcohol S1f ( $400 \mathrm{mg}, 2.63 \mathrm{mmol}, 1.0$ equiv) was oxidized according to General Procedure C to afford the corresponding $\beta, \gamma$-unsaturated ketone S2f that was carried forward without further purification.

According to General Procedure E, ketone S2f was reacted with vinylmagnesium bromide (1.0 M in THF, $6.5 \mathrm{~mL}, 6.5 \mathrm{mmol}, 2.5$ equiv) to afford the crude addition product as a yellow oil and in $>19: 1 \mathrm{dr}$ in favor of the title compound. The crude material was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to
provide S3f as a pale yellow oil ( $246 \mathrm{mg}, 1.4 \mathrm{mmol}, 52 \%$ yield, 2 steps). $\mathrm{R} f=0.43(10 \%$ $\mathrm{Et}_{2} \mathrm{O}$ in hexanes, $\mathrm{KMnO}_{4}$ ); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.85$ (dd, $J=17.17,10.76$ Hz, 1 H) 5.20 (dd, $J=17.40,1.37 \mathrm{~Hz}, 1 \mathrm{H}) 5.00(\mathrm{dd}, J=10.53,1.37 \mathrm{~Hz}, 1 \mathrm{H}) 4.89-4.94$ (m, 1H) $4.77(\mathrm{~s}, 1 \mathrm{H}) 4.65-4.68(\mathrm{~m}, 1 \mathrm{H}) 4.62-4.65(\mathrm{~m}, 1 \mathrm{H}) 2.54(\mathrm{td}, J=13.05,1.37 \mathrm{~Hz}$, $1 \mathrm{H}) 2.38-2.50(\mathrm{~m}, 1 \mathrm{H}) 2.17(\mathrm{dd}, J=13.28,3.66 \mathrm{~Hz}, 1 \mathrm{H}) 2.13$ (dquin, $J=13.28,1.83 \mathrm{~Hz}$, 1 H) 2.05 (ddd, $J=13.30,3.66,1.83 \mathrm{~Hz}, 1 \mathrm{H}) 1.82(\mathrm{~d}, J=1.83 \mathrm{~Hz}, 1 \mathrm{H}) 1.75$ (s, 3 H$) 1.72$ (dd, $J=4.81,2.52 \mathrm{~Hz}, 1 \mathrm{H}) 1.56(\mathrm{tdd}, J=13.74,4.58,1.83 \mathrm{~Hz}, 1 \mathrm{H}){ }^{13} \mathrm{C}$ NMR ( 126 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 148.70,147.41,145.50,112.07,111.33,107.32,72.68,53.60,39.12,36.12$, 30.05, 25.54; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3547 (br, m), 3072 (m), 2981 (m), 2938 (m), 2918 (m), 2849 (w), 1843 (w), 1786 (w), 1650 (m), 1639 (m), 1438 (m), 1374 (m), 1281 (m), 1135 (m), $997(\mathrm{~m}), 950(\mathrm{~s}), 888(\mathrm{~s}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{16}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 161.1; found: 161.1.


39f

## (E)-5-methyl-8-methylenecyclodec-5-enone (39f)

According to General Procedure F, divinyl alcohol S3f (200 mg, 1.12 mmol , 1 equiv) underwent an anionic oxy-Cope rearrangement. The crude material was purified by flash column chromatography (Davisil ${ }^{\mathrm{TM}}$, Biotage, 0 to $5 \%$ $\mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to provide cyclodecenone 39 f as a clear oil ( $95 \mathrm{mg}, 0.53 \mathrm{mmol}, 47$ yield). $\mathrm{R} f=0.31\left(5 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, 23{ }^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.09(\mathrm{t}$, $J=7.33 \mathrm{~Hz}, 1 \mathrm{H}) 4.73-4.76(\mathrm{~m}, 1 \mathrm{H}) 4.72(\mathrm{~s}, 1 \mathrm{H}) 1.54-3.14(\mathrm{~m}, 12 \mathrm{H}) 1.46(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{1} \mathrm{H}$ NMR (399 MHz, $-20^{\circ} \mathrm{C}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.08(\mathrm{~d}, J=10.53 \mathrm{~Hz}, 1 \mathrm{H}) 4.73(\mathrm{~s}, 1 \mathrm{H}) 4.70(\mathrm{~s}, 1$ H) $2.71-2.86(\mathrm{~m}, 1 \mathrm{H}) 2.51-2.71(\mathrm{~m}, 2 \mathrm{H}) 2.41(\mathrm{dd}, \mathrm{J}=14.43,9.75 \mathrm{~Hz}, 2 \mathrm{H}) 2.10-2.34$ (m, 4 H) 2.04 (d, $J=12.48 \mathrm{~Hz}, 1 \mathrm{H}) 1.77(\mathrm{td}, J=12.48,3.51 \mathrm{~Hz}, 1 \mathrm{H}) 1.57-1.70(\mathrm{~m}, 1 \mathrm{H})$
$1.44(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 209.2,149.2,138.8,124.9,113.0,45.2$, $43.0,41.0,37.8,30.9,25.0,15.8 ;$ FTIR (neat, $\mathrm{cm}^{-1}$ ) 3071 (w), 2924 (m), 2856 (m), 1703 (s), 1638 (m), 1443 (m), 1426 (m), 1381 (w), 1351 (m), 1260 (w), 1175 (w), 1103 (s), 1081 (m), 1020 (w), 907 (s), 846 (m), 804 (m), 633 (m). MS (ESI) $m / z$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{ONa}[\mathrm{M}+\mathrm{Na}]^{+}$201.1250, found 201.1259.

Scheme for the Synthesis of Transannular Ketone-Ene Substrate 57

 MS. The sieves were activated by flame-drying under reduced pressure (1 torr) and cooled under argon. $\mathrm{CH}_{2} \mathrm{Cl}_{2}(86 \mathrm{~mL})$ was added by syringe, followed by aldehyde $\mathbf{S 1 1}$ ( $6.1 \mathrm{~g}, 43 \mathrm{mmol}, 1$ equiv). The resultant suspension was cooled to $-78{ }^{\circ} \mathrm{C}$, and $\mathrm{SnCl}_{4}$ ( $4.4 \mathrm{~mL}, 38 \mathrm{mmol}, 0.90$ equiv) was added neat, dropwise. The flask was transferred to a $-60^{\circ} \mathrm{C}$ cryocool and the mixture was stirred at this temperature overnight. The flask was transferred to a $0{ }^{\circ} \mathrm{C}$ bath, and the reaction was quenched by slow addition of saturated aqueous $\mathrm{NaHCO}_{3}(50 \mathrm{~mL})$. The contents were diluted with an additional 50 mL DI $\mathrm{H}_{2} \mathrm{O}$, and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 50 \mathrm{~mL})$. The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to afford the crude product as a yellow oil and a 1.8:1.0 mixture of diastereomeric alcohols (S5, 2.8 g ). This crude product was taken on to the next step without further purification.

[^26]The crude product S5 was oxidized according to General Procedure C to afford S6, which was carried forward without further purification.

According to General Procedure D, the intermediate ketone S6 was reacted with vinylmagnesium bromide ( 1.0 M in THF, $23.6 \mathrm{~mL}, 23.6 \mathrm{mmol}, 1.2$ equiv) to afford the crude addition product in $3.9: 1 \mathrm{dr}$ in favor of the title compound. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $50 \% \mathrm{EtOAc} /$ hexanes $)$ to afford divinyl alcohol $\mathbf{S 6}$ as a clear oil ( $1.2 \mathrm{~g}, 7.1 \mathrm{mmol}, 17 \%$ over 3 steps). $\mathrm{Rf}=0.32$ (20\% EtOAc/hexanes); ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 5.89(\mathrm{dd}, J=17.13,10.69 \mathrm{~Hz}$, $1 \mathrm{H}) 5.25(\mathrm{dd}, J=17.13,1.03 \mathrm{~Hz}, 1 \mathrm{H}) 5.07(\mathrm{dd}, J=10.69,1.03 \mathrm{~Hz}, 2 \mathrm{H}) 4.97(\mathrm{~d}, J=1.17$ $\mathrm{Hz}, 1 \mathrm{H}) 4.69(\mathrm{~s}, 1 \mathrm{H}) 3.74-3.86(\mathrm{~m}, 2 \mathrm{H}) 3.61-3.72(\mathrm{~m}, 2 \mathrm{H}) 2.37(\mathrm{dd}, \mathrm{J}=11.42$, 4.69 Hz, 1 H) 1.89 (d, $J=2.34 \mathrm{~Hz}, 1 \mathrm{H}) 1.83$ (dddd, $J=13.95,11.31,6.66,2.34 \mathrm{~Hz}, 1 \mathrm{H}) 1.77$ (s, $3 \mathrm{H}) 1.52(\mathrm{~d}, \mathrm{~J}=13.77 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 144.8,143.9,113.0$, 112.1, 70.6, 66.8, 63.5, 50.9, 37.0, 26.6; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3436 (br m) 3085 (w) 2954 (m) 2869 (m) 1639 (m) 1374 (m) 1289 (w) 1215 (w) 1114 (s) 968 (s) 917 (s) 867 (s) 815 (m) $734(\mathrm{~m})$; MS (APCI) $\mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{O}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$151.1; found 151.2.


## (E)-8-methyl-5,6,7,10-tetrahydro-2H-oxecin-4(3H)-one (57)

According to General Procedure G, divinyl alcohol S6 (1.1 g, $6.5 \mathrm{mmol}, 1.0$ equiv) underwent the palladium-catalyzed oxy-Cope rearrangement. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}, 0$ to $40 \% \mathrm{EtOAc} /$ hexanes) to afford keto-olefin 57 ( $528 \mathrm{mg}, 3.14 \mathrm{mmol}, 48 \%$ ) as a white solid. $\mathrm{R} f=0.56(25 \%$ EtOAc/hexanes, $\left.\mathrm{Al}_{2} \mathrm{O}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 5.22-5.40(\mathrm{~m}, 1 \mathrm{H}) 4.13(\mathrm{~d}$, $J=12.70 \mathrm{~Hz}, 1 \mathrm{H}) 3.86-3.98(\mathrm{~m}, 2 \mathrm{H}) 3.59-3.77(\mathrm{~m}, 1 \mathrm{H}) 2.94(\mathrm{dd}, J=15.38,8.55 \mathrm{~Hz}, 1$
H) $2.36-2.50(\mathrm{~m}, 2 \mathrm{H}) 2.31(\mathrm{dd}, J=15.14,7.81 \mathrm{~Hz}, 1 \mathrm{H}) 2.16-2.26(\mathrm{~m}, 1 \mathrm{H}) 2.10(\mathrm{~d}$, $J=11.23 \mathrm{~Hz}, 1 \mathrm{H}) 1.83-1.99(\mathrm{~m}, 1 \mathrm{H}) 1.78(\mathrm{~d}, J=11.72 \mathrm{~Hz}, 1 \mathrm{H}) 1.51(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 208.6,143.1,123.9,68.6,66.8,47.4,43.5,41.1,26.3,16.3$; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2931 (m) 2868 (m) 1692 (s) 1422 (w) 1354 (m) 1297 (m) 1259 (m) 1241 (m) 1103 (s) 1071 (s) 1044 (s) 859 (m) 808 (m) 791 (m); MS (ESI) m/z calc'd for $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}$169.1223, found 169.1227 ; calc'd for $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{O}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$ 151.1117, found 151.1114 .

Scheme for the Synthesis of Planar Chiral Transannular Ketone-Ene Substrate 61



## ( $\pm$ )-(1S,2R)-2-methyl-2-(prop-1-en-2-yl)-1-vinylcyclohexanol (S13)

According to General Procedure F, ketone S12 ( $1.16 \mathrm{~g}, 7.62 \mathrm{mmol}, 1$ equiv) was reacted with vinylmagnesium bromide $(1.0 \mathrm{M}$ in $\mathrm{THF}, 18.8 \mathrm{~mL}, 18.8 \mathrm{mmol}, 2.5$ equiv) to afford the desired divinyl alcohol in $>19: 1 \mathrm{dr}$. The crude product was purified (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford divinyl alcohol S 13 ( 476 mg , $2.64 \mathrm{mmol}, 35 \%)$ as a yellow oil. $\mathrm{Rf}=0.34\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{Al}_{2} \mathrm{O}_{3}\right) ;{ }^{1} \mathrm{H}$ NMR ( 500 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \operatorname{ppm} 6.10(\mathrm{dd}, J=17.09,10.74 \mathrm{~Hz}, 1 \mathrm{H}) 5.19(\mathrm{dd}, J=17.09,1.46 \mathrm{~Hz}, 1 \mathrm{H})$ $5.07(\mathrm{t}, J=1.50 \mathrm{~Hz}, 1 \mathrm{H}) 5.00(\mathrm{dd}, J=10.74,1.47 \mathrm{~Hz}, 1 \mathrm{H}) 4.96(\mathrm{~s}, 1 \mathrm{H}) 2.18(\mathrm{td}, J=12.45$, $5.37 \mathrm{~Hz}, 1 \mathrm{H}) 2.07(\mathrm{~d}, \mathrm{~J}=2.44 \mathrm{~Hz}, 1 \mathrm{H}) 1.79(\mathrm{~s}, 3 \mathrm{H}) 1.72-1.78(\mathrm{~m}, 1 \mathrm{H}) 1.65-1.71(\mathrm{~m}$, $1 \mathrm{H}) 1.53-1.59(\mathrm{~m}, 2 \mathrm{H}) 1.47-1.53(\mathrm{~m}, 1 \mathrm{H}) 1.39-1.46(\mathrm{~m}, 1 \mathrm{H}) 1.22(\mathrm{~s}, 3 \mathrm{H}) 1.13-$ $1.20(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm}$ 151.0, 144.4, 114.1, 112.0, 74.2, 46.4, 33.2, 32.9, 23.9, 21.5, 20.9, 19.3; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3540 (br m) 2088 (w) 2929 (s) 2966
(m) 1623 (m) 1447 (m) 1379 (m) 1315 (m) 1195 (w) 1088 (m) 1040 (m) 1000 (m) 975 (s)

917 (s) 901 (s) 888 (s) $684(\mathrm{~m}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{19}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}: 163.1$; found: 163.2.

$( \pm)$-(E)-5,6-dimethylcyclodec-5-enone (61)
According to General Procedure F, divinyl alcohol S13 (243 mg, $1.34 \mathrm{mmol}, 1$ equiv) underwent an anionic oxy-Cope rearrangement. The crude residue was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}, 0$ to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford planar chiral cyclodecenone $61(124 \mathrm{mg}, 0.69 \mathrm{mmol}, 51 \%)$ as a clear oil. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 2.52(\mathrm{ddt}, J=16.03,8.70,0.90,0.90 \mathrm{~Hz}, 1 \mathrm{H}) 2.33-2.48(\mathrm{~m}, 3$ H) 2.22-2.30(m, 2 H) $2.00(\mathrm{dd}, J=14.65,6.41 \mathrm{~Hz}, 1 \mathrm{H}) 1.82(\mathrm{~s}, 3 \mathrm{H}) 1.50-1.86(\mathrm{~m}, 7$ H) $1.48(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 208.5 ; 132.0,129.1,43.1,41.5$, 34.4, 34.2, 26.5, 26.0, 22.4, 19.1, 18.8; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3382 (br m) 2958 (m) 2952 (s) 2861 (s) 1701 (s) 1445 (m) 1428 (m) 1372 (m) 1353 (m) 1199 (w) 1126 (s) 1061 (m) 893 (w) 788 (w). MS (ESI) $m / z$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{19}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$163.1481; found 163.1484; calc'd for $\mathrm{C}_{12} \mathrm{H}_{20} \mathrm{NaO}[\mathrm{M}+\mathrm{Na}]^{+}$203.1406; found 203.1418.

## D. Enantioselective Transannular Ketone-Ene Reactions

General Procedure H - Enantioselective Cr(III)-Catalyzed Transannular Ketone-Ene Reaction

An oven-dried 0.5 dram screw-top vial was charged with a stir bar, activated $4 \AA$ MS (10 mg ) and was sealed with a cap containing a Teflon-lined septum. The sieves were flamedried under vacuum (1 torr) and allowed to cool to room temperature under $\mathrm{N}_{2}$. To the cooled vial was added catalyst $50(12.7 \mathrm{mg}, 0.02 \mathrm{mmol}, 5 \mathrm{~mol} \%$, which is $10 \mathrm{~mol} \%$
based on Cr). The keto-olefin substrate (either 39b, 39d, 39e, 57, and 59) ( 0.2 mmol ) was added as a solid to the vial, followed by toluene $(50 \mu \mathrm{~L})$ by microliter syringe. For keto-olefin substrates 39a, 39c, and 39f: toluene ( $50 \mu \mathrm{~L}$ ) was first added, followed by the substrate, which was added neat by microliter syringe. The $\mathrm{N}_{2}$ line was removed, the cap was wrapped with parafilm, and the reaction mixture was stirred at room temperature for 48 h . At this point, an aliquot $(\sim 2 \mu \mathrm{~L})$ was removed from the vial and diluted into an NMR tube with $\mathrm{CDCl}_{3}$ to determine the product diastereomeric ratio. The NMR sample along with the remainder of the crude reaction mixture was directly loaded onto a column $\left(\mathrm{SiO}_{2}\right.$, neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, or Davisil $\left.{ }^{\mathrm{TM}}\right)$ and eluted to isolate the bicyclic alcohol product.

## (4aR,8aS)-1-methylenedecahydronaphthalen-4a-ol (40a)



Following General Procedure H, cyclodecenone 39a ( $33.3 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ equiv) underwent a transannular ketone-ene rearrangement to afford 40a as a single diastereomer. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes, followed by $10 \%$ to $50 \%$ EtOAc/hexanes) to afford 40a ( $27.1 \mathrm{mg}, 0.163 \mathrm{mmol}, 81 \%$ yield) as a pale yellow oil. $\mathrm{R} f=0.16\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{SiO}_{2}, \mathrm{KMnO}_{4}\right) \cdot[\alpha]_{D}^{23}=+33.2^{\circ}\left(\mathrm{c}=0.82, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 4.86-4.92(\mathrm{~m}, 1 \mathrm{H}) 4.63(\mathrm{~d}, J=0.98 \mathrm{~Hz}, 1 \mathrm{H}) 2.33$ (dquin, $J=12.70,2.40,1 \mathrm{H}) 1.92-2.06(\mathrm{~m}, 2 \mathrm{H}) 1.80$ (dquin, $J=13.18,3.40 \mathrm{~Hz}, 1 \mathrm{H}) 1.66-1.75$ (m, 2 H) $1.54-1.66(\mathrm{~m}, 3 \mathrm{H}) 1.38-1.54(\mathrm{~m}, 4 \mathrm{H}) 1.33(\mathrm{td}, J=13.31,4.15 \mathrm{~Hz}, 1 \mathrm{H}) 1.21-$ $1.37(\mathrm{~m}, 1 \mathrm{H}){ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 150.4, 108.6, 72.0, 49.5, 40.0, 38.7, 36.7, 26.1, 24.0, 23.9, 21.4; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3474 (br m), 2930 (s) 2853 (m) 1643 (w) 1446 (m) 1251 (w) 1186 (w) 1089 (m) 949 (s) 893 (m) 756 (m) 700 (m). MS (APCI) m/z calc'd for $\mathrm{C}_{11} \mathrm{H}_{19} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 167.2; found: 167.1. The enantiomeric excess was
determined to be $93 \%$ by chiral GC analysis (CHIRALDEX $\beta-\mathrm{PH}, 100^{\circ} \mathrm{C}, 14 \mathrm{psi}, 20: 1$ split $) \mathrm{t}_{\mathrm{R}}($ minor $)=21.47 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=22.60 \mathrm{~min}$.


## (4aS,8aS)-7,7-dimethyl-1-methylenedecahydronaphthalen-4a-ol (40b)

Following General Procedure H, cyclodecenone 39b ( $38.9 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ 40b equiv) underwent a transannular ketone-ene rearrangement to afford 40b as a single diastereomer. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes ) to afford $\mathbf{4 0 b}$ as a clear oil ( $37.7 \mathrm{mg}, 0.19 \mathrm{mmol}$, $97 \%$ yield $) . \mathrm{R} f=0.34\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes, $\left.\mathrm{KMnO}_{4}\right) \cdot[\alpha]_{D}{ }^{23}=+17.4\left(c=0.43, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \operatorname{ppm} 4.90(\mathrm{q}, J=1.53 \mathrm{~Hz}, 1 \mathrm{H}) 4.65(\mathrm{~d}, J=0.92 \mathrm{~Hz}, 1 \mathrm{H}) 2.36$ (ddt, $J=12.93,4.01,2.06,2.06 \mathrm{~Hz}, 1 \mathrm{H}) 2.18(\mathrm{~d}, J=14.19 \mathrm{~Hz}, 1 \mathrm{H}) 2.04(\mathrm{td}, J=13.16,4.81$ $\mathrm{Hz}, 1 \mathrm{H}) 1.53-1.78(\mathrm{~m}, 7 \mathrm{H}) 1.41-1.50(\mathrm{~m}, 2 \mathrm{H}) 1.15-1.21(\mathrm{~m}, 2 \mathrm{H}) 0.99(\mathrm{~s}, 3 \mathrm{H}) 0.94$ (s, 3 H ); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 150.3, 108.5, 71.6, 45.1, 39.6, 36.83, 36.75, 34.9, 34.0, 33.4, 30.6, 24.3, 24.0; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3471 (br m), 3083 (w), 2931 (s), 1644 (m), 1441 (m), 1364 (m), 1252 (w), 1194 (w), 1093 (m), 1039 (w), 970 (m), 948 (m), $923(\mathrm{~m}), 893(\mathrm{~s}), 758(\mathrm{w}) . \mathrm{MS}(\mathrm{ESI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{23} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 195.1743$; found: 195.1736; calc'd for $\mathrm{C}_{13} \mathrm{H}_{26} \mathrm{NO}\left[\mathrm{M}+\mathrm{NH}_{4}\right]^{+}$212.2009; found 212.2007. The enantiomeric excess was determined to be $94 \%$ by chiral GC analysis (CHIRALDEX $\beta$ $\left.\mathrm{PH}, 100^{\circ} \mathrm{C}, 14 \mathrm{psi}, 20: 1 \mathrm{split}\right) \mathrm{t}_{\mathrm{R}}($ minor $)=28.24 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=30.18 \mathrm{~min}$.


40c
(4aR,8aS)-2,2-dimethyl-1-methylenedecahydronaphthalen-4a-ol (40c)
Following General Procedure H, cyclodecenone 39c ( $38.9 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$
equiv) underwent a transannular ketone-ene rearrangement to afford 40c as a single diastereomer. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes, followed by $10 \%$ to $50 \% \mathrm{EtOAc} /$ hexanes) to afford 40c ( $32.8 \mathrm{mg}, 0.169 \mathrm{mmol}, 84 \%$ yield $)$ as a pale yellow oil. $[\alpha]_{D}{ }^{24}=+16.2^{\circ}(c=1.0$, $\mathrm{CHCl}_{3}$ ). ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.91-4.98(\mathrm{~m}, 1 \mathrm{H}) 4.70(\mathrm{~s}, 1 \mathrm{H}) 2.19-2.29$ (m, 1 H) 1.78-1.87 (m, 1 H ) 1.72 (dquin, $J=13.74,2.30 \mathrm{~Hz}, 1 \mathrm{H}) 1.54-1.69(\mathrm{~m}, 2 \mathrm{H})$ $1.42-1.54(\mathrm{~m}, 4 \mathrm{H}) 1.33-1.40(\mathrm{~m}, 2 \mathrm{H}) 1.22-1.33(\mathrm{~m}, 2 \mathrm{H}) 1.12(\mathrm{~s}, 3 \mathrm{H}) 1.08(\mathrm{~s}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 156.8,106.9,72.1,45.3,38.9,36.99,36.93,36.4$, 29.7, 26.3, 26.0, 24.7, 21.5; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3474 (br m) 3096 (w) 2930 (s) 2854 (m) 1707 (w) 1632 (m) 1449 (m) 1364 (m) 1179 (w) 1081 (m) 990 (m) 955 (s) 915 (m) 898 (s) $857(\mathrm{~m})$; MS (ESI) $\mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 177.1638; found: 177.1639; calc'd for $\mathrm{C}_{13} \mathrm{H}_{22} \mathrm{NaO}[\mathrm{M}+\mathrm{Na}]^{+}$217.1563; found 217.1567. The enantiomeric excess was determined to be $94 \%$ by chiral GC analysis (CHIRALDEX $\beta-\mathrm{PH}, 100^{\circ} \mathrm{C}, 14 \mathrm{psi}, 20: 1$ $\operatorname{split}) \mathrm{t}_{\mathrm{R}}($ minor $)=40.28 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=41.89 \mathrm{~min}$.


40d

## (4aR,8aS)-3,3-dimethyl-1-methylenedecahydronaphthalen-4a-ol (40d)

Following General Procedure H, cyclodecenone 39d (38.9 mg, $0.2 \mathrm{mmol}, 1$ equiv) underwent a transannular ketone-ene rearrangement to afford 40d, as a single diastereomer but as a mixture of regioisomers. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes, followed by $10 \%$ to $50 \% \mathrm{EtOAc} /$ hexanes). The product was isolated as a mixture with an inseparable olefin isomer in a combined yield of $32 \%$ and was formed as a racemate. The characterization data provided here were measured on a racemic sample. ${ }^{1} \mathrm{H}$ NMR
( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 4.85(\mathrm{~d}, \mathrm{~J}=1.83 \mathrm{~Hz}, 1 \mathrm{H}) 4.71$ (s, 1 H$) 2.04$ (dd, $J=12.82,2.29$ Hz, 1 H) 1.99 (d, $J=12.82 \mathrm{~Hz}, 0 \mathrm{H}) 1.90(\mathrm{dd}, J=10.99,4.58 \mathrm{~Hz}, 1 \mathrm{H}) 1.74-1.86(\mathrm{~m}, 1 \mathrm{H})$ $1.64-1.72(\mathrm{~m}, 1 \mathrm{H}) 1.41-1.64(\mathrm{~m}, 5 \mathrm{H}) 1.36(\mathrm{~d}, J=14.19 \mathrm{~Hz}, 1 \mathrm{H}) 1.15-1.33(\mathrm{~m}, 3 \mathrm{H})$ $1.01(\mathrm{~s}, 3 \mathrm{H}) 0.95(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 148.4, 109.3, 73.0, 52.2, 50.4, 49.4, 39.7, 34.0, 33.4, 27.4, 26.1, 23.7, 21.1; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3491 (br m) 2081 (w) 2927 (s) 2861 (m) 1648 (m) 1450 (m) 1365 (m) 1162 (m) 1073 (m) 972 (s) 156 (m) 889 (s) 812 (m) $697(w) . M S(E S I) ~ m / z$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{21}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}: 177.2$, found: 177.1.

(4a'S,8a'S)-8'-methyleneoctahydro-1'H-spiro[[1,3]dioxolane-2,2'-
40e naphthalen]-4a'-ol (40e)
Following General Procedure H, cyclodecenone 39e ( $44.9 \mathrm{mg}, 0.2 \mathrm{mmol}$, 1 equiv) underwent a transannular ketone-ene rearrangement to afford 40e as a single diastereomer. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $25 \%$ EtOAc/hexanes) to afford $40 \mathrm{e}(38.9 \mathrm{mg}, 0.173 \mathrm{mmol}, 87 \%$ yield) as a clear oil.; $[\alpha]_{D}{ }^{23}=+58.3^{\circ}\left(\mathrm{c}=0.107, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.89(\mathrm{~d}$, $J=1.37 \mathrm{~Hz}, 1 \mathrm{H}) 4.59(\mathrm{~s}, 1 \mathrm{H}) 3.84-4.06(\mathrm{~m}, 3 \mathrm{H}) 2.32(\mathrm{dd}, \mathrm{J}=13.05,1.60 \mathrm{~Hz}, 2 \mathrm{H}) 1.86-$ $2.06(\mathrm{~m}, 2 \mathrm{H}) 1.81(\mathrm{t}, \mathrm{J}=12.82 \mathrm{~Hz}, 1 \mathrm{H}) 1.63-1.76(\mathrm{~m}, 3 \mathrm{H}) 1.50-1.63(\mathrm{~m}, 3 \mathrm{H}) 1.44(\mathrm{td}$, $J=13.30,4.12 \mathrm{~Hz}, 1 \mathrm{H}) 1.47$ (br. s., 1 H ); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 149.2, 109.7, 108.8, 71.1, 64.4, 46.9, 38.9, 36.1, 36.0, 32.9, 30.2, 23.8; FTIR (neat, $\left.\mathrm{cm}^{-1}\right) 3491$ (br w), 2932 (s) 2879 (m) 1646 (w) 1441 (w) 1358 (m) 1296 (m) 1270 (m) 1153 (m) 1091 (s) 1031 (m) 988 (m) 965 (m) 950 (m) 932 (m) 898 (m) 836 (m) 757 (m); MS (ESI) $m / z$ calc'd for $\mathrm{C}_{13} \mathrm{H}_{19} \mathrm{O}_{2} \quad\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 207.1380; found: 207.1370; calc'd for
$\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{NaO}_{3}[\mathrm{M}+\mathrm{Na}]^{+} 247.1305$; found 247.1297. The enantiomeric excess was determined to be $96 \%$ by chiral GC analysis (CHIRALDEX $\beta$-Cyclodex, $140^{\circ} \mathrm{C}$, 14 psi , $20: 1 \mathrm{split}) \mathrm{t}_{\mathrm{R}}($ minor $)=38.63 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=40.96 \mathrm{~min}$.

$40 f$
(4aS,8aS)-1,7-dimethylenedecahydronaphthalen-4a-ol (40f)
Following General Procedure H, cyclodecenone $39 \mathrm{f}(35.7 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ equiv) underwent a transannular ketone-ene rearrangement to afford $\mathbf{4 0 f}$ as a single diastereomer. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $5 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford $40 \mathrm{f}(22.2 \mathrm{mg}, 0.124 \mathrm{mmol}, 62 \%$ yield) as a clear oil.; $[\alpha]_{D}{ }^{24}=+107.8^{\circ}\left(\mathrm{c}=0.66, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.93(\mathrm{~d}$, $J=1.46 \mathrm{~Hz}, 1 \mathrm{H}) 4.66-4.69(\mathrm{~m}, 2 \mathrm{H}) 4.64-4.66(\mathrm{~m}, 1 \mathrm{H}) 2.42(\mathrm{tdd}, J=13.70,13.70,4.88$, $1.95 \mathrm{~Hz}, 1 \mathrm{H}) 2.35$ (dquin, $J=13.18,2.00 \mathrm{~Hz}, 1 \mathrm{H}) 2.26-2.38(\mathrm{~m}, 1 \mathrm{H}) 2.04-2.17(\mathrm{~m}, 3$ H) $1.98(\mathrm{td}, J=13.18,4.39 \mathrm{~Hz}, 1 \mathrm{H}) 1.85(\mathrm{ddd}, J=13.43,4.88,2.20 \mathrm{~Hz}, 1 \mathrm{H}) 1.65-1.78$ (m, 2 H) 1.49-1.65 (m, 2 H) $1.43(\mathrm{tdd}, \mathrm{J}=13.49,13.49,9.16,4.39 \mathrm{~Hz}, 2 \mathrm{H})^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 149.7,148.9,108.9,107.5,71.8,50.6,39.8,39.4,36.3,32.9$, 30.2, 23.7; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3471 (br m) 3071 (w) 2932 (s) 2850 (m) 1724 (w) 1648 (m) 1441 (m) 1270 (m) 1095 (m) 937 (s) 887 (s) 838 (w) 655 (m). MS (ESI) $\mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{17}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}: 161.1325$; found: 161.1325. The enantiomeric excess was determined to be $94 \%$ by chiral GC analysis (CHIRALDEX $\beta$-Cyclodex, $100^{\circ} \mathrm{C}, 14 \mathrm{psi}$, $20: 1 \mathrm{split}) \mathrm{t}_{\mathrm{R}}($ minor $)=44.84 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=48.31 \mathrm{~min}$.

Following General Procedure H, with the exception of a 24 h reaction time, ether 57 ( $33.6 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ equiv) underwent a transannular ketone-ene rearrangement to afford 58 as a single diastereomer. The crude product was purified by flash column chromatography ( $\mathrm{SiO}_{2}$, Biotage, 0 to $40 \% \mathrm{EtOAc} /$ hexanes $)$ to afford 58 (4.4 $\mathrm{mg}, 0.026 \mathrm{mmol}, 13 \%$ yield) as a clear oil. $\mathrm{R} f=0.40(25 \% \mathrm{EtOAc} /$ hexanes, CAM); $[\alpha]_{D}{ }^{23}=+15.3^{\circ}\left(\mathrm{c}=0.36, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.90(\mathrm{~s}, 1 \mathrm{H}) 4.40(\mathrm{~s}$, 1 H) $3.71-3.85(\mathrm{~m}, 3 \mathrm{H}) 3.66(\mathrm{t}, \mathrm{J}=11.20 \mathrm{~Hz}, 1 \mathrm{H}) 2.26-2.36(\mathrm{~m}, 2 \mathrm{H}) 2.06(\mathrm{td}, J=13.18$, $4.88 \mathrm{~Hz}, 1 \mathrm{H}) 1.54-1.80(\mathrm{~m}, 6 \mathrm{H}) 1.42-1.54(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 146.5, 108.9, 69.9, 65.0, 64.0, 48.6, 38.9, 38.2, 36.3, 23.5; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3448 (br m) 2934 (m) 2867 (m) 1647 (m) 1439 (w) 1391 (w) 1250 (w) 1170 (m) 1120 (m) 1081 (s) 1025 (m) 967 (s) 945 (m) 888 (s) 854 (s) 832 (w). MS (APCI) m/z calc'd for $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{O}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 151.1; found: 151.1. The enantiomeric excess was determined to be $49 \%$ by chiral GC analysis (CHIRALDEX $\gamma$-TA, $100^{\circ} \mathrm{C}, 14 \mathrm{psi}, 20: 1$ split) $\mathrm{t}_{\mathrm{R}}$ (major) $=26.30 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ minor $)=29.25 \mathrm{~min}$.


## (3aR,7aS)-7-methyleneoctahydro-1H-inden-3a-ol (60)

Following General Procedure H, with the exception of a 24 h reaction time, 60 cyclononenone 59 ( $30.4 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ equiv) underwent a transannular ketone-ene rearrangement to afford $\mathbf{6 0}$ as a single diastereomer. The crude product was purified by flash column chromatography $\left(\mathrm{SiO}_{2}\right.$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes $)$ to afford 60 (5.6 $\mathrm{mg}, 0.037 \mathrm{mmol}, 18 \%$ yield $)$ as a clear oil. $\mathrm{R} f=0.42\left(10 \% \mathrm{Et}_{2} \mathrm{O} /\right.$ hexanes $) ;[\alpha]_{D}{ }^{23}=+6.1^{\circ}$ $\left(\mathrm{c}=0.17, \mathrm{CHCl}_{3}\right) .{ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.93(\mathrm{q}, J=1.76 \mathrm{~Hz}, 1 \mathrm{H}) 4.69(\mathrm{q}$,
$J=1.76 \mathrm{~Hz}, 1 \mathrm{H}) 2.32(\mathrm{ddd}, J=15.55,3.81,1.76 \mathrm{~Hz}, 1 \mathrm{H}) 2.13(\mathrm{dd}, J=12.03,6.16 \mathrm{~Hz}, 1 \mathrm{H})$ 1.90-2.01(m, 2H) 1.72-1.87(m, 4 H) 1.63-1.71(m, 2H) $1.60(\mathrm{dt}, J=13.50,4.40 \mathrm{~Hz}$, $1 \mathrm{H}) 1.52-1.57(\mathrm{~m}, 1 \mathrm{H}) 1.43$ (td, $J=13.21,4.70 \mathrm{~Hz}, 1 \mathrm{H}) 1.34$ (br. s., 1 H$) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 148.5,108.5,80.5,53.9,38.0,36.3,35.2,24.0,23.7,20.3$. FTIR (neat, $\mathrm{cm}^{-1}$ ) 3476 (br m), 2930 (s) 1650 (m) 1439 (m) 1287 (w) 1246 (m) 1188 (w) $1056(\mathrm{~m}) 964$ (s) 893 (s) 873 (s) $756(\mathrm{~s}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{10} \mathrm{H}_{15}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$: 135.1; found: 135.1. The enantiomeric excess was determined to be $68 \%$ by chiral GC analysis (CHIRALDEX $\beta$-Cyclosil, $\left.90{ }^{\circ} \mathrm{C}, 14 \mathrm{psi}, 100: 1 \mathrm{split}\right) \mathrm{t}_{\mathrm{R}}($ minor $)=29.16 \mathrm{~min}$, $\mathrm{t}_{\mathrm{R}}($ major $)=29.62 \mathrm{~min}$.


## (4aR,8aS)-8a-methyl-1-methylenedecahydronaphthalen-4a-ol (62)

An oven-dried 0.5 dram screw-top vial was charged with a stir bar, activated 4 $\AA$ MS (10 mg) and was sealed with a cap containing a Teflon-lined septum. The sieves were flame-dried under vacuum (1 torr) and allowed to cool to room temperature under $\mathrm{N}_{2}$. To the cooled vial was added catalyst $50(12.7 \mathrm{mg}, 0.02 \mathrm{mmol}, 5$ $\mathrm{mol} \%$, which is $10 \mathrm{~mol} \%$ based on Cr$)$. Toluene $(50 \mu \mathrm{~L})$ was first added, followed by the cyclodecenone 61 ( $36.0 \mathrm{mg}, 0.2 \mathrm{mmol}, 1$ equiv), which was added neat by microliter syringe. The $\mathrm{N}_{2}$ line was removed, the cap was wrapped with electrical tape, and the vial was immersed in an oil bath at $50^{\circ} \mathrm{C}$ and stirred at this temperature for $24 \mathrm{~h} .1,3,5-$ trimethoxybenzene ( $3.4 \mathrm{mg}, 0.02 \mathrm{mmol}, 0.1$ equiv) was added as a solid followed by $\mathrm{CDCl}_{3}(\sim 1 \mathrm{~mL})$. The conversion was determined to be $19 \%$, based on integration of the ${ }^{1} \mathrm{H}$ NMR spectrum. The crude product was purified by flash column chromatography (neutral $\mathrm{Al}_{2} \mathrm{O}_{3}$, Biotage, 0 to $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes). Recovered 61 eluted first and was
isolated as a clear oil ( $24.6 \mathrm{mg}, 0.137 \mathrm{mmol}, 69 \%$ ), and decalinol $\mathbf{6 2}$ was isolated as a clear oil ( $4.3 \mathrm{mg}, 0.024 \mathrm{mmol}, 12 \%$ yield). $\mathrm{R} f=0.3$ ( $10 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes). ${ }^{1} \mathrm{H}$ NMR ( 600 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 4.90(\mathrm{t}, \mathrm{J}=1.76 \mathrm{~Hz}, 1 \mathrm{H}) 4.72(\mathrm{~s}, 1 \mathrm{H}) 2.40-2.54(\mathrm{~m}, 1 \mathrm{H}) 2.10-$ $2.17(\mathrm{~m}, 1 \mathrm{H}) 1.82-1.93(\mathrm{~m}, 1 \mathrm{H}) 1.64-1.80(\mathrm{~m}, 3 \mathrm{H}) 1.53-1.63(\mathrm{~m}, 3 \mathrm{H}) 1.44-1.52$ (m, 1 H$) 1.40(\mathrm{~m}, J=13.50 \mathrm{~Hz}, 1 \mathrm{H}) 1.23-1.32(\mathrm{~m}, 3 \mathrm{H}) 1.19(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 154.9,109.3,74.1,44.0,34.2,33.2,31.8,30.8,29.8,23.3,22.7$, 21.4; FTIR (neat, $\mathrm{cm}^{-1}$ ) 3433 (br w) 2922 (s) 2852 (m) 1718 (w) 1642 (w) 1462 (m) 1377 (w) 1260 (w) 1103 (m) $803(\mathrm{w}) . \mathrm{MS}(\mathrm{APCI}) \mathrm{m} / \mathrm{z}$ calc'd for $\mathrm{C}_{12} \mathrm{H}_{19}\left[\mathrm{M}-\mathrm{H}_{2} \mathrm{O}+\mathrm{H}\right]^{+}$163.1; found 163.2. The enantiomeric excess was determined to be $73 \%$ by chiral GC analysis $\left(\right.$ CHIRALDEX $\gamma$-TA, $\left.90^{\circ} \mathrm{C}, 14 \mathrm{psi}, 20: 1 \mathrm{split}\right) \mathrm{t}_{\mathrm{R}}($ minor $)=33.28 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=34.94$ $\min$.
 recovered 61 (CHIRALCEL OD-H, $2 \% \mathrm{IPA} /$ hexanes, $1 \mathrm{~mL} / \mathrm{min}, 210 \mathrm{~nm}) \mathrm{t}_{\mathrm{R}}($ major $)=5.89$ $\min , \mathrm{t}_{\mathrm{R}}($ minor $)=6.32 \mathrm{~min}$.

## E. Determination of Absolute Configuration

A solution of KHMDS in THF ( $1.0 \mathrm{M}, 0.36 \mathrm{~mL}, 0.36 \mathrm{mmol}, 5$ equiv) was added dropwise to a stirred solution of enantioenriched (+)-40a (93\% ee, 12 $\mathrm{mg}, 0.072 \mathrm{mmol}, 1$ equiv) in THF at $0{ }^{\circ} \mathrm{C}$ and under a positive pressure of $\mathrm{N}_{2}$. s14
The resultant solution was stirred at $0^{\circ} \mathrm{C}$ for 30 m , at which point a solution of $p$-bromo-
benzoyl chloride in THF ( $0.86 \mathrm{M}, 0.5 \mathrm{~mL}, 0.43 \mathrm{mmol}, 6$ equiv) was added in one portion. The reaction vial was sealed with parafilm and stirred at $4{ }^{\circ} \mathrm{C}$ for 16 h , after which it was quenched by slow addition of DI $\mathrm{H}_{2} \mathrm{O}(1 \mathrm{~mL})$ and extracted with $\mathrm{Et}_{2} \mathrm{O}(3 \times 0.5 \mathrm{~mL})$. The combined organics were diluted with dichloromethane ( 1 mL ), dried with $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated to afford a white solid. The crude product was purified by column chromatography (Biotage, $\mathrm{SiO}_{2}, 0$ to $5 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes) to afford a clear oil, which was re-evaporated from hexanes twice to afford the desired benzoate S14 as a white solid ( $13.3 \mathrm{mg}, 0.038 \mathrm{mmol}, 53 \%$ yield). $\mathrm{R} f=0.53$ ( $5 \% \mathrm{Et}_{2} \mathrm{O} /$ hexanes); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 7.87$ (d, $\left.J=8.30 \mathrm{~Hz}, 2 \mathrm{H}\right) 7.55(\mathrm{~d}, J=8.79 \mathrm{~Hz}, 2 \mathrm{H}) 4.87$ (d, $J=1.46 \mathrm{~Hz}, 1 \mathrm{H}) 4.76(\mathrm{~d}, J=1.46 \mathrm{~Hz}, 1 \mathrm{H}) 2.82-2.98(\mathrm{~m}, 2 \mathrm{H}) 2.33-2.45(\mathrm{~m}, 1 \mathrm{H}) 2.11$ (td, $J=12.70,4.88 \mathrm{~Hz}, 1 \mathrm{H}) 1.96(\mathrm{t}, J=7.81 \mathrm{~Hz}, 1 \mathrm{H}) 1.82(\mathrm{dd}, J=12.21,3.42 \mathrm{~Hz}, 1 \mathrm{H}) 1.71$ $-1.79(\mathrm{~m}, 2 \mathrm{H}) 1.62-1.70(\mathrm{~m}, 1 \mathrm{H}) 1.52-1.60(\mathrm{~m}, 1 \mathrm{H}) 1.27-1.51(\mathrm{~m}, 5 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 164.5,149.4,131.7$ (2 C), 131.3 (2 C), 127.7, 107.5, 85.5, 50.1, 36.5, 34.5, 34.4, 25.8, 24.4, 23.2, 21.5; FTIR (neat, $\mathrm{cm}^{-1}$ ) 2932 (s) 2855 (m) 1715 (s) 1590 (m) 1484 (w) 1446 (m) 1397 (w) 1279 (s) 1259 (s) 1225 (w) 1173 (m) 1070 (m) 1012 (s) 911 (m) 848 (w) 758 (s). MS (ESI) $m / z$ calc'd for $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{BrO}_{2}[\mathrm{M}+\mathrm{H}]^{+}$: 349.0798; found: 349.0803. $[\alpha]_{D}{ }^{25}=-17.1^{\circ}\left(\mathrm{c}=0.41, \mathrm{CHCl}_{3}\right)$. Slow evaporation of a hexanes solution of S14 at room temperature afforded single crystals (white needles) suitable for X-ray analysis.

### 1.8. X-Ray Crystallographic Analysis of para-Br-Benzoate S14

## Acknowledgment

We thank Dr. Shao-Liang Zheng at the Center for Crystallographic Studies at Harvard University for X-ray data collection and structure determination.

## Procedure

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 DUO CCD diffractometer $\left(\mathrm{Cu}_{\mathrm{K} \alpha}\right.$ radiation, $\lambda=1.54178 \AA$ ), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved $1.0^{\circ}$ scans in $\omega$ at $30^{\circ}, 55^{\circ}, 80^{\circ}$ and $115^{\circ}$ in 2日. Data integration down to $0.84 \AA$ resolution was carried out using SAINT V8.30 A (Bruker diffractometer, 2013) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2013). The structure was solved by the direct methods procedure and refined by least-squares methods again $F^{2}$ using SHELXS-2013 and SHELXL-2013 (Sheldrick, 2008). Nonhydrogen 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 1.5, and geometric parameters are shown in Table 1.6. The Ortep plots produced with SHELXL-2013 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 1.5. Experimental details

|  | NSR-9-086 |
| :---: | :---: |
| Crystal data |  |
| Chemical formula | $\mathrm{C}_{72} \mathrm{H}_{84} \mathrm{Br}_{4} \mathrm{O}_{8}$ |
| $M_{\mathrm{r}}$ | 1397.03 |
| Crystal system, space group | Monoclinic, C2 |
| Temperature (K) | 100 |
| $a, b, c(\AA)$ | 34.7369 (6), 7.4593 (1), 30.4529 (5) |
| $\left.\beta{ }^{( }\right)$ | 124.346 (1) |
| $V\left(\AA^{3}\right)$ | 6514.95 (19) |
| Z | 4 |
| Radiation type | Cu Ka |
| $\mu\left(\mathrm{mm}^{-1}\right)$ | 3.45 |
| Crystal size (mm) | $0.01 \times 0.01 \times 0.01$ |
| Data collection |  |
| Diffractometer | Bruker D8 goniometer with CCD area detector diffractometer |
| Absorption correction | Multi-scan SADABS |
| $T_{\text {min }}, T_{\text {max }}$ | 0.672, 0.806 |
| No. of measured, independent and observed $[I>2 \sigma(I)]$ reflections | 68346, 10935, 10256 |
| $R_{\text {int }}$ | 0.060 |
| $(\sin \theta / \lambda)_{\text {max }}\left(\AA^{-1}\right)$ | 0.596 |
| Refinement |  |
| $R\left[F^{2}>2 \sigma\left(F^{2}\right)\right], w R\left(F^{2}\right), S$ | 0.051, 0.104, 1.14 |
| No. of reflections | 10935 |
| No. of parameters | 791 |
| No. of restraints | 78 |
| H -atom treatment | H -atom parameters constrained |
| $\Delta \rho_{\text {max }}, \Delta \rho_{\text {min }}\left(\mathrm{e} \AA^{-3}\right)$ | 0.59, -0.60 |
| Absolute structure | Flack x determined using 4289 quotients $[(\mathrm{I}+)-(\mathrm{I}-)] /[(\mathrm{I}+)+(\mathrm{I}-)]$ (Parsons and Flack (2004), Acta Cryst. A60, s61). |
| Flack parameter | -0.007 (10) |

Computer programs: APEX2 v2013.4.1 (Bruker-AXS, 2013), SAINT 8.30A (Bruker-AXS, 2012),
SHELXS2013 (Sheldrick, 2013), SHELXL2013 (Sheldrick, 2013), Bruker SHELXTL (Sheldrick, 2013).
Table 1.6. Geometric parameters $\left(\AA,{ }^{\circ}\right)$

| C1-C2 | 1.383 (11) | C48-C49 | 1.519 (10) |
| :---: | :---: | :---: | :---: |
| C1-C6 | 1.395 (11) | C48-C57 | 1.527 (11) |
| $\mathrm{C} 1-\mathrm{H} 1$ | 0.9500 | C48-C53 | 1.536 (11) |
| C2-C3 | 1.364 (11) | C49-C50 | 1.533 (11) |
| C2-H2 | 0.9500 | C49-H49A | 0.9900 |
| C3-C4 | 1.393 (12) | C49-H49B | 0.9900 |
| C3-Br1 | 1.915 (8) | C50-C51 | 1.509 (12) |
| C4-C5 | 1.377 (12) | C50-H50A | 0.9900 |
| C4-H4 | 0.9500 | C50-H50B | 0.9900 |
| C5-C6 | 1.387 (10) | C51-C52 | 1.497 (11) |
| C5-H5 | 0.9500 | C51-H51A | 0.9900 |
| C6-C7 | 1.500 (11) | C51-H51B | 0.9900 |
| C7-O2 | 1.218 (10) | C52-C58 | 1.322 (11) |
| C7-O1 | 1.321 (9) | C52-C53 | 1.528 (10) |
| C8-O1 | 1.472 (9) | C53-C54 | 1.521 (10) |
| C8-C9 | 1.518 (10) | C53-H53 | 1.0000 |
| C8-C17 | 1.519 (10) | C54-C55 | 1.533 (12) |
| C8-C13 | 1.549 (10) | C54-H54A | 0.9900 |
| C9-C10 | 1.526 (10) | C54-H54B | 0.9900 |
| C9—H9A | 0.9900 | C55-C56 | 1.534 (13) |
| C9—H9B | 0.9900 | C55-H55A | 0.9900 |
| C10-C11 | 1.513 (12) | C55-H55B | 0.9900 |
| C10-H10A | 0.9900 | C56-C57 | 1.522 (12) |
| C10-H10B | 0.9900 | C56-H56A | 0.9900 |
| C11-C12 | 1.512 (11) | C56-H56B | 0.9900 |
| C11-H11A | 0.9900 | C57-H57A | 0.9900 |
| C11-H11B | 0.9900 | C57-H57B | 0.9900 |
| C12-C18 | 1.321 (12) | C58-H58A | 0.9500 |
| C12-C13 | 1.530 (10) | C58-H58B | 0.9500 |

Table 1.6. (Continued)

| C13-C14 | 1.521 (10) | C61-C66 | 1.387 (10) |
| :---: | :---: | :---: | :---: |
| C13-H13 | 1.0000 | C61-C62 | 1.395 (10) |
| C14-C15 | 1.517 (11) | C61-H61 | 0.9500 |
| C14-H14A | 0.9900 | C62-C63 | 1.378 (10) |
| C14-H14B | 0.9900 | C62-H62 | 0.9500 |
| C15-C16 | 1.519 (10) | C63-C64 | 1.377 (10) |
| C15-H15A | 0.9900 | C63-Br4 | 1.898 (7) |
| C15-H15B | 0.9900 | C64-C65 | 1.387 (11) |
| C16-C17 | 1.520 (10) | C64-H64 | 0.9500 |
| C16-H16A | 0.9900 | C65-C66 | 1.380 (10) |
| C16-H16B | 0.9900 | C65-H65 | 0.9500 |
| C17-H17A | 0.9900 | C66-C67 | 1.512 (11) |
| C17-H17B | 0.9900 | C67-08 | 1.204 (11) |
| C18-H18A | 0.9500 | C67-07 | 1.336 (11) |
| C18-H18B | 0.9500 | O7-C68A | 1.520 (17) |
| C21-C26 | 1.391 (11) | O7-C68 | 1.525 (15) |
| C21-C22 | 1.391 (11) | C68-C69 | 1.511 (17) |
| C21-H21 | 0.9500 | C68-C77 | 1.513 (16) |
| C22-C23 | 1.364 (12) | C68-C73 | 1.526 (17) |
| C22-H22 | 0.9500 | C69-C70 | 1.518 (18) |
| C23-C24 | 1.382 (11) | C69-H69A | 0.9900 |
| C23-Br2 | 1.903 (8) | C69-H69B | 0.9900 |
| C24-C25 | 1.380 (12) | C70-C71 | 1.522 (17) |
| C24-H24 | 0.9500 | C70-H70A | 0.9900 |
| C25-C26 | 1.391 (12) | C70-H70B | 0.9900 |
| C25-H25 | 0.9500 | C71-C72 | 1.520 (18) |
| C26-C27 | 1.509 (11) | C71-H71A | 0.9900 |
| C27-O4 | 1.209 (10) | C71-H71B | 0.9900 |
| C27-O3 | 1.331 (10) | C72-C78 | 1.29 (2) |
| C28-O3 | 1.474 (9) | C72-C73 | 1.510 (18) |
| C28-C37 | 1.521 (12) | C73-C74 | 1.531 (15) |

Table 1.6. (Continued)

| C28-C29 | 1.531 (10) | C73-H73 | 1.0000 |
| :---: | :---: | :---: | :---: |
| C28-C33 | 1.556 (11) | C74-C75 | 1.496 (19) |
| C29-C30 | 1.509 (10) | C74-H74A | 0.9900 |
| C29-H29A | 0.9900 | C74-H74B | 0.9900 |
| C29-H29B | 0.9900 | C75-C76 | 1.49 (2) |
| C30-C31 | 1.532 (11) | C75-H75A | 0.9900 |
| C30-H30A | 0.9900 | C75-H75B | 0.9900 |
| C30-H30B | 0.9900 | C76-C77 | 1.529 (17) |
| C31-C32 | 1.511 (12) | C76-H76A | 0.9900 |
| C31-H31A | 0.9900 | C76-H76B | 0.9900 |
| C31-H31B | 0.9900 | C77-H77A | 0.9900 |
| C32-C38 | 1.293 (11) | C77-H77B | 0.9900 |
| C32-C33 | 1.500 (12) | C78-H78A | 0.9500 |
| C33-C34 | 1.536 (12) | C78-H78B | 0.9500 |
| C33-H33 | 1.0000 | C68A-C69A | 1.509 (18) |
| C34-C35 | 1.522 (15) | C68A-C77A | 1.523 (17) |
| C34-H34A | 0.9900 | C68A-C73A | 1.532 (18) |
| C34-H34B | 0.9900 | C69A-C70A | 1.517 (19) |
| C35-C36 | 1.517 (17) | C69A-H69C | 0.9900 |
| C35-H35A | 0.9900 | C69A-H69D | 0.9900 |
| C35-H35B | 0.9900 | C70A-C71A | 1.51 (2) |
| C36-C37 | 1.525 (14) | C70A-H70C | 0.9900 |
| C36-H36A | 0.9900 | C70A-H70D | 0.9900 |
| C36-H36B | 0.9900 | C71A-C72A | 1.52 (2) |
| C37-H37A | 0.9900 | C71A-H71C | 0.9900 |
| C37-H37B | 0.9900 | C71A-H71D | 0.9900 |
| C38-H38A | 0.9500 | C72A-C78A | 1.33 (2) |
| C38-H38B | 0.9500 | C72A-C73A | 1.499 (18) |
| C41-C46 | 1.380 (11) | C73A-C74A | 1.535 (18) |
| C41-C42 | 1.382 (12) | C73A-H73A | 1.0000 |
| C41-H41 | 0.9500 | C74A-C75A | 1.50 (2) |

Table 1.6. (Continued)

| C42-C43 | 1.365 (12) | C74A-H74C | 0.9900 |
| :---: | :---: | :---: | :---: |
| C42-H42 | 0.9500 | C74A-H74D | 0.9900 |
| C43-C44 | 1.400 (11) | C75A-C76A | 1.50 (2) |
| C43-Br3 | 1.896 (8) | C75A-H75C | 0.9900 |
| C44-C45 | 1.389 (12) | C75A-H75D | 0.9900 |
| C44-H44 | 0.9500 | C76A-C77A | 1.523 (18) |
| C45-C46 | 1.388 (11) | C76A-H76C | 0.9900 |
| C45-H45 | 0.9500 | C76A-H76D | 0.9900 |
| C46-C47 | 1.512 (11) | C77A-H77C | 0.9900 |
| C47-O6 | 1.213 (10) | C77A-H77D | 0.9900 |
| C47-O5 | 1.318 (10) | C78A-H78C | 0.9500 |
| C48-O5 | 1.475 (10) | C78A-H78D | 0.9500 |
| C2-C1-C6 | 121.0 (7) | C50-C49-H49B | 109.3 |
| C2- $\mathrm{C} 1-\mathrm{H} 1$ | 119.5 | H49A-C49-H49B | 108.0 |
| C6-C1-H1 | 119.5 | C51-C50-C49 | 111.0 (7) |
| C3-C2-C1 | 118.0 (7) | C51-C50-H50A | 109.4 |
| $\mathrm{C} 3-\mathrm{C} 2-\mathrm{H} 2$ | 121.0 | C49-C50-H50A | 109.4 |
| C1-C2-H2 | 121.0 | C51-C50-H50B | 109.4 |
| C2-C3-C4 | 122.9 (8) | C49-C50-H50B | 109.4 |
| $\mathrm{C} 2-\mathrm{C} 3-\mathrm{Br} 1$ | 119.5 (6) | H50A-C50-H50B | 108.0 |
| C4-C3-Br1 | 117.6 (7) | C52-C51-C50 | 112.3 (7) |
| C5-C4-C3 | 118.0 (8) | C52-C51-H51A | 109.1 |
| C5- $44-\mathrm{H} 4$ | 121.0 | C50-C51-H51A | 109.1 |
| C3-C4-H4 | 121.0 | C52-C51-H51B | 109.1 |
| C4-C5-C6 | 120.8 (8) | C50-C51-H51B | 109.1 |
| C4-C5-H5 | 119.6 | H51A-C51-H51B | 107.9 |
| C6-C5-H5 | 119.6 | C58-C52-C51 | 122.9 (8) |
| C5-C6-C1 | 119.2 (8) | C58-C52-C53 | 123.1 (8) |
| C5-C6-C7 | 119.1 (7) | C51-C52-C53 | 113.9 (7) |
| C1-C6-C7 | 121.7 (7) | C54-C53-C52 | 115.1 (7) |

Table 1.6. (Continued)

| O2-C7-O1 | 126.6 (8) | C54-C53-C48 | 111.6 (6) |
| :---: | :---: | :---: | :---: |
| O2-C7- 66 | 122.5 (7) | C52-C53-C48 | 109.5 (6) |
| O1-C7-C6 | 110.9 (6) | C54-C53-H53 | 106.7 |
| O1-C8-C9 | 111.6 (6) | C52-C53-H53 | 106.7 |
| O1-C8-C17 | 109.7 (6) | C48-C53-H53 | 106.7 |
| C9-C8-C17 | 111.5 (6) | C53-C54-C55 | 111.6 (7) |
| O1-C8-C13 | 101.6 (6) | C53-C54-H54A | 109.3 |
| C9-C8-C13 | 111.5 (7) | C55-C54-H54A | 109.3 |
| C17-C8-C13 | 110.5 (6) | C53-C54-H54B | 109.3 |
| C8-C9-C10 | 112.9 (6) | C55-C54-H54B | 109.3 |
| C8-C9-H9A | 109.0 | H54A-C54—H54B | 108.0 |
| C10-C9-H9A | 109.0 | C54-C55-C56 | 110.7 (7) |
| C8-C9-H9B | 109.0 | C54-C55-H55A | 109.5 |
| C10-C9-H9B | 109.0 | C56-C55-H55A | 109.5 |
| H9A-C9-H9B | 107.8 | C54-C55-H55B | 109.5 |
| C11-C10-C9 | 109.6 (7) | C56-C55-H55B | 109.5 |
| C11-C10-H10A | 109.8 | H55A-C55-H55B | 108.1 |
| C9-C10-H10A | 109.8 | C57-C56-C55 | 110.4 (8) |
| C11-C10-H10B | 109.8 | C57-C56-H56A | 109.6 |
| C9-C10-H10B | 109.8 | C55-C56-H56A | 109.6 |
| H10A-C10-H10B | 108.2 | C57-C56-H56B | 109.6 |
| C12-C11-C10 | 112.1 (7) | C55-C56-H56B | 109.6 |
| C12-C11-H11A | 109.2 | H56A-C56-H56B | 108.1 |
| C10-C11-H11A | 109.2 | C56-C57-C48 | 112.9 (7) |
| C12-C11-H11B | 109.2 | C56-C57-H57A | 109.0 |
| C10-C11-H11B | 109.2 | C48-C57-H57A | 109.0 |
| H11A-C11-H11B | 107.9 | C56-C57-H57B | 109.0 |
| C18-C12-C11 | 122.4 (8) | C48-C57-H57B | 109.0 |
| C18-C12-C13 | 123.5 (8) | H57A-C57-H57B | 107.8 |
| C11-C12-C13 | 114.1 (7) | C52-C58-H58A | 120.0 |
| C14-C13-C12 | 115.1 (7) | C52-C58-H58B | 120.0 |

Table 1.6. (Continued)

| C14-C13-C8 | 111.3 (6) | H58A-C58-H58B | 120.0 |
| :---: | :---: | :---: | :---: |
| C12-C13-C8 | 108.4 (6) | C47-O5-C48 | 123.5 (6) |
| C14-C13-H13 | 107.2 | C66-C61-C62 | 120.2 (6) |
| C12-C13-H13 | 107.2 | C66-C61-H61 | 119.9 |
| C8-C13-H13 | 107.2 | C62-C61-H61 | 119.9 |
| C15-C14-C13 | 110.9 (6) | C63-C62-C61 | 117.8 (7) |
| C15-C14-H14A | 109.5 | C63-C62-H62 | 121.1 |
| C13-C14-H14A | 109.5 | C61-C62-H62 | 121.1 |
| C15-C14-H14B | 109.5 | C64-C63-C62 | 122.8 (7) |
| C13-C14-H14B | 109.5 | C64-C63-Br4 | 118.3 (5) |
| H14A-C14-H14B | 108.0 | C62-C63-Br4 | 118.8 (5) |
| C14-C15-C16 | 112.1 (6) | C63-C64-C65 | 118.6 (7) |
| C14-C15-H15A | 109.2 | C63-C64-H64 | 120.7 |
| C16-C15-H15A | 109.2 | C65-C64-H64 | 120.7 |
| C14-C15-H15B | 109.2 | C66-C65-C64 | 120.0 (7) |
| C16-C15-H15B | 109.2 | C66-C65-H65 | 120.0 |
| H15A-C15-H15B | 107.9 | C64-C65-H65 | 120.0 |
| C15-C16-C17 | 111.0 (6) | C65-C66-C61 | 120.5 (7) |
| C15-C16-H16A | 109.4 | C65-C66-C67 | 117.9 (7) |
| C17-C16-H16A | 109.4 | C61-C66-C67 | 121.6 (7) |
| C15-C16-H16B | 109.4 | O8-C67-07 | 126.4 (8) |
| C17-C16-H16B | 109.4 | O8-C67-C66 | 122.9 (9) |
| H16A-C16-H16B | 108.0 | O7-C67-C66 | 110.7 (7) |
| C8-C17-C16 | 113.1 (6) | C67-O7-C68A | 110.9 (9) |
| C8-C17-H17A | 109.0 | C67-O7-C68 | 130.9 (8) |
| C16-C17-H17A | 109.0 | C69-C68-C77 | 113.6 (12) |
| C8-C17-H17B | 109.0 | C69-C68-O7 | 107.5 (17) |
| C16-C17-H17B | 109.0 | C77-C68-O7 | 105.3 (11) |
| H17A-C17-H17B | 107.8 | C69-C68-C73 | 111.7 (14) |
| C12-C18-H18A | 120.0 | C77-C68-C73 | 111.9 (12) |
| C12-C18-H18B | 120.0 | O7-C68-C73 | 106.3 (11) |

Table 1.6. (Continued)

| H18A-C18-H18B | 120.0 | C68-C69-C70 | 113.1 (17) |
| :---: | :---: | :---: | :---: |
| C7-O1-C8 | 123.5 (6) | C68-C69-H69A | 109.0 |
| C26- $221-\mathrm{C} 22$ | 119.6 (8) | C70-C69-H69A | 109.0 |
| C26- $21-\mathrm{H} 21$ | 120.2 | C68-C69-H69B | 109.0 |
| C22-C21-H21 | 120.2 | C70-C69-H69B | 109.0 |
| C23-C22-C21 | 118.8 (8) | H69A-C69-H69B | 107.8 |
| C23-C22-H22 | 120.6 | C69-C70-C71 | 109.9 (16) |
| C21-C22-H22 | 120.6 | C69-C70-H70A | 109.7 |
| C22-C23-C24 | 122.7 (8) | C71-C70-H70A | 109.7 |
| C22-C23-Br2 | 118.6 (6) | C69-C70-H70B | 109.7 |
| $\mathrm{C} 24-\mathrm{C} 23-\mathrm{Br} 2$ | 118.7 (7) | C71-C70-H70B | 109.7 |
| C25-C24-C23 | 118.6 (8) | H70A-C70-H70B | 108.2 |
| C25-C24-H24 | 120.7 | C72-C71-C70 | 110.9 (14) |
| C23-C24-H24 | 120.7 | C72-C71-H71A | 109.5 |
| C24-C25-C26 | 120.0 (8) | C70-C71-H71A | 109.5 |
| C24-C25-H25 | 120.0 | C72-C71-H71B | 109.5 |
| C26-C25-H25 | 120.0 | C70-C71-H71B | 109.5 |
| C25-C26-C21 | 120.3 (8) | H71A-C71-H71B | 108.1 |
| C25-C26-C27 | 119.1 (7) | C78-C72-C73 | 122.4 (17) |
| C21-C26-C27 | 120.7 (8) | C78-C72-C71 | 123.0 (17) |
| O4-C27-O3 | 126.1 (8) | C73-C72-C71 | 114.5 (13) |
| O4-C27-C26 | 123.3 (8) | C72-C73-C68 | 111.4 (11) |
| O3-C27-C26 | 110.6 (7) | C72-C73-C74 | 116.8 (13) |
| O3-C28-C37 | 110.7 (7) | C68-C73-C74 | 111.2 (12) |
| O3-C28-C29 | 110.4 (6) | C72-C73-H73 | 105.5 |
| C37-C28-C29 | 112.8 (7) | C68-C73-H73 | 105.5 |
| O3-C28-C33 | 100.9 (6) | C74-C73-H73 | 105.5 |
| C37-C28-C33 | 112.0 (7) | C75-C74-C73 | 113.3 (13) |
| C29-C28-C33 | 109.4 (7) | C75-C74-H74A | 108.9 |
| C30-C29-C28 | 113.3 (6) | C73-C74-H74A | 108.9 |
| C30-C29-H29A | 108.9 | C75-C74-H74B | 108.9 |

Table 1.6. (Continued)

| C28-C29-H29A | 108.9 | C73-C74-H74B | 108.9 |
| :---: | :---: | :---: | :---: |
| C30-C29-H29B | 108.9 | H74A-C74-H74B | 107.7 |
| C28-C29-H29B | 108.9 | C76-C75-C74 | 114.1 (14) |
| H29A-C29-H29B | 107.7 | C76-C75-H75A | 108.7 |
| C29-C30-C31 | 110.5 (6) | C74-C75-H75A | 108.7 |
| C29-C30-H30A | 109.6 | C76-C75-H75B | 108.7 |
| C31-C30-H30A | 109.6 | C74-C75-H75B | 108.7 |
| C29-C30-H30B | 109.6 | H75A-C75-H75B | 107.6 |
| C31-C30-H30B | 109.6 | C75-C76-C77 | 109.2 (12) |
| H30A-C30-H30B | 108.1 | C75-C76-H76A | 109.8 |
| C32-C31-C30 | 110.2 (7) | C77-C76-H76A | 109.8 |
| C32-C31-H31A | 109.6 | C75-C76-H76B | 109.8 |
| C30-C31-H31A | 109.6 | C77-C76-H76B | 109.8 |
| C32-C31-H31B | 109.6 | H76A-C76-H76B | 108.3 |
| C30-C31-H31B | 109.6 | C68-C77-C76 | 114.4 (12) |
| H31A-C31-H31B | 108.1 | C68-C77-H77A | 108.7 |
| C38-C32-C33 | 124.7 (10) | C76-C77-H77A | 108.7 |
| C38-C32-C31 | 120.7 (10) | C68-C77-H77B | 108.7 |
| C33-C32-C31 | 114.6 (7) | C76-C77-H77B | 108.7 |
| C32-C33-C34 | 116.2 (8) | H77A-C77-H77B | 107.6 |
| C32-C33-C28 | 110.9 (6) | C72-C78-H78A | 120.0 |
| C34-C33-C28 | 110.4 (7) | C72-C78-H78B | 120.0 |
| C32-C33-H33 | 106.2 | H78A-C78-H78B | 120.0 |
| C34-C33-H33 | 106.2 | C69A-C68A-O7 | 105 (2) |
| C28-C33-H33 | 106.2 | C69A-C68A-C77A | 113.2 (14) |
| C35-C34-C33 | 112.2 (9) | O7-C68A-C77A | 119.5 (13) |
| C35-C34-H34A | 109.2 | C69A-C68A-C73A | 112.5 (17) |
| C33-C34-H34A | 109.2 | O7-C68A-C73A | 94.2 (12) |
| C35-C34-H34B | 109.2 | C77A-C68A-C73A | 110.6 (14) |
| C33-C34-H34B | 109.2 | C68A-C69A-C70A | 116.0 (19) |
| H34A-C34-H34B | 107.9 | C68A-C69A-H69C | 108.3 |

Table 1.6. (Continued)

| C36-C35-C34 | 112.3 (9) | C70A-C69A-H69C | 108.3 |
| :---: | :---: | :---: | :---: |
| C36-C35-H35A | 109.1 | C68A-C69A-H69D | 108.3 |
| C34-C35-H35A | 109.1 | C70A-C69A-H69D | 108.3 |
| C36-C35-H35B | 109.1 | H69C-C69A-H69D | 107.4 |
| C34-C35-H35B | 109.1 | C71A-C70A-C69A | 111.1 (18) |
| H35A-C35-H35B | 107.9 | C71A-C70A-H70C | 109.4 |
| C35-C36-C37 | 109.6 (10) | C69A-C70A-H70C | 109.4 |
| C35-C36-H36A | 109.8 | C71A-C70A-H70D | 109.4 |
| C37-C36-H36A | 109.8 | C69A-C70A-H70D | 109.4 |
| C35-C36-H36B | 109.8 | H70C-C70A-H70D | 108.0 |
| C37-C36-H36B | 109.8 | C70A-C71A-C72A | 114.7 (16) |
| H36A-C36-H36B | 108.2 | C70A-C71A-H71C | 108.6 |
| C28-C37-C36 | 112.8 (9) | C72A-C71A-H71C | 108.6 |
| C28-C37-H37A | 109.0 | C70A-C71A-H71D | 108.6 |
| C36-C37-H37A | 109.0 | C72A-C71A-H71D | 108.6 |
| C28-C37-H37B | 109.0 | H71C-C71A-H71D | 107.6 |
| C36-C37-H37B | 109.0 | C78A-C72A-C73A | 121 (2) |
| H37A-C37-H37B | 107.8 | C78A-C72A-C71A | 123 (2) |
| C32-C38-H38A | 120.0 | C73A-C72A-C71A | 116.4 (15) |
| C32-C38-H38B | 120.0 | C72A-C73A-C68A | 112.0 (15) |
| H38A-C38-H38B | 120.0 | C72A-C73A-C74A | 117.8 (15) |
| C27-O3-C28 | 122.5 (6) | C68A-C73A-C74A | 112.7 (14) |
| C46-C41-C42 | 120.1 (8) | C72A-C73A-H73A | 104.2 |
| C46-C41-H41 | 120.0 | C68A-C73A-H73A | 104.2 |
| C42- $\mathrm{C} 41-\mathrm{H} 41$ | 120.0 | C74A-C73A-H73A | 104.2 |
| C43-C42-C41 | 119.4 (7) | C75A-C74A-C73A | 112.1 (14) |
| C43-C42-H42 | 120.3 | C75A-C74A-H74C | 109.2 |
| C41-C42-H42 | 120.3 | C73A-C74A-H74C | 109.2 |
| C42-C43-C44 | 122.4 (8) | C75A-C74A-H74D | 109.2 |
| C42-C43-Br3 | 119.5 (6) | C73A-C74A-H74D | 109.2 |
| C44-C43-Br3 | 118.1 (7) | H74C-C74A-H74D | 107.9 |

Table 1.6. (Continued)

| C45-C44-C43 | 117.1 (8) | C74A-C75A-C76A | 112.5 (17) |
| :---: | :---: | :---: | :---: |
| C45-C44-H44 | 121.5 | C74A-C75A-H75C | 109.1 |
| C43-C44-H44 | 121.5 | C76A-C75A-H75C | 109.1 |
| C46-C45-C44 | 121.1 (9) | C74A-C75A-H75D | 109.1 |
| C46-C45-H45 | 119.4 | C76A-C75A-H75D | 109.1 |
| C44-C45-H45 | 119.4 | H75C-C75A-H75D | 107.8 |
| C41-C46-C45 | 119.9 (8) | C75A-C76A-C77A | 109.0 (14) |
| C41-C46-C47 | 120.7 (8) | C75A-C76A-H76C | 109.9 |
| C45-C46-C47 | 119.3 (7) | C77A-C76A-H76C | 109.9 |
| O6- $\mathrm{C} 47-\mathrm{O} 5$ | 126.6 (8) | C75A-C76A-H76D | 109.9 |
| O6-C47-C46 | 122.5 (8) | C77A-C76A-H76D | 109.9 |
| O5-C47-C46 | 110.9 (7) | H76C-C76A-H76D | 108.3 |
| O5-C48-C49 | 111.0 (7) | C76A-C77A-C68A | 113.3 (14) |
| O5-C48-C57 | 109.7 (7) | C76A-C77A-H77C | 108.9 |
| C49-C48-C57 | 111.0 (6) | C68A-C77A-H77C | 108.9 |
| O5-C48-C53 | 102.0 (6) | C76A-C77A-H77D | 108.9 |
| C49-C48-C53 | 112.2 (6) | C68A-C77A-H77D | 108.9 |
| C57-C48-C53 | 110.7 (7) | H77C-C77A-H77D | 107.7 |
| C48-C49-C50 | 111.6 (6) | C72A-C78A-H78C | 120.0 |
| C48-C49-H49A | 109.3 | C72A-C78A-H78D | 120.0 |
| C50-C49-H49A | 109.3 | H78C-C78A-H78D | 120.0 |
| C48-C49-H49B | 109.3 |  |  |
| C6- $\mathrm{C} 1-\mathrm{C} 2-\mathrm{C} 3$ | 1.5 (12) | C49-C50-C51-C52 | 53.5 (10) |
| $\mathrm{C} 1-\mathrm{C} 2-\mathrm{C} 3-\mathrm{C} 4$ | -2.2 (13) | C50-C51-C52-C58 | 123.5 (9) |
| $\mathrm{C} 1-\mathrm{C} 2-\mathrm{C} 3-\mathrm{Br} 1$ | 177.5 (6) | C50-C51-C52-C53 | -54.1 (10) |
| $\mathrm{C} 2-\mathrm{C} 3-\mathrm{C} 4-\mathrm{C} 5$ | 1.5 (14) | C58-C52-C53-C54 | 1.9 (12) |
| Br1-C3-C4-C5 | -178.3 (6) | C51-C52-C53-C54 | 179.5 (7) |
| C3-C4-C5-C6 | 0.0 (13) | C58-C52-C53-C48 | -124.8 (9) |
| C4- $55-\mathrm{C} 6-\mathrm{C} 1$ | -0.7 (12) | C51-C52-C53-C48 | 52.8 (9) |
| C4-C5-C6-C7 | 179.4 (7) | O5-C48-C53-C54 | -63.1 (8) |
| $\mathrm{C} 2-\mathrm{C} 1-\mathrm{C} 6-\mathrm{C} 5$ | -0.1 (11) | C49-C48-C53-C54 | 178.1 (7) |

Table 1.6. (Continued)

| C2- $\mathrm{C} 1-\mathrm{C} 6-\mathrm{C} 7$ | 179.8 (7) | C57-C48-C53-C54 | 53.5 (9) |
| :---: | :---: | :---: | :---: |
| C5-C6-C7-O2 | 8.7 (11) | O5-C48-C53-C52 | 65.5 (7) |
| C1-C6-C7-O2 | -171.2 (7) | C49-C48-C53-C52 | -53.3 (9) |
| C5-C6-C7-O1 | -172.5 (7) | C57-C48-C53-C52 | -177.9 (7) |
| C1-C6-C7-O1 | 7.7 (10) | C52-C53-C54-C55 | 178.9 (7) |
| $\mathrm{O} 1-\mathrm{C} 8-\mathrm{C} 9-\mathrm{C} 10$ | -56.0 (9) | C48-C53-C54-C55 | -55.5 (10) |
| C17-C8-C9-C10 | -179.1 (7) | C53-C54-C55-C56 | 56.6 (11) |
| C13-C8-C9-C10 | 56.8 (9) | C54-C55-C56-C57 | -55.9 (11) |
| C8-C9-C10-C11 | -55.5 (10) | C55-C56-C57-C48 | 55.7 (11) |
| C9-C10-C11-C12 | 53.8 (9) | O5-C48-C57-C56 | 57.6 (10) |
| C10-C11-C12-C18 | 125.1 (10) | C49-C48-C57-C56 | -179.5 (8) |
| C10-C11-C12-C13 | -55.6 (10) | C53-C48-C57-C56 | -54.2 (10) |
| C18-C12-C13-C14 | -1.5 (12) | O6-C47-O5-C48 | 8.0 (12) |
| C11-C12-C13-C14 | 179.3 (7) | C46-C47-O5-C48 | -171.5 (6) |
| C18-C12-C13-C8 | -126.9 (9) | C49-C48-O5-C47 | -63.8 (9) |
| C11-C12-C13-C8 | 53.9 (9) | C57-C48-O5-C47 | 59.2 (9) |
| O1-C8-C13-C14 | -62.3 (7) | C53-C48-O5-C47 | 176.5 (6) |
| C9-C8-C13-C14 | 178.7 (6) | C66-C61-C62-C63 | 0.2 (12) |
| C17-C8-C13-C14 | 54.1 (9) | C61-C62-C63-C64 | -0.2 (12) |
| $\mathrm{O} 1-\mathrm{C} 8-\mathrm{C} 13-\mathrm{C} 12$ | 65.3 (7) | C61-C62-C63-Br4 | -178.4 (6) |
| C9-C8-C13-C12 | -53.7 (8) | C62-C63-C64-C65 | 1.1 (13) |
| C17-C8-C13-C12 | -178.3 (7) | Br4-C63-C64-C65 | 179.4 (6) |
| C12-C13-C14-C15 | -179.7 (6) | C63-C64-C65-C66 | -2.0 (12) |
| C8-C13-C14-C15 | -55.8 (9) | C64-C65-C66-C61 | 2.0 (12) |
| C13-C14-C15-C16 | 56.3 (9) | C64-C65-C66-C67 | -178.9 (7) |
| C14-C15-C16-C17 | -54.6 (9) | C62-C61-C66-C65 | -1.1 (12) |
| O1-C8-C17-C16 | 57.9 (8) | C62-C61-C66-C67 | 179.9 (7) |
| C9-C8--C17-C16 | -178.0 (7) | C65-C66-C67-O8 | -9.5 (12) |
| C13-C8-C17-C16 | -53.4 (9) | C61-C66-C67-O8 | 169.5 (8) |
| C15-C16-C17-C8 | 53.7 (9) | C65-C66-C67-O7 | 172.9 (7) |
| O2-C7-O1-C8 | 4.2 (12) | C61-C66-C67-O7 | -8.0 (11) |

Table 1.6. (Continued)

| C6-C7-O1-C8 | -174.7 (6) | O8-C67-O7-C68A | -2.9 (14) |
| :---: | :---: | :---: | :---: |
| C9-C8-O1-C7 | -61.2 (9) | C66-C67-O7-C68A | 174.6 (9) |
| C17-C8-O1-C7 | 62.9 (8) | O8-C67-O7-C68 | -3.9 (16) |
| C13-C8-O1-C7 | 179.9 (6) | C66-C67-O7-C68 | 173.6 (10) |
| C26-C21-C22-C23 | 0.3 (12) | C67-O7-C68-C69 | -50.2 (15) |
| C21-C22-C23-C24 | 0.6 (13) | C68A-O7-C68-C69 | -53 (3) |
| C21-C22-C23-Br2 | 179.6 (6) | C67-O7-C68-C77 | 71.2 (14) |
| C22-C23-C24-C25 | -1.6 (14) | C68A-O7-C68-C77 | 68 (3) |
| Br2-C23-C24-C25 | 179.4 (6) | C67-O7-C68-C73 | -170.0 (9) |
| C23-C24-C25-C26 | 1.6 (13) | C68A-O7-C68-C73 | -173 (4) |
| C24-C25-C26-C21 | -0.7 (12) | C77-C68-C69-C70 | -177.6 (18) |
| C24-C25-C26-C27 | 178.4 (8) | O7-C68-C69-C70 | -61 (2) |
| C22-C21-C26-C25 | -0.2 (12) | C73-C68-C69-C70 | 55 (3) |
| C22-C21-C26-C27 | -179.4 (7) | C68-C69-C70-C71 | -57 (3) |
| C25-C26-C27-O4 | -1.1 (12) | C69-C70-C71-C72 | 55 (2) |
| C21-C26-C27-O4 | 178.0 (8) | C70-C71-C72-C78 | 125.0 (19) |
| C25-C26-C27-O3 | 178.8 (7) | C70-C71-C72-C73 | -53 (2) |
| C21-C26-C27-O3 | -2.1 (10) | C78-C72-C73-C68 | -127.7 (16) |
| O3-C28-C29-C30 | -54.7 (9) | C71-C72-C73-C68 | 50.6 (17) |
| C37-C28-C29-C30 | -179.2 (7) | C78-C72-C73-C74 | 2 (2) |
| C33-C28-C29-C30 | 55.5 (8) | C71-C72-C73-C74 | 179.9 (13) |
| C28-C29-C30-C31 | -57.0 (8) | C69-C68-C73-C72 | -50.1 (19) |
| C29-C30-C31-C32 | 54.3 (8) | C77-C68-C73-C72 | -178.7 (12) |
| C30-C31-C32-C38 | 123.3 (10) | O7-C68-C73-C72 | 66.9 (14) |
| C30-C31-C32-C33 | -54.8 (9) | C69-C68-C73-C74 | 177.7 (16) |
| C38-C32-C33-C34 | 3.3 (14) | C77-C68-C73-C74 | 49.2 (16) |
| C31-C32-C33-C34 | -178.6 (8) | O7-C68-C73-C74 | -65.3 (14) |
| C38-C32-C33-C28 | -123.8 (10) | C72-C73-C74-C75 | -179.5 (13) |
| C31-C32-C33-C28 | 54.3 (9) | C68-C73-C74-C75 | -50.1 (17) |
| O3-C28-C33-C32 | 63.9 (8) | C73-C74-C75-C76 | 54.0 (19) |
| C37-C28-C33-C32 | -178.2 (7) | C74-C75-C76-C77 | -53.7 (19) |

Table 1.6. (Continued)

| C29-C28-C33-C32 | -52.4 (8) | C69-C68-C77-C76 | 179.8 (18) |
| :---: | :---: | :---: | :---: |
| O3-C28-C33-C34 | -66.3 (8) | O7-C68-C77-C76 | 62.4 (14) |
| C37-C28-C33-C34 | 51.5 (9) | C73-C68-C77-C76 | -52.7 (16) |
| C29-C28-C33-C34 | 177.3 (7) | C75-C76-C77-C68 | 53.6 (18) |
| C32-C33-C34-C35 | -179.8 (8) | C67-O7-C68A-C69A | -78.2 (16) |
| C28-C33-C34-C35 | -52.4 (11) | C68-O7-C68A-C69A | 100 (3) |
| C33-C34-C35-C36 | 56.4 (13) | C67-O7-C68A-C77A | 50.4 (17) |
| C34-C35-C36-C37 | -56.6 (13) | C68-O7-C68A-C77A | -132 (4) |
| O3-C28-C37-C36 | 57.4 (10) | C67-O7-C68A-C73A | 167.1 (9) |
| C29-C28-C37-C36 | -178.3 (8) | C68-O7-C68A-C73A | -15 (3) |
| C33-C28-C37-C36 | -54.4 (11) | O7-C68A-C69A-C70A | -50 (3) |
| C35-C36-C37-C28 | 56.0 (12) | C77A-C68A-C69A-C70A | 177 (3) |
| O4-C27-O3-C28 | -1.0 (12) | C73A-C68A-C69A-C70A | 51 (4) |
| C26-C27-O3-C28 | 179.1 (6) | C68A-C69A-C70A-C71A | -49 (4) |
| C37-C28-O3-C27 | 64.6 (9) | C69A-C70A-C71A-C72A | 45 (3) |
| C29-C28-O3-C27 | -61.0 (9) | C70A-C71A-C72A-C78A | 132 (2) |
| C33-C28-O3-C27 | -176.6 (6) | C70A-C71A-C72A-C73A | -46 (3) |
| C46-C41-C42-C43 | 0.5 (11) | C78A-C72A-C73A-C68A | -131.9 (19) |
| C41-C42-C43-C44 | 0.1 (12) | C71A-C72A-C73A-C68A | 46 (2) |
| C41-C42-C43-Br3 | -179.4 (6) | C78A-C72A-C73A-C74A | 1 (3) |
| C42-C43-C44-C45 | -0.5 (12) | C71A-C72A-C73A-C74A | 179.3 (17) |
| Br3-C43-C44-C45 | 179.0 (6) | C69A-C68A-C73A-C72A | -48 (2) |
| C43-C44-C45-C46 | 0.3 (12) | O7-C68A-C73A-C72A | 61.0 (16) |
| C42-C41-C46-C45 | -0.7 (11) | C77A-C68A-C73A-C72A | -175.3 (15) |
| C42-C41-C46-C47 | 177.1 (7) | C69A-C68A-C73A-C74A | 177 (2) |
| C44-C45-C46-C41 | 0.3 (11) | O7-C68A-C73A-C74A | -74.6 (15) |
| C44-C45-C46-C47 | -177.5 (7) | C77A-C68A-C73A-C74A | 49.2 (19) |
| C41-C46-C47-O6 | -170.2 (8) | C72A-C73A-C74A-C75A | 176.6 (17) |
| C45-C46-C47-O6 | 7.6 (11) | C68A-C73A-C74A-C75A | -51 (2) |
| C41-C46-C47-O5 | 9.4 (10) | C73A-C74A-C75A-C76A | 55 (2) |
| C45-C46-C47-O5 | -172.8(7) | C74A-C75A-C76A-C77A | -58 (2) |

Table 1.6. (Continued)

| $\mathrm{O} 5-\mathrm{C} 48-\mathrm{C} 49-\mathrm{C} 50$ | $-57.9(9)$ | C75A-C76A-C77A-C68A | $57(2)$ |
| :--- | :--- | :--- | :--- |
| $\mathrm{C} 57-\mathrm{C} 48-\mathrm{C} 49-\mathrm{C} 50$ | $179.8(7)$ | C69A-C68A-C77A-C76A | $179(2)$ |
| $\mathrm{C} 53-\mathrm{C} 48-\mathrm{C} 49-\mathrm{C} 50$ | $55.4(9)$ | O7-C68A-C77A-C76A | $54(2)$ |
| $\mathrm{C} 48-\mathrm{C} 49-\mathrm{C} 50-\mathrm{C} 51$ | $-54.5(10)$ | C73A-C68A-C77A-C76A | $-53.5(18)$ |



Figure 1.5. Perspective views showing 50\% probability displacement.


Figure 1.6. Three-dimensional supramolecular architecture viewed along the $b$-axis direction.

## Chapter 2

## Enantioselective Total Synthesis of (+)-Reserpine ${ }^{1}$

[^27]
### 2.1. Introduction

Reserpine (1, Figure 2.1) is a biologically active indole alkaloid natural product that has, since its isolation six decades ago, represented an iconic target for organic synthesis. ${ }^{2}$ Its stereochemically complex pentacyclic structure has inspired some of the most important work in the history of stereoselective synthesis, and it


Figure 2.1. Reserpine (-)-1 continues to inspire new synthetic methodologies today. ${ }^{3,4}$ Woodward and coworkers disclosed the first total synthesis of reserpine in $1956,{ }^{5 a}$ and since then a number of synthetic studies have been published. At the outset of this project there were ten reported total syntheses along with numerous partial synthetic studies. ${ }^{5}$ Despite the scope of this effort, each successful approach to this molecule has relied on the same fundamental strategy, namely a late-stage generation of the C-ring and its embedded C3

[^28]${ }^{5}$ (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. J. Am. Chem. Soc. 1956, 78, 2023. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Kierstead, R. W. Tetrahedron 1958, 2, 1. (c) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. J. Am. Chem. Soc. 1956, 78, 2657. (d) Pearlman, B. A. J. Am. Chem. Soc. 1979, 101, 6398. (e) Wender, P. A.; Schaus, J. M.; White, A. W. J. Am. Chem. Soc. 1980, 102, 6157. (f) Wender, P. A.; Schaus, J. M.; White, A. W. Heterocycles 1987, 25, 263. (g) Martin, S. F.; Grzejszczak, S.; Rueger, H.; Williamson, S. A. J. Am. Chem. Soc. 1985, 107, 4072. (h) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszczak, S. J. Am. Chem. Soc. 1987, 109, 6124. (i) Stork, G. Pure \& Appl. Chem. 1989, 61, 439. (j) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. J. Org. Chem. 1994, 59, 4048. (k) Gomez, A. M.; Lopez, J. C.; Fraser-Reid, B. J. Org. Chem. 1995, 60, 3859. (1) Chu, C.S.; Liao, C.-C.; Rao, P. D. Chem. Commun. 1996, 1537. (m) Hanessian, S.; Pan, J. W.; Carnell, A.; Bouchard, H.; Lesage, L. J. Org. Chem. 1997, 62, 465. (n) Mehta, G.; Reddy, D. S. J. Chem. Soc., Perkin Trans. 1 2000, 1399. (o) Sparks, S. M.; Shea, K. J. Org. Lett. 2001, 3, 2265. (p) Sparks, S. M.; Gutierrez, A. J.; Shea, K. J. J. Org. Chem. 2003, 68, 5274. (q) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. J. Am. Chem. Soc. 2005, 127, 16255.
stereocenter from a 2,3-seco-derivative (2, Scheme 2.1). ${ }^{6}$ These approaches target five of the molecule's six stereogenic centers through the formation of an appropriately functionalized E-ring or cis-fused D/E-ring fragment. However, the late-stage C-ring installation is generally complicated by preferential formation of the final C3 stereocenter with the undesired, thermodynamically favored relative stereochemistry. ${ }^{7}$ As an introduction to this chapter, key strategies that have been employed to address this undesired outcome are reviewed, and a recently reported alternative approach to the reserpine framework is presented.


Scheme 2.1. Synthetic Strategies Common to All Previous Successful Approaches to Reserpine

### 2.2. Previous Strategies to Obtain the Desired C3 Configuration of Reserpine

### 2.2.1. The Woodward Approach: Conformational Biasing and C3 Epimerization

[^29]Woodward's landmark synthesis of reserpine involved a Bischler-Napieralski cyclization of lactam 3 and reduction of the resultant iminium ion with sodium borohydride (Scheme 2.2). ${ }^{5 a}$ However, nucleophilic addition selectively produced pentacycle 4 , which contains the undesired configuration at C 3 . Woodward reasoned that the C 3 center could be epimerized after fixing the molecule in an unstable conformation. To this end, intermediate 4 was converted into rigid lactone 5, and an equilibration of the C 3 center under acidic conditions provided the correct relative stereochemistry of reserpine.


4
$\downarrow \begin{aligned} & \text { 1. } \mathrm{KOH}, \mathrm{MeOH} \\ & \text { 2. } \mathrm{DCC}, \text { pyridine }\end{aligned}$




Scheme 2.2. Woodward's Synthesis of the C-ring and C3 Epimerization

### 2.2.2. The Stork Approach: Kinetic Cyclization of an Amino-Nitrile

The challenge posed by the C3 stereocenter of reserpine was overcome in a notable and most elegant manner by Stork and coworkers (Scheme 2.3). ${ }^{5 \mathrm{i}, \mathrm{q}}$ They predicted that cyclization of amino-nitrile $\mathbf{6}$ would generate a dialkyl iminium ion that could be trapped through a kinetic nucleophilic attack by the pendant indole to access methyl reserpate (10). However, in refluxing acetonitrile, 6 underwent a C2-C3 bond formation to furnish pentacycle 8, which contains the undesired C3 stereochemistry. This
unexpected outcome was rationalized as occurring through a tight ion pair (7), in which the cyanide counterion blocks the desired trajectory of nucleophilic addition. Based on this hypothesis, amino-nitrile 6 was treated with either dilute HCl or silver tetrafluoroborate to generate a loose ion pair (9), which underwent a kinetically controlled cyclization to afford methyl reserpate (10). ${ }^{8}$


Scheme 2.3. Cyclizations of Amino-Nitrile 6 in the Stork Synthesis of Reserpine

### 2.2.3. The Kwon Approach: C3 Stereochemical Relay via a $6 \pi$-Electrocyclization

The complex architecture of reserpine continues to serve as a forum for exploring the frontiers of stereoselective synthesis. In 2012, Kwon and coworkers reported progress towards the synthesis of $( \pm)$-reserpine (1) through the application of a diastereoselective $6 \pi$-electrocyclization. ${ }^{9}$ Kwon's strategy is relevant to the work presented in this chapter as it also represents a fundamental departure from the previous syntheses of reserpine in that the C3 stereocenter is generated at an early stage in the route. Racemic bromides ( $\mathbf{Z} / \boldsymbol{E} \mathbf{)}$-12 were generated in a 1:2 ratio of olefin isomers in 11

[^30]steps from methyl ester 11. A Negishi cross-coupling of vinyl zinc species 13 with bromide (Z/E)-12 afforded triene $\mathbf{1 4}$ which underwent an in situ $6 \pi$-electrocyclization to directly afford acetonide 15 in good yield and as a single diastereomer (Scheme 2.4). Pentacycle 15 was advanced to olefin 16 through hydrolysis of the acetonide followed by a $\mathrm{PtO}_{2}$-catalyzed hydrogenation of the resultant $\alpha$-keto-ester. Through the cascade Negishi/ $6 \pi$-electrocyclization, the authors demonstrated an efficient and unprecedented relay of stereochemical information from the C3 stereocenter of triene $\mathbf{1 4}$ to the remote C18 center of a highly functionalized pentacycle (15). However, the product was selectively generated with the undesired relative stereochemistry, and this outcome may present challenges for advancing 16 to reserpine (1).


Scheme 2.4. Kwon's Diastereoselective $6 \pi$-Electrocyclization

### 2.3. Previous Work towards the Synthesis of (+)-Reserpine in the Jacobsen Group

Meredeth McGowan, a former graduate student in the Jacobsen group, became interested in investigating a new approach to reserpine based on a recently developed asymmetric formal aza-Diels-Alder (FADA) method. The motivations for pursuing the synthesis were to demonstrate the synthetic utility of the transformation and to address the historically problematic C3 stereocenter by using the newly developed method to install the problematic stereocenter with catalyst control. Together with Mathieu Lalonde, another former graduate student, she developed a highly diastereo- and enantioselective synthesis of chiral benzo- and indoloquinolizidine frameworks via FADA reactions of enones and cyclic imines (Scheme 2.5). ${ }^{10}$ This transformation is catalyzed by bifunctional primary aminothiourea $\mathbf{1 7}$ that is proposed to activate the enone as its corresponding dienamine and simultaneously associate with the imine as a thiourea-bound iminium ion.


Scheme 2.5. Enantioselective Primary Aminothiourea-Catalyzed FADA Reactions of Enones and Cyclic Imines

[^31]Meredeth devised an alternative approach to the reserpine framework that proposed a catalyst-controlled diastereoselective FADA reaction between two components of comparable size, imine 18 and chiral enone 19 (Scheme 2.6). ${ }^{11}$ Her progress is summarized in this section.


Scheme 2.6. Retrosynthetic Analysis of Reserpine
The synthetic efforts toward requisite enone component 19 began with a highly selective alcoholic kinetic resolution of racemic terminal epoxide 20. Differentially protected 4-carbon triol 21 was obtained in $96 \%$ ee through the use of oligomeric cobalt salen catalyst 23, ${ }^{12}$ employing benzyl alcohol as the nucleophile (Scheme 2.7). Elaboration of protected alcohol 21 to aldehyde 22 was accomplished in a 3-step sequence consisting of methylation of the secondary alcohol, subsequent hydrogenolysis of the benzyl ether, and Swern oxidation of the resulting primary alcohol. The $\alpha$-methoxy group of aldehyde 22 then served to direct a chelation-controlled diastereoselective allylation, thereby installing the adjacent C18 stereogenic center and providing vinyl bromide 24 as a single diastereomer. ${ }^{13}$ Following protection of the C 18 alcohol, lithium-

[^32]halogen exchange and subsequent addition to acetaldehyde afforded an inconsequential mixture of diastereomeric alcohols (25/26) which was oxidized with the Dess-Martin periodinane to afford enone 19. Efforts to directly access enone 19 through addition of the vinyllithium species derived from 24 to $N$-methoxy- $N$-methylacetamide proved less efficient due to competitive formation of the terminal olefin via protonolysis.


Scheme 2.7. Synthesis of Enantioenriched Enone 19

The key coupling of enone 19 and 6-methoxytryptamine-derived dihydro- $\beta$ carboline $18^{14}$ to generate the D-ring of reserpine was then examined under a series of conditions (Scheme 2.8). The FADA reaction employing just a slight excess of complex enone 19 (1.2 equivalents) relative to imine 18 was only successful under the influence

[^33]of primary amine catalysts, consistent with previous observations employing simple, hindered enone derivatives and with the mechanistic hypothesis of enamine formation. ${ }^{15}$ The degree of intrinsic substrate-induced diastereocontrol was evaluated using achiral amine promoters. With stoichiometric $n$-hexylamine, ${ }^{16}$ ketones 27 and 28, which contain a trans-relationship between the newly formed C3 and C20 stereocenters, were generated in a $1: 1$ diastereomeric ratio (entry 1). In contrast, high levels of chiral catalystcontrolled diastereoselectivity were observed in the presence of $20 \mathrm{~mol} \%$ aminothiourea 17, providing the desired diastereomer 27 in $76 \%$ isolated yield. Notably, the enantiomeric primary aminothiourea ent-17 induced a reversal of diastereoselectivity in the FADA reaction to afford ketone 28 selectively (entry 3).

[^34]


(76\% isolated yield with 17)



| entry | amine (mol \%) | AcOH (mol \%) | time (d) | conv (\%) | dr (27:28:29:30) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | $n$-hexylamine (100) | 100 | 9 | 90 | $1.0: 1.0: 0: 0$ |
| 2 | $\mathbf{1 7}(20)$ | 20 | 6 | $>99$ | $11.5: 1.0: 1.8: 0$ |
| 3 | $e n t-17(20)$ | 20 | 6 | $>99$ | $1.0: 11.9: 0: 2.1$ |

Scheme 2.8. Diastereoselective FADA Reactions of Imine 18 and Enone 19

Closure of the E-ring to complete the carbon skeleton of reserpine could be accomplished by an intramolecular aldol reaction of keto-aldehyde 31 (Scheme 2.9). Intermediate 31 was obtained in two steps from FADA adduct 27 through cleavage of the primary TBS ether with pyridine-buffered HF and oxidation of the resulting primary alcohol with the Dess-Martin periodinane. Treatment of crude aldehyde 31 with piperidine and catalytic TsOH resulted in an intramolecular enamine aldol reaction to afford C15 tertiary alcohol 32 as a single diastereomer that contains trans-fused D- and E-rings.


Scheme 2.9. Elaboration of the FADA Adduct to a Pentacyclic Framework Through an Aldol Cyclization

The most fruitful strategy evaluated for obtaining the correct oxidation state at C15 was an elimination-hydrogenation sequence (Scheme 2.10). Upon treatment of alcohol 32 with mesyl chloride and triethylamine, an in situ regioselective, albeit lowyielding, elimination took place to afford conjugated enal 33. The C15-C16 olefin could be hydrogenated with $\mathrm{PtO}_{2}$ in the presence of a mesyl chloride-derived additive. ${ }^{17}$ Ultimately, however, compound 34 was not obtained in sufficient quantities to determine the stereochemical outcome of the hydrogenation.


Scheme 2.10. Deoxygenation of 32 via an Elimination-Hydrogenation Sequence

### 2.4. Remaining Challenges

The previous synthetic work on this project established a route for generating four of the six stereocenters present in reserpine. The desired C18 and C17 stereocenters were installed by means of an enantioselective epoxide-opening reaction and a chelation-

[^35]controlled allylation. Additionally, the primary aminothiourea-catalyzed FADA reaction of enone 19 and imine 18 introduced the desired stereochemistry at C3 and C20 to provide ketone 27 with a high degree of catalyst-induced diastereoselectivity. The primary goal of the work described herein was to develop a successful route for elaborating this key tetracyclic intermediate to $(+)$-reserpine. The remaining challenges included formation of the E-ring of the molecule and installation of the final two stereocenters at C15 and C16. As our overall synthetic strategy is a clear departure from previously published routes to reserpine, we anticipated completion of the synthesis would require developing an understanding of factors that influence the diastereoselectivity of transformations performed in such a complex setting. Additionally, while generating material to explore strategies to complete the synthesis, a secondary goal was to improve upon the synthesis of enone 19. In particular, we investigated the direct conversion of vinyl bromide 24 to enone 19.

### 2.5. Improved Synthesis of Enone $19{ }^{18}$

As previously mentioned, attempts to form enone 19 directly from bromide 24 through a lithium-halogen exchange and subsequent addition to $N$-methoxy- $N$ methylacetamide (35a) ${ }^{19}$ were unsatisfactory. This reaction formed a roughly $1: 1$ mixture of the desired enone and terminal olefin byproduct 36, which is generated via protonolysis of the vinyllithium species (Table 2.1). This outcome contrasts with the analogous addition into acetaldehyde, which generates a diastereomeric mixture of secondary alcohols (25/26) in good yield and without formation of 36 (Scheme 2.7).

[^36]Table 2.1. Optimization of the Synthesis of Enone 19



We speculated that formation of 36 directly involved electrophile 35a, since efforts to rigorously exclude water did not suppress terminal olefin formation. We considered two possible scenarios for the formation of 36: 1) incomplete consumption of the vinyllithium during the reaction, perhaps due to the formation of aggregates,,${ }^{20}$ or 2) protonation of the vinyllithium species by amide 35a. We ruled out the former possibility by quenching the reaction with $\mathrm{D}_{2} \mathrm{O}$ (entry 2 ). The absence of deuterated olefin 37 and the observation that protonated olefin 36 was still formed indicated that the vinyllithium species was completely consumed during the reaction. Evidence against the latter possibility was provided through analogous reactions performed with deuterated

[^37]amide 35b and $N$-tert-butoxy- $N$-methylacetamide $\mathbf{3 5 c}$. Both reactions still afforded terminal olefin 36, and without formation of 37. These results suggested that electrophile 35a was not undergoing deprotonation at the acetyl or alkoxy positions. ${ }^{21}$ Although the proton source could not be determined, byproduct formation was suppressed through optimization of the reaction solvent (Table 2.1, entries 1, 6-8) and vinyl bromide concentration (entries 1 vs. 3). The reaction conducted in ether and at an initial vinyl bromide concentration of 0.05 M formed the enone in a ratio of 5.3:1 with olefin $\mathbf{3 6}$. When the addition was performed on a preparative scale, the ratio improved to 6.7:1 and enone 19 was isolated in $76 \%$ yield. With this procedure, the synthesis of FADA coupling partner 19 could be accomplished in seven steps and in $33 \%$ overall yield from racemic epoxide 20 (Scheme 2.7).

### 2.6. Strategies for the Completion of the Reserpine Synthesis

We evaluated alternative strategies to an aldol cyclization for advancing FADA adduct 27 to the pentacyclic core of reserpine. Although the aldol cyclization was efficient and diastereoselective, the poor efficiency of the mesyl chloride-induced elimination and the capricious nature of the enal hydrogenation prompted us to consider an alternative intramolecular enamine-alkylation route.

### 2.6.1. Attempted Closure of the E-Ring Via Enamine Alkylation ${ }^{22}$

An alkylation strategy was particularly attractive as cyclization of an appropriately functionalized aldehyde (38) would afford a pentacycle with the C 15 center

[^38]at the desired oxidation state (Scheme 2.11). Additionally, the stereospecificity of the transformation ensures that the C15 center would be formed with the desired stereochemistry.


Scheme 2.11. Intramolecular Alkylation Strategy to Effect E-Ring Formation

Secondary mesylate $\mathbf{4 0}$ was synthesized from FADA adduct 27 through reduction of the ketone to afford a separable 3.4:1 mixture of alcohol diastereomers favoring the desired equatorial alcohol, and a subsequent mesylation. The proposed alkylation precursor 41 was obtained by removal of the silyl protecting group with TBAF, and oxidation of the resultant primary alcohol with the Dess-Martin Periodinane. However, treatment of aldehyde 41 with a variety of secondary amines only resulted in elimination of the C17 methoxy group to form $(E)$-olefin 43 , which still contains the C15 mesylate (Scheme 2.12).



Scheme 2.12. Synthesis of Mesylate 41 and Attempted Enamine Alkylation

Although aldol precursor 31 and aldehyde 41 presumably access similar enamine intermediates upon exposure to a secondary amine and acid, the reaction outcomes are very different. Whereas the aldol cyclization afforded pentacycle 32 in high yield, the attempted alkylation did not afford any of the desired cyclization product (39, Scheme 2.13A).

An analysis of these results provided information about the reactivity of these intermediates and helped inform future routes. Aldol cyclization of keto-aldehyde 31 afforded trans-fused 32 as a single diastereomer, and without any elimination of the C17 methoxy group. This outcome corresponded to nucleophilic attack of the enamine occurring exclusively from the top face of the C15 ketone. ${ }^{23}$ In contrast, the proposed

[^39]alkylation route would require the enamine derived from $\mathbf{4 1}$ to displace the C15 mesylate from the bottom face of the intermediate. Additionally, the enamine intermediate would need to access an unfavorable conformation (corresponding to 43b) that places the C 15 mesylate in an axial orientation. Unfavorable steric interactions between the C-ring and the C15 substituent may have rendered this pathway energetically inaccessible. Without a productive cyclization pathway available, the intermediate underwent an elimination of the C17 methoxy group to provide the only observed product, 42. Together, these data strongly suggest that the top face of these tetracyclic intermediates is more accessible for nucleophilic attack. Based on this analysis, we moved forward with the aldol product 32 and investigated radical-based methods of obtaining the desired C15 oxidation state, since this same strong facial preference might render the mechanistically unselective radical pathway highly selective.
(A) Successful Enamine Aldol Cyclization

vs.
(B) Unsuccessful Enamine Alkylation


Scheme 2.13. Comparison of Aldol and Alkylation Routes

### 2.6.2. Radical Deoxygenation Attempts for Installing the C15 Stereocenter

The insight that these polycyclic intermediates may selectively undergo reactions on the top face encouraged us to pursue a radical deoxygenation approach to install the C15 center from aldol adduct 32. In particular, we envisioned that if a C15 tertiary radical could be generated, it would likely react with a hydrogen radical from the top face of the intermediate, thereby affording the corresponding product that contains the correct oxidation state and configuration at C 15 . Because previous attempts to derivatize the C15 alcohol of 32 were met with limited success, an intramolecular activation strategy was employed (Scheme 2.14). Cyclic thiocarbonate 45 was identified as an appropriate
radical precursor, and literature precedent suggested that deoxygenation should occur via the more stable C15 tertiary radical instead of the C22 primary radical. ${ }^{24,25}$ Thiocarbonate 45 was obtained in two steps from aldehyde 32 through a sodium borohydride reduction and cyclization of the resultant diol with thiocarbonyl diimidazole.


Scheme 2.14. Synthesis of Cyclic Thiocarbonate 45

However, upon subjecting 45 to radical deoxygenation conditions (AIBN and tributyltin hydride) and then hydrolysis conditions, C15 tertiary alcohol 46 was obtained exclusively. We reasoned that the radical process may be under Curtin-Hammett control (Scheme 2.15), wherein 48, the less-hindered of the two equilibrating radical species preferentially reacts with a hydrogen radical. ${ }^{26}$

[^40]

45 desired product observed I



47


46



48

Scheme 2.15. Possible Curtin-Hammett Control in Radical Deoxygenation of 45

Fortunately, we were successful in obtaining the C15 trifluoroacetate 49 as another possible precursor for radical deoxygenation (Scheme 2.16). ${ }^{27}$ Trifluoroacetic anhydride, in contrast to several other derivatizing reagents, cleanly and quantitatively reacted with aldol adduct 32. However, attempted purification of intermediate 49 revealed that it readily underwent hydrolysis back to alcohol 32 and elimination to yield conjugated enal 33. This fortuitous discovery along with the prediction that enal 33 should selectively undergo reactions from the top face of the intermediate encouraged us to re-visit the hydrogenation strategy for setting the C15 and C16 stereocenters of reserpine.

[^41]

Scheme 2.16. Synthesis of C 15 Trifluoroacetate and a $\mathrm{SiO}_{2}$-Promoted Elimination

### 2.6.3. Re-evaluation of an Enal Hydrogenation

Through optimization studies, it was found that treatment of crude C15 trifluoroacetate 49 with diisopropylamine induced a regioselective elimination to afford enal 33 in $63 \%$ yield from aldol adduct 32 (Scheme 2.17). ${ }^{28}$


Scheme 2.17. Optimized Synthesis of Conjugated Enal 33

Hydrogenation of enal 33 with $\mathrm{PtO}_{2}$ occurred only at high hydrogen pressures (14-48 atm) and afforded products 34 and 50-52, corresponding to reduction of the C15C16 olefin, the carbonyl group, and the aromatic ring of the PMB ether (Scheme 2.18). After subjecting the crude hydrogenation product mixture to Dess-Martin oxidation

[^42]conditions, saturated aldehyde 34 was obtained as a single diastereomer and in $40 \%$ yield over the two steps. ${ }^{29}$


Scheme 2.18. $\mathrm{PtO}_{2}$-Catalyzed Hydrogenation of Conjugated Enal 33

The stereochemical outcome of olefin hydrogenation was determined by analysis of the corresponding methyl ester (53), obtained by subjecting aldehyde 34 to Pinnick oxidation conditions followed by treatment of the crude acid with diazomethane (Scheme 2.19). NMR studies performed on this intermediate led to the determination that it had the desired C 15 configuration but the incorrect C 16 configuration. The relevant nOe data from the proton at C16 of methyl ester 53 are summarized in Scheme 2.19. PMB- and Ts-protecting group removals were carried out with DDQ and magnesium in MeOH , respectively, to access 16-epi-methyl reserpate (54).

[^43]


Scheme 2.19. Stereochemical Determination of the Enal Hydrogenation

A plausible explanation for this outcome is that hydrogen delivery occurred from the top face of the olefin, as predicted, to generate saturated aldehyde 55 but that unfavorable steric interactions between the C 16 substituent and the tosyl protecting group drove epimerization at C16 (Scheme 2.20).


Scheme 2.20 Potential Explanation for the Hydrogenation Outcome

Based on this hypothesis, we proposed two strategies to prevent epimerization during hydrogenation of a C15-C16 olefin (Scheme 2.21). The first strategy involved the removal of the tosyl protecting group. It was proposed that if unfavorable steric interactions between the tosyl group and the C 16 aldehyde substituent were responsible
for epimerization, then hydrogenation of the free indole substrate may proceed without epimerization (Scheme 2.22A). The second strategy involved modification of the C16 substituent to either an ester or primary alcohol, such that hydrogenation would generate a product that was less prone to epimerization at C16.
(A) Remove unfavorable steric interactions: Hydrogenation of an intermediate containing an unprotected indole

(B) Generate a less epimerizable product: Hydrogenation of an allylic alcohol or unsaturated ester


Scheme 2.21. Strategies for Preventing C16 Epimerization

### 2.6.4. Hydrogenation of an Unprotected Indole Intermediate

Through experimentation, we found that the unprotected methoxy indole of related intermediates was unstable to even mildly oxidative conditions. This observation suggested that oxidative manipulations, such as installation of the C16 ester and removal of the PMB protecting group should take place prior to removal of the tosyl group. Thus, we targeted unsaturated ester 58 as a hydrogenation substrate to evaluate our first strategy. Pinnick oxidation of aldehyde 32 to the corresponding carboxylic acid, followed by esterification with diazomethane provided methyl ester 56 (Scheme 2.22). The C15
alcohol of intermediate 56 proved very resistant to derivatization, and as with aldol adduct 32, trifluoroacetylation was found to be the most effective strategy. Derivatization of 56 to a C15 tertiary trifluoroacetate was accomplished with $n-\mathrm{BuLi}$ and trifluoroacetic anhydride, and the crude product was subjected to DBU in refluxing toluene to effect a regioselective elimination forming enoate $57 .{ }^{30}$ The PMB protecting group was cleaved using DDQ, and the tosyl protecting group was removed using a 5\% sodium/mercury amalgam to provide the free indole 58.

32 (aldol adduct)


Scheme 2.22. Synthesis of Enoate 58

C15-C16 olefin 58 underwent hydrogenation with $\mathrm{PtO}_{2}$ at 1 atm of hydrogen pressure to afford saturated ester 59 (Scheme 2.23). ${ }^{31}$ The stereochemical outcome of the hydrogenation was determined through NMR analysis of free indole 59, and by comparing its spectrum to those of saturated ester 54 (obtained through the enal

[^44]hydrogenation, Scheme 2.19), and methyl reserpate (10), obtained through saponification of a commercially available sample of (-)-reserpine. Through this analysis we determined that hydrogenation occurred with undesired selectivity from the bottom face of intermediate 58, providing the incorrect configurations at both C15 and C16.


58
15,16-di-epi-(+)-methyl reserpate
Scheme 2.23. Hydrogenation of 58 Occurs with Undesired Facial Selectivity

In comparing the two hydrogenation approaches and the outcomes, we determined that the facial selectivity of hydrogen delivery was influenced by the conformation of the intermediate, and this in turn was dependent on the presence or absence of an indole protecting group (Scheme 2.24). Substrate 33 containing a protected indole underwent hydrogenation exclusively from its top face, as the bottom face appears to be shielded by the bulky tosyl protecting group. In contrast, unprotected substrate $\mathbf{5 8}$, which lacks this directing effect, underwent hydrogenation primarily from the bottom face of the olefin. These observations are in agreement with a series of hydrogenation studies done by Lounasmaa on tetracyclic indole-containing substrates. ${ }^{32}$ Taking these results into consideration, we decided to move on to our second proposed endgame strategy and to carry out a hydrogenation in the presence of an indole protecting group and a C16 substituent that is unlikely to be susceptible to epimerization (Scheme 2.21B).

[^45]We predicted that this strategy would allow for hydrogenation to occur with the desired facial selectivity and without C16 epimerization.


33


protected indole
vs.

unprotected indole


Scheme 2.24. Protecting-Group Dependent Hydrogenation Facial Selectivities

### 2.7. Completion of the Synthesis of (+)-Reserpine

We anticipated that allylic alcohol 52, obtained through reduction of enal 33, might be capable of coordinating to a homogeneous hydrogenation catalyst and thereby enable hydrogenation of the hindered C15-C16 olefin. Unfortunately, an evaluation of both homogeneous and heterogeneous hydrogenation catalysts was unfruitful, either returning unreacted alcohol 52 or resulting in reduction of the aromatic ring of the PMB ether (Scheme 2.25).


Scheme 2.25. Unsuccessful Attempts at Reducing Allylic Alcohol 52

We therefore instead focused on hydrogenation of unsaturated ester 57, obtained via elimination of a tertiary trifluoroacetate (Scheme 2.23), which maintains the PMB and Ts protecting groups. This olefin proved to be a particularly challenging hydrogenation substrate as it is hindered, tetrasubstituted, and electron-deficient. After an extensive evaluation of both homogeneous and heterogeneous catalytic systems under a range of conditions, cationic iridium complex 64, bearing the noncoordinating BArF counteranion, was identified as uniquely effective in the reduction of the C15-C16 olefin of enoate 57 (Table 2.2). ${ }^{33}$

[^46]Table 2.2. Catalyst Screen for Hydrogenation of Enoate 57


Variation of the stoichiometry of enoate 57 to iridium complex 64 indicated that the catalytic use of $\mathbf{6 4}$ provided low amounts of conversion to the reduction product (Scheme Table 2.3, entries 1-2). However, hydrogenation with one full equivalent of complex 64 resulted in $54 \%$ conversion of 57 and proceeded with a significant degree of facial selectivity (6:1 dr), ultimately affording saturated ester $\mathbf{6 0}$ in $44 \%$ isolated yield $\left(81 \%\right.$ based on recovered olefin 57) (entry 3)..$^{34}$ The use of super stoichiometric amounts of iridium complex $\mathbf{6 4}$ offered a slight increase in yield but at the expense of recovered enoate (entry 4). The stereochemical outcome of the hydrogenation was determined by ${ }^{1} \mathrm{H}$ NMR analysis and indicated that the C15 and C16 stereogenic centers had been obtained in the correct configuration. The identity of saturated ester $\mathbf{6 0}$ was further confirmed by X-ray crystallographic analysis (Figure 2.2).

[^47]Table 2.3. Loading Studies of Complex 64


Figure 2.2. ORTEP Diagram of 60 Showing 50\% Probability Displacement

With the fully elaborated pentacycle in hand, completion of the synthesis required only a global deprotection and installation of the trimethoxybenzoyl ester on the E-ring. Thus, treatment of $\mathbf{6 0}$ sequentially with TfOH and sodium/mercury amalgam resulted in cleavage of the PMB ether and tosyl protecting groups, respectively (Scheme 2.26).

Resulting C18 secondary alcohol $\mathbf{1 0}$ was esterified using conditions reported by Stork to deliver reserpine $((+)-\mathbf{1}) .{ }^{5 q}$


Scheme 2.26. Completion of the Synthesis of (+)-Reserpine

### 2.8. Conclusions

The enantioselective total synthesis of reserpine was accomplished in 19 steps in the longest linear sequence from racemic epoxide 20 (Scheme 2.27). The convergent approach relied on chiral catalysis to provide access to coupling component 19 and to address the historically problematic installation of the C3 stereogenic center. The insights we gained about substrate-controlled diastereoselectivity in reactions performed on highly functionalized tetracyclic and pentacyclic intermediates guided us to pursue a diastereoselective hydrogenation that enabled completion of the synthesis. Furthermore, through this process, we were able to identify synthetic routes to access intermediates corresponding to two unnatural diastereomers of $(+)$-methyl reserpate: 16-epi-(+)-methyl reserpate (54) and 15,16-di-epi-(+)-methyl reserpate (59).


1. HF, pyr
2. DMP
3. piperidine, TsOH
80\%




(+)-reserpine

Scheme 2.27. Synthetic Route to (+)-Reserpine

### 2.9. Experimental Section

A. General Information.

Unless otherwise noted, all reactions were performed under a positive pressure of anhydrous nitrogen or argon in flame- or oven-dried glassware. Moisture- and airsensitive reagents were dispensed using oven-dried stainless steel syringes or cannulae and were introduced to reaction flasks through rubber septa. Reactions conducted below ambient temperature were cooled by external baths (dry ice/acetone for $-78{ }^{\circ} \mathrm{C}$ and ice/water for $0{ }^{\circ} \mathrm{C}$ ). Reactions conducted above ambient temperature were heated by a silicone oil bath.

Analytical thin layer chromatography (TLC) was performed on glass plates precoated with silica $60 \mathrm{~F}_{254}$ plates, 0.25 mm ). Visualization was carried out by exposure to a UV-lamp (short wave 254 nm , long wave 365 nm ), and by heating after staining the plate with a ceric ammonium molybdate or a potassium permanganate solution. Extraction and chromatography solvents were reagent or HPLC grade and were used without further purification. Flash chromatography was carried out over silica gel ( $60 \AA$, 230-400 mesh) from EM Science or Davisil ${ }^{\mathrm{TM}}$. Where indicated, chromatography was conducted on a Biotage Isolera automated chromatography system.

Materials. Commercial reagents and solvents were used with the following exceptions: tetrahydrofuran, diethyl ether, toluene, dichloromethane, acetonitrile, and methanol employed as reaction solvents were dried by passage through columns of activated alumina. Pyridine and triethylamine were distilled from calcium hydride at 760 torr prior
to use. The Dess-Martin Periodinane was prepared according to known procedures. ${ }^{35}$ Diazomethane was prepared as a 0.5 M solution in ether according to the known procedure. ${ }^{36}$ 2-bromoallyltrimethylsilane was prepared according to the reported procedure. ${ }^{37}$ Epoxide ( $\pm$ )-20 was prepared according to the reported procedure and was distilled from calcium hydride prior to use. ${ }^{38}$ Oligomeric cobalt salen catalyst $(R, R)-23$ was prepared according to the reported procedure and stored over calcium sulfate in a $-78{ }^{\circ} \mathrm{C}$ freezer. ${ }^{12}$ Imine 18, catalyst 17 , and catalyst ent-17, were prepared according to the reported procedures. ${ }^{10 a}$ Chloroform-d was dried over $3 \AA$ MS prior to use. Iridium complex 64 was prepared according to the reported procedure and was stored in a glove box under a $\mathrm{N}_{2}$ atmosphere. ${ }^{33 \mathrm{a}}$

Instrumentation. Proton nuclear magnetic resonance ( ${ }^{1} \mathrm{H} \mathrm{NMR}$ ) spectra and carbon nuclear magnetic resonance ( ${ }^{13} \mathrm{C}$ NMR) spectra were recorded on a Varian Mercury-400 $(400 \mathrm{MHz})$, Inova- $500(500 \mathrm{MHz})$, or an Inova- $600(600 \mathrm{MHz})$ spectrometer at $23{ }^{\circ} \mathrm{C}$. Chemical shifts for protons are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent $\left(\mathrm{CHCl}_{3}: 7.26 \mathrm{ppm} ; \mathrm{C}_{6} \mathrm{H}_{6}: 7.16 \mathrm{ppm}\right)$. Chemical shifts for carbons are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane and are referenced to the NMR solvent $\left(\mathrm{CDCl}_{3}: 77.16 \mathrm{ppm}\right)$. Data are represented as follows: chemical shift, multiplicity $(\mathrm{s}=$ singlet, $\mathrm{d}=$ doublet, $\mathrm{t}=$ triplet, $\mathrm{q}=$ quartet, $\mathrm{m}=$ multiplet, $\mathrm{br}=$ broad,

[^48]app $=$ apparent $)$, integration, and coupling constant $(J)$ in Hertz (Hz). Infrared (IR) spectroscopy was performed on the neat compounds on a Brucker Tensor 27 FT-IR Spectrometer using OPUS software. Data are represented as follows: frequency of absorption $\left(\mathrm{cm}^{-1}\right)$, intensity of absorption ( $\mathrm{s}=$ strong, $\mathrm{m}=$ medium, $\mathrm{w}=$ weak). Mass spectra were obtained on an Agilent 1200 series 6120 Quadrupole LC/MS. Optical rotation data were collected using either a $2-\mathrm{mL}$ cell with a 1 dm path length or a $1-\mathrm{mL}$ cell using a 0.5 dm path length on a Jasco P-2000 polarimeter and are reported as $[\alpha]_{\mathrm{D}}{ }^{23}$ (concentration in grams $/ 100 \mathrm{~mL}$ solvent). Reported rotations are the average of 3-5 measurements per sample.
B. Experimental procedures and characterization data.


## (S)-1-(benzyloxy)-4-(tert-butyldimethylsilyloxy)butan-2-ol (21)

A $50-\mathrm{mL}$ round-bottom flask was charged with a stir bar, epoxide $( \pm)-20(10.0 \mathrm{~g}, 49.7$ mmol, 1 equiv.), $\mathrm{CH}_{3} \mathrm{CN}(2.4 \mathrm{~mL})$, and anhydrous $\mathrm{BnOH}(2.32 \mathrm{~mL}, 22.4 \mathrm{mmol}, 0.45$ equiv.). The flask was cooled to $0^{\circ} \mathrm{C}$, and $(R, R)-23(185 \mathrm{mg}, 0.227 \mathrm{mmol}, 0.45 \mathrm{~mol} \%$ based on Co) was added in one portion. The flask was sealed with a plastic cap and allowed to stir at $4{ }^{\circ} \mathrm{C}$ for 96 h , at which point pyridinium para-toluenesulfonate (PPTS) ( $60 \mathrm{mg}, 0.240 \mathrm{mmol}$ ) was added in one portion. The reaction mixture was filtered through a silica gel plug, eluting with $\mathrm{Et}_{2} \mathrm{O}(400 \mathrm{~mL})$. The filtrate was concentrated in vacuo to provide a dark orange oil which was purified immediately via flash
chromatography (silica gel, Biotage, $10 \% \mathrm{Et}_{2} \mathrm{O}$ in hexanes) to provide the desired secondary alcohol 21 as a clear oil $(6.28 \mathrm{~g}, 20.2 \mathrm{mmol}, 41 \%$ yield $) . \quad \mathrm{R} f=0.44(25 \%$ EtOAc in hexanes); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 7.24-7.42(\mathrm{~m}, 5 \mathrm{H}) 4.58(\mathrm{~d}, J=12.4$ $\mathrm{Hz}, 1 \mathrm{H}) 4.55(\mathrm{~d}, J=11.9 \mathrm{~Hz}, 1 \mathrm{H}) 4.03(\mathrm{ddd}, J=11.40,6.90,4.60 \mathrm{~Hz}, 1 \mathrm{H}) 3.86(\mathrm{~m}, 1 \mathrm{H})$ 3.79 (m, 1 H ) 3.48 (dd, $J=9.77,4.39 \mathrm{~Hz}, 1 \mathrm{H}) 3.43$ (dd, $J=8.79,6.84 \mathrm{~Hz}, 1 \mathrm{H}) 3.17$ (br. s., $1 \mathrm{H}) 1.70(\mathrm{~m}, 2 \mathrm{H}) 0.90(\mathrm{~s}, 9 \mathrm{H}) 0.06(\mathrm{~s}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta: 138.13$, 128.36 (2C), 127.69 (2C), 127.64, 74.36, 73.32, 69.63, 61.32, 35.42, 25.85 (3C), 18.14, 5.52, -5.55 ; FTIR (neat, $\mathrm{cm}^{-1}$ ); 3400(br m), 2953(m), 2928(m), 2857(m), 1497(w), 1471(w), 1463(w), 1389(w), 1362(w), 1253(m), 1205(w), 1090(s), 1005(m), 908(m), 833(s), 775(s), 733(s), 697(s), 663(m); LRMS (APCI) $311.2[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}-1.2(c$ $\left.1.77, \mathrm{CHCl}_{3}\right)$.

To assess the enantiomeric purity, the epoxide-opened product was elaborated to the corresponding diol in the following manner: Silyl ether $21(22.7 \mathrm{mg}, 0.073 \mathrm{mmol}, 1$ equiv.) was dissolved in THF ( 0.47 mL ) and TBAF ( 1 M in THF, $0.152 \mathrm{~mL}, 2.1$ equiv.) was added at $0^{\circ} \mathrm{C}$. The solution was allowed to come to rt and stir 1 h . The reaction was then diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \mathrm{~mL})$ and the organic layer was washed with $\mathrm{H}_{2} \mathrm{O}(3 \times 5 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to provide the diol as a clear oil. The enantiomeric excess was determined to be $96 \%$ by chiral SFC analysis (OD-H, $5 \% \mathrm{MeOH}, 4.0 \mathrm{ml} / \mathrm{min}$ ) $\mathrm{t}_{\mathrm{R}}$ (minor) $=6.88 \mathrm{~min}, \mathrm{t}_{\mathrm{R}}($ major $)=7.52 \mathrm{~min}$.

(5S,6S)-8-(tert-butyldimethylsilyloxy)-6-methoxy-5-(4-methoxybenzyloxy)-3-
methyleneoctan-2-one (19)
Vinyl bromide 24 ( $286 \mathrm{mg}, 0.60 \mathrm{mmol}, 1$ equiv.) was azeotroped from benzene twice and placed on high vacuum 2 h in a $50-\mathrm{mL}$ round-bottomed flask. $\mathrm{Et}_{2} \mathrm{O}(12 \mathrm{~mL})$ was then added under $\mathrm{N}_{2}$, and the flask was cooled to $-78^{\circ} \mathrm{C}$. Tert-butyllithium ( $741 \mu \mathrm{~L}$ of a 1.7 M solution in pentane, 1.26 mmol , 2.1 equiv.) was added dropwise over 5 min . The yellow solution was stirred for 30 min , after which $N$-methoxy- $N$-methylacetamide (138 $\mu \mathrm{L}, 0.90 \mathrm{mmol}, 1.5$ equiv.) was added. The reaction was stirred for an additional 1.5 h at $-78{ }^{\circ} \mathrm{C}$, and was then quenched by addition of $\mathrm{H}_{2} \mathrm{O}(5 \mathrm{~mL})$ and immediately warmed to rt . The reaction mixture was diluted with $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$, and the aqueous layer was extracted with EtOAc ( $2 \times 15 \mathrm{~mL}$ ). The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The resultant oil was purified by flash chromatography (silica gel, 0 to $15 \%$ EtOAc in hexanes) to provide 19 as a clear oil (199 $\mathrm{mg}, 0.46 \mathrm{mmol}, 76 \%$ yield). $\mathrm{R} f=0.19$ ( $15 \%$ EtOAc in hexanes); ${ }^{1} \mathrm{H}$ NMR ( 600 MHz , $\left.\mathrm{CDCl}_{3}\right) \delta: 7.21(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}) 6.84(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}) 6.03(\mathrm{~s}, 1 \mathrm{H}) 5.87(\mathrm{~s}, 1 \mathrm{H})$ $4.48(\mathrm{~d}, J=11.42 \mathrm{~Hz}, 1 \mathrm{H}) 4.40(\mathrm{~d}, J=11.42 \mathrm{~Hz}, 1 \mathrm{H}) 3.79(\mathrm{~s}, 3 \mathrm{H}) 3.52-3.69(\mathrm{~m}, 3 \mathrm{H})$ 3.43 (dt, $J=8.42,4.14 \mathrm{~Hz}, 1 \mathrm{H}) 3.39(\mathrm{~s}, 3 \mathrm{H}) 2.64(\mathrm{ddd}, J=13.55,4.61,0.88 \mathrm{~Hz}, 1 \mathrm{H}) 2.37$ (dd, $J=13.62,8.35 \mathrm{~Hz}, 1 \mathrm{H}) 2.28(\mathrm{~s}, 3 \mathrm{H}) 1.78$ (dddd, $J=14.06,8.20,5.86,4.10 \mathrm{~Hz}, 1 \mathrm{H})$ 1.61 (ddt, $J=13.79,8.67,5.13,5.13 \mathrm{~Hz}, 1 \mathrm{H}) 0.85-0.90(\mathrm{~m}, 9 \mathrm{H}) 0.03$ (s, 3 H ) 0.02 (s, 3 H) ${ }^{13}{ }^{1} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 199.65,159.10,146.09,130.72,129.71$ (2C) 127.52, 113.59 (2C) 77.89, 76.81, 71.90, 59.46, 58.17, 55.22, 32.66, 31.89, 25.91 (3C), 25.85,
18.21, $-5.35,-5.41$; IR 2949(m), 2929(s), 2856(m), 1678(s), 1613(m), 1586(w), 1464(m), 1441(w), 1362(m), 1324(w), 1032(w), 1247(s), 1090(s), 1036(m), 938(m), 833(s), 775(s), 662(m); LRMS (ESI) $459.2[\mathrm{M}+\mathrm{Na}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}-16.1\left(c 3.03, \mathrm{CHCl}_{3}\right)$.

(3S,12bS)-3-((2S,3S)-5-(tert-butyldimethylsilyloxy)-3-methoxy-2-(4-
methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-
aךquinolizin-2(12H)-one (27)
An oven-dried $25-\mathrm{mL}$ round-bottom flask with stir-bar was charged with enone 19 (788 $\mathrm{mg}, 1.80 \mathrm{mmol}, 1.2$ equiv.), imine $18(533 \mathrm{mg}, 1.50 \mathrm{mmol}, 1$ equiv.), and aminothiourea 17 ( $140 \mathrm{mg}, 0.30 \mathrm{mmol}, 20 \mathrm{~mol} \%$ ). The flask was placed under $\mathrm{N}_{2}$ and toluene ( 4.5 mL ) was added, followed by $\mathrm{AcOH}(17.2 \mu \mathrm{l}, 0.30 \mathrm{mmol}, 20 \mathrm{~mol} \%)$ in one portion. The reaction was allowed to stir at rt 4.5 d , and then at $45^{\circ} \mathrm{C}$ for 2 h . Analysis of the crude reaction mixture by ${ }^{1} \mathrm{H}$ NMR (comparison of a combination of C 3 and PMB Bn signals) showed a 11.5:1.0:1.8:0 diastereomeric ratio of 27:28:29:30. The crude reaction mixture was directly purified by flash chromatography (silica gel, Biotage, $0-50 \%$ EtOAc in hexanes gradient) to provide the desired diastereomer as a pale yellow solid ( 909 mg , $1.15 \mathrm{mmol}, 76 \%$ yield). $\mathrm{R} f=0.19$ ( $50 \%$ EtOAc in hexanes); ${ }^{1} \mathrm{H}$ NMR ( $399 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.65(\mathrm{~d}, J=2.20 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 12) 7.47(\mathrm{~d}, J=8.42 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}) 7.17-7.25(\mathrm{~m}, 3 \mathrm{H}, \mathrm{PMB}$, C10) $7.10(\mathrm{~d}, J=7.68 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}) 6.77-6.91(\mathrm{~m}, 3 \mathrm{H}, \mathrm{PMB}, \mathrm{C} 9) 4.61(\mathrm{~d}, J=11.34 \mathrm{~Hz}, 1$ H, PMB Bn) 4.51 (dd, $J=11.34,2.20 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 3) 4.31$ (d, $J=11.34 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn})$
3.87 (s, 3 H, PMB OMe) 3.85 (ddd, $J=10.61,4.76,2.56 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 18) 3.75$ (dd, $J=7.87$, $\left.4.57 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{OTBS}\right) 3.70(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.54$ (ddd, $\left.J=9.51,4.57,2.38 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 17\right)$ $3.50(\mathrm{~s}, 3 \mathrm{H}, \mathrm{C} 17 \mathrm{MeO}) 3.31(\mathrm{dd}, J=13.17,5.86 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 21) 3.10-3.20(\mathrm{~m}, 2 \mathrm{H}, \mathrm{C} 14$, C5) $2.94(\mathrm{t}, J=12.44 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 21) 2.78-2.86(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 5) 2.68-2.78(\mathrm{~m}, 3 \mathrm{H}, \mathrm{C} 6(2)$, C20) $2.39(\mathrm{t}, J=12.26 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 2.28(\mathrm{~s}, 3 \mathrm{H}, \mathrm{Ts}) 2.05(\mathrm{ddd}, J=13.80,9.15,2.38 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{C} 19) 1.85$ (dtd, $J=14.00,7.70,7.70,2.60 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 16) 1.58$ (ddt, $J=14.00,9.38$, 4.62, 4.62 Hz, 1 H, C16) 1.04 (ddd, $J=13.80,10.30,3.40 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 19) 0.90-0.93(\mathrm{~m}, 9$ H, TBS) $0.08(\mathrm{~s}, 3 \mathrm{H}, \mathrm{TBS}) 0.08(\mathrm{~s}, 3 \mathrm{H}, \mathrm{TBS}) ;{ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 208.55$, $159.21,158.02,144.63,138.37,134.52,134.41,130.76,129.83$ (2C), 129.61 (2C), 126.29 (2C), 123.97, 118.92, 118.81, 113.78 (2C), 112.73, 100.33, 78.22, 76.77, 72.43, $61.10,59.59,58.95,58.37,55.79,55.17,45.17,44.56,43.00,32.82,26.86,25.94$ (3C), $22.25,21.49,18.25,-5.29,-5.37$; IR 2592(m), 2927(m), 2856(m), 1706(s), 1612(m), 1582(w), 1513(m), 1493(m), 1463(m), 1440(w), 1364(s), 1304(w), 1248(s), 1172(s), $1145(\mathrm{~m}), 1088(\mathrm{~s}), 1035(\mathrm{~m}), 975(\mathrm{~m}), 834(\mathrm{~s}), 775(\mathrm{~m}), 674(\mathrm{~s}), 626(\mathrm{~m}) ;$ LRMS (APCI) $791.4[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{24}{ }_{\mathrm{D}}+65.8^{\circ}\left(c\right.$ 1.11, $\left.\mathrm{CHCl}_{3}\right)$.

The 1-D NOESY spectrum ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) displayed the following nOe transfers: Irradiation of C14 ( $\delta 2.39$ ): 0.3\% C3 ( $\delta 4.51$ ),

$$
1.2 \% \mathrm{C} 20(\delta 2.75)
$$

Irradiation of C3 ( $\delta 4.51$ ): $0.9 \% \mathrm{Ts}(\delta 7.47), 1.7 \% \mathrm{C} 14(\delta 3.15)$,

$$
1.9 \% \text { C21 ( } \delta 2.94 \text { ) }
$$



Irradiation of C21 ( $\delta 2.94$ ): 1.2\% C3 ( $\delta 4.51$ )
Irradiation of C21 ( $\delta 3.31$ ): 2.6\% C5 ( $\delta 2.81$ ), 4.5\% C20 ( $\delta 2.74$ )

(3R,12b $R)$-3-((2S,3S)-5-(tert-butyldimethylsilyloxy)-3-methoxy-2-(4-
methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin- $2(12 \mathrm{H})$-one (28)
$\mathrm{R} f=0.28\left(50 \%\right.$ EtOAc in hexanes); ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 7.65(\mathrm{~d}, J=2.29 \mathrm{~Hz}, 1$ H) $7.48(\mathrm{~d}, J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 7.30(\mathrm{~d}, J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 7.20(\mathrm{~d}, J=8.24 \mathrm{~Hz}, 1 \mathrm{H}) 7.10(\mathrm{~d}$, $J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 6.88$ (d, $J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 6.85(\mathrm{dd}, J=8.47$, $2.06 \mathrm{~Hz}, 1 \mathrm{H}) 4.63$ (d, $J=11.90 \mathrm{~Hz}, 1 \mathrm{H}) 4.49(\mathrm{~m}, 2 \mathrm{H}) 3.87(\mathrm{~s}, 3 \mathrm{H}) 3.80(\mathrm{~s}, 3 \mathrm{H}) 3.69(\mathrm{td}, J=9.27,5.27 \mathrm{~Hz}, 1 \mathrm{H})$ $3.62-3.66(\mathrm{~m}, 1 \mathrm{H}) 3.60(\mathrm{dt}, J=8.59,4.64 \mathrm{~Hz}, 1 \mathrm{H}) 3.54(\mathrm{dt}, J=8.47,4.01 \mathrm{~Hz}, 1 \mathrm{H}) 3.39$ (s, 3 H$) 3.21-3.34(\mathrm{~m}, 2 \mathrm{H}) 3.06-3.16(\mathrm{~m}, 1 \mathrm{H}) 2.89(\mathrm{t}, J=12.36 \mathrm{~Hz}, 1 \mathrm{H}) 2.65-2.83$ (m, 4 H) $2.46-2.58(\mathrm{dd}, J=12.4,11.8 \mathrm{~Hz}, 1 \mathrm{H}) 2.29(\mathrm{~s}, 3 \mathrm{H}) 2.17$ (ddd, $J=14.19$, 8.70, $5.04 \mathrm{~Hz}, 1 \mathrm{H}) 1.74-1.88(\mathrm{~m}, 1 \mathrm{H}) 1.55-1.69(\mathrm{~m}, 1 \mathrm{H}) 1.32-1.46(\mathrm{~m}, 1 \mathrm{H}) 0.90(\mathrm{~s}, 9 \mathrm{H})$ $0.05(\mathrm{~s}, 3 \mathrm{H}) 0.04(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm}$ 208.31, 159.39, 158.22, $144.78,138.68,134.81,134.53,130.98,129.95$ (2C), 129.75 (2C), 126.53 (2C), 124.21, 119.37, 119.08, 113.92 (2C), 112.98, 100.62, 78.22, 74.89, 71.33, 60.14, 59.61, 59.00, $58.55,56.00,55.41,45.45,45.25,43.22,32.95,26.31,26.10$ (3C), 22.49, 21.68, 18.41, 5.15, -5.21; IR 3008 (w), 2928 (m), 2856 (m), 1708 (m), 1613 (m), 1513 (m), 1494 (w), 1367 ( s), 1250 (s), 1216 (w), 1173 (s), 1147 (m), 1090 (s), 1037 (m), 836 (s), 759 (s); LRMS (APCI) $791.4[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{24}{ }_{\mathrm{D}}+16.9^{\circ}\left(c 0.29, \mathrm{CHCl}_{3}\right)$.

(3R,12bS)-3-((2S,3S)-5-(tert-butyldimethylsilyloxy)-3-methoxy-2-(4-
methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin- $2(12 \mathrm{H})$-one (29)
$\mathrm{R} f=0.36(50 \%$ EtOAc in hexanes $) ;{ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 7.60(\mathrm{~d}, J=2.20 \mathrm{~Hz}, 1$ H, C12) $7.44(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}) 7.25(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{PMB}) 7.12(\mathrm{~d}, J=8.49 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{C} 10) 7.08(\mathrm{~d}, J=8.35 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}) 6.86(\mathrm{~d}, J=8.64 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{PMB}) 6.81(\mathrm{dd}, J=8.49$, $2.34 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 9) 4.43$ (d, $J=10.84 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn}) 4.32(\mathrm{~d}, J=10.69 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB}$ Bn) 4.04 (dd, $J=11.10,2.40 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 3) 3.86(\mathrm{~s}, 3 \mathrm{H}, \mathrm{PMB} \mathrm{MeO}) 3.78(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO})$ $3.62-3.73$ (m, 2 H, C18, CHHOTBS) $3.51-3.59$ (m, 2 H, CHHOTBS, C17) 3.40 (s, 3 H, C17 MeO) 3.36 (ddd, $J=14.57,2.78,1.40 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 2.98(\mathrm{~m}, 2 \mathrm{H}, \mathrm{C} 5, \mathrm{C} 21) 2.91$ (dd, $J=11.57,2.78 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 5) 2.75(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 6) 2.54-2.64(\mathrm{~m}, 3 \mathrm{H}, \mathrm{C} 14, \mathrm{C} 20, \mathrm{C} 21)$ 2.47 (dd, $J=15.96,2.30 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 6) 2.28(\mathrm{~s}, 3 \mathrm{H}, \mathrm{Ts}) 2.07(\mathrm{dt}, J=14.31,8.80 \mathrm{~Hz}, 1 \mathrm{H}$, C19) $1.76-1.85(\mathrm{~m}, 2 \mathrm{H}, \mathrm{C} 16, \mathrm{C} 19) 1.56-1.44(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 16) 0.87-0.91(\mathrm{~m}, 9 \mathrm{H}$, TBS) 0.04 ( $\mathrm{s}, 3 \mathrm{H}, \mathrm{TBS}) 0.04(\mathrm{~s}, 3 \mathrm{H}, \mathrm{TBS}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 210.75$, $159.13,157.97,144.48,139.42,134.90,133.39,130.48,129.97$ (2C) 129.23 (2C) 126.59 (2C) 124.57, 122.59, 118.83, 113.69 (2C) 112.92, 101.18, 77.17, 75.89, 71.30, 59.53, 59.33, 58.54, 58.32, 55.81, 55.24, 49.90, 48.26, 46.43, 32.51, 32.03, 25.93 (3C) 22.90, 21.52, 18.25, -5.31, -5.41; IR 2929 (m), 2857 (m), 1709 (m), 1613 (m), 1514 (m), 1368 (s), 1305 (w), 1249 (s), 1216 (s), 1090 (s), 1038 (m), 971 (w), 836 (m), 759 (s); LRMS (APCI) $791.4[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{24}{ }_{\mathrm{D}}+38.6^{\circ}\left(c\right.$ 1.72, $\left.\mathrm{CHCl}_{3}\right)$.

The 1-D NOESY spectrum ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) displayed the following nOe transfers:
Irradiation of C19 ( $\delta 2.07$ ): 3.0\% C14 ( $\delta 2.57$ ),
2.3\% C17 ( $\delta 2.57$ )

Irradiation of C3 ( $\delta 4.04$ ): 3.7\% C14 ( $\delta 3.36$ ), 4.7\% C5 ( $\delta 2.98$ ),

$$
5.4 \% \text { C21 ( } \delta 2.58 \text { ) }
$$


(3S,12bR)-3-((2S,3S)-5-(tert-butyldimethylsilyloxy)-3-methoxy-2-(4-
methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin- $2(12 \mathrm{H})$-one ( $\mathbf{3 0}$ )
$\mathrm{R} f=0.61\left(50 \% \mathrm{EtOAc}\right.$ in hexanes); ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 7.63(\mathrm{~d}, J=2.05 \mathrm{~Hz}, 1$ H) $7.45(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}) 7.32(\mathrm{~d}, J=8.79 \mathrm{~Hz}, 2 \mathrm{H}) 7.14(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 1 \mathrm{H}) 7.08(\mathrm{~d}$, $J=8.20 \mathrm{~Hz}, 2 \mathrm{H}) 6.89(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}) 6.82(\mathrm{dd}, J=8.35,2.20 \mathrm{~Hz}, 1 \mathrm{H}) 4.58(\mathrm{~d}$, $J=10.84 \mathrm{~Hz}, 1 \mathrm{H}) 4.48(\mathrm{~d}, J=10.54 \mathrm{~Hz}, 1 \mathrm{H}) 4.14(\mathrm{dd}, J=10.69,2.49 \mathrm{~Hz}, 1 \mathrm{H}) 3.87(\mathrm{~s}, 3$ H) $3.80(\mathrm{~s}, 3 \mathrm{H}) 3.69(\mathrm{dd}, J=7.76,4.54 \mathrm{~Hz}, 2 \mathrm{H}) 3.60(\mathrm{ddd}, J=10.40,4.25,2.34 \mathrm{~Hz}, 1 \mathrm{H})$ $3.48-3.52(\mathrm{~m}, 1 \mathrm{H}) 3.42(\mathrm{dd}, J=15.08,3.08 \mathrm{~Hz}, 1 \mathrm{H}) 3.33(\mathrm{~s}, 3 \mathrm{H}) 3.17(\mathrm{dd}, J=11.42$, $5.86 \mathrm{~Hz}, 1 \mathrm{H}) 3.02$ (ddd, $J=11.00,4.69,2.05 \mathrm{~Hz}, 1 \mathrm{H}) 2.96(\mathrm{dd}, J=11.42,3.22 \mathrm{~Hz}, 1 \mathrm{H})$ $2.74-2.85(\mathrm{~m}, 2 \mathrm{H}) 2.60(\mathrm{td}, J=10.54,3.51 \mathrm{~Hz}, 1 \mathrm{H}) 2.46-2.53(\mathrm{~m}, 2 \mathrm{H}) 2.29(\mathrm{~s}, 3 \mathrm{H})$ $2.12-2.18(\mathrm{~m}, 1 \mathrm{H}) 1.79-1.84(\mathrm{~m}, 1 \mathrm{H}) 1.47-1.58(\mathrm{~m}, 2 \mathrm{H}) 0.90(\mathrm{~s}, 9 \mathrm{H}) 0.05(\mathrm{~s}, 3 \mathrm{H})$ $0.05(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta: 210.99,159.42,158.24,144.72,139.62$,
$135.01,133.61,130.87,130.04$ (2C) 129.44 (2C) 126.75 (2C) $124.75,122.80,119.08$, 114.00 (2C) $113.18,101.40,77.51,76.45,72.61,59.76,59.54,59.00,58.47,56.01$, $55.44,49.97,46.52,32.71,32.13,29.86,26.12,22.95,21.69,18.44,-5.13,-5.22$; IR 2929 (m), 2856 (m), 1711 (m), 1613 (m), 1514 (m), 1465 (w), 1369 (m), 1249 (s), 1173 (s), 1144 (m), 1090 (s), 1036 (m), 970 (w), 836 (s), 760 (s). LRMS (APCI) $791.4[\mathrm{M}+$ $\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}-2.46^{\circ}\left(c 0.69, \mathrm{CHCl}_{3}\right)$.

(3S,4S)-3-methoxy-5-((3S,12bS)-10-methoxy-2-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-3-yl)-4-(4-methoxybenzyloxy)pentanal (31) Alcohol S1 (442 mg, $0.653 \mathrm{mmol}, 1$ equiv.) was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(65 \mathrm{~mL})$ in a $300-$ mL round-bottom flask at rt . To this was added the Dess-Martin periodinane ( 305 mg , $0.72 \mathrm{mmol}, 1.1$ equiv.) in one portion, and the solution was stirred 1 h , after which the reaction solution was diluted with $\mathrm{Et}_{2} \mathrm{O}(60 \mathrm{~mL})$. The reaction mixture was poured into a $500-\mathrm{mL}$ Erlenmeyer flask containing 120 mL of a $1: 1$ aqueous solution of sat. $\mathrm{NaHCO}_{3}: 10 \% \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$. The biphasic mixture was stirred vigorously 1 h , after which additional $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added $(50 \mathrm{~mL})$ and the layers were separated. The aqueous was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 50 \mathrm{~mL})$, and the combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and concentrated in vacuo to provide the crude aldehyde (31), which was carried forward without further purification. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 9.81(\mathrm{t}, J=1.71 \mathrm{~Hz}, 1$
H) $7.65(\mathrm{~d}, J=1.95 \mathrm{~Hz}, 1 \mathrm{H}) 7.47(\mathrm{~d}, J=8.30 \mathrm{~Hz}, 2 \mathrm{H}) 7.16-7.23(\mathrm{~m}, 3 \mathrm{H}) 7.10(\mathrm{~d}, J=7.81$ $\mathrm{Hz}, 2 \mathrm{H}) 6.80-6.89(\mathrm{~m}, 3 \mathrm{H}) 4.54(\mathrm{~d}, J=11.23 \mathrm{~Hz}, 1 \mathrm{H}) 4.50(\mathrm{dd}, J=11.23,2.44 \mathrm{~Hz}, 1 \mathrm{H})$ $4.31(\mathrm{~d}, J=11.23 \mathrm{~Hz}, 1 \mathrm{H}) 3.90-3.98(\mathrm{~m}, 2 \mathrm{H}) 3.87(\mathrm{~s}, 3 \mathrm{H}) 3.70(\mathrm{~s}, 3 \mathrm{H}) 3.48-3.50(\mathrm{~m}$, $3 \mathrm{H}) 3.29$ (dd, $J=13.18,6.35 \mathrm{~Hz}, 1 \mathrm{H}) 3.15(\mathrm{~m}, 2 \mathrm{H}) 2.94(\mathrm{t}, J=12.45 \mathrm{~Hz}, 1 \mathrm{H}) 2.83(\mathrm{dt}$, $J=10.74,4.64 \mathrm{~Hz}, 1 \mathrm{H}) 2.64-2.77(\mathrm{~m}, 4 \mathrm{H}) 2.59(\mathrm{ddd}, J=16.60,7.81,1.95 \mathrm{~Hz}, 1 \mathrm{H}) 2.37$ (t, $J=12.20 \mathrm{~Hz}, 1 \mathrm{H}) 2.28(\mathrm{~s}, 3 \mathrm{H}) 2.04$ (ddd, $J=14.16,9.28,2.20 \mathrm{~Hz}, 1 \mathrm{H}) 1.01$ (ddd, $J=13.18,9.77,2.93 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 208.50,201.11,159.38$, $158.04,144.68,138.37,134.36,134.31,129.95$ (2C), 129.62 (2C), 126.28 (2C), 123.94, $118.94,118.87,113.87$ (2C), 112.75, 100.31, 76.45, 75.92, 72.59, 60.94, 58.93, 57.99, $55.80,55.18,45.18,44.62,43.92,42.77,29.66,26.64,22.24,21.50 ;$ LRMS (APCI) 675.3 $[\mathrm{M}+\mathrm{H}]^{+}$


## Pentacyclic aldehyde (32)

A flame-dried, $100-\mathrm{mL}$ round-bottom flask was charged with crude aldehyde 31 (0.653 mmol, 1 equiv.), which was azeotroped twice from benzene and placed on high vacuum 30 min . A stir bar was then added under a positive pressure of nitrogen, followed by toluene $(21 \mathrm{~mL})$. To a separate $10-\mathrm{mL}$ flask was charged with toluene $(2 \mathrm{~mL})$, piperidine $(129 \mu \mathrm{~L})$ and $p$-toluenesulfonic acid ( 24.8 mg ), and 1 mL of this solution was transferred to the first flask (piperidine addition: $65.7 \mu \mathrm{~L}, 0.65 \mathrm{mmol}, 1$ equiv). The reaction was
allowed to stir overnight, after which it was quenched by the addition of saturated aqueous $\mathrm{NaHCO}_{3}(10 \mathrm{~mL})$. The reaction mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 15$ mL ), and the combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. ${ }^{39}$ The residue was azeotroped twice from benzene to aid in the removal of residual piperidine, after which the residue was dissolved in a $1: 1$ solution of hexanes:EtOAc. The solution was filtered to remove any precipitate, and the filtrate was concentrated in vacuo to provide 32 as a single diastereomer ( $382 \mathrm{mg}, 0.56 \mathrm{mmol}, 86 \%$ yield). ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}$ ) $\delta: 9.83(\mathrm{~d}, J=2.44 \mathrm{~Hz}, 1 \mathrm{H}) 8.16(\mathrm{~d}, J=2.44 \mathrm{~Hz}, 1 \mathrm{H})$ 7.59 (d, $J=8.30 \mathrm{~Hz}, 2 \mathrm{H}) 7.33$ (d, $J=8.80 \mathrm{~Hz}, 2 \mathrm{H}) 6.99(\mathrm{~d}, J=8.30 \mathrm{~Hz}, 1 \mathrm{H}) 6.88$ (d, $J=8.80 \mathrm{~Hz}, 1 \mathrm{H}) 6.88(\mathrm{~d}, J=8.30 \mathrm{~Hz}, 2 \mathrm{H}) 6.38(\mathrm{~d}, J=7.81,2 \mathrm{H}) 4.83(\mathrm{dd}, J=11.5,1.5 \mathrm{~Hz}$, 1 H) 4.59 (d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}) 4.51$ (d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}) 4.07$ (dd, $J=10.99,9.03 \mathrm{~Hz}, 1$ H) $3.45(\mathrm{~s}, 3 \mathrm{H}) 3.45(\mathrm{~s}, 3 \mathrm{H}) 3.38-3.51(\mathrm{~m}, 1 \mathrm{H}) 3.33(\mathrm{~s}, 3 \mathrm{H}) 3.25(\mathrm{t}, J=11.96,1 \mathrm{H}) 3.12$ (br. s, 1 H ), 2.91 (dd, $J=13.18,1.95 \mathrm{~Hz}, 1 \mathrm{H}) 2.69-2.81$ (m, 1 H$) 2.41-2.57$ (m, 2 H ) $2.34-2.41(\mathrm{~m}, 1 \mathrm{H}) 2.29(\mathrm{dd}, J=10.99,2.20,1 \mathrm{H}) 1.83(\mathrm{ddd}, J=12.30,12.30,12.30,1 \mathrm{H})$ $1.53(\mathrm{~s}, 3 \mathrm{H}) 1.47-1.52(\mathrm{~m}, 1 \mathrm{H}) 1.42(\mathrm{dd}, J=13.18,11.23 \mathrm{~Hz}, 1 \mathrm{H}) 1.33(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta: 206.34,159.39,158.08,144.80,139.10,135.86,134.26$, 130.97, 129.71 (2C), 129.44 (2C), 126.70 (2C), 124.83, 120.42, 118.89, 114.05 (2C), 112.94, 101.09, 82.33, 82.13, 72.51, 71.67, 62.61, 61.21, 56.08, 55.52, 55.39, 53.68, 46.76, 40.03, 38.24, 28.99, 22.68, 21.76; IR 3500 (br m), 2956(m), 2926(s), 2853(m), 1721(m), 1612(m), 1583(w), 1513(m), 1492(m), 1462(m), 1441(w), 1363(s), 1278(m), 1247(s), 1170(s), 1144(m), 1102(s), 1087(s), 1033(s), 973(m), 909(w), 846(w), 810(s),

[^49]731(m), 703(w), 657(m), 627(w); LRMS (APCI) $675.3[M+H]^{+} ;[\alpha]^{24}{ }_{D}+70.8^{\circ}(c 1.00$, $\mathrm{CHCl}_{3}$ ).

The 1-D NOESY spectra ( $600 \mathrm{MHz}, \mathrm{C}_{6} \mathrm{D}_{6}$ ) displayed the following nOe transfers:
Irradiation of C17 ( $\delta 4.07$ ): $1.79 \% 19 \alpha(\delta 1.83)$
Irradiation of C16 ( $\delta 2.29$ ): 1.69\% CHO ( $\delta 9.83$ ),

$$
3.34 \% \mathrm{C} 20(\delta 1.33)
$$



32
$3.63 \% \mathrm{C} 21 \alpha(\delta 3.25), 2.55 \% \mathrm{C} 14 \alpha(\delta 2.91)$
Irradiation of C20 ( $\delta 1.33$ ): 2.00\% C18 ( $\delta 3.41$ ),
$0.75 \% \mathrm{C} 5 \beta(\delta 2.72) .1 .94 \% \mathrm{C} 21 \beta(\delta 2.44)$


## Enal (33)

A flame-dried $50-\mathrm{mL}$ round-bottom flask was charged with aldol adduct 32 ( 208 mg , $0.31 \mathrm{mmol}, 1$ equiv) and azeotroped twice with benzene and placed on high vacuum for 15 min . A stir bar and and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(7 \mathrm{~mL})$ were added and the flask was cooled to $0{ }^{\circ} \mathrm{C}$. To the stirred solution under nitrogen at $0{ }^{\circ} \mathrm{C}$ was added 7 mL of the following stock solution: ( 39 mg DMAP, $520 \mu \mathrm{LEt}_{3}$, and $14 \mathrm{~mL} \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ). The amounts added were: DMAP ( $19.5 \mathrm{mg}, 0.16 \mathrm{mmol}, 0.5$ equiv) and $\mathrm{NEt}_{3}(260 \mu \mathrm{~L}, 3.5 \mathrm{mmol}, 11.4$ equiv).

TFAA was added to the cooled solution, neat via microliter syringe ( $236 \mu \mathrm{~L}, 0.75 \mathrm{mmol}$, 2.4 equiv) which caused an immediate color change from pale yellow to dark orange-red. After addition was complete, the ice bath was removed and the reaction was stirred at rt for 30 m . The stir bar was removed and the contents of the flask were concentrated in vacuo. The flask containing the crude product was charged with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(20 \mathrm{~mL})$ and diisopropyl amine ( $135 \mu \mathrm{~L}, 1.85 \mathrm{mmol}, 6.0$ equiv), and the contents were stirred at room temperature overnight. The contents were washed twice with DI $\mathrm{H}_{2} \mathrm{O}(10 \mathrm{~mL})$, and the aqueous layer was re-extracted twice with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 10 \mathrm{~mL})$. The combined organics were dried over Na2SO4, filtered, and concentrated. The residue was purified by flash chromatography (Biotage, 20-50\% EtOAc/hexanes) to afford enal 33 as an orange solid $\left(131 \mathrm{mg}, 0.19 \mathrm{mmol}, 63 \%\right.$ yield). $\mathrm{R} f=0.54$ ( $100 \% \mathrm{EtOAc}$ ); ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 10.46(\mathrm{~s}, 1 \mathrm{H}, \mathrm{CHO}) 7.67(\mathrm{~d}, J=2.34 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 12) 7.46(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}) 7.26$ (d, $J=8.79 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{PMB}) 7.19$ (d, $J=8.49 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 10) 7.08$ (d, $J=8.49 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{Ts}$ ) 6.86-6.89 (m, 2 H, PMB) 6.85 (dd, $J=8.49,2.34 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 9) 4.53$ (sk d, $J=11.42 \mathrm{~Hz}, 1$ H, PMB Bn) 4.51 (sk d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn}) 4.39$ (dd, $J=3.22,0.88 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 17)$ 4.36 (br. d, $J=10.54 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 3) 4.23$ (dd, $J=12.89,2.34 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 3.87$ (s, 3 H , PMB) $3.84(\mathrm{q}, J=3.22 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 18) 3.78(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeOAr}) 3.43-3.51(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 21)$ 3.45 (s, $3 \mathrm{H}, \mathrm{C} 17 \mathrm{OMe}$ ) 3.27 (ddd, $J=11.50,8.57,5.42 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 5) 3.14$ (dd, $J=12.89$, $4.98 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 21) 2.84$ (ddd, $J=11.42,5.56,3.80 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 5) 2.65-2.75(\mathrm{~m}, 3 \mathrm{H}$, C6(2), C20) 2.32 (dd, $J=12.89,10.84 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 2.28(\mathrm{~s}, 3 \mathrm{H}, \mathrm{Ts}) 2.14$ (ddd, $J=14.64$, 7.61, $2.93 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 19) 1.57-1.60(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 19) .{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ : $190.23,161.72,159.01,158.03,144.64,138.32,134.58,134.29,130.53,130.50,129.63$ (2C), 128.96 (2C), 126.27 (2C), 123.97, 119.15, 118.91, 113.73 (2C), 112.70, 100.33,
$72.27,70.38,70.29,62.87,59.67,58.38,55.79,55.17,44.81,33.95,32.24,25.39,22.23$, 21.45; FTIR (neat, $\left.\mathrm{cm}^{-1}\right) 2924(\mathrm{~m}), 2874(\mathrm{~m}), 2835(\mathrm{~m}), 1726(\mathrm{w}), 1663(\mathrm{~s}), 1612(\mathrm{~s})$, 1581(w), 1512(m), 1493(m), 1453(m), 1440(m), 1361(s), 1304(w), 1245(s), 1170(s), 1103(s), 1080(s), 1034(s), 983(m), 946(w), 924(m), 845(w), 811(m), 731(m), 674(s), 657(s), 617(w); LRMS (APCI) $657.3[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}} 224.8^{\circ}\left(c 0.83, \mathrm{CHCl}_{3}\right)$.


## Saturated Aldehyde (34)

A $20-\mathrm{mL}$ vial equipped with a stir bar was charged sequentially with enal $33(10 \mathrm{mg}$, $0.015 \mathrm{mmol}, 1$ equiv), $\mathrm{EtOH}(2.5 \mathrm{~mL})$, and $\mathrm{PtO}_{2}(9 \mathrm{mg}, 0.040 \mathrm{mmol}, 2.6$ equiv). The uncapped vial was placed in a Paar hydrogenation bomb over a stir place, and the bomb was charged with $\mathrm{H}_{2}$ gas ( 48 atm ). The solution was stirred at room temperature at this pressure for 65 h , after which point the bomb was carefully vented. The contents of the vial were filtered through a short plug of Celite ${ }^{\circledR}$ into a $10-\mathrm{mL}$ round-bottom flask and concentrated in vacuo to afford an orange solid that was carried on to the next step without purification. [The ${ }^{1} \mathrm{H}$ NMR spectrum of one of the products, saturated alcohol $\mathbf{5 0}$, is: ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta \mathrm{ppm} 7.58(\mathrm{~d}, J=2.34 \mathrm{~Hz}, 1 \mathrm{H}) 7.46(\mathrm{~d}, J=8.20 \mathrm{~Hz}, 2 \mathrm{H})$ $7.30(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 2 \mathrm{H}) 7.12(\mathrm{~d}, J=8.49 \mathrm{~Hz}, 1 \mathrm{H}) 7.07(\mathrm{~d}, J=7.91 \mathrm{~Hz}, 2 \mathrm{H}) 6.87-6.94(\mathrm{~m}$, 2 H) 6.79 (dd, $J=8.49,2.05 \mathrm{~Hz}, 1 \mathrm{H}) 4.58$ (d, $J=11.42 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn}) 4.44$ (d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn}) 4.35$ (d, $J=11.42 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 3) 4.30$ (br. s., $1 \mathrm{H}, \mathrm{CHHOH})$
$4.03(\mathrm{~d}, J=10.54 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CHHOH}) 3.84(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.82(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.78(\mathrm{t}$, $J=13.03 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 21) 3.72-3.75(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 18) 3.71$ (br. s., $1 \mathrm{H}, \mathrm{C} 17) 3.39(\mathrm{~s}, 3 \mathrm{H}$, MeO) 3.23-3.30(m, 1H) 2.81 (dd, $J=13.18,3.81 \mathrm{~Hz}, 1 \mathrm{H}) 2.57-2.77(\mathrm{~m}, 4 \mathrm{H}) 2.53(\mathrm{~d}$, $J=14.35 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 2.40-2.47(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 16) 2.33-2.40(\mathrm{~m}, 1 \mathrm{H}, \mathrm{C} 15) 2.21-2.30(\mathrm{~m}$, $1 \mathrm{H}, \mathrm{C} 20) 2.27$ (s, $3 \mathrm{H}, \mathrm{Ts}$ ) 1.86 (ddd, $J=14.86,6.08,3.37 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 19) 1.76$ (ddd, $J=14.13,11.79,4.83 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 14) 1.68(\mathrm{~d}, J=14.94 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 19)]$.

The flask containing the crude hydrogenation product was charged with a stir bar and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{~mL})$ and cooled to $0{ }^{\circ} \mathrm{C}$. To this solution was added the Dess-Martin periodinane ( $19.3 \mathrm{mg}, 0.046 \mathrm{mmol}, 3.0$ equiv). The reaction mixture was stirred for 2 h , at which point it was first diluted with $\mathrm{Et}_{2} \mathrm{O}(3 \mathrm{~mL})$ and then quenched by pouring the solution into 6 mL of a $1: 1$ mixture of saturated aqueous $\mathrm{NaHCO}_{3}$ and $10 \%$ aqueous sodium thiosulfate. The contents were stirred vigorously for 1 h and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 5 \mathrm{~mL})$. The organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated. The crude residue was purified by flash chromatography (Davisil ${ }^{\mathrm{TM}}, 20-50 \% \mathrm{EtOAc} /$ hexanes ) to afford saturated aldehyde $34(4.0 \mathrm{mg}, 0.0061 \mathrm{mmol}, 40 \%$ yield $)$.


Saturated Ester (53)
A 1-dram vial containing aldehyde $34(4.0 \mathrm{mg}, 0.0061 \mathrm{mmol}, 1$ equiv) was charged with a stir bar, $t$ - $\mathrm{BuOH}(300 \mu \mathrm{~L}), \mathrm{H}_{2} \mathrm{O}(200 \mu \mathrm{~L})$ and 2-methyl-2-butene $(91 \mu \mathrm{~L}, 0.86 \mathrm{mmol}$,

140 equiv). To this mixture, cooled to $0{ }^{\circ} \mathrm{C}$, were added $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ ( $3.8 \mathrm{mg}, 0.027 \mathrm{mmol}$, 4.5 equiv) followed by $\mathrm{NaClO}_{2}$ ( $80 \%$ technical grade, $3.1 \mathrm{mg}, 0.027 \mathrm{mmol}, 4.5$ equiv) as solids. After 2 h , the reaction was determined to be complete (based on consumption of starting material by LC/MS). The reaction was diluted with DI $\mathrm{H}_{2} \mathrm{O}$ and extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \times 1 \mathrm{~mL})$. The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo to afford the crude carboxylic acid as a pale yellow solid. The crude product, in an uncapped vial, was dissolved in EtOAc $(\sim 3 \mathrm{~mL})$ and treated with a solution of $\mathrm{CH}_{2} \mathrm{~N}_{2}\left(1 \mathrm{M}\right.$ in $\left.\mathrm{Et}_{2} \mathrm{O}\right)$ dropwise (8 drops) until a bright yellow color persisted. The solution was stirred for 2 min , after which excess $\mathrm{CH}_{2} \mathrm{~N}_{2}$ and the solvent were removed by a positive pressure of $\mathrm{N}_{2}$. The resultant residue was purified by flash column chromatography (DavisilTM, 20-50\% EtOAc/hexanes) to afford saturated ester 53 as a yellow-orange solid ( $3.6 \mathrm{mg}, 0.005 \mathrm{mmol}, 86 \%$ yield). ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ ppm 7.58 (d, $J=1.95 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 12) 7.45(\mathrm{~d}, J=8.79 \mathrm{~Hz}, 2 \mathrm{H}) 7.31(\mathrm{~d}, J=8.30 \mathrm{~Hz}, 2 \mathrm{H})$ 7.12 (d, $J=8.30 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 9) 7.07$ (d, $J=8.30 \mathrm{~Hz}, 2 \mathrm{H}) 6.86-6.96$ (m, 2 H$) 6.79$ (dd, $J=8.55,2.20 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 10) 4.56$ (d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{PMB} \mathrm{Bn}) 4.50$ (d, $J=11.72 \mathrm{~Hz}, 1 \mathrm{H}$, PMB Bn) $4.14(\mathrm{~d}, J=11.23 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 3) 3.84(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.83(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.80(\mathrm{~s}, 3$ H, MeO) 3.78-3.80 (m, 1 H, C17) $3.72(\mathrm{~d}, J=2.90 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 18) 3.63(\mathrm{t}, J=12.94 \mathrm{~Hz}, 1$ H, C21) $3.40(\mathrm{dd}, J=12.70,2.93 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 16) 3.30(\mathrm{~s}, 3 \mathrm{H}, \mathrm{MeO}) 3.14-3.23(\mathrm{~m}, 1 \mathrm{H}$, C5) 2.76 (dd, $J=13.43,4.15 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 21) 2.63-2.72(\mathrm{~m}, 2 \mathrm{H}, \mathrm{C} 6, \mathrm{C} 5) 2.50-2.63(\mathrm{~m}, 3$ H, C6, C15, C14) 2.20-2.31 (m, $1 \mathrm{H}, \mathrm{C} 20$ ) 2.27 (s, $3 \mathrm{H}, \mathrm{Ts}-\mathrm{Me}$ ) $1.84-1.94$ (m, 1 H , C19) 1.73-1.84 (m, $1 \mathrm{H}, \mathrm{C} 14) 1.64(\mathrm{~d}, J=15.14 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{C} 19)$.

The 1-D NOESY spectra ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) displayed the following nOe transfers: Irradiation of C21 ( $\delta 3.63$ ): 5.2\% C3 ( $\delta 4.14$ ),


$$
0.94 \% \mathrm{C} 16(\delta 2.25)
$$

Irradiation of C3 ( $\delta 4.50$ ): 2.1\% C16 ( $\delta 2.25$ ),

$$
1.4 \% o \text {-CHTs ( } \delta 7.45 \text { ) }
$$

Irradiation of C16 ( $\delta 3.40): 2.3 \% \mathrm{C} 3$ (4.14), 3.4\% C21 $\alpha$ (3.63), 3.0\% C17 (3.80)


32


56

Pentacyclic methyl ester (56)
Aldol adduct 32 ( $100 \mathrm{mg}, 0.148 \mathrm{mmol}$, 1 equiv.) was dissolved in $t-\mathrm{BuOH}(2.5 \mathrm{~mL}), \mathrm{H}_{2} \mathrm{O}$ $(2.5 \mathrm{~mL})$ and acetone $(1.4 \mathrm{~mL})$ in a $25-\mathrm{mL}$ round-bottom flask. 2-methyl-2-butene (58 $\mu \mathrm{L}, 0.55 \mathrm{mmol}, 3.7$ equiv.) was then added via microliter syringe, followed by $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ ( $92 \mathrm{mg}, 0.67 \mathrm{mmol}, 4.5$ equiv.) and $\mathrm{NaClO}_{2}(80 \%$ technical grade, $75 \mathrm{mg}, 0.67 \mathrm{mmol}, 4.5$ equiv.) as solids. The biphasic reaction was stirred vigorously 1.5 h , after which saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(5 \mathrm{~mL})$ was added. The reaction mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \mathrm{x}$ 10 mL ) and the combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The resultant yellow solid was suspended in EtOAc $(10 \mathrm{~mL})$, to which EtOH was added dropwise until the reaction mixture was homogenous ( $\sim 4 \mathrm{~mL}$ ). To this was added a solution of $\mathrm{CH}_{2} \mathrm{~N}_{2}\left(1 \mathrm{M}\right.$ in $\left.\mathrm{Et}_{2} \mathrm{O}\right)$ dropwise until a bright yellow color persisted ( $\sim 200$ $\mu \mathrm{L}$ ). Excess $\mathrm{CH}_{2} \mathrm{~N}_{2}$ and solvent were removed by evaporation under a steady stream of nitrogen, followed by high vacuum ( $\sim 5 \mathrm{~min}$ ). The residue was purified by flash chromatography (silica gel, $20-100 \% \mathrm{EtOAc}$ in hexanes) to provide the ester 56 (74.9
$\mathrm{mg}, 0.11 \mathrm{mmol}, 72 \%$ yield $) . \mathrm{R} f=0.44(100 \% \mathrm{EtOAc}) ;{ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 7.66 (d, $J=2.29 \mathrm{~Hz}, 1 \mathrm{H}) 7.48$ (d, $J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 7.29$ (d, $J=8.70 \mathrm{~Hz}, 2 \mathrm{H}) 7.12$ (d, $J=8.24 \mathrm{~Hz}, 1 \mathrm{H}) 7.08(\mathrm{~d}, J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 6.88(\mathrm{~d}, J=8.70 \mathrm{~Hz}, 2 \mathrm{H}) 6.81(\mathrm{dd}, J=8.70,2.29$ Hz, 1 H) $4.63(\mathrm{~d}, J=11 \mathrm{~Hz}, 1 \mathrm{H}) 4.60(\mathrm{~d}, J=11.45 \mathrm{~Hz}, 1 \mathrm{H}) 4.54(\mathrm{~d}, J=10.53 \mathrm{~Hz}, 1 \mathrm{H}) 3.84$ $-3.89(\mathrm{~m}, 1 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}) 3.80(\mathrm{~s}, 3 \mathrm{H}) 3.54(\mathrm{~s}, 3 \mathrm{H}) 3.39-3.48(\mathrm{~m}, 1$ H) $3.22(\mathrm{~s}, 1 \mathrm{H}) 3.16(\mathrm{t}, J=11.68 \mathrm{~Hz}, 1 \mathrm{H}) 3.02-3.11(\mathrm{~m}, 1 \mathrm{H}) 2.62-2.75(\mathrm{~m}, 3 \mathrm{H}) 2.52$ - 2.62 (m, 1 H) 2.37 (dd, $J=12.36,1.83 \mathrm{~Hz}, 1 \mathrm{H}) 2.34(\mathrm{~d}, J=10.99 \mathrm{~Hz}, 1 \mathrm{H}) 2.27(\mathrm{~s}, 3 \mathrm{H})$ $1.61-1.76(\mathrm{~m}, 3 \mathrm{H}) 1.57(\mathrm{dd}, J=13.05,11.22 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(126 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ : $174.09,159.23,157.91,144.66,138.86,134.30,130.98,129.63$ (2C), 129.32 (2C), 126.57 (2C), $124.71,119.92,118.75,113.91$ (2C), 112.77, 100.89, 83.52, 81.57, 71.72, $70.98,61.12,57.76,55.95,55.41,55.35,53.54,52.34,46.30,39.62,37.76,31.71,29.23$, 22.54, 21.65; IR 3004 (w), 2929 (m), 1717 (m), 1613 (m), 1514 (m), 1493 (m), 1439 (m), 1365 (s), 1280 (m), 1211 (m), 1172 (s), 1147 (m), 1108 (m), 1036 (m), 992 (w), 848 (m), 757 (s), 667 (s) LRMS (APCI) $705.3[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}+142.7^{\circ}\left(c 1.04, \mathrm{CHCl}_{3}\right)$.


## Unsaturated methyl ester (57)

A $25-\mathrm{mL}$ round-bottom flask with stir bar was charged with tertiary alcohol 56 ( 50.9 mg , $0.072 \mathrm{mmol}, 1$ equiv.), which had been azeotroped from benzene twice and placed under high vacuum for 30 min . The alcohol was dissolved in THF ( 3.6 mL ), and the flask was
cooled to $-78^{\circ} \mathrm{C}$ under a positive pressure of argon. A $1.3 \mathrm{M} n$-butyllithium solution in hexanes ( $110 \mu \mathrm{~L}, 0.144 \mathrm{mmol}, 2$ equiv.) was added dropwise, and the solution was stirred 10 min , after which trifluoroacetic anhydride ( $50.9 \mu \mathrm{~L}, 0.36 \mathrm{mmol}, 5$ equiv.) was added. The reaction mixture was allowed to come to rt over 3 h and was then quenched at $0{ }^{\circ} \mathrm{C}$ by slow addition of $\mathrm{H}_{2} \mathrm{O}$. The crude reaction mixture was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ ( $3 \times 5$ mL ), and the combined organics were washed with a saturated aqueous $\mathrm{NaHCO}_{3}$ solution (1 x 5 mL ), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo to afford 60.4 mg of an orange solid. This material consisted of a 3:1 mixture of the tertiary trifluoroacetate to alcohol starting material and was carried forward without further purification. The crude trifluoroacetate, which was azeotroped twice from benzene and placed under high vacuum for 30 min , was transferred to a $25-\mathrm{mL}$ sealed tube and dissolved in 11.5 mL toluene. To this solution was added a stir bar and freshly distilled DBU ( $86 \mu \mathrm{~L}, 10$ equiv.) at rt. The flask was then sealed and immersed in a $110{ }^{\circ} \mathrm{C}$ oil bath, and the solution was stirred at this temperature for 15 h . The reaction was removed from the oil bath and the solution was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, $1 \% \mathrm{EtOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ ) to provide the unsaturated methyl ester 57 as a pale yellow solid $(18.0 \mathrm{mg}, 0.026 \mathrm{mmol}, 36 \%$ yield $) .{ }^{1} \mathrm{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ 7.64 (d, $J=1.83 \mathrm{~Hz}, 1 \mathrm{H}) 7.47$ (d, $J=8.42 \mathrm{~Hz}, 2 \mathrm{H}) 7.31$ (d, $J=8.42 \mathrm{~Hz}, 2 \mathrm{H}) 7.16$ (d, $J=8.78 \mathrm{~Hz}, 1 \mathrm{H}) 7.07(\mathrm{~d}, J=8.05 \mathrm{~Hz}, 2 \mathrm{H}) 6.88(\mathrm{~d}, J=8.78 \mathrm{~Hz}, 2 \mathrm{H}) 6.82(\mathrm{dd}, J=8.42,2.20$ Hz, 1 H) $4.61(\mathrm{~s}, 2 \mathrm{H}) 4.27(\mathrm{~d}, J=6.59 \mathrm{~Hz}, 1 \mathrm{H}) 4.08(\mathrm{~d}, J=11.34 \mathrm{~Hz}, 1 \mathrm{H}) 3.88$ ( $\mathrm{s}, 3 \mathrm{H})$ $3.86(\mathrm{~s}, 3 \mathrm{H}) 3.80(\mathrm{~s}, 3 \mathrm{H}) 3.63-3.75(\mathrm{~m}, 2 \mathrm{H}) 3.54(\mathrm{~s}, 3 \mathrm{H}) 3.06-3.25(\mathrm{~m}, 1 \mathrm{H}) 3.12(\mathrm{dd}$, $J=12.81,5.12 \mathrm{~Hz}, 1 \mathrm{H}) 2.88(\mathrm{t}, J=12.08 \mathrm{~Hz}, 1 \mathrm{H}) 2.67-2.79(\mathrm{~m}, 2 \mathrm{H}) 2.54-2.67(\mathrm{~m}, 2$ H) $2.27(\mathrm{~s}, 3 \mathrm{H}) 2.16-2.25(\mathrm{~m}, 1 \mathrm{H}) 1.94-2.07(\mathrm{~m}, 1 \mathrm{H}) 1.27-1.41(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR
(126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta 168.60,159.12,157.87,144.43,143.76,138.52,135.39,134.38$, $130.71,129.47,129.24,126.60,126.43,124.24,119.22,118.79,113.79,112.59,100.54$, $80.01,71.10,61.99,59.89,58.96,55.82,55.25,51.72,45.59,34.25,33.71,29.68,29.12$, 22.31, 21.49; IR 2925(m), 1720 (m), 1613 (w), 1513 (m), 1366 (m), 1248 (m), 1172 (m), $1115(\mathrm{~m}), 911(\mathrm{~s}), 813(\mathrm{~m}), 734(\mathrm{~s}), 669(\mathrm{~m}) ;$ LRMS (APCI) $687.4[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{24}{ }_{\mathrm{D}}$ $+162.4\left(c \quad 1.01, \mathrm{CHCl}_{3}\right)$.

$N$-tosyl, 18-(4-methoxybenzyloxy)-methyl reserpate (60)
A 2-mL Biotage microwave vial was brought into a glove box and charged with a stir bar and unsaturated ester 57 ( $5.0 \mathrm{mg}, 7.3 \mu \mathrm{~mol}, 1$ equiv.) which had been azeotroped from benzene (3x) and placed under high vacuum for 30 min . Iridium complex $64(11.0 \mathrm{mg}$, $7.3 \mu \mathrm{~mol}, 1$ equiv.) was added to the vial followed by $\mathrm{CH}_{2} \mathrm{Cl}_{2}(360 \mu \mathrm{~L})$, which had been degassed through three freeze-pump-thaw cycles. The vial was sealed with a Teflon-lined pressure seal cap and transferred out of the glove box. The vial was evacuated and backfilled with $\mathrm{H}_{2}(4 \mathrm{x})$, after which it was stirred 16 h at rt under a balloon of $\mathrm{H}_{2}$. The reaction mixture was then concentrated in vacuo. Analysis of the crude reaction mixture by ${ }^{1} \mathrm{H}$ NMR (comparison of the PMB Bn signals) showed a 6:1 diastereomeric ratio of olefin hydrogenation products. The mixture was purified by preparatory thin layer chromatography to provide recovered unsaturated ester $57(2.3 \mathrm{mg}, 3.3 \mu \mathrm{~mol}, 46 \%$
recovered starting material) and the desired saturated ester $\mathbf{6 0}$ as a white solid ( 2.2 mg , $3.2 \mu \mathrm{~mol}, 44 \%$ yield, $81 \%$ based on recovered starting material). $\mathrm{R} f=0.51$ (EtOAc); ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 7.61(\mathrm{~d}, J=2.29 \mathrm{~Hz}, 1 \mathrm{H}) 7.32(\mathrm{~d}, J=8.24 \mathrm{~Hz}, 2 \mathrm{H}), 7.32(\mathrm{~m}, 2$ H), 7.05 (d, $J=8.70 \mathrm{~Hz}, 1 \mathrm{H}) 7.02$ (d, $J=8.24 \mathrm{~Hz}, 2 \mathrm{H}) 6.90(\mathrm{~d}, J=8.70 \mathrm{~Hz}, 2 \mathrm{H}) 6.80$ (dd, $J=8.24,2.29 \mathrm{~Hz}, 1 \mathrm{H}) 4.64(\mathrm{~d}, J=10.99 \mathrm{~Hz}, 1 \mathrm{H}) 4.58(\mathrm{~d}, J=10.99 \mathrm{~Hz}, 1 \mathrm{H}) 4.40$ (dd, $J=5.27,2.52 \mathrm{~Hz}, 1 \mathrm{H}) 3.89(\mathrm{~s}, 3 \mathrm{H}) 3.88(\mathrm{~s}, 3 \mathrm{H}) 3.83(\mathrm{~s}, 3 \mathrm{H}) 3.72(\mathrm{dd}, J=10.99,9.16 \mathrm{~Hz}$, $1 \mathrm{H}) 3.67(\mathrm{~s}, 3 \mathrm{H}) 3.33-3.42(\mathrm{~m}, 1 \mathrm{H}) 3.12(\mathrm{dd}, J=13.28,5.49 \mathrm{~Hz}, 1 \mathrm{H}) 2.93-3.03(\mathrm{~m}, 1$ H) $2.79(\mathrm{dd}, J=11.45,4.58 \mathrm{~Hz}, 1 \mathrm{H}) 2.85(\mathrm{ddt}, J=17.06,5.72,2.80,2.80 \mathrm{~Hz}, 1 \mathrm{H}) 2.64(\mathrm{dt}$, $J=14.54,3.03 \mathrm{~Hz}, 1 \mathrm{H}) 2.52(\mathrm{dd}, J=10.99,5.04 \mathrm{~Hz}, 1 \mathrm{H}) 2.34(\mathrm{dd}, J=11.68,1.60 \mathrm{~Hz}, 1 \mathrm{H})$ $2.27(\mathrm{~s}, 3 \mathrm{H}) 2.15-2.26(\mathrm{~m}, 2 \mathrm{H}) 2.09(\mathrm{td}, J=13.28,11.90 \mathrm{~Hz}, 1 \mathrm{H}) 1.92-2.01(\mathrm{~m}, 1 \mathrm{H})$ $1.87(\mathrm{dt}, J=13.16,3.95 \mathrm{~Hz}, 1 \mathrm{H}) 1.72(\mathrm{~d}, J=12.36 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 172.51,159.01,157.97,144.23,140.33,135.72,132.38,131.12,129.12$ (2C), 128.82 (2C), 126.74, 125.65, 123.95, 118.49, 113.72, 113.06, 102.50, 82.88, 79.37, 71.19, 61.13, $56.27,55.89,55.26,52.06,51.89,50.66,50.08,33.63,32.33,30.36,26.27,21.49,18.15$.; FTIR (neat, $\mathrm{cm}^{-1}$ ); 2930 (br m), 1737 (m), 1614 (m), 1514 (m), 1364 (m), 1278 (m), 1171 (s), $1093(\mathrm{~m}), 911(\mathrm{w}), 814(\mathrm{w}), 735(\mathrm{~s}) ;$ LRMS (APCI) $689.3[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}+166.0(c$ $\left.1.35, \mathrm{CHCl}_{3}\right)$.

$N$-tosyl-methyl reserpate (S2)

A 2-dram vial with a septum cap and stir bar was charged with PMB ether $60(11.4 \mathrm{mg}$, $16.5 \mu \mathrm{~mol}$, 1 equiv.), followed by $\mathrm{CH}_{2} \mathrm{Cl}_{2}(1.1 \mathrm{~mL})$ and 1,3-dimethoxybenzene ( $6.5 \mu \mathrm{~L}$, $49.5 \mu \mathrm{~mol}$, 3 equiv.). The vial was cooled to $0{ }^{\circ} \mathrm{C}$, and a TfOH solution in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(44 \mu \mathrm{~L}$ of a $50 \mu \mathrm{~L} \mathrm{TfOH} / 1 \mathrm{~mL} \mathrm{CH}_{2} \mathrm{Cl}_{2}, 24.7 \mu \mathrm{~mol}, 1.5$ equiv.) was added dropwise via microliter syringe. Consumption of the starting material was monitored using LC/MS (APCI). Upon completion ( $\sim 30 \mathrm{~min}$ after addition of TfOH ), the reaction was quenched with a half-saturated aqueous solution of $\mathrm{NaHCO}_{3}(1 \mathrm{~mL})$ and diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(0.5 \mathrm{~mL})$. The layers were separated and the aqueous layer was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(3 \times 1 \mathrm{~mL})$. The combined organic layers were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The resultant residue was purified (silica gel, $5-10 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$, followed by an eluent of 10:1:1:1 EtOAc: $\mathrm{H}_{2} \mathrm{O}: \mathrm{MeOH}$ : acetone), to afford alcohol $\mathbf{S 2}$ as a pale yellow solid ( $8.1 \mathrm{mg}, 14.2 \mu \mathrm{~mol}, 86 \%$ yield). $\mathrm{R} f=0.28$ (10:1:1:1 EtOAc: $\mathrm{H}_{2} \mathrm{O}: \mathrm{MeOH}$ : acetone); ${ }^{1} \mathrm{H} \operatorname{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta: 7.60(\mathrm{~d}, J=1.95 \mathrm{~Hz}, 1 \mathrm{H}) 7.31(\mathrm{~d}, J=8.30 \mathrm{~Hz}, 2 \mathrm{H}) 7.04(\mathrm{~d}$, $J=8.30 \mathrm{~Hz}, 1 \mathrm{H}) 7.01$ (d, $J=7.81 \mathrm{~Hz}, 2 \mathrm{H}) 6.78$ (dd, $J=8.30,2.44 \mathrm{~Hz}, 1 \mathrm{H}) 4.39$ (br. s., 1 H) $3.88(\mathrm{~s}, 3 \mathrm{H}) 3.87(\mathrm{~s}, 3 \mathrm{H}) 3.65(\mathrm{~s}, 3 \mathrm{H}) 3.58(\mathrm{td}, J=10.74,8.79 \mathrm{~Hz}, 1 \mathrm{H}) 3.52(\mathrm{~m}, 1 \mathrm{H})$ 3.11 (dd, $J=12.94,5.62 \mathrm{~Hz}, 1 \mathrm{H}) 2.96(\mathrm{td}, J=12.33,4.64 \mathrm{~Hz}, 1 \mathrm{H}) 2.76-2.87(\mathrm{~m}, 1 \mathrm{H})$ 2.79 (dd, $J=11.23,4.88 \mathrm{~Hz}, 1 \mathrm{H}) 2.64(\mathrm{dt}, J=14.41,3.30 \mathrm{~Hz}, 1 \mathrm{H}) 2.50(\mathrm{dd}, J=10.74,4.88$ Hz, 1 H) $2.35(\mathrm{~d}, J=11.72 \mathrm{~Hz}, 1 \mathrm{H}) 2.26(\mathrm{~s}, 3 \mathrm{H}) 2.07-2.23(\mathrm{~m}, 3 \mathrm{H}) 1.93-2.03(\mathrm{~m}, 1 \mathrm{H})$ $1.71-1.84(\mathrm{~m}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\left.\mathrm{CDCl}_{3}\right) \delta: 172.57,157.99,144.29,140.33$, $135.65,132.38,128.86$ (2C), 126.74 (2C), 125.64, 123.97, 118.54, 113.07, 102.51, 81.35, $75.30,61.18,56.27,55.90,51.98,51.44,50.65,50.05,33.79,32.79,32.52,26.43,21.50$, 18.21; FTIR (neat, $\mathrm{cm}^{-1}$ ); 1737 (m), 1614 (m), 1493 (w), 1365 (m), 1278 (w), 1254 (w),
$1172(\mathrm{~s}), 1089(\mathrm{~m}), 909(\mathrm{~m}), 812(\mathrm{w}), 735(\mathrm{~s}) ;$ LRMS (APCI) $569.2[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{23}{ }_{\mathrm{D}}{ }^{+}$ $211.3\left(c 0.81, \mathrm{CHCl}_{3}\right)$.


## (+)-Methyl reserpate (10)

A $20-\mathrm{mL}$ vial was charged with a stir bar, $\mathbf{S} 2(10.0 \mathrm{mg}, 0.018 \mathrm{mmol}, 1$ equiv.), and $\mathrm{MeOH}(3.2 \mathrm{~mL})$ under a positive pressure of $\mathrm{N}_{2}$. To this was added $\mathrm{Na}_{2} \mathrm{HPO}_{4}(75.1 \mathrm{mg}$, $0.51 \mathrm{mmol}, 30$ equiv.) as a solid in one portion, followed by $5 \%$-sodium/mercury amalgam ( $32 \mathrm{mg}, 0.070 \mathrm{mmol}, 4$ equiv.). The heterogeneous mixture was stirred vigorously at rt and consumption of the $\mathbf{S 2}$ was monitored using LC/MS (APCI). After 4 h, a second portion of $\mathrm{Na}_{2} \mathrm{HPO}_{4}(38 \mathrm{mg}, 0.26 \mathrm{mmol}, 15$ equiv.) was added, followed by 5\%-sodium/mercury amalgam ( $20 \mathrm{mg}, 0.043 \mathrm{mmol}, 2.7$ equiv.). Upon completion ( 1 h after second addition of reagents), the reaction mixture was transferred away from the bead of mercury that had formed, using $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$ to complete the transfer. The solution was washed with $\mathrm{H}_{2} \mathrm{O}(2 \times 5 \mathrm{~mL})$ and brine $(5 \mathrm{~mL})$, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The resultant residue was purified by flash chromatography $\left(10 \% \mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$ to afford, as a white solid, $\mathbf{1 0}(5.0 \mathrm{mg}, 0.012 \mathrm{mmol}, 69 \%) . \mathrm{R} f=$ 0.19 (10:1:1:1 EtOAc $: \mathrm{H}_{2} \mathrm{O}: \mathrm{MeOH}:$ acetone) $;{ }^{1} \mathrm{H}$ NMR data were in agreement with literature values. ${ }^{40}{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta$ : 173.17, 156.38, 136.78, 128.84,

[^50]$121.63,118.51,109.31,107.13,95.24,80.95,75.00,60.93,55.79,54.20,51.97,51.15$, $51.04,49.00,33.97,32.40,32.12,23.97,16.48$; FTIR (neat, $\mathrm{cm}^{-1}$ ); $3372(\mathrm{~m}), 2929(\mathrm{~m})$, 2852 (w), 1723 (m), 1629 (w), 1463 (m), 1279 (w), 910 (s), 732 (s); LRMS (APCI) 415.1 $[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{22}{ }_{\mathrm{D}}+96.8\left(c 0.23, \mathrm{CHCl}_{3}\right)$.


## Reserpine ( + )-( $\mathbf{( 1 )}{ }^{41}$

A 1-dram vial with a screw-top septum cap was charged with a stir bar, secondary alcohol (+)-10 ( $5.0 \mathrm{mg}, 0.012 \mathrm{mmol}, 1$ equiv.) and 3,4,5-trimethoxybenzoyl chloride ( $16.7 \mathrm{mg}, 0.072 \mathrm{mmol}, 5$ equiv). Freshly distilled pyridine ( $300 \mu \mathrm{~L}$ ) was added under argon, the vial was wrapped in aluminum foil, and the reaction mixture was allowed to stir at rt 4 d under argon. Upon completion of the reaction, the pyridine was removed in vacuo. The crude residue was cooled to $0{ }^{\circ} \mathrm{C}$, dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \mathrm{~mL})$ and treated dropwise with a saturated aqueous solution of $\mathrm{Na}_{2} \mathrm{CO}_{3}(2 \mathrm{~mL})$. The layers were separated, and the aqueous layer was extracted twice with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The combined organics were washed once with deionized water, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The resultant solid was purified by flash chromatography (silica gel, $70 \%$ EtOAc in hexanes) to provide (+)-reserpine ( $6.6 \mathrm{mg}, 0.011 \mathrm{mmol}, 90 \%$ yield) as an off-white solid. The synthetic sample of (+)-reserpine gave identical TLC $\mathrm{R} f,{ }^{1} \mathrm{H}$

[^51]NMR, and ${ }^{13} \mathrm{C}$ NMR data to a commercial sample of (-)-reserpine from Aldrich, and were in agreement with literature values ( $\left.{ }^{1} \mathrm{H} \mathrm{NMR},{ }^{13} \mathrm{C} \mathrm{NMR}\right) .{ }^{40,42} \mathrm{R} f=0.21$ (EtOAc) ${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta: 7.48$ (br. s, 1 H$) 7.34$ (d, $\left.J=8.79 \mathrm{~Hz}, 1 \mathrm{H}\right) 7.32$ (s, 2 H$) 6.85$ (d, $J=2.05 \mathrm{~Hz}, 1 \mathrm{H}) 6.78(\mathrm{dd}, J=8.64,2.20 \mathrm{~Hz}, 1 \mathrm{H}) 5.06(\mathrm{ddd}, J=11.64,9.45,4.98 \mathrm{~Hz}, 1$ H) 4.48 (br. s., 1 H$) 3.92(\mathrm{~s}, 9 \mathrm{H}) 3.91(\mathrm{~m}, 1 \mathrm{H}) 3.85(\mathrm{~s}, 3 \mathrm{H}) 3.82(\mathrm{~m}, 3 \mathrm{H}) 3.51(\mathrm{~s}, 3 \mathrm{H})$ 3.12 - 3.25 (m, 2 H) 3.06 (dd, $J=12.15,2.78 \mathrm{~Hz}, 1 \mathrm{H}) 2.96(\mathrm{~m}, 1 \mathrm{H}) 2.70(\mathrm{dd}, J=11.13$, $4.69 \mathrm{~Hz}, 1 \mathrm{H}) 2.44-2.54(\mathrm{~m}, 2 \mathrm{H}) 2.28-2.41(\mathrm{~m}, 2 \mathrm{H}) 2.04-2.12(\mathrm{~m}, 1 \mathrm{H}) 2.00(\mathrm{ddd}$, $J=12.67,4.17,0.73 \mathrm{~Hz}, 1 \mathrm{H}) 1.92(\mathrm{~d}, J=11.72 \mathrm{~Hz}, 1 \mathrm{H}) 1.80(\mathrm{~d}, J=14.64 \mathrm{~Hz}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (126 MHz, $\mathrm{CDCl}_{3}$ ) $\delta: 172.79,165.39,156.28,152.98,142.28,136.31,130.36$, $125.39,122.20,118.59,109.09,108.23,106.78,95.19,77.98,77.82,60.93,60.77,56.27$, $55.83,53.72,51.84,51.77,51.23,49.06,34.04,32.31,29.75,24.35,16.81$; IR 3433 (w), 2987 (w), 1730 (m), 1711 (m), 1587 (m), 1499 (m), 1456 (m), 1412 (m), 1331 (s), 1273 (s), 1249 (m), 1225 (s), 1186 (w), 1120 (s), 1062 (m), 1002 (m), 976 (m), 763 (m). LRMS (APCI) $609.2[\mathrm{M}+\mathrm{H}]^{+} ;[\alpha]^{22}{ }_{\mathrm{D}}+114.6\left(c 0.20, \mathrm{CHCl}_{3}\right)$.

[^52]2.10. Spectroscopic Comparisons of Synthetic (+)- and Commercial (-)-Reserpine
${ }^{1} \mathrm{H}$ NMR Spectra $\left(\mathrm{CDCl}_{3}, 600 \mathrm{MHz}\right)$


${ }^{13}$ C NMR Spectra $\left(\mathrm{CDCl}_{3}, 126 \mathrm{MHz}\right)$


## Circular Dichroism Spectra $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$



### 2.11. X-Ray Crystallographic Analysis of 60

## Acknowledgment

We thank Dr. Shao-Liang Zheng at the Center for Crystallographic Studies at Harvard University for X-ray data collection and structure determination. We thank Dr. Yu-Sheng Chen at ChemMatCARS, APS, for his assistance with single-crystal data. ChemMatCARS Sector 15 is principally supported by the National Science Foundation/Department of Energy under grant number NSF/CHE-0822838. Use of the Advanced Photon Source was supported by the U. S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357." (See: http://cars9.uchicago.edu/chemmat/pages/acknowledge.html)

## Procedure

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 along with the D8 Diffractometer ( $30 \mathrm{KeV}, \lambda=0.413280 \AA$ ), and equipped with an Oxford Cryosystems
nitrogen open flow apparatus. The collection method involved $0.5^{\circ}$ scans in Phi at $-5^{\circ}$ in 2日. Data integration down to $0.82 \AA$ resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again $F^{2}$ using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). 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 1, while geometric parameters are shown in Tables 2. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table 2.4. Experimental details

|  |  |
| :--- | :--- |
| naomil101_APS |  |
| Chemical formula data | $\mathrm{C}_{38} \mathrm{H}_{44} \mathrm{~N}_{2} \mathrm{O}_{8} \mathrm{~S}$ |
| $M_{\mathrm{r}}$ | 688.81 |
| Crystal system, space group | Triclinic, $P 1$ |
| Temperature (K) | 15 |
| $a, b, c(\AA)$ | $10.5400(9), 13.2962(12), 13.7619(13)$ |
| $\alpha, \beta, \gamma\left({ }^{\circ}\right)$ | $71.577(2), 89.697(2), 69.957(2)$ |
| $V\left(\AA^{3}\right)$ | $1707.4(3)$ |
| $Z$ | 2 |
| Radiation type | Synchrotron, $\lambda=0.41328 \AA$ |
| $\mu\left(\mathrm{~mm}{ }^{-1}\right)$ | 0.09 |
| Crystal size (mm) | $0.02 \times 0.01 \times 0.01$ |
| Data collection | Bruker D8 goniometer with CCD area detector diffractometer |
| Diffractometer | Multi-scan <br> $S A D A B S$ <br> Absorption correction <br> $T_{\text {min }}, T_{\text {max }}$ |

Table 2.4. (Continued).

| No. of measured, independent <br> and observed $[I>2 \sigma(I)]$ <br> reflections | $35992,11719,10083$ |
| :--- | :--- |
| $R_{\text {int }}$ | 0.075 |
| Refinement | $0.045,0.102,1.02$ |
| $R\left[F^{2}>2 \sigma\left(F^{2}\right)\right], w R\left(F^{2}\right), S$ | 11719 |
| No. of reflections | 887 |
| No. of parameters | 3 |
| No. of restraints | H-atom parameters constrained |
| H-atom treatment | $0.28,-0.34$ |
| $\Delta \rho_{\text {max }}, \Delta \rho_{\text {min }}\left(\right.$ e $\left.\AA^{-3}\right)$ | Flack H D (1983), Acta Cryst. A39, 876-881 |
| Absolute structure | $-0.28(16)$ |
| Flack parameter |  |

Computer programs: APEX2 v2009.3.0 (Bruker-AXS, 2009), SAINT 7.46A (Bruker-AXS, 2009), SHELXS97 (Sheldrick, 2008), SHELXL97 (Sheldrick, 2008), Bruker SHELXTL.

Table 2.5. Geometric parameters ( $\AA$, ${ }^{\circ}$ )

| S1-O1 | $1.424(2)$ | $\mathrm{S} 2-\mathrm{O} 12$ | $1.424(2)$ |
| :--- | :--- | :--- | :--- |
| $\mathrm{S} 1-\mathrm{O} 2$ | $1.429(2)$ | $\mathrm{S} 2-\mathrm{O} 11$ | $1.426(2)$ |
| $\mathrm{S} 1-\mathrm{N} 1$ | $1.679(2)$ | $\mathrm{S} 2-\mathrm{N} 3$ | $1.694(3)$ |
| $\mathrm{S} 1-\mathrm{C} 20$ | $1.757(3)$ | $\mathrm{S} 2-\mathrm{C} 60$ | $1.766(3)$ |
| $\mathrm{O} 3-\mathrm{C} 13$ | $1.433(4)$ | $\mathrm{O} 13-\mathrm{C} 43$ | $1.376(4)$ |
| $\mathrm{O} 3-\mathrm{C} 28$ | $1.433(4)$ | $\mathrm{O} 13-\mathrm{C} 67$ | $1.432(4)$ |
| $\mathrm{O} 4-\mathrm{C} 32$ | $1.360(4)$ | $\mathrm{O} 14-\mathrm{C} 68$ | $1.415(4)$ |
| $\mathrm{O} 4-\mathrm{C} 35$ | $1.435(4)$ | $\mathrm{O} 14-\mathrm{C} 53$ | $1.438(4)$ |
| $\mathrm{O} 5-\mathrm{C} 36$ | $1.409(4)$ | $\mathrm{O} 15-\mathrm{C} 72$ | $1.371(4)$ |
| $\mathrm{O} 5-\mathrm{C} 14$ | $1.441(4)$ | $\mathrm{O} 15-\mathrm{C} 75$ | $1.433(4)$ |
| $\mathrm{O} 6-\mathrm{C} 37$ | $1.354(4)$ | $\mathrm{O} 16-\mathrm{C} 76$ | $1.402(4)$ |
| $\mathrm{O} 6-\mathrm{C} 38$ | $1.450(4)$ | $\mathrm{O} 16-\mathrm{C} 54$ | $1.429(4)$ |
| $\mathrm{O} 7-\mathrm{C} 37$ | $1.193(4)$ | $1.349(4)$ |  |

Table 2.5. (Continued).

| O8-C3 | 1.365 (4) | O17-C78 | 1.438 (3) |
| :---: | :---: | :---: | :---: |
| O8-C27 | 1.414 (4) | O18-C77 | 1.202 (4) |
| N1-C1 | 1.438 (4) | N3-C41 | 1.431 (4) |
| N1-C19 | 1.446 (4) | N3-C59 | 1.447 (4) |
| N2-C9 | 1.465 (4) | N4-C49 | 1.463 (4) |
| N2-C10 | 1.474 (4) | N4-C50 | 1.480 (4) |
| N2-C18 | 1.479 (4) | N4-C58 | 1.483 (4) |
| C1-C6 | 1.388 (4) | C41-C42 | 1.390 (4) |
| $\mathrm{C} 1-\mathrm{C} 2$ | 1.394 (4) | C41-C46 | 1.394 (4) |
| C2-C3 | 1.396 (4) | C42-C43 | 1.385 (4) |
| C2-H2 | 0.9500 | C42-H42 | 0.9500 |
| C3-C4 | 1.390 (5) | C43-C44 | 1.403 (4) |
| C4-C5 | 1.377 (5) | C44-C45 | 1.387 (4) |
| C4-H4 | 0.9500 | C44-H44 | 0.9500 |
| C5-C6 | 1.398 (4) | C45-C46 | 1.396 (4) |
| C5-H5 | 0.9500 | C45-H45 | 0.9500 |
| C6-C7 | 1.448 (4) | C46-C47 | 1.440 (4) |
| C7-C19 | 1.349 (4) | C47-C59 | 1.346 (4) |
| C7-C8 | 1.498 (4) | C47-C48 | 1.496 (4) |
| C8-C9 | 1.539 (4) | C48-C49 | 1.534 (4) |
| C8-H8A | 0.9900 | C48-H48A | 0.9900 |
| С8-H8B | 0.9900 | C48-H48B | 0.9900 |
| C9—H9A | 0.9900 | C49-H49A | 0.9900 |
| C9—H9B | 0.9900 | C49-H49B | 0.9900 |
| C10-C11 | 1.518 (4) | C50-C51 | 1.516 (4) |
| C10-H10A | 0.9900 | C50-H50A | 0.9900 |
| C10-H10B | 0.9900 | C50-H50B | 0.9900 |
| C11-C16 | 1.526 (4) | C51-C52 | 1.520 (4) |
| C11-C12 | 1.527 (4) | C51-C56 | 1.540 (4) |
| C11-H11 | 1.0000 | C51-H51 | 1.0000 |
| C12-C13 | 1.525 (4) | C52-C53 | 1.515 (4) |

Table 2.5. (Continued).

| C12-H12A | 0.9900 | C52-H52A | 0.9900 |
| :---: | :---: | :---: | :---: |
| C12-H12B | 0.9900 | C52-H52B | 0.9900 |
| C13-C14 | 1.518 (4) | C53-C54 | 1.533 (4) |
| C13-H13 | 1.0000 | C53-H53 | 1.0000 |
| C14-C15 | 1.523 (4) | C54-C55 | 1.524 (4) |
| C14-H14 | 1.0000 | C54-H54 | 1.0000 |
| C15-C37 | 1.514 (4) | C55-C77 | 1.521 (4) |
| C15-C16 | 1.535 (4) | C55-C56 | 1.545 (4) |
| C15-H15 | 1.0000 | C55-H55 | 1.0000 |
| C16-C17 | 1.537 (4) | C56-C57 | 1.535 (4) |
| C16-H16 | 1.0000 | C56-H56 | 1.0000 |
| C17-C18 | 1.522 (4) | C57-C58 | 1.529 (4) |
| C17-H17A | 0.9900 | C57-H57A | 0.9900 |
| C17-H17B | 0.9900 | C57-H57B | 0.9900 |
| C18-C19 | 1.518 (4) | C58-C59 | 1.517 (4) |
| C18-H18 | 1.0000 | C58-H58 | 1.0000 |
| C20-C21 | 1.389 (4) | C60-C65 | 1.388 (4) |
| C20-C25 | 1.396 (4) | C60-C61 | 1.391 (4) |
| C21-C22 | 1.394 (4) | C61-C62 | 1.384 (4) |
| C21-H21 | 0.9500 | C61-H61 | 0.9500 |
| C22-C23 | 1.384 (5) | C62-C63 | 1.392 (4) |
| $\mathrm{C} 22-\mathrm{H} 22$ | 0.9500 | C62-H62 | 0.9500 |
| C23-C24 | 1.391 (5) | C63-C64 | 1.390 (4) |
| C23-C26 | 1.514 (4) | C63-C66 | 1.509 (4) |
| C24-C25 | 1.383 (4) | C64-C65 | 1.397 (4) |
| C24-H24 | 0.9500 | C64-H64 | 0.9500 |
| C25-H25 | 0.9500 | C65-H65 | 0.9500 |
| C26-H26A | 0.9800 | C66-H66A | 0.9800 |
| C26-H26B | 0.9800 | C66-H66B | 0.9800 |
| C26-H26C | 0.9800 | C66-H66C | 0.9800 |
| C27-H27A | 0.9800 | C67-H67A | 0.9800 |

Table 2.5. (Continued).

| C27-H27B | 0.9800 | C67-H67B | 0.9800 |
| :---: | :---: | :---: | :---: |
| C27-H27C | 0.9800 | C67-H67C | 0.9800 |
| C28-C29 | 1.505 (4) | C68-C69 | 1.511 (4) |
| C28-H28A | 0.9900 | C68-H68A | 0.9900 |
| C28-H28B | 0.9900 | C68-H68B | 0.9900 |
| C29-C30 | 1.377 (5) | C69-C70 | 1.382 (5) |
| C29-C34 | 1.396 (4) | C69-C74 | 1.388 (4) |
| C30-C31 | 1.394 (4) | C70-C71 | 1.379 (5) |
| C30-H30 | 0.9500 | C70-H70 | 0.9500 |
| C31-C32 | 1.383 (4) | C71-C72 | 1.393 (4) |
| C31-H31 | 0.9500 | C71-H71 | 0.9500 |
| C32-C33 | 1.395 (4) | C72-C73 | 1.401 (4) |
| C33-C34 | 1.365 (4) | C73-C74 | 1.382 (5) |
| C33-H33 | 0.9500 | C73-H73 | 0.9500 |
| C34-H34 | 0.9500 | C74-H74 | 0.9500 |
| C35-H35A | 0.9800 | C75-H75A | 0.9800 |
| C35-H35B | 0.9800 | C75-H75B | 0.9800 |
| C35-H35C | 0.9800 | C75-H75C | 0.9800 |
| C36-H36A | 0.9800 | C76-H76A | 0.9800 |
| C36-H36B | 0.9800 | C76-H76B | 0.9800 |
| C36-H36C | 0.9800 | C76-H76C | 0.9800 |
| C38-H38A | 0.9800 | C78-H78A | 0.9800 |
| C38-H38B | 0.9800 | C78-H78B | 0.9800 |
| C38-H38C | 0.9800 | C78-H78C | 0.9800 |
| $\mathrm{O} 1-\mathrm{S} 1-\mathrm{O} 2$ | 120.14 (13) | O12-S2-O11 | 119.84 (13) |
| $\mathrm{O} 1-\mathrm{S} 1-\mathrm{N} 1$ | 105.64 (13) | O12-S2-N3 | 106.48 (12) |
| $\mathrm{O} 2-\mathrm{S} 1-\mathrm{N} 1$ | 107.84 (12) | O11-S2-N3 | 106.65 (12) |
| $\mathrm{O} 1-\mathrm{S} 1-\mathrm{C} 20$ | 108.92 (14) | O12-S2-C60 | 109.36 (13) |
| $\mathrm{O} 2-\mathrm{S} 1-\mathrm{C} 20$ | 107.56 (14) | O11-S2-C60 | 108.82 (14) |
| N1—S1-C20 | 105.88 (13) | N3-S2-C60 | 104.61 (13) |
| C13-O3-C28 | 116.6 (2) | C43-O13-C67 | 116.4 (3) |

Table 2.5. (Continued).

| C32-O4-C35 | 118.1 (2) | C68-O14-C53 | 113.9 (2) |
| :---: | :---: | :---: | :---: |
| C36-O5-C14 | 115.5 (3) | C72-O15-C75 | 116.5 (2) |
| C37-O6-C38 | 115.2 (2) | C76-O16-C54 | 114.8 (2) |
| C3-O8- C 27 | 117.4 (3) | C77-O17-C78 | 115.9 (2) |
| C1-N1-C19 | 106.1 (2) | C41-N3-C59 | 105.1 (2) |
| $\mathrm{C} 1-\mathrm{N} 1-\mathrm{S} 1$ | 114.53 (19) | C41-N3-S2 | 113.43 (19) |
| C19-N1-S1 | 122.8 (2) | C59-N3-S2 | 116.58 (19) |
| C9-N2-C10 | 109.9 (2) | C49-N4-C50 | 109.3 (2) |
| C9-N2-C18 | 111.1 (2) | C49-N4-C58 | 109.9 (2) |
| C10-N2-C18 | 113.0 (2) | C50-N4-C58 | 112.9 (2) |
| C6- $\mathrm{C} 1-\mathrm{C} 2$ | 122.9 (3) | C42-C41-C46 | 123.1 (3) |
| C6- $\mathrm{C} 1-\mathrm{N} 1$ | 108.4 (3) | C42-C41-N3 | 128.2 (3) |
| $\mathrm{C} 2-\mathrm{C} 1-\mathrm{N} 1$ | 128.7 (3) | C46-C41-N3 | 108.6 (3) |
| C1-C2-C3 | 116.3 (3) | C43-C42-C41 | 116.9 (3) |
| $\mathrm{C} 1-\mathrm{C} 2-\mathrm{H} 2$ | 121.8 | C43-C42-H42 | 121.6 |
| C3-C2-H2 | 121.8 | C41-C42-H42 | 121.6 |
| O8-C3-C4 | 115.9 (3) | O13-C43-C42 | 123.2 (3) |
| O8-C3-C2 | 122.9 (3) | O13-C43-C44 | 115.2 (3) |
| C4-C3-C2 | 121.2 (3) | C42-C43-C44 | 121.6 (3) |
| C5-C4-C3 | 121.7 (3) | C45-C44-C43 | 120.1 (3) |
| C5-C4-H4 | 119.2 | C45-C44-H44 | 119.9 |
| C3-C4-H4 | 119.2 | C43-C44-H44 | 119.9 |
| C4-C5-C6 | 118.2 (3) | C44-C45-C46 | 119.5 (3) |
| C4-C5-H5 | 120.9 | C44-C45-H45 | 120.2 |
| C6-C5-H5 | 120.9 | C46-C45-H45 | 120.2 |
| C1-C6-C5 | 119.6 (3) | C41-C46-C45 | 118.7 (3) |
| C1-C6-C7 | 107.4 (3) | C41-C46-C47 | 107.9 (3) |
| C5-C6-C7 | 133.0 (3) | C45-C46-C47 | 133.4 (3) |
| C19-C7-C6 | 109.1 (3) | C59-C47-C46 | 108.0 (3) |
| C19-C7-C8 | 123.7 (3) | C59-C47-C48 | 123.0 (3) |
| C6-C7-C8 | 127.2 (3) | C46-C47-C48 | 128.9 (3) |

Table 2.5. (Continued).

| C7-C8-C9 | 108.8 (3) | C47-C48-C49 | 108.7 (2) |
| :---: | :---: | :---: | :---: |
| C7-C8-H8A | 109.9 | C47-C48-H48A | 109.9 |
| C9-C8-H8A | 109.9 | C49-C48-H48A | 109.9 |
| C7-C8-H8B | 109.9 | C47-C48-H48B | 109.9 |
| C9-C8-H8B | 109.9 | C49-C48-H48B | 109.9 |
| H8A-C8-H8B | 108.3 | H48A-C48-H48B | 108.3 |
| N2-C9-C8 | 113.3 (3) | N4-C49-C48 | 114.6 (3) |
| N2-C9-H9A | 108.9 | N4-C49-H49A | 108.6 |
| C8-C9-H9A | 108.9 | C48-C49-H49A | 108.6 |
| N2-C9-H9B | 108.9 | N4-C49-H49B | 108.6 |
| C8-C9-H9B | 108.9 | C48-C49-H49B | 108.6 |
| H9A-C9-H9B | 107.7 | H49A-C49-H49B | 107.6 |
| N2-C10-C11 | 112.7 (2) | N4-C50-C51 | 114.1 (2) |
| N2-C10-H10A | 109.1 | N4-C50-H50A | 108.7 |
| C11-C10-H10A | 109.1 | C51-C50-H50A | 108.7 |
| N2-C10-H10B | 109.1 | N4-C50-H50B | 108.7 |
| C11-C10-H10B | 109.1 | C51-C50-H50B | 108.7 |
| H10A-C10-H10B | 107.8 | H50A-C50-H50B | 107.6 |
| C10-C11-C16 | 109.9 (2) | C50-C51-C52 | 114.0 (3) |
| C10-C11-C12 | 113.2 (3) | C50-C51-C56 | 109.0 (2) |
| C16-C11-C12 | 111.3 (2) | C52-C51-C56 | 111.7 (3) |
| C10-C11-H11 | 107.4 | C50-C51-H51 | 107.3 |
| C16-C11-H11 | 107.4 | C52-C51-H51 | 107.3 |
| C12- $\mathrm{C} 11-\mathrm{H} 11$ | 107.4 | C56- $\mathrm{C} 51-\mathrm{H} 51$ | 107.3 |
| C13-C12-C11 | 110.1 (3) | C53-C52-C51 | 109.9 (2) |
| C13-C12-H12A | 109.6 | C53-C52-H52A | 109.7 |
| $\mathrm{C} 11-\mathrm{C} 12-\mathrm{H} 12 \mathrm{~A}$ | 109.6 | C51-C52-H52A | 109.7 |
| C13-C12-H12B | 109.6 | C53-C52-H52B | 109.7 |
| C11-C12-H12B | 109.6 | C51-C52-H52B | 109.7 |
| H12A-C12-H12B | 108.2 | H52A-C52-H52B | 108.2 |
| O3-C13-C14 | 113.1 (2) | O14-C53-C52 | 114.6 (2) |

Table 2.5. (Continued).

| O3-C13-C12 | 113.8 (3) | O14-C53-C54 | 111.6 (3) |
| :---: | :---: | :---: | :---: |
| C14-C13-C12 | 111.1 (2) | C52-C53-C54 | 111.0 (2) |
| $\mathrm{O} 3-\mathrm{C} 13-\mathrm{H} 13$ | 106.0 | O14-C53-H53 | 106.3 |
| C14-C13-H13 | 106.0 | C52-C53-H53 | 106.3 |
| C12-C13-H13 | 106.0 | C54-C53-H53 | 106.3 |
| O5-C14-C13 | 109.1 (2) | O16-C54-C55 | 105.7 (2) |
| O5-C14-C15 | 106.1 (3) | O16-C54-C53 | 110.8 (2) |
| C13-C14-C15 | 111.5 (2) | C55-C54-C53 | 111.2 (3) |
| O5-C14-H14 | 110.0 | O16-C54-H54 | 109.7 |
| C13-C14-H14 | 110.0 | C55-C54-H54 | 109.7 |
| C15-C14-H14 | 110.0 | C53-C54-H54 | 109.7 |
| C37-C15-C14 | 114.4 (3) | C77-C55-C54 | 110.3 (3) |
| C37-C15-C16 | 108.6 (2) | C77-C55-C56 | 109.3 (2) |
| C14-C15-C16 | 115.3 (3) | C54-C55-C56 | 114.5 (2) |
| C37-C15-H15 | 105.9 | C77-C55-H55 | 107.5 |
| C14-C15-H15 | 105.9 | C54-C55-H55 | 107.5 |
| C16-C15-H15 | 105.9 | C56-C55-H55 | 107.5 |
| C11-C16-C15 | 111.6 (2) | C57-C56-C51 | 110.6 (2) |
| C11-C16-C17 | 109.7 (2) | C57-C56-C55 | 112.7 (2) |
| C15-C16-C17 | 112.6 (2) | C51-C56-C55 | 110.9 (2) |
| C11-C16-H16 | 107.6 | C57-C56-H56 | 107.5 |
| C15-C16-H16 | 107.6 | C51-C56-H56 | 107.5 |
| C17-C16-H16 | 107.6 | C55-C56-H56 | 107.5 |
| C18-C17-C16 | 113.3 (2) | C58-C57-C56 | 111.7 (2) |
| C18-C17-H17A | 108.9 | C58-C57-H57A | 109.3 |
| C16-C17-H17A | 108.9 | C56-C57-H57A | 109.3 |
| C18-C17-H17B | 108.9 | C58-C57-H57B | 109.3 |
| C16-C17-H17B | 108.9 | C56-C57-H57B | 109.3 |
| H17A-C17-H17B | 107.7 | H57A-C57-H57B | 107.9 |
| N2-C18-C19 | 109.0 (2) | N4-C58-C59 | 109.1 (2) |
| N2-C18-C17 | 108.0 (2) | N4-C58-C57 | 109.5 (2) |

Table 2.5. (Continued).

| C19-C18-C17 | 118.9 (3) | C59-C58-C57 | 116.0 (2) |
| :---: | :---: | :---: | :---: |
| N2-C18-H18 | 106.8 | N4-C58-H58 | 107.3 |
| C19-C18-H18 | 106.8 | C59-C58-H58 | 107.3 |
| C17-C18-H18 | 106.8 | C57-C58-H58 | 107.3 |
| C7-C19-N1 | 109.0 (3) | C47-C59-N3 | 110.3 (3) |
| C7-C19-C18 | 123.5 (3) | C47-C59-C58 | 124.2 (3) |
| N1-C19-C18 | 127.3 (3) | N3-C59-C58 | 125.1 (3) |
| C21-C20-C25 | 121.4 (3) | C65-C60-C61 | 121.3 (3) |
| C21-C20-S1 | 119.9 (2) | C65-C60-S2 | 119.4 (2) |
| C25-C20-S1 | 118.6 (2) | C61-C60-S2 | 119.3 (2) |
| C20-C21-C22 | 118.7 (3) | C62-C61-C60 | 118.2 (3) |
| C20-C21-H21 | 120.6 | C62-C61-H61 | 120.9 |
| C22-C21-H21 | 120.6 | C60-C61-H61 | 120.9 |
| C23-C22-C21 | 120.9 (3) | C61-C62-C63 | 122.3 (3) |
| C23-C22-H22 | 119.5 | C61-C62-H62 | 118.8 |
| C21-C22-H22 | 119.5 | C63-C62-H62 | 118.8 |
| C22-C23-C24 | 119.0 (3) | C64-C63-C62 | 118.2 (3) |
| C22-C23-C26 | 120.4 (3) | C64-C63-C66 | 121.5 (3) |
| C24-C23-C26 | 120.6 (3) | C62-C63-C66 | 120.2 (3) |
| C25-C24-C23 | 121.5 (3) | C63-C64-C65 | 120.9 (3) |
| C25- $\mathrm{C} 24-\mathrm{H} 24$ | 119.2 | C63-C64-H64 | 119.6 |
| C23-C24-H24 | 119.2 | C65-C64-H64 | 119.6 |
| C24-C25-C20 | 118.4 (3) | C60-C65-C64 | 119.0 (3) |
| C24-C25-H25 | 120.8 | C60-C65-H65 | 120.5 |
| C20-C25-H25 | 120.8 | C64-C65-H65 | 120.5 |
| C23-C26-H26A | 109.5 | C63-C66-H66A | 109.5 |
| C23-C26-H26B | 109.5 | C63-C66-H66B | 109.5 |
| H26A-C26-H26B | 109.5 | H66A-C66-H66B | 109.5 |
| C23-C26-H26C | 109.5 | C63-C66-H66C | 109.5 |
| H26A-C26-H26C | 109.5 | H66A-C66-H66C | 109.5 |
| H26B-C26-H26C | 109.5 | H66B-C66-H66C | 109.5 |

Table 2.5. (Continued).

| O8-C27-H27A | 109.5 | O13-C67-H67A | 109.5 |
| :---: | :---: | :---: | :---: |
| O8-C27-H27B | 109.5 | O13-C67-H67B | 109.5 |
| H27A-C27-H27B | 109.5 | H67A-C67-H67B | 109.5 |
| O8-C27-H27C | 109.5 | O13-C67-H67C | 109.5 |
| H27A-C27-H27C | 109.5 | H67A-C67-H67C | 109.5 |
| H27B-C27-H27C | 109.5 | H67B-C67-H67C | 109.5 |
| O3-C28-C29 | 107.0 (2) | O14-C68-C69 | 110.3 (3) |
| O3-C28-H28A | 110.3 | O14-C68-H68A | 109.6 |
| C29-C28-H28A | 110.3 | C69-C68-H68A | 109.6 |
| O3-C28-H28B | 110.3 | O14-C68-H68B | 109.6 |
| C29-C28-H28B | 110.3 | C69-C68-H68B | 109.6 |
| H28A-C28-H28B | 108.6 | H68A-C68-H68B | 108.1 |
| C30-C29-C34 | 117.4 (3) | C70-C69-C74 | 117.9 (3) |
| C30-C29-C28 | 122.2 (3) | C70-C69-C68 | 118.4 (3) |
| C34-C29-C28 | 120.4 (3) | C74-C69-C68 | 123.6 (3) |
| C29-C30-C31 | 122.0 (3) | C71-C70-C69 | 122.2 (3) |
| C29-C30-H30 | 119.0 | C71-C70-H70 | 118.9 |
| C31-C30-H30 | 119.0 | C69-C70-H70 | 118.9 |
| C32-C31-C30 | 119.7 (3) | C70-C71-C72 | 119.7 (3) |
| C32-C31-H31 | 120.2 | C70-C71-H71 | 120.2 |
| C30-C31-H31 | 120.2 | C72-C71-H71 | 120.2 |
| O4-C32-C31 | 125.3 (3) | O15-C72-C71 | 124.3 (3) |
| O4-C32-C33 | 116.1 (3) | O15-C72-C73 | 116.8 (3) |
| C31-C32-C33 | 118.6 (3) | C71-C72-C73 | 118.9 (3) |
| C34-C33-C32 | 121.0 (3) | C74-C73-C72 | 120.0 (3) |
| C34-C33-H33 | 119.5 | C74-C73-H73 | 120.0 |
| C32-C33-H33 | 119.5 | C72-C73-H73 | 120.0 |
| C33-C34-C29 | 121.4 (3) | C73-C74-C69 | 121.3 (3) |
| C33-C34-H34 | 119.3 | C73-C74-H74 | 119.3 |
| C29-C34-H34 | 119.3 | C69-C74-H74 | 119.3 |
| O4-C35-H35A | 109.5 | O15-C75-H75A | 109.5 |

Table 2.5. (Continued).

| O4-C35-H35B | 109.5 | O15-C75-H75B | 109.5 |
| :---: | :---: | :---: | :---: |
| H35A-C35-H35B | 109.5 | H75A-C75-H75B | 109.5 |
| O4-C35-H35C | 109.5 | O15-C75-H75C | 109.5 |
| H35A-C35-H35C | 109.5 | H75A-C75-H75C | 109.5 |
| H35B-C35-H35C | 109.5 | H75B-C75-H75C | 109.5 |
| O5-C36-H36A | 109.5 | O16-C76-H76A | 109.5 |
| O5-C36-H36B | 109.5 | O16-C76-H76B | 109.5 |
| H36A-C36-H36B | 109.5 | H76A-C76-H76B | 109.5 |
| O5-C36-H36C | 109.5 | O16-C76-H76C | 109.5 |
| H36A-C36-H36C | 109.5 | H76A-C76-H76C | 109.5 |
| H36B-C36-H36C | 109.5 | H76B-C76-H76C | 109.5 |
| O7-C37-O6 | 123.6 (3) | O18-C77-O17 | 123.6 (3) |
| O7-C37-C15 | 124.6 (3) | O18-C77-C55 | 127.2 (3) |
| O6-C37-C15 | 111.7 (3) | O17-C77-C55 | 109.2 (3) |
| O6-C38-H38A | 109.5 | O17-C78-H78A | 109.5 |
| O6-C38-H38B | 109.5 | O17-C78-H78B | 109.5 |
| H38A-C38-H38B | 109.5 | H78A-C78-H78B | 109.5 |
| O6-C38-H38C | 109.5 | O17-C78-H78C | 109.5 |
| H38A-C38-H38C | 109.5 | H78A-C78-H78C | 109.5 |
| H38B-C38-H38C | 109.5 | H78B-C78-H78C | 109.5 |
| O1-S1-N1-C1 | -62.8 (2) | O12-S2—N3-C41 | -58.6 (2) |
| $\mathrm{O} 2-\mathrm{S} 1-\mathrm{N} 1-\mathrm{C} 1$ | 167.6 (2) | O11-S2-N3-C41 | 172.4 (2) |
| C20-S1-N1-C1 | 52.7 (2) | C60-S2-N3-C41 | 57.2 (2) |
| O1—S1-N1-C19 | 166.1 (2) | O12-S2-N3-C59 | 179.1 (2) |
| O2-S1-N1-C19 | 36.5 (3) | O11-S2-N3-C59 | 50.0 (2) |
| C20-S1-N1-C19 | -78.4 (2) | C60-S2-N3-C59 | -65.2 (2) |
| C19-N1-C1-C6 | 0.8 (3) | C59-N3-C41-C42 | -175.2 (3) |
| S1-N1-C1-C6 | -137.9 (2) | S2-N3-C41-C42 | 56.4 (4) |
| C19-N1-C1-C2 | -178.0 (3) | C59-N3-C41-C46 | 2.7 (3) |
| S1-N1-C1-C2 | 43.3 (4) | S2-N3-C41-C46 | -125.8 (2) |
| $\mathrm{C} 6-\mathrm{C} 1-\mathrm{C} 2-\mathrm{C} 3$ | 1.2 (5) | C46-C41-C42-C43 | 0.8 (4) |

Table 2.5. (Continued).

| N1-C1-C2-C3 | 179.8 (3) | N3-C41-C42-C43 | 178.4 (3) |
| :---: | :---: | :---: | :---: |
| C27-O8-C3-C4 | -176.5 (3) | C67-O13-C43-C42 | 0.5 (4) |
| C27-O8-C3-C2 | 3.5 (4) | C67-O13-C43-C44 | -179.2 (3) |
| C1-C2-C3-O8 | -179.6 (3) | C41-C42-C43-O13 | -179.5 (3) |
| C1-C2-C3-C4 | 0.3 (5) | C41-C42-C43-C44 | 0.1 (4) |
| O8-C3-C4-C5 | 178.1 (3) | O13-C43-C44-C45 | 179.1 (3) |
| C2-C3-C4-C5 | -1.9 (5) | C42-C43-C44-C45 | -0.5 (5) |
| C3-C4-C5-C6 | 1.8 (5) | C43-C44-C45-C46 | 0.0 (4) |
| C2- $\mathrm{C} 1-\mathrm{C} 6-\mathrm{C} 5$ | -1.2 (5) | C42-C41-C46-C45 | -1.3 (4) |
| N1-C1-C6-C5 | 179.9 (3) | N3-C41-C46-C45 | -179.3 (2) |
| C2-C1-C6-C7 | 177.5 (3) | C42-C41-C46-C47 | 176.4 (3) |
| N1-C1-C6-C7 | -1.4 (3) | N3-C41-C46-C47 | -1.6 (3) |
| C4-C5-C6-C1 | -0.3 (5) | C44-C45-C46-C41 | 0.8 (4) |
| C4-C5-C6-C7 | -178.6 (3) | C44-C45-C46-C47 | -176.2 (3) |
| C1-C6-C7-C19 | 1.5 (4) | C41-C46-C47-C59 | -0.3 (3) |
| C5-C6-C7-C19 | 179.9 (3) | C45-C46-C47-C59 | 177.0 (3) |
| C1-C6-C7-C8 | -175.3 (3) | C41-C46-C47-C48 | -177.6 (3) |
| C5-C6-C7-C8 | 3.1 (6) | C45-C46-C47-C48 | -0.3 (5) |
| C19-C7-C8-C9 | 10.2 (4) | C59-C47-C48-C49 | 4.9 (4) |
| C6-C7-C8-C9 | -173.4 (3) | C46-C47-C48-C49 | -178.1 (3) |
| C10-N2-C9-C8 | -59.8 (3) | C50-N4-C49-C48 | -58.4 (3) |
| C18-N2-C9-C8 | 65.9 (3) | C58-N4-C49-C48 | 66.1 (3) |
| C7-C8-C9-N2 | -42.4 (4) | C47-C48-C49-N4 | -41.0 (3) |
| C9-N2-C10-C11 | -176.7 (2) | C49-N4-C50-C51 | 178.6 (2) |
| C18-N2-C10-C11 | 58.6 (3) | C58-N4-C50-C51 | 55.9 (3) |
| $\mathrm{N} 2-\mathrm{C} 10-\mathrm{C} 11-\mathrm{C} 16$ | -55.0 (3) | N4-C50-C51-C52 | 71.8 (3) |
| N2-C10-C11-C12 | 70.1 (3) | N4-C50-C51-C56 | -53.8 (3) |
| C10-C11-C12-C13 | 176.5 (2) | C50-C51-C52-C53 | 176.3 (2) |
| C16-C11-C12-C13 | -59.2 (3) | C56-C51-C52-C53 | -59.5 (3) |
| C28-O3-C13-C14 | 78.6 (3) | C68-O14-C53-C52 | -53.0 (3) |
| C28-O3-C13-C12 | -49.5 (3) | C68-O14-C53-C54 | 74.4 (3) |

Table 2.5. (Continued).

| C11-C12-C13-O3 | -170.6 (2) | C51-C52-C53-O14 | -171.9 (3) |
| :---: | :---: | :---: | :---: |
| C11-C12-C13-C14 | 60.3 (3) | C51-C52-C53-C54 | 60.5 (3) |
| C36-O5-C14-C13 | -110.9 (3) | C76-O16-C54-C55 | 146.1 (3) |
| C36-O5-C14-C15 | 128.9 (3) | C76-O16-C54-C53 | -93.3 (3) |
| O3-C13-C14-O5 | 59.8 (3) | O14-C53-C54-O16 | 58.5 (3) |
| C12-C13-C14-O5 | -170.8 (3) | C52-C53-C54-O16 | -172.3 (2) |
| O3-C13-C14-C15 | 176.6 (3) | O14-C53-C54-C55 | 175.7 (2) |
| C12-C13-C14-C15 | -53.9 (3) | C52-C53-C54-C55 | -55.1 (3) |
| O5-C14-C15-C37 | -66.5 (3) | O16-C54-C55-C77 | -66.5 (3) |
| C13-C14-C15-C37 | 174.8 (3) | C53-C54-C55-C77 | 173.1 (2) |
| O5-C14-C15-C16 | 166.5 (2) | O16-C54-C55-C56 | 169.6 (2) |
| C13-C14-C15-C16 | 47.8 (4) | C53-C54-C55-C56 | 49.3 (3) |
| C10-C11-C16-C15 | 178.0 (3) | C50-C51-C56-C57 | 53.6 (3) |
| C12-C11-C16-C15 | 51.7 (3) | C52-C51-C56-C57 | -73.3 (3) |
| C10-C11-C16-C17 | 52.5 (3) | C50-C51-C56-C55 | 179.4 (2) |
| C12-C11-C16-C17 | -73.7 (3) | C52-C51-C56-C55 | 52.4 (3) |
| C37-C15-C16-C11 | -176.7 (2) | C77-C55-C56-C57 | -47.7 (3) |
| C14-C15-C16-C11 | -46.8 (4) | C54-C55-C56-C57 | 76.7 (3) |
| C37-C15-C16-C17 | -52.8 (3) | C77-C55-C56-C51 | -172.2 (3) |
| C14-C15-C16-C17 | 77.1 (3) | C54-C55-C56-C51 | -47.9 (3) |
| C11-C16-C17-C18 | -55.5 (3) | C51-C56-C57-C58 | -56.7 (3) |
| C15-C16-C17-C18 | 179.6 (2) | C55-C56-C57-C58 | 178.6 (2) |
| C9-N2-C18-C19 | -50.6 (3) | C49-N4-C58-C59 | -49.5 (3) |
| C10-N2-C18-C19 | 73.4 (3) | C50-N4-C58-C59 | 72.9 (3) |
| C9-N2-C18-C17 | 179.0 (3) | C49-N4-C58-C57 | -177.4 (2) |
| $\mathrm{C} 10-\mathrm{N} 2-\mathrm{C} 18-\mathrm{C} 17$ | -57.0 (3) | C50-N4-C58-C57 | -55.0 (3) |
| C16-C17-C18-N2 | 56.3 (3) | C56-C57-C58-N4 | 56.2 (3) |
| C16-C17-C18-C19 | -68.4 (3) | C56-C57-C58-C59 | -67.9 (3) |
| C6-C7-C19-N1 | -0.9 (3) | C46-C47-C59-N3 | 2.1 (3) |
| C8-C7-C19—N1 | 176.0 (3) | C48-C47-C59-N3 | 179.6 (3) |
| C6-C7-C19-C18 | -176.5 (3) | C46-C47-C59-C58 | -170.6 (3) |

Table 2.5. (Continued).

| C8-C7-C19-C18 | 0.5 (5) | C48-C47-C59-C58 | 6.9 (5) |
| :---: | :---: | :---: | :---: |
| $\mathrm{C} 1-\mathrm{N} 1-\mathrm{C} 19-\mathrm{C} 7$ | 0.1 (3) | C41-N3-C59-C47 | -3.0 (3) |
| S1-N1-C19-C7 | 134.5 (2) | S2-N3-C59-C47 | 123.6 (2) |
| C1-N1-C19-C18 | 175.4 (3) | C41-N3-C59-C58 | 169.6 (3) |
| S1-N1-C19-C18 | -50.2 (4) | S2-N3-C59-C58 | -63.8 (3) |
| N2-C18-C19-C7 | 19.2 (4) | N4-C58-C59-C47 | 15.7 (4) |
| C17-C18-C19-C7 | 143.5 (3) | C57-C58-C59-C47 | 140.0 (3) |
| N2-C18-C19-N1 | -155.4 (3) | N4-C58-C59-N3 | -155.9 (2) |
| C17-C18-C19-N1 | -31.2 (4) | C57-C58-C59-N3 | -31.6 (4) |
| O1—S1-C20-C21 | 4.9 (3) | O12-S2-C60-C65 | 27.4 (3) |
| $\mathrm{O} 2-\mathrm{S} 1-\mathrm{C} 20-\mathrm{C} 21$ | 136.6 (2) | O11-S2-C60-C65 | 160.0 (2) |
| N1—S1-C20-C21 | -108.3 (2) | N3-S2-C60-C65 | -86.3 (3) |
| O1-S1-C20-C25 | -171.7 (2) | O12-S2-C60-C61 | -154.1 (2) |
| O2-S1-C20-C25 | -40.0 (3) | O11-S2-C60-C61 | -21.5 (3) |
| N1—S1-C20-C25 | 75.1 (3) | N3-S2-C60-C61 | 92.2 (3) |
| C25-C20-C21-C22 | 0.5 (4) | C65-C60-C61-C62 | -0.8 (5) |
| S1-C20-C21-C22 | -176.0 (2) | S2-C60-C61-C62 | -179.2 (2) |
| C20-C21-C22-C23 | -0.5 (5) | C60-C61-C62-C63 | 0.9 (5) |
| C21-C22-C23-C24 | 0.1 (5) | C61-C62-C63-C64 | 0.2 (5) |
| C21-C22-C23-C26 | 179.1 (3) | C61-C62-C63-C66 | -178.2 (3) |
| C22-C23-C24-C25 | 0.5 (5) | C62-C63-C64-C65 | -1.4 (5) |
| C26-C23-C24-C25 | -178.6 (3) | C66-C63-C64-C65 | 177.0 (3) |
| C23-C24-C25-C20 | -0.5 (5) | C61-C60-C65-C64 | -0.4 (5) |
| C21-C20-C25-C24 | 0.0 (4) | S2-C60-C65-C64 | 178.0 (2) |
| S1-C20-C25-C24 | 176.6 (2) | C63-C64-C65-C60 | 1.5 (5) |
| C13-O3-C28-C29 | -175.4 (2) | C53-O14-C68-C69 | -163.1 (2) |
| O3-C28-C29-C30 | -119.7 (3) | O14-C68-C69-C70 | 166.7 (3) |
| O3-C28-C29-C34 | 59.5 (4) | O14-C68-C69-C74 | -17.5 (4) |
| C34-C29-C30-C31 | -0.4 (5) | C74-C69-C70-C71 | -2.1 (5) |
| C28-C29-C30-C31 | 178.8 (3) | C68-C69-C70-C71 | 173.9 (3) |
| C29-C30-C31-C32 | 0.3 (5) | C69-C70-C71-C72 | -0.3 (5) |

Table 2.5. (Continued).

| $\mathrm{C} 35-\mathrm{O} 4-\mathrm{C} 32-\mathrm{C} 31$ | $2.1(4)$ | $\mathrm{C} 75-\mathrm{O} 15-\mathrm{C} 72-\mathrm{C} 71$ | $-1.7(4)$ |
| :--- | :--- | :--- | :--- |
| $\mathrm{C} 35-\mathrm{O} 4-\mathrm{C} 32-\mathrm{C} 33$ | $-178.5(3)$ | $\mathrm{C} 75-\mathrm{O} 15-\mathrm{C} 72-\mathrm{C} 73$ | $177.4(3)$ |
| $\mathrm{C} 30-\mathrm{C} 31-\mathrm{C} 32-\mathrm{O} 4$ | $179.9(3)$ | $\mathrm{C} 70-\mathrm{C} 71-\mathrm{C} 72-\mathrm{O} 15$ | $-179.1(3)$ |
| $\mathrm{C} 30-\mathrm{C} 31-\mathrm{C} 32-\mathrm{C} 33$ | $0.6(5)$ | $\mathrm{C} 70-\mathrm{C} 71-\mathrm{C} 72-\mathrm{C} 73$ | $1.9(5)$ |
| $\mathrm{O} 4-\mathrm{C} 32-\mathrm{C} 33-\mathrm{C} 34$ | $179.2(3)$ | $\mathrm{O} 15-\mathrm{C} 72-\mathrm{C} 73-\mathrm{C} 74$ | $179.9(3)$ |
| $\mathrm{C} 31-\mathrm{C} 32-\mathrm{C} 33-\mathrm{C} 34$ | $-1.4(5)$ | $\mathrm{C} 71-\mathrm{C} 72-\mathrm{C} 73-\mathrm{C} 74$ | $-1.0(4)$ |
| $\mathrm{C} 32-\mathrm{C} 33-\mathrm{C} 34-\mathrm{C} 29$ | $1.3(5)$ | $\mathrm{C} 72-\mathrm{C} 73-\mathrm{C} 74-\mathrm{C} 69$ | $-1.5(5)$ |
| $\mathrm{C} 30-\mathrm{C} 29-\mathrm{C} 34-\mathrm{C} 33$ | $-0.4(5)$ | $\mathrm{C} 70-\mathrm{C} 69-\mathrm{C} 74-\mathrm{C} 73$ | $3.0(5)$ |
| $\mathrm{C} 28-\mathrm{C} 29-\mathrm{C} 34-\mathrm{C} 33$ | $-179.6(3)$ | $\mathrm{C} 68-\mathrm{C} 69-\mathrm{C} 74-\mathrm{C} 73$ | $-172.8(3)$ |
| $\mathrm{C} 38-\mathrm{O} 6-\mathrm{C} 37-\mathrm{O} 7$ | $1.6(4)$ | $\mathrm{C} 78-\mathrm{O} 17-\mathrm{C} 77-\mathrm{O} 18$ | $-2.4(4)$ |
| $\mathrm{C} 38-\mathrm{O} 6-\mathrm{C} 37-\mathrm{C} 15$ | $-174.3(2)$ | $\mathrm{C} 78-\mathrm{O} 17-\mathrm{C} 77-\mathrm{C} 55$ | $174.3(2)$ |
| $\mathrm{C} 14-\mathrm{C} 15-\mathrm{C} 37-\mathrm{O} 7$ | $159.7(3)$ | $\mathrm{C} 54-\mathrm{C} 55-\mathrm{C} 77-\mathrm{O} 18$ | $-11.8(4)$ |
| $\mathrm{C} 16-\mathrm{C} 15-\mathrm{C} 37-\mathrm{O} 7$ | $-69.9(4)$ | $\mathrm{C} 56-\mathrm{C} 55-\mathrm{C} 77-\mathrm{O} 18$ | $115.0(3)$ |
| $\mathrm{C} 14-\mathrm{C} 15-\mathrm{C} 37-\mathrm{O} 6$ | $-24.4(4)$ | $\mathrm{C} 54-\mathrm{C} 55-\mathrm{C} 77-\mathrm{O} 17$ | $171.6(2)$ |
| $\mathrm{C} 16-\mathrm{C} 15-\mathrm{C} 37-\mathrm{O} 6$ | $106.0(3)$ | $\mathrm{C} 55-\mathrm{C} 77-\mathrm{O} 17$ | $-61.6(3)$ |



Figure 2.3. Perspective views showing 50\% probability displacement.


Figure 2.4. Three-dimensional supramolecular architecture viewed along the $a$-axis direction.

Chapter 3

## Synthesis of Chiral Bisthiourea Catalysts

### 3.1. Introduction

Recent mechanistic investigations of a thiourea-catalyzed asymmetric alkylation of $\alpha$-chloroethers with silyl ketene acetals have led to the hypothesis that two molecules of catalyst are involved in both productive electrophile activation and in nonproductive ground state aggregation. This chapter describes our efforts to synthesize chiral bisthioureas that can activate electrophiles but cannot self-aggregate. Ongoing efforts are presented and future directions are suggested.

### 3.2. Hydrogen Bond Donor-Assisted Anion-Abstraction

Chiral dual hydrogen bond donors have been shown to catalyze a number of enantioselective transformations of cationic electrophiles through mechanisms involving catalyst-bound ion pairs. ${ }^{1,2}$ A particularly effective strategy for generating such electrophiles is through hydrogen bond donor-assisted abstraction of anions from neutral precursors. This mechanism was first investigated in the context of a thiourea-catalyzed Pictet-Spengler-type reaction of in situ generated $\alpha$-chlorolactams (Scheme 3.1A), ${ }^{3}$ and since then has been used as a guiding principle to develop asymmetric transformations involving carbenium ions (Scheme 3.1B) ${ }^{4}$ and oxocarbenium ions (Scheme 3.1C). ${ }^{5}$

[^53](A) Thiourea-Catalyzed Enantioselective Pictet-Spengler-type Cyclization

(B) Primary Aminothiourea-Catalyzed Enantioselective $\alpha$-Alkylation of Aldehydes



## Scheme 3.1. Anion-Abstraction in Thiourea-Catalyzed Transformations

With the goal of gaining insight into the anion-abstraction process, David Ford and Dr. Dan Lehnherr, current Jacobsen group members, have undertaken mechanistic studies on the enantioselective thiourea-catalyzed addition of silyl ketene acetal $\mathbf{1}$ to preformed $\alpha$-chloroether 2 (Scheme 3.2). ${ }^{6}$ This transformation is conducted with $10 \mathrm{~mol} \%$ of arylpyrrolidino-thiourea 3 and provides isochroman 4 in $85 \%$ ee.

[^54]

Scheme 3.2. Model Reaction for Mechanistic Investigations

### 3.3. Proposed Mechanistic Scenario

Through these investigations it was determined that the reaction has a first order kinetic dependence on thiourea at high catalyst concentrations and a second order kinetic dependence at low concentrations. These results are consistent with the involvement of two thiourea molecules in the rate-determining transition state along with a dimeric catalyst resting state at high concentrations and a monomeric catalyst resting state at low concentrations. X-ray crystallographic data, in combination with NMR data, have been used to characterize the dimeric resting state (5) in which the hydrogen bond donor functionality of each thiourea is bound to the amide of the other (Figure 3.1). A second thiourea dimerization mode became apparent through analysis of an X-ray crystal structure of the thiourea co-crystallized with tetramethylammonium chloride in a $2: 1$ stoichiometry (6) (Figure 3.2).


inactive dimer (5), consisting of two molecules of ent-3

Figure 3.1. Crystal Structure Depicting the Dimeric Resting State of ent-3



2:1 complex of ent $-3: \mathrm{NMe}_{4} \mathrm{Cl}(6)$

Figure 3.2. Crystal Structure of a $2: 1$ ent-3: $\mathrm{NMe}_{4} \mathrm{Cl}$ Complex ( $\left[\mathrm{NMe}_{4}\right]^{+}$has been omitted from the left structure for clarity)

Together, these data suggest that the ground state dimer must dissociate and recombine in a productive geometry to allow for dual electrophile activation of $\alpha$ chloroether substrates via anion-abstraction (Scheme 3.3). Furthermore, this mechanistic scenario raised the possibility that covalently linking two thiourea moieties could prevent inactive dimer formation while allowing for cooperative electrophile activation. Such a
dimer would effectively increase the concentration of active catalyst, potentially allowing for the use of a lower catalyst loading and more efficient catalysis.


Scheme 3.3. Proposed Mechanistic Scenario for the Thiourea-Catalyzed Addition to Oxocarbenium Ions

With this goal in mind, Dan Lehnherr has investigated various symmetrical tethering strategies (represented as $\mathrm{S} 1-\mathrm{S} 3$, Figure 3.3) and has identified dimeric catalysts that afford higher reactivity than monomer 3 while maintaining comparable selectivity. An examination of crystal structures 5 and 6 suggests that an unsymmetrical linking strategy may better accomplish the goal of selectively disfavoring thioureathiourea interactions while enhancing cooperative electrophile activation. The proximity of the amino acid $t$-Bu group of one molecule of catalyst to the aniline-derived portion of
the second catalyst in crystal structure 6, and the relatively far distance between them in the unproductive aggregate 5 , led to the proposal that tethering these two portions would be beneficial (Figure 3.4). We targeted the synthesis of bisthioureas 7 and $\mathbf{8}{ }^{7}$ The ester functionality was introduced to aid in the synthetic accessibility of the bisthioureas while maintaining the electron-deficient nature of the parent 3,5-bis(trifluoromethyl)phenyl group. Computational modeling studies using DFT calculations indicated that a 1-2 atom linker ( $\mathrm{n}=1-2$, Figure 3.4) would be optimal to achieve cooperative electrophile activation and conformationally restrict access to the geometry of the unproductive aggregate. For the remainder of the chapter, the top portion of the bisthioureas, as drawn in Figure 3.4, will be referred to as "thiourea A" and the bottom as "thiourea B".


Figure 3.3. Symmetrical Linking Strategies Evaluated



Figure 3.4. Proposed Tethering Strategy and Target Bisthioureas

[^55]
### 3.4. Synthetic Strategies

Three potential synthetic routes to access 7 were identified: (1) esterification of two monomeric thioureas, (2) late-stage installation of thiourea B, and (3) late-stage installation of thiourea A (Figure 3.5). Ultimately, the third strategy proved successful. In this section, the problems encountered with the first two routes are described and a successful final route is presented.


Figure 3.5. Retrosynthetic Analysis of Bisthiourea 7

### 3.4.1. Strategy 1: Esterification of Two Functionalized Thiourea Monomers

The most attractive strategy in terms of convergency is an esterification of two functionalized analogs of 3, carboxylic acid 9 and neopentyl alcohol 10 (Scheme 3.4). ${ }^{8}$



Scheme 3.4. Proposed Esterification Route to Bisthiourea 7

[^56]Carboxylic acid $\mathbf{9}$ was readily obtained through saponification of methyl ester $\mathbf{1 1}$ with LiOH (Scheme 3.5); ${ }^{9}$ however, alcohol $\mathbf{1 0}$ proved more challenging to access. Dan Lehnherr identified a route to the required amide fragment 14 from $(R)$-pantolactone (12) that employs a trimethylaluminum-mediated lactone opening with arylpyrrolidine $\mathbf{1 3}$ (Scheme 3.6). ${ }^{10,11,12}$ Attempted elaboration of Boc-protected amine $\mathbf{1 4}$ to $\mathbf{1 0}$ under conditions used for synthesis of monomer 3 furnished undesired thioureas 18 and 19. Lactone 18 was obtained in $70 \%$ yield and was characterized by ${ }^{1} \mathrm{H}$ NMR and LRMS. The outcome indicates that amine deprotection using acidic conditions also effected amide bond cleavage to afford 16 and $\mathbf{1 7}$, which subsequently react with isothiocyanate 15. These results were unexpected because acidic conditions have been used to effect the deprotection of Boc-amines on related primary alcohol intermediates without amide hydrolysis. ${ }^{13,14}$


Scheme 3.5. Synthesis of Carboxylic Acid 9

[^57]

## Scheme 3.6. Amide Bond Cleavage During Amine Deprotection

Based on these results, we protected primary alcohol 14 as the corresponding benzyl ether 20 to access thiourea 21 (Scheme 3.7). However, attempted hydrogenolysis of the benzyl ether to obtain primary alcohol 10 was unsuccessful. ${ }^{15}$ Because we were encountering problems obtaining alcohol 10, we chose to focus on two alternative routes to bisthiourea 7: a late-stage installation of thiourea B and a late-stage installation of thiourea A .


Scheme 3.7. Synthesis of Benzyl Ether 21

[^58]
### 3.4.2. Strategy 2: Late-Stage Installation of Thiourea B

Our second strategy, late-stage installation of thiourea B (Scheme 3.8), also presented a problematic amine deprotection.


Scheme 3.8. Proposed Late-Stage Installation of Thiourea B

Alcohol 14 was elaborated to isothiocyanate 24 through a three-step sequence consisting of esterification, transfer hydrogenation of the aromatic nitro group, and a subsequent reaction with thiophosgene (Scheme 3.9). The crude isothiocyanate 24 was treated with amine 25 to complete installation of thiourea A. Unfortunately, deprotection of intermediate 26 was accompanied by undesired reactions, resulting in a complex mixture of products (Scheme 3.10). Although the byproducts were not rigorously characterized, mass spectrometric analysis of the crude reaction mixture indicated that loss of an arylpyrrolidine fragment occurred during removal of the Boc group. ${ }^{16}$ We did not determine which of the two amide bonds of 26 was cleaved, but based on literature precedent we hypothesize that it was the amide of thiourea A. ${ }^{17}$ In analogy to the outcome of the attempted deprotection of Boc-amine 14 in the presence of a free primary

[^59]alcohol (Scheme 3.6), it is likely that the thiourea functionality serves as an internal nucleophile under the deprotection conditions to generate 5 -membered cyclic product 28 (or a related tautomeric structure). With a different protecting group choice, this route may be viable. Ultimately, with the success of the third route, we did not investigate this strategy any further.







Scheme 3.9. Synthesis of Intermediate 26



Scheme 3.10. Potential Rearrangement during the Deprotection of Intermediate 26

### 3.4.3. Strategy 3: Late-Stage Installation of Thiourea A

The route that proved to be most fruitful was a late-stage installation of thiourea A (Scheme 3.11).


Scheme 3.11. Proposed Late-Stage Installation of Thiourea A

From intermediate 23, removal of the Boc group followed by a subsequent reaction with isothiocyanate 15 installed thiourea B (Scheme 3.12). The success of the amine deprotection in this context lends support to the hypothesis that amide bond
cleavage only occurs under acidic conditions when the intermediate contains an internal nucleophile. Hydrogenation of the nitro group of 29 could be accomplished with palladium on carbon at $50{ }^{\circ} \mathrm{C}$. ${ }^{18}$ Aniline $\mathbf{3 0}$ was treated with 1,1'thiocarbonyldiimidazole to access an isothiocyanate that was reacted with amine 25 to furnish desired bisthiourea 7 .






Scheme 3.12. Synthetic Route to Bisthiourea 7

### 3.4.4. Synthesis of Bisthiourea 8

We used the same strategy to access bisthiourea 8, which contains a 2-carbon linker between the two thiourea moieties. We obtained the necessary primary alcohol 35

[^60]through the sequence presented in Scheme 3.13. Amino acid 32 was obtained in $93 \%$ ee and was synthesized according to the procedure reported by Rossi. ${ }^{19}$ This route uses an Ireland-Claisen rearrangement of Boc-glycine ester 31 and a classical resolution of the resultant racemic amino acid with (S)-phenylglycinol 33. Amide 34 was formed using EDC and HOBt, and a subsequent hydroboration-oxidation sequence afforded primary alcohol 35. The completion of the synthesis of bisthiourea $\mathbf{8}$ is shown in Scheme 3.14.


Scheme 3.13. Synthesis of arylpyrrolidino-amide fragment 35

[^61]






Scheme 3.14. Synthesis of Bisthiourea 8

This sequence was first used to generate approximately 90 mg of bisthiourea 8. After we obtained encouraging preliminary data on the reactivity of this catalyst (see Section 3.4), Dr. Masayuki Wasa, a postdoctoral fellow in the group, investigated the scalability of this route. Through this effort, he was able to synthesize 1.3 g of bisthiourea 8, and he also used isothiocyanate 39 as a diversification point to prepare bisthioureas 40 and 41 (Scheme 3.15).



8 (1.3g prepared)


40 ( 70 mg prepared)


41 (90mg prepared)

Scheme 3.15. Gram-scale Preparation of Bisthiourea 8

### 3.5. Comparison of Bisthioureas 7 and 8 with Monomer 3

The thiourea-catalyzed asymmetric alkylation of $\alpha$-chloroether $\mathbf{1}$ with silyl ketene acetal $\mathbf{2}$ was evaluated with the standard monomeric catalyst (3) and bisthioureas $\mathbf{7}$ and $\mathbf{8}$ (Scheme 3.16). ${ }^{20}$ In order to determine the relative reactivity of the three thioureas, a low catalyst loading ( $1 \mathrm{~mol} \%$, based on thiourea moiety) and a short reaction time ( 1 hour) were used in this assay. Under these conditions, thiourea 3 afforded isochroman 4 in $6 \%$ yield and $81 \%$ ee. Bisthioureas 7 and $\mathbf{8}$ afforded significantly higher conversions, albeit

[^62]with slightly diminished selectivity. Bisthiourea 8, with a 2 -atom linker, was more reactive and marginally more selective than 7 , providing $95 \%$ conversion and $77 \%$ ee.



60\% conversion, 76\% ee

>95\% conversion, $77 \%$ ee

Scheme 3.16. Comparison of monomer $\mathbf{3}$ and bisthioureas 7 and 8

### 3.6. Conclusions and Outlook

The syntheses of bisthioureas $\mathbf{7}$ and $\mathbf{8}$ were accomplished through sequential installations of thiourea B and thiourea A . The final route is scalable and has been used to access 1.3 grams of bisthiourea 8. Most importantly, these covalently tethered thioureas demonstrate substantially higher reactivity than analogous monomeric thioureas in the asymmetric alkylation of $\alpha$-chloroethers. Current efforts in the Jacobsen group are focused on probing the generality of these observations. Dr. Kaid Harper, a postdoctoral fellow in the group, has recently made a comparison of monomer $\mathbf{3}$ and bisthiourea $\mathbf{8}$ in a catalyst-controlled diastereoselective glycosylation of propargyl alcohol with $\alpha$ chloroether 42 (Scheme 3.17). The background reaction of chloroether $42(9: 1 \alpha: \beta)$ with
propargyl alcohol provides the corresponding product 43 in a 3:1 diastereomeric ratio in favor of the $\alpha$-anomer. The product ratio is unchanged in the presence of monomeric thiourea 3, but it is reversed to $1: 5.7$ in the presence of bisthiourea 8. Although the basis for this reversal of diastereoselectivity is not well understood at this time, it is clear that there is a benefit to using bisthiourea 8 .




Scheme 3.17. Preliminary Results in a Thiourea-Catalyzed Glycosylation

Ongoing work in the group involves the modification of various portions of bisthiourea 8 to enhance reactivity and selectivity. Because an esterification of two thiourea monomers (Strategy 1, section 3.3.1) is potentially the most convergent route to bisthioureas, this strategy should be revisited. It is possible that the problems encountered in the synthesis of $\mathbf{7}$ will be alleviated with the longer tether length of $\mathbf{8}$.

Additionally, the symmetrical orientation of the two monomeric catalysts in the 2:1 complex with tetramethylammonium chloride (6, Figure 3.2) suggests that a cyclic dimer scaffold may provide an optimal geometry for productive electrophile activation
(Scheme 3.18). Although macrocyclization to obtain large cyclic structures is often challenging, we envision that chloride-binding properties of thioureas can be exploited in a templated macrolactonization to provide access to 22 -membered cyclic dimer $\mathbf{4 4} .^{21,22}$


Scheme 3.18. Proposed Template-Induced Macrolactonization

Our progress towards this dimer, a cyclic analog of bisthiourea 7, is summarized in Scheme 3.19. Isothiocyanate $\mathbf{4 7}$ was prepared from ester $\mathbf{2 3}$ according to the developed route. The remaining steps, installation of thiourea A and macrocyclization, will likely be challenging and may require protecting group manipulations. As such, it will be best to pursue a cyclic dimerization once an optimal bisthiourea is identified.

[^63]



Scheme 3.19. Progress towards Cyclic Dimer 44

### 3.7. Experimental Section

A. General Information.

Unless otherwise noted, all reactions were performed under a positive pressure of anhydrous nitrogen or argon in flame- or oven-dried glassware. Moisture- and airsensitive reagents were dispensed using oven-dried stainless steel syringes or cannulae and were introduced to reaction flasks through rubber septa. Reactions conducted below ambient temperature were cooled by external baths (dry ice/acetone for $-78{ }^{\circ} \mathrm{C}$ and ice/water for $0^{\circ} \mathrm{C}$ ). Reactions conducted above ambient temperature were heated by an oil bath.

Analytical thin layer chromatography (TLC) was performed on glass plates precoated with silica $60 \mathrm{~F}_{254}$ plates, 0.25 mm ). Visualization was carried out by exposure to a UV-lamp (short wave 254 nm , long wave 365 nm ), and by heating after staining the plate with a ceric ammonium molybdate or a potassium permanganate solution. Extraction and chromatography solvents were reagent or HPLC grade and were used without further purification. Flash chromatography was carried out over silica gel ( $60 \AA$, 230-400 mesh) from EM Science. Where indicated, chromatography was conducted on a Biotage Isolera automated chromatography system.

Materials. Commercial reagents and solvents were used with the following exceptions: tetrahydrofuran, dichloromethane, and 1,4-dioxane employed as reaction solvents were dried by passage through columns of activated alumina. Triethylamine was distilled from calcium hydride at 760 torr prior to use. Chloroform-d was dried over $3 \AA$ MS prior to use.

Instrumentation. Proton nuclear magnetic resonance ( ${ }^{1} \mathrm{H}$ NMR) spectra and carbon nuclear magnetic resonance ( ${ }^{13} \mathrm{C}$ NMR) spectra were recorded on a Varian Mercury-400 $(400 \mathrm{MHz})$, Inova- $500(500 \mathrm{MHz})$, or an Inova- $600(600 \mathrm{MHz})$ spectrometer at $23{ }^{\circ} \mathrm{C}$. Chemical shifts for protons are reported in parts per million (ppm, $\delta$ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent $\left(\mathrm{CHCl}_{3}: 7.26 \mathrm{ppm}\right)$.
B. Preparation and Characterization of Selected Intermediates

(S)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(4,4-dimethyl-2-oxotetrahydrofuran-3-
yl)thiourea (18)
A flame-dried $10-\mathrm{mL}$ round-bottom flask was charged with alcohol $14(50 \mathrm{mg}, 0.127$ $\mathrm{mmol}, 1.0$ equiv) and dioxane $(1.27 \mathrm{~mL})$. The flask was cooled to $0{ }^{\circ} \mathrm{C}$ and a solution of HCl in dioxane ( $127 \mu \mathrm{~L}, 0.508 \mathrm{mmol}, 4.0$ equiv) was added dropwise under an atmosphere of $\mathrm{N}_{2}$. The reaction mixture was allowed to gradually warm to room temperature over a period of 2 h . At this point, the reaction mixture was concentrated in vacuo to provide a sticky oil. The crude product was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(650 \mu \mathrm{~L}) . \mathrm{NEt}_{3}$ ( $53 \mu \mathrm{~L}, 3.0$ equiv) and isothiocyanate 15 ( $26 \mu \mathrm{~L}, 0.143 \mathrm{mmol}, 1.1$ equiv) were added sequentially and the reaction mixture was stirred at room temperature overnight. The
contents were concentrated in vacuo and purified via flash column chromatography (Biotage, $\mathrm{SiO}_{2}, 0-50 \% \mathrm{EtOAc} /$ hexanes) to afford 18 as a pale yellow solid ( 35.2 mg , $0.088 \mathrm{mmol}, 70 \%$ yield). $\mathrm{Rf}=0.47$ ( $50 \% \mathrm{EtOAc} /$ hexanes). ${ }^{1} \mathrm{H} \mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 7.76-7.98(m, 5H) $4.24(\mathrm{~s}, 1 \mathrm{H}) 3.73(\mathrm{~d}, J=10.74 \mathrm{~Hz}, 1 \mathrm{H}) 3.56(\mathrm{~d}, J=10.74 \mathrm{~Hz}, 1$ H) $1.18(\mathrm{~s}, 3 \mathrm{H}) 1.11-1.14(\mathrm{~m}, 3 \mathrm{H})$.



## Aniline (30)

A flame-dried $50-\mathrm{mL}$ round-bottom flask was charged with a stir bar and $10 \% \mathrm{Pd} / \mathrm{C}(44$ $\mathrm{mg}, 0.4$ equiv). The flask was fitted with a septum, evacuated, and refilled with argon. $\mathrm{MeOH}(4.0 \mathrm{~mL})$ was added to the flask under an atmosphere of argon, followed by a solution of nitro aromatic 29 ( $152 \mathrm{mg}, 0.19 \mathrm{mmol}, 1$ equiv) in $\mathrm{MeOH}(4.1 \mathrm{~mL})$. The flask was evacuated and refilled with $\mathrm{H}_{2}$ gas (3x) and then maintained under an atmosphere of $\mathrm{H}_{2}$. The flask was immersed in an oil bath set at $50^{\circ} \mathrm{C}$ and stirred at this temperature overnight. The hydrogen balloon was removed and the contents of the flask were filtered through a short pad of Celite ${ }^{\circledR}$. The filtrate was concentrated in vacuo to provide a dark brown product, which was carried forward without further purification. In $\mathrm{CDCl}_{3}$ the compound exists as a 1.7:1 mixture of rotamers. One of the resonances in the ${ }^{1} \mathrm{H}$ NMR spectrum corresponding to a proton of the minor rotamer was integrated to 1 , and all other integration data are reported relative to it. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3} \delta\right.$
ppm 9.24 (s, 1.4 H$) 8.92$ (br. s., 2.1 H ) 7.94 (s, 2 H ) 7.80 (s, 3.7 H ) $7.51-7.70$ (m, 9.7 H ) $7.42(\mathrm{~m}, 1.1 \mathrm{H}) 7.23(\mathrm{~m}, 1.8 \mathrm{H}) 7.05(\mathrm{~s}, 1.7 \mathrm{H}) 6.92-7.01(\mathrm{~m}, 6 \mathrm{H}) 6.66-6.74(\mathrm{~m}, 3.6 \mathrm{H})$ $5.93(\mathrm{~d}, J=9.62 \mathrm{~Hz}, 1.7 \mathrm{H}) 5.89(\mathrm{~d}, J=7.78 \mathrm{~Hz}, 1 \mathrm{H}) 5.61(\mathrm{~d}, J=10.07 \mathrm{~Hz}, 1 \mathrm{H}) 5.05-5.10$ (m, 1.9 H) 4.47-4.55 (m, 2 H) 4.28-4.33(m, 1.8 H$) 4.22-4.28(\mathrm{~m}, 1.9 \mathrm{H}) 4.07(\mathrm{~s}, 3.1$ H) 3.98-4.03(m, 1.7 H) 3.79-3.89 (m, 2.9 H) 3.51-3.66(m, 2.4 H) 2.26-2.38(m, 1.6 H) $2.14-2.24(\mathrm{~m}, 2.4 \mathrm{H}) 1.91-2.01(\mathrm{~m}, 4.0 \mathrm{H}) 1.75-1.89(\mathrm{~m}, 5 \mathrm{H}) 1.28(\mathrm{~s}, 4.3 \mathrm{H}) 1.26$ (s, 4.3 H$) 0.96-1.00(\mathrm{~m}, 3 \mathrm{H}) 0.70(\mathrm{~s}, 3 \mathrm{H})$.

tert-butyl (S)-1-((R)-2-(4-fluorophenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxopent-4-en-2-
ylcarbamate (34)
A flame-dried $100-\mathrm{mL}$ round-bottom flask was charged with arylpyrrolidine 15 (3.46 mmol, 1.0 equiv), amino acid 32 ( $884 \mathrm{mg}, 3.63 \mathrm{mmol}, 1.05$ equiv), HOBt ( $583 \mathrm{mg}, 3.80$ mmol, 1.1 equiv), and EDC ( $728 \mathrm{mg}, 3.80 \mathrm{mmol}, 1.1$ equiv) and DMF ( 17.3 mL ). The reaction mixture was stirred overnight, after which it was diluted with DI $\mathrm{H}_{2} \mathrm{O}(20 \mathrm{~mL})$ and extracted with EtOAc (3x). The combined organics were washed with saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}(1 \mathrm{x})$ and brine (1x), dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (Biotage $\circledR, 0-50 \%$ EtOAc/hexanes) to afford amide 34 as a white solid ( $859 \mathrm{mg}, 2.20 \mathrm{mmol}, 64 \%$ yield). In $\mathrm{CDCl}_{3}$ the compound exists as a $4.0: 1$ mixture of rotamers. One of the resonances in the ${ }^{1} \mathrm{H}$ NMR spectrum corresponding to a proton of the minor rotamer $\left(\mathrm{C}(\mathrm{Me})_{2} \mathrm{CHCH}_{2}\right)$ was integrated to 1 , and all other integration data are reported relative to it. ${ }^{1} \mathrm{H}$ NMR ( 600
$\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 7.28-7.35(\mathrm{~m}, 3 \mathrm{H}) 7.04-7.16(\mathrm{~m}, 11 \mathrm{H}) 6.95(\mathrm{t}, \mathrm{J}=8.79 \mathrm{~Hz}, 8 \mathrm{H})$ 6.08 (dd, $J=17.28,10.84 \mathrm{~Hz}, 4 \mathrm{H}) 5.89(\mathrm{dd}, J=17.57,10.84 \mathrm{~Hz}, 1 \mathrm{H}) 5.48(\mathrm{dd}, J=8.05$, $2.20 \mathrm{~Hz}, 1 \mathrm{H}) 5.19$ (dd, $J=7.91,2.34 \mathrm{~Hz}, 5 \mathrm{H}) 5.08-5.15$ (m, 13 H$) 5.05$ (s, 1 H$) 4.98$ (dd, $J=10.84,1.17 \mathrm{~Hz}, 1 \mathrm{H}) 4.89$ (dd, $J=17.57,1.17 \mathrm{~Hz}, 1 \mathrm{H}) 4.39(\mathrm{~d}, J=9.96 \mathrm{~Hz}, 4 \mathrm{H}) 4.20$ $4.27(\mathrm{~m}, 4 \mathrm{H}) 4.12-4.20(\mathrm{~m}, 1 \mathrm{H}) 3.64-3.83(\mathrm{~m}, 7 \mathrm{H}) 2.37(\mathrm{~s}, 1 \mathrm{H}) 2.21-2.32(\mathrm{~m}, 4 \mathrm{H})$ 1.90-2.06(m, 13 H$) 1.79-1.90(\mathrm{~m}, 5 \mathrm{H}) 1.45-1.55(\mathrm{~m}, 52 \mathrm{H}) 1.14-1.21(\mathrm{~m}, 27 \mathrm{H})$ 0.81 (s, 3 H ) 0.67 (s, 3 H ).

tert-butyl (S)-1-((R)-2-(4-fluorophenyl)pyrrolidin-1-yl)-5-hydroxy-3,3-dimethyl-1-oxopentan-2-ylcarbamate (35)

An oven-dried $200-\mathrm{mL}$ round-bottom flask was charged with alkene $34(802 \mathrm{mg}, 2.05$ mmol, 1 equiv) and THF ( 20.5 mL ). The flask was cooled to 0 oC and stirred at that temperature for 5 min , after which $9-\mathrm{BBN}(0.4 \mathrm{M}$ hexanes, $15.4 \mathrm{~mL}, 6.16 \mathrm{mmol}, 3.0$ equiv) was added dropwise over 10 min . The reaction was allowed to warm to room temperature overnight. The flask was returned to 0 oC and 2 N NaOH (4 drops) was cautiously added, resulting in vigorous bubbling. Another 9.25 mL 2 N NaOH were slowly added followed by $30 \% \mathrm{H}_{2} \mathrm{O}_{2}(8.2 \mathrm{~mL})$. The ice bath was removed and the contents were stirred rapidly at room temperature for 4 h . The contents were diluted with $\mathrm{H}_{2} \mathrm{O}$ and extracted with EtOAc (3x). The combined organics were washed sequentially with DI $\mathrm{H}_{2} \mathrm{O}, 10 \%$ aqueous sodium thiosulfate, and brine, dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered,
and concentrated. The crude residue was purified by flash chromatography (Biotage ${ }^{\circledR}$, $\mathrm{SiO}_{2}, 20-80 \% \mathrm{EtOAc} /$ hexanes) to afford primary alcohol 35 as a white foamy solid (757 $\mathrm{mg}, 90 \%$ yield). $\mathrm{R} f=0.19$ ( $50 \% \mathrm{EtOAc} /$ hexanes, CAM ). $\mathrm{In}_{\mathrm{CDCl}}^{3}$ the compound exists as a 2.3:1 mixture of rotamers. One of the resonances in the ${ }^{1} \mathrm{H}$ NMR spectrum corresponding to a proton of the minor rotamer was integrated to 1 , and all other integration data are reported relative to it. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 7.29(\mathrm{~m}$, 1.9 H) $7.00-7.14(\mathrm{~m}, 5.6 \mathrm{H}) 6.93(\mathrm{t}, \mathrm{J}=8.47 \mathrm{~Hz}, 4.3 \mathrm{H}) 6.34-6.50(\mathrm{~m}, 3.2 \mathrm{H}) 5.47(\mathrm{~d}$, $J=7.33 \mathrm{~Hz}, 1 \mathrm{H}) 5.19(\mathrm{~d}, J=7.33 \mathrm{~Hz}, 2.3 \mathrm{H}) 4.53(\mathrm{~d}, J=10.07 \mathrm{~Hz}, 2.3 \mathrm{H}) 4.25-4.35(\mathrm{~m}$, $2.3 \mathrm{H}) 4.22(\mathrm{~d}, \mathrm{~J}=10.53 \mathrm{~Hz}, 1.1 \mathrm{H}) 4.04$ (br s., 2.3 H$) 3.70-3.80(\mathrm{~m}, 4.9 \mathrm{H}) 3.58-3.70$ $(\mathrm{m}, 3.8 \mathrm{H}) 3.45-3.58(\mathrm{~m}, 1.5 \mathrm{H}) 2.29-2.40(\mathrm{~m}, 1.3 \mathrm{H}) 2.29(\mathrm{~s}, 2.6 \mathrm{H}) 1.76-2.01(\mathrm{~m}$, $10.8 \mathrm{H}) 1.44-1.51(\mathrm{~m}, 21.9 \mathrm{H}) 1.1(\mathrm{~s}, 4.9 \mathrm{H}) 1.08(\mathrm{~s}, 4.9 \mathrm{H}) 0.68(\mathrm{~s}, 2.2 \mathrm{H}) 0.49(\mathrm{~s}, 2.2$ H); ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) All observed resonances are reported: $\delta \mathrm{ppm}$ 172.7, $171.4,171.2,163.1,162.6,161.2,160.7,156.8,156.1,139.8(\mathrm{~d}, J=3.66 \mathrm{~Hz}), 138.1$ (d, $J=3.66 \mathrm{~Hz}), 128.3(\mathrm{~d}, J=8.24 \mathrm{~Hz}), 126.8(\mathrm{~d}, J=7.32 \mathrm{~Hz}) 115.6(\mathrm{~d}, J=22.0 \mathrm{~Hz}), 115.3(\mathrm{~d}$, $J=21.1 \mathrm{~Hz}), 79.62,79.57,61.0,60.4,60.1,58.6,58.5,58.3,57.3,48.3,47.3,41.64,41.60$, $36.2,36.1,35.8,34.3,28.43,28.40,26.9,26.6,25.0,24.6,23.1,21.7,21.0,14.2$.


An oven-dried 2-dram vial was charged with a stir bar, alcohol 35 ( $195 \mathrm{mg}, 0.478 \mathrm{mmol}$, 1.0 equiv), and acid 22 ( $135 \mathrm{mg}, 0.573 \mathrm{mmol}, 1.2$ equiv). $\mathrm{CH} 2 \mathrm{Cl} 2(1.5 \mathrm{~mL})$ and DMF ( 1 mL ) were added, followed by EDC ( $275 \mathrm{mg}, 1.4 \mathrm{mmol}, 3.0$ equiv) and DMAP ( 175 mg , $1.4 \mathrm{mmol}, 3.0$ equiv). The reaction mixture was stirred at room temperature overnight. It was then diluted with DI $\mathrm{H}_{2} \mathrm{O}$ and extracted with EtOAc (3x). The combined organics were dried over $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography to afford ester 36 as a white foamy solid ( $248 \mathrm{mg}, 83 \%$ yield). In $\mathrm{CDCl}_{3}$ the compound exists as a $1.7: 1$ mixture of rotamers. One of the resonances in the ${ }^{1} \mathrm{H}$ NMR spectrum corresponding to a proton of the minor rotamer was integrated to 1 , and all other integration data are reported relative to it. ${ }^{1} \mathrm{H}$ NMR (500 $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta \mathrm{ppm} 9.01(\mathrm{~d}, \mathrm{~J}=1.83 \mathrm{~Hz}, 1.7 \mathrm{H}) 8.88-8.96(\mathrm{~m}, 1 \mathrm{H}) 8.66(\mathrm{~d}, \mathrm{~J}=1.83 \mathrm{~Hz}$, $2.3 \mathrm{H}) 8.60(\mathrm{~s}, 1.6 \mathrm{H}) 8.53(\mathrm{~s}, 1.1 \mathrm{H}) 7.26-7.36(\mathrm{~m}, 2 \mathrm{H}) 6.96-7.08(\mathrm{~m}, 4.5 \mathrm{H}) 6.91(\mathrm{t}$, $J=8.70 \mathrm{~Hz}, 3.2 \mathrm{H}) 5.34(\mathrm{~d}, J=5.95 \mathrm{~Hz}, 1 \mathrm{H}) 5.06-5.20(\mathrm{~m}, 3.9 \mathrm{H}) 4.53$ (t, $J=7.33 \mathrm{~Hz}, 3$ H) 4.49 (br. s., 1.7 H ) $4.15-4.30(\mathrm{~m}, 3.6 \mathrm{H}) 3.60-3.81(\mathrm{~m}, 3.6 \mathrm{H}) 2.20-2.44(\mathrm{~m}, 3 \mathrm{H})$ 1.77-2.10(m, 11.5 H) 1.50-1.60(m, 2 H) 1.40-1.50(m, 17.4 H$) 1.09-1.18(\mathrm{~m}, 7.8 \mathrm{H})$ $0.88(\mathrm{~s}, 2 \mathrm{H}) 0.68(\mathrm{~s}, 2 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) All observed resonances are reported: $\delta \mathrm{ppm} 171.6,171.2,170.2,163.3,163.0,162.7,161.2,160.7,156.4,155.8$, $148.6,140.10,140.08,138.51,138.48,133.6,133.5,133.1,132.8,131.99,131.96,131.9$, $128.5,128.4,127.6,127.5,126.8,126.7,124.54,124.51,123.61,115.8,115.6,115.4$, $115.2,80.16,63.6,63.4,61.1,60.5,60.4,58.2,56.8,48.5,47.2,37.1,37.0,36.7,36.5$, $36.0,34.3,28.40,28.37,23.8,23.4,23.3,23.2,22.1,21.1,14.3$.


Thiourea (37)
A $50-\mathrm{mL}$ round-bottom flask was charged with Boc-protected amine $36(248 \mathrm{mg}, 0.40$ mmol, 1.0 equiv) and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(10 \mathrm{~mL})$. The flask was cooled to $0{ }^{\circ} \mathrm{C}$ and TFA ( 3.3 mL ) was added dropwise under an atmosphere of $\mathrm{N}_{2}$. The reaction mixture was stirred at this temperature for 2 h , at which point the contents were concentrated in vacuo. The crude amine salt was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(4 \mathrm{~mL})$, and 1.3 mL of this solution was removed (for use in a different reaction). The solution was cooled to $0{ }^{\circ} \mathrm{C}$, and $\mathrm{NEt}_{3}(110 \mu \mathrm{~L}, 3.0$ equiv) and isothiocyanate 15 ( $97 \mu \mathrm{~L}, 2.0$ equiv) were sequentially added to the flask dropwise. The reaction mixture was stirred and allowed to warm to room temperature over a period of 4 h , at which point the contents were concentrated in vacuo. The crude reside was purified by flash chromatography (Biotage ${ }^{\circledR}, 15-70 \% \mathrm{EtOAc} /$ hexanes ) to afford thiourea 37 as a white foam ( $204 \mathrm{mg}, 97 \%, 2$ steps). In $\mathrm{CDCl}_{3}$ the compound exists as a 1.3:1 mixture of rotamers. One of the resonances in the ${ }^{1} \mathrm{H}$ NMR spectrum corresponding to a proton of the minor rotamer was integrated to 1 , and all other integration data are reported relative to it. ${ }^{1} \mathrm{H}$ NMR $\left(500 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ ppm 9.51 (br. s., 1 H$) 9.42$ (br. s., $1.3 \mathrm{H}) 8.94-9.08(\mathrm{~m}, 1.4 \mathrm{H}) 8.88-8.94(\mathrm{~m}, 1 \mathrm{H}) 8.65-8.74(\mathrm{~m}, 1.97 \mathrm{H}) 8.61(\mathrm{~s}, 1.3 \mathrm{H})$
$8.52(\mathrm{~s}, 1.1 \mathrm{H}) 8.06(\mathrm{~s}, 1.87 \mathrm{H}) 7.92(\mathrm{~s}, 2.3 \mathrm{H}) 7.69(\mathrm{~s}, 0.9 \mathrm{H}) 7.64(\mathrm{~s}, 1.3 \mathrm{H}) 7.42-7.58$ (m, 2.2 H) $7.31-7.40(\mathrm{~m}, 1.8 \mathrm{H}) 7.04(\mathrm{t}, \mathrm{J}=8.70 \mathrm{~Hz}, 1.9 \mathrm{H}) 6.89(\mathrm{dd}, J=8.01,5.27 \mathrm{~Hz}$, $2.3 \mathrm{H}) 6.70(\mathrm{t}, J=8.47 \mathrm{~Hz}, 2.4 \mathrm{H}) 5.84(\mathrm{~d}, J=7.78 \mathrm{~Hz}, 1 \mathrm{H}) 5.69(\mathrm{~d}, J=9.62 \mathrm{~Hz}, 1.3 \mathrm{H})$ 5.47 (d, $J=9.62 \mathrm{~Hz}, 1 \mathrm{H}) 5.09(\mathrm{~d}, \mathrm{~J}=6.87 \mathrm{~Hz}, 1.3 \mathrm{H}) 4.58-4.70(\mathrm{~m}, 2.3 \mathrm{H}) 4.47-4.58(\mathrm{~m}$, 1.4 H) 4.35 (ddd, $J=11.22,8.01,5.95 \mathrm{~Hz}, 1.3 \mathrm{H}) 3.78-3.91(\mathrm{~m}, 1.4 \mathrm{H}) 3.50-3.66(\mathrm{~m}, 2$ H) 2.20-2.47 (m, 2.7 H) 2.09-2.18(m, 1 H) 1.73-2.02 (m, 6.3 H) 1.57-1.71 (m, 1.5 H) $1.34-1.49(\mathrm{~m}, 1.5 \mathrm{H}) 1.28(\mathrm{~d}, \mathrm{~J}=2.29 \mathrm{~Hz}, 6 \mathrm{H}) 1.00-1.10(\mathrm{~m}, 2.4 \mathrm{H}) 0.68(\mathrm{~s}, 2.3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( $126 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) All observed resonances are reported: $\delta \mathrm{ppm}$ 182.0, 181.6, $172.3,171.5,170.3,163.3,163.0,162.5,160.5,148.62,148.59,140.4,139.8,139.15$, $139.13,137.07,137.05,133.4,133.3,133.2,132.9,132.4,132.2,132.15,132.0,131.95$, $131.9,131.87,128.5,128.4,127.5,127.4,124.7,124.6,124.1,124.0,122.1,122.0,121.4$, $118.9,118.8,116.1,115.9,115.2,115.0,63.3,62.2,62.0,60.9,60.6,60.4,49.1,48.0$, $38.1,37.8,37.7,37.4,35.4,34.3,24.4,24.2,24.1,23.5,23.1,21.6,21.2,14.3$.


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    ${ }^{7}$ Epimerization of reserpine (1) to 3-epi-reserpine (isoreserpine) occurs under acidic or basic conditions and is driven by the removal of unfavorable streic interactions between the axial C3 indole group and the D-ring. Subjecting 1 to AcOH under reflux affords an equilibrium mixture of 1.0:3.5 (reserpine:isoresrepine). For details, see: a) Gaskell, A. J.; Joule, J. A. Tetrahedron 1967, 23, 4053. b) Zhang, L.-H.; Gupta, A. K.; Cook, J. M. J. Org. Chem. 1989, 54, 4708. c) Sakai, S.; Ogawa, M. Chem. Pharm. Bull. 1978, 26, 678. d) Lounasmaa, M.; Berner, M.; Tolvanen, A. Heterocycles 1998, 48, 1275.

[^30]:    ${ }^{8}$ A related cyclization of amino-nitriles was recently employed in the syntheses of C3-epimeric natural products venenatine and alstovenine: Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. Nat. Chem. 2013, 5, 126.
    ${ }^{9}$ a) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. Org. Lett. 2012, 14, 5388. b) Patel, A.; Barcan, G. A.; Kwon, O.; Houk, K. N. J. Am. Chem. Soc. 2013, 135, 4878.

[^31]:    ${ }^{10}$ a) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. J. Am. Chem. Soc. 2013, 135, 1891. b) For further details regarding the developing and scope of this transformation, see: Lalonde, M. P. Ph.D. Dissertation, Harvard University, 2008.

[^32]:    ${ }^{11}$ Meredeth McGowan also applied an enantioselective FADA reaction of dihydroisoquinone and enone fragments to an asymmetric total synthesis of (-)-tubulosine. See reference 3a.
    ${ }^{12}$ White, D. E.; Jacobsen, E.N. Tetrahedron: Asymmetry 2003, 14, 3633.
    ${ }^{13}$ The sequence of allylsilane addition and subsequent PMB protection was adapted from: Evans, D. A.; Rajapakse, H. A.; Stenkemp, D. Angew. Chem., Int. Ed. 2002, 41, 4569.

[^33]:    ${ }^{14}$ Imine 18 was synthesized from 6-methoxy-tryptamine through a formylation, Bischler-Napieralski cyclization, and tosylation with TsF. See refs. 10a,b for details.

[^34]:    ${ }^{15}$ No catalysis was observed with proline or related secondary amine catalysts. The proline-catalyzed formal aza-Diels-Alder reaction between dihydro- $\beta$-carboline and enones has been shown to require a large excess of enone ( 30 equivalents) relative to imine in those cases where catalysis is observed, see: Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. Org. Lett. 2006, 8, 1533.
    ${ }^{16}$ Very low conversions ( $<10 \%$ after 6 d ) were obtained using $20 \mathrm{~mol} \% \mathrm{n}$-hexylamine and $20 \mathrm{~mol} \%$ acetic acid.

[^35]:    ${ }^{17}$ The beneficial additive was generated during the mesylation/elimination, and its identity was not conclusively determined. In the absence of the additive, enal decomposition was observed, and with excess (3 equiv) of the additive, lower conversion was obtained.

[^36]:    ${ }^{18}$ This work was done in collaboration with Matthew Rienzo.
    ${ }^{19}$ Nahm, S.; Weinreb, S. M. Tetrahedron Lett. 1981, 22, 3815.

[^37]:    ${ }^{20}$ In a related addition of an alkynyllithium species to a Weinreb amide, Collum and coworkers identified 1:1 aggregates that form between the tetrahedral adduct and unreacted organolithium reagent: Qu, B.; Collum, D. B. J. Org. Chem. 2006, 71, 7117.

[^38]:    ${ }^{21}$ Similar Weinreb amide deprotonation pathways have been identified: a) Mentzel, M.; Hoffman, H. M. R. J. Prakt. Chem. 1997, 339, 517. b) Sibi, M. P. Org. Prep. Proced. Int. 1993, 25, 15.
    ${ }^{22}$ This work was done in collaboration with Meredeth McGowan.

[^39]:    ${ }^{23}$ The enamine aldol reaction installs the C16 center of $\mathbf{3 2}$ via protonation of an enamine intermediate, also from the top face. ${ }^{1}$ H NMR and NOESY analysis of this intermediate (see the experimental section and ref. 3 b ) indicates that the E -ring is in a chair conformation, with all substituents in equatorial positions.

[^40]:    ${ }^{24}$ For a review of thiocarbonyl radical chemistry, see: Crich, D.; Quintero, L. Chem. Rev. 1989, 89, 1413.
    ${ }^{25}$ Radical deoxygenation of cyclic thiocarbonyl derivatives typically occurs through the more stable of the two possible radicals. For relevant examples, see: a) Barton, D. H. R.; Subramanian, R. J. Chem. Soc. Perkin I, 1977, 1718. b) Liang, D.; Paula, H. W.; Fraser-Reid, B. J. Chem. Soc.; Chem. Commun. 1984, 1123. c) Kangani, C. O.; Brückner, A. N.; Curran, D. P. Org. Lett. 2005, 7, 379.
    ${ }^{26}$ A similar radical equilibration mechanism was proposed to account for the significant selectivity for radical deoxygenation at the secondary center from a cyclic thiocarbamate derived from a secondary/ tertiary diol: Redlich, H.; Sudau, W.; Paulsen, H. Tetrahedron 1985, 41, 4253.

[^41]:    ${ }^{27}$ a) Kim, J.-G.; Cho, D. H.; Jang, D. O. Tetrahedron Lett. 2004, 45, 3031. b) Jang, D. O.; Kim, J.; Cho, D. H.; Chung, C.-M. Tetrahedron Lett. 2001, 42, 1073. c) Flyer, A. N.; Si, C.; Myers, A. G. Nat. Chem. 2010, 2, 886 .

[^42]:    ${ }^{28}$ The elimination of the C15 trifluoroacetate $\mathbf{4 9}$ was faster with secondary amines than with tertiary amine bases, suggesting that enamine intermediates may be involved. Based on this possibility, we attempted a cascade aldol-elimination sequence from keto-aldehyde 31. However, enal 33 was formed as a minor product and in a $1: 14$ ratio with the aldol adduct 32 , so we moved forward with the two-step sequence.

[^43]:    ${ }^{29}$ Hydrogenation product 34 was equivalent to the one Meredeth McGowan had previously obtained (Scheme 2.10).

[^44]:    ${ }^{30}$ Attempted radical deoxygenation of the tertiary trifluoroacetate under conditions reported by Jang (Refs.25a,b ) or Myers (Ref.25c ) resulted in decomposition, hydrolysis, and elimination products.
    ${ }^{31}$ Although a diastereomeric ratio was not measured on the crude hydrogenation product, the high yield of hydrogenation product indicates that the dr must at least be $4: 1$ in favor of the observed product 59 .

[^45]:    ${ }^{32}$ a) Lounasmaa, M. Tetrahedron 1995, 51, 11892. b) Lounasmaa, M.; Jokela, R. Tetrahedron 1990, 46, 615.

[^46]:    ${ }^{33}$ a) Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. Inorg. Chim. Acta 2006, 359, 2786. b)
    Wüstenberg, B.; Pfaltz, A. Adv. Synth. Catal. 2008, 350, 174.\#

[^47]:    ${ }^{34}$ Although improvements in the turnover of iridium hydrogenation catalysts have been accomplished through the formation of substrate amine salts or by the use of borate additives, these strategies were ineffective for the hydrogenation of 57 with 64. For precedents, see: a) Trost, B. M.; Rudd, M. T. Org. Lett. 2003, 5, 1467. b) Maimone, T. J.; Shi, J.; Ashida, S. Baran, P. S. J. Am. Chem. Soc. 2009, 131, 17066.

[^48]:    ${ }^{35}$ Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. Org. Synth. 2000, 77, 141.
    ${ }^{36}$ Sigma Aldrich, 2003, "AL-180: Diazald, MNNG and Diazomethane Generators." http://www.sigmaaldrich.com/aldrich/bulletin/AL-180.pdf
    ${ }^{37}$ Trost, B. M.; Grese, T. A.; Chan, D. M. T. J. Am. Chem. Soc. 1991, 113, 7350.
    ${ }^{38}$ Ficini, J.; Barbara, C.; Desmaële, D.; Ourfelli, O. Heterocycles 1987, 25, 329.

[^49]:    ${ }^{39}$ The product can be chromatographed on Davisil ${ }^{\mathrm{TM}}$, but small amounts of decomposition are observed, and thus the reported workup procedure was devised to provide the pure product without need for flash chromatography.

[^50]:    ${ }^{40}$ Lounasmaa, M.; Tolvanen, A.; Kan, S.-K. Heterocycles 1985, 23, 371-375.

[^51]:    ${ }^{41}$ This procedure was adapted the Stork synthesis of reserpine: See ref. 5q

[^52]:    ${ }^{42}$ Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. J. Am. Chem. Soc. 1987, 109, 6124.

[^53]:    ${ }^{1}$ a) Doyle, A. G.; Jacobsen, E. N. Chem. Rev. 2007, 107, 5713. b) Brak, K.; Jacobsen, E. N. Angew. Chem., Int. Ed. 2013, 52, 534. c) Mahlau, M.; List, B. Angew. Chem., Int. Ed. 2013, 52, 518. d) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. Nat. Chem. 2012, 4, 603.
    ${ }^{2}$ For a review on catalysis via thiourea-bound ion pairs, see: Zhang, Z.; Schreiner, P. R. Chem. Soc. Rev. 2009, 38, 1187.
    ${ }^{3}$ Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. J. Am. Chem. Soc. 2007, 129, 13404.
    ${ }^{4}$ Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. J. Am. Chem. Soc. 2010, 132, 9286.
    ${ }^{5}$ Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N.; J. Am. Chem. Soc. 2008, 130, 7198.

[^54]:    ${ }^{6}$ Ford, D. D.; Lehnherr, D.; Jacobsen, E. N. Manuscript in preparation.

[^55]:    ${ }^{7}$ Bisthioureas 7 and $\mathbf{8}$ were proposed by Dan Lehnherr.

[^56]:    ${ }^{8}$ Another possible coupling strategy is a Mitsunobu reaction of $\mathbf{9}$ and $\mathbf{1 0}$; however, the conditions would likely result in cyclization of thiourea 10: Lee, G.-J.; Kim, J. N.; Kim, T. H. Bull Korean Chem. Soc. 2002, 23, 19.

[^57]:    ${ }^{9}$ Hydrolysis of symmetrical thiourea dimers linked through the aniline-derived portion also provided a route to carboxylic acid 9 . The analogous hydrolysis of dimers linked through the hydroxy-tert-leucine amino acid residues did not afford alcohol 10.
    ${ }^{10}$ Freskos, J. N. Synth. Commun. 1994, 24, 557.
    ${ }^{11}$ Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. J. Org. Chem. 2003, 68, 1771.
    ${ }^{12}$ Arylpyrrolidine 13 was synthesized according to the reported procedure: Reddy, L. R.; Das, S. G.; Liu, Y.; Prashad, M. J. Org. Chem. 2010, 75, 2236.
    ${ }^{13}$ Augeri, D. J. et al. J. Med. Chem. 2005, 48, 5025.
    ${ }^{14}$ We also attempted a ring-opening of lactone $\mathbf{1 8}$ with arylpyrrolidine $\mathbf{1 3}$ in the presence of $\mathrm{AlMe}_{3}$; however, the desired amide was not formed.

[^58]:    ${ }^{15}$ Recent results obtained by Dr. Kaid Harper, a postdoctoral fellow in the group, indicate that cleavage of a silyl ether related to 21 is also problematic.

[^59]:    ${ }^{16}$ When the reaction was monitored by LC/MS, the peaks corresponding to the masses of $[\mathbf{2 6} \text { - Boc }]^{+},[26$ - arylpyrrolidine $]^{+}$, and [ 26 - Boc - arylpyrrolidine] ${ }^{+}$were all present, suggesting that amide bond cleavage occurs competitively with removal of the Boc group.
    ${ }^{17}$ Analogous acid-promoted cyclizations have been reported: a) Lehmann, J.; Linden, A.; Heimgartner, H. Tetrahedron 1998, 54, 8721. b) Breitenmoser, R. A.; Linden, A.; Heimgartner, H. Helv. Chim. Acta 2002, 85, 990.

[^60]:    ${ }^{18}$ Hydrogenation of 29 with $\mathrm{Pd} / \mathrm{C}$ at room temperature and $20 \mathrm{~atm} \mathrm{H}_{2}$ resulted in over reduction to the corresponding cyclohexylamine. Other reductions evaluated (e.g. $\mathrm{NH}_{2} \mathrm{HCO}_{2}$ transfer hydrogenation, $\mathrm{SnCl}_{2}$, room temperature hydrogenation) stalled at the hydroxylamine stage (determined by LRMS). The difficulty of this reduction is in contrast to the straightforward reduction of 23 (Scheme 3.9) and suggests that thiourea B may be poisoning the reagents or interacting with the nitro group.

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[^62]:    ${ }^{20}$ These results were obtained by Dan Lehnherr.

[^63]:    ${ }^{21}$ For a general review of templated macrocylizations, see: Laughrey, Z. R.; Gibb, B. C. in Top. Curr. Chem. Vol. 249 (Eds. Schalley, C. A.; Vögtle, F.; Dötz, K. H.) Springer-Verlag, Heidelberg, 2005, 67.
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