PROGRESS TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF VARIECOLIN

AND

GAS-PHASE STUDIES OF THE TWISTED AMIDE 2-QUINUCLIDONE

Thesis by

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To my mother
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was intrigued by his labs that were a constant exercise in creativity, critical thinking, and fun.

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ABSTRACT

Biologically active natural products and pharmaceuticals often present intriguing structural features that can challenge the state of the art in catalysis and synthetic methodology for their preparation. The identification of unique targets thus stimulates the development of new strategies and methods for chemical synthesis. The complex architecture representative of the variecolin family of sesterterpenes has inspired our pursuit of new tactics that has enabled the expansion of methods from our laboratory.

First, progress toward the asymmetric total synthesis of variecolin is discussed. Our convergent synthetic approach bisects the target into two complex fragments to address the main structural challenges. A microwave-promoted tandem Wolff/Cope rearrangement of vinyl cyclobutyl diazocarbonyls has been developed that provides access to functionalized, fused eight-membered rings and is used to construct the central B ring of variecolin. In addition, the utility of our Pd-catalyzed enantioselective alkylation method is extended to a new vinylogous ester substrate class to produce a quaternary ketone in excellent yield with high selectivity that is an exceptional substrate for an efficient ring contraction to the cyclopentene D ring system. The successful asymmetric preparation of our two devised fragments has facilitated initial studies toward their coupling and completion of variecolin.

Second, a preliminary examination of the substrate scope for the asymmetric alkylation of the vinylogous β-ketoester substrate class is described. Derivatives that perturb substrate electronics display enhanced reactivity and selectivity, generating products with excellent selectivities and expanding the potential of this versatile class of substrates. Furthermore, their utility is underscored as the key enantioselective transformation en route to the synthesis of the sesquiterpenoid (+)-carissone.

Finally, gas-phase studies of the twisted amide 2-quinuclidone are described. Proton affinity experiments have quantified its high basicity, which is comparable to a tertiary amine. A gas-phase synthesis of 2-quinuclidione via elimination of water and subsequent fragmentation further highlight the unusual characteristics of extremely twisted amides.
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**APPENDIX 6**

An Improved and Highly Efficient Copper(I)-Catalyzed Preparation of (S)-t-Bu-PHOX

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APPENDIX 8
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Figure A8.1.1. (S)-t-Bu-PHOX ((S)-55) is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 646767.

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<th>Definition</th>
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<tbody>
<tr>
<td>Å</td>
<td>Ångstrom</td>
</tr>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation at wavelength of sodium D line</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Anal.</td>
<td>combustion elemental analysis</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
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<td>aq</td>
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</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
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<tr>
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<tr>
<td>ca.</td>
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<td>------------</td>
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<tr>
<td>CAN</td>
<td>ceric ammonium nitrate</td>
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<tr>
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<td>CCDC</td>
<td>Cambridge Crystallographic Data Centre</td>
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<tr>
<td>CDI</td>
<td>1,1'-carbonyldiimidazole</td>
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<tr>
<td>cf.</td>
<td>compare (Latin confer)</td>
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<td>CID</td>
<td>collision-induced dissociation</td>
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<td>complex</td>
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<td>doublet</td>
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<tr>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>dmdba</td>
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<td>N,N-dimethylformamide</td>
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<tr>
<td>DNA</td>
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<td>1,4-bis(diphenylphosphino)butane</td>
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<td>dppf</td>
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</tr>
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<td>dr</td>
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$E_a$  
activation energy

EC$_{50}$  
median effective concentration (50%)

EDC  
$N$-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide

ee  
enantiomeric excess

EI  
electron impact

e.g.  
for example (Latin exempli gratia)

equiv  
equivalent

ESI  
electrospray ionization

Et  
ethyl

FAB  
fast atom bombardment

FID  
flame ionization detector

g  
gram(s)

GC  
gas chromatography

gCOSY  
gradientselected correlation spectroscopy

h  
hour(s)

HIV  
human immunodeficiency virus

HMDS  
1,1,1,3,3,3-hexamethyldisilazane

HMPA  
hexamethylphosphoramide

HOBt  
1-hydroxybenzotriazole

HPLC  
high-performance liquid chromatography

HRMS  
high-resolution mass spectroscopy

HSV  
herpes simplex virus

$h\nu$  
light

Hz  
hertz

IC$_{50}$  
median inhibition concentration (50%)

i.e.  
that is (Latin id est)

IR  
infrared (spectroscopy)
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<td>$J$</td>
<td>coupling constant</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>KDA</td>
<td>potassium diisopropylamide</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>wavelength</td>
</tr>
<tr>
<td>L</td>
<td>liter</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature value</td>
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<tr>
<td>LTQ</td>
<td>linear trap quadrupole</td>
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<tr>
<td>m</td>
<td>multiplet; milli</td>
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<tr>
<td>$m$</td>
<td>meta</td>
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<tr>
<td>$m/z$</td>
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<td>metal; molar; molecular ion</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>$\mu$</td>
<td>micro</td>
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<td>nbd</td>
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<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
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<td>NIST</td>
<td>National Institute of Standards and Technology</td>
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<tr>
<td>NMO</td>
<td>$N$-methylmorpholine $N$-oxide</td>
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<tr>
<td>NMR</td>
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
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<td>nuclear Overhauser enhancement spectroscopy</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<tr>
<td>[O]</td>
<td>oxidation</td>
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<tr>
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<td>ortho</td>
</tr>
<tr>
<td>p</td>
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<tr>
<td>PA</td>
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<td>pyridinium dichromate</td>
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<td>Ph</td>
<td>phenyl</td>
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<td>pH</td>
<td>hydrogen ion concentration in aqueous solution</td>
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<tr>
<td>Piv</td>
<td>pivaloyl</td>
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<tr>
<td>p$K_a$</td>
<td>$pK$ for association of an acid</td>
</tr>
<tr>
<td>PMB</td>
<td>$p$-methoxybenzyl</td>
</tr>
<tr>
<td>pmdba</td>
<td>bis(4-methoxybenzyldene)acetone</td>
</tr>
<tr>
<td>PPL</td>
<td>porcine pancreas lipase</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium $p$-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>$i$-Pr</td>
<td>isopropyl</td>
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Py    pyridine
q    quartet
ref    reference
R    generic for any atom or functional group
$R_f$    retention factor
rt    room temperature
s    singlet or strong or selectivity factor
sat.    saturated
SET    single electron transfer
$S_{\text{n2}}$    second-order nucleophilic substitution
sp.    species
t    triplet
TBAF    tetrabutylammonium fluoride
TBHP    tert-butyl hydroperoxide
TBS    tert-butyldimethylsilyl
TCDI    1,1’-thiocarbonyldiimidazole
TCNE    tetracyanoethylene
Tf    trifluoromethanesulfonyl (trifyl)
TFA    trifluoroacetic acid
TFE    2,2,2-trifluoroethanol
THF    tetrahydrofuran
TIPS    triisopropylsilyl
TLC    thin-layer chromatography
TMEDA    $N,N,N',N'$-tetramethylethlenediamine
TMS    trimethylsilyl
TOF    time-of-flight
Tol    tolyl
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<tr>
<td>TON</td>
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<tr>
<td>$t_R$</td>
<td>retention time</td>
</tr>
<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>$v/v$</td>
<td>volume to volume</td>
</tr>
<tr>
<td>w</td>
<td>weak</td>
</tr>
<tr>
<td>$w/v$</td>
<td>weight to volume</td>
</tr>
<tr>
<td>X</td>
<td>anionic ligand or halide</td>
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CHAPTER 1

Natural Products and Pharmaceuticals as Inspiration for the Development of Enantioselective Catalysis†

1.1 INTRODUCTION

Biologically active natural products and pharmaceuticals often contain particularly challenging structural features and functionalities in terms of synthesis. Perhaps the greatest difficulties are those caused by issues of stereochemistry. A useful strategy for synthesizing such molecules is to devise methods of bond formation that provide opportunities for using enantioselective catalysis. In using this tactic, the desire for a particular target structure ultimately drives the development of catalytic methods. New enantioselective catalytic methods contribute to a greater fundamental understanding of how bonds can be constructed and lead to valuable synthetic technologies that are useful for a variety of applications. The lack of methods available for installing functionalities or structural motifs during chemical synthesis can at first be frustrating. However,

† This review was written in collaboration with Justin T. Mohr and a similar version has been published. See: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. Nature 2008, 455, 323–332.
retrosynthetic analysis,\textsuperscript{1} a way of viewing the target molecule as a series of structurally simpler precursors, can greatly aid in planning how to generate a valuable chemical substance. Despite this, difficulties in preparing materials enriched in a particular enantiomer persist because of the limited number of catalytic enantioselective transformations available.\textsuperscript{2} One fruitful strategy is to design a synthesis that depends on a bond-forming reaction for which there is no known enantioselective variant. This approach thus provides the impetus for developing novel transformations and leads to a greater understanding of methods of bond construction and catalysis. Herein, several recent examples of novel catalytic enantioselective transformations are described in order to illustrate the effectiveness of this strategy for preparing important structural motifs found in biologically active molecules. Each of these transformations has contributed not only an effective means of generating a particular target structure but also a useful new tool for a variety of applications in synthetic chemistry.

\section*{1.2 HISTORICAL OVERVIEW OF ENANTIOSELECTIVE METHODS}

To provide an overview of established catalytic enantioselective methods that have been developed for total synthesis, several notable examples of enantioselective reactions in total synthesis are highlighted in Scheme 1.2.1 through Scheme 1.2.4. In each of these cases, the target molecules posed particular challenges that had yet to be solved by enantioselective catalysis. Although, in some instances (e.g., the Diels–Alder reaction, Scheme 1.2.1), the methods were developed before their first application in total synthesis, the demonstrated value of the transformation highlighted the need for enantioselective variants. Following the development of the [4 + 2] cycloaddition
reaction in the 1920s, studies of this transformation elucidated several key facets of the stereochemical outcome of the reaction (e.g., the “endo rule,” regioselectivity, and diastereoselectivity). These intrinsic stereochemical control elements proved useful when the Diels–Alder reaction was first featured in a total synthesis with Stork’s stereocontrolled synthesis of cantharidin in 1951. Subsequently, the thermal Diels–Alder reaction was used for several total syntheses, perhaps most famously in Woodward’s landmark synthesis of reserpine. Enantioselectivity in this transformation remained elusive, however, and perhaps was considered unattainable at the time.

Scheme 1.2.1. Enantioselective Diels–Alder cycloaddition and enantioselective ketone reduction en route to prostaglandins

One key practical improvement in the Diels–Alder reaction was the discovery that Lewis acids markedly increased the reaction rate. Many laboratories sought to exploit this and to develop asymmetric versions of the Diels–Alder reaction catalyzed by chiral Lewis acids, culminating in a report of the first highly enantioselective catalytic Diels–
Alder reaction in 1979. The interface between reaction development, study of the mechanism, and synthesis is readily apparent from the multitude of chiral Diels–Alder catalysts and accompanying enantioselective total syntheses that have been reported. These successes validate the extensive efforts directed at realizing this important goal.

Other methods were developed to address more general problems in synthesis (e.g., synthesis of chiral alcohols by means of enantioselective ketone reduction, Scheme 1.2.1); however, the key structures are embedded in a variety of important natural products and pharmaceutical compounds. In the case of Corey’s approach to the synthesis of prostaglandins first reported in the 1960s, control of the configuration of the sidechain allylic alcohol at C(15) required stoichiometric chiral reducing agents until a solution to this long-standing problem was found in the 1980s. Interestingly, the oxazaborolidine catalyst discovered in these explorations has had other varied applications in synthesis and catalysis, demonstrating the versatility of privileged molecular frameworks for enantioselective catalysis.

The practical application of enantioselective catalysis is apparent in myriad industrial applications (e.g., Scheme 1.2.2), for which the limits of catalysis must be examined to minimize costs. Important industrial applications include the synthesis of chiral building blocks (e.g., amino acids (10)), novel biologically active pharmaceuticals (e.g., Crixivan (indinavir sulfate, 13)), and commodity chemicals (cheap chemicals sold in bulk) with various important uses (e.g., menthol (17)). Only the most efficient methods are feasible for large-scale industrial synthesis, and in many ways these protocols represent the pinnacle of modern enantioselective catalysis. A viable commercial operation must account for more than simply effective asymmetric induction; factors
including turnover frequency, catalyst availability, catalyst recovery, catalyst toxicity, and feasible large-scale handling procedures must all be considered for industrial applications. These daunting challenges underscore the demand for increasingly efficient catalyst systems.

Scheme 1.2.2. a) Enantioselective enamide hydrogenation toward $\alpha$-amino acids. b) Enantioselective alkene epoxidation toward Crixivan. c) Enantioselective isomerization of an allyl amine toward menthol

To maximize the usefulness of the stereochemistry attained by these key asymmetric transformations, subsequent diastereoselective reactions may be used to control the formation of many stereocenters based on a single enantioselective transformation (e.g., Scheme 1.2.3). The Hajos–Parrish ketone (19), first prepared in the context of steroid synthesis, has been used extensively in other synthetic efforts and has proved to be a
versatile chiral-pool starting material.\textsuperscript{17} The amino acid catalyst system developed for this intramolecular aldol condensation provided a sound basis for the recent use of organic molecules as catalysts for a variety of enantioselective transformations (see subsection 1.3.4).

\textit{Scheme 1.2.3. Enantioselective intramolecular aldol condensation toward steroids}

The use of several different enantioselective reactions to prepare enantioenriched fragments of complex molecules improves efficiency through convergency. The importance of this strategy is shown by the variety of extraordinarily complex polyketide natural products that have been prepared through asymmetric intermolecular aldol reactions (e.g., phorboxazole B\textsuperscript{18} (27), Scheme 1.2.4). The challenging structure of these molecules has required the development of several related protocols to address the subtle differences in substitution patterns and functionality present in substrates, and, despite many successes, studies are ongoing.\textsuperscript{19}
1.3 RECENT DEVELOPMENTS IN ENANTIOSELECTIVE CATALYSIS

In this section, recent representative developments made by using this approach—that is, by using target structures to inspire the development of enantioselective catalysts—for the construction of biologically important target molecules are described. Most of these methods involve the formation of a carbon–carbon bond, the fundamental structure of organic molecules. These cases were selected to illustrate some of the latest developments in enantioselective catalysis for complex molecule synthesis. Special
attention has been given to reactions that address some of the most important challenges in synthetic chemistry today: increasing functional group tolerance, generating new carbocyclic and heterocyclic rings, and forming all-carbon quaternary stereocenters. The examples are also intended to show the important symbiosis between total synthesis and method development, and to show that improvements in one branch of synthetic chemistry have an impact on the others.

### 1.3.1 β-ENAMINO AMIDE HYDROGENATIONS — JANUVIA

Catalytic enantioselective hydrogenation has become one of the most effective and powerful methods for the synthesis of chiral α-amino acids for numerous applications. Over the past decade, the usefulness of the homologous building blocks, β-amino acids, in pharmaceutical, agrochemical, β-peptide, and natural substances has become evident, highlighting the need for a general and effective means for their preparation. Undoubtedly, the implementation of a catalytic asymmetric hydrogenation of N-acyl-β-enamino esters seemed to be the most efficient pathway toward their synthesis, although initial investigations achieved poor selectivities. Additional syntheses using the chiral pool, auxiliaries, and more recently the catalytic asymmetric generation of C–C and C–N bonds have been successful in satisfying the increased demand for β-amino acids. These valuable methods allow flexible strategies for the synthesis of a variety of analogs; however, most examples are limited by the requirement for further chemical manipulation that is often necessary to produce the functionality of the desired β-amino acids.
Despite initial difficulties, the asymmetric hydrogenation of $N$-acyl-$\beta$-enamino esters has been developed into a useful method over the past 15 years.\textsuperscript{22} This fruitful endeavor has demonstrated that several transition metal and ligand combinations are competent for preparing $N$-acyl-$\beta$-amino acids with good-to-excellent enantioselectivities. A notable drawback to this strategy, however, is the requirement for the seemingly indispensable $N$-acyl group on the $\beta$-enamino esters; this group is needed for metal chelation, which improves reactivity and selectivity. The introduction of this moiety often produces enamine alkene isomers that can be difficult to separate, and, importantly, the individual isomers are typically hydrogenated with differing rates and selectivities. Moreover, these difficulties are magnified by the necessary removal of this group, a seemingly cumbersome artifact of an otherwise powerful strategy. Nonetheless, this advance has allowed a variety of $\beta$-amino acids to be prepared.\textsuperscript{20b}

An innovative solution to this problem was demonstrated by a group at Merck en route to synthesizing Januvia (sitagliptin phosphate; \textbf{40}, Scheme 1.3.1), which has recently been approved by the U. S. Food and Drug Administration for the treatment of type 2 diabetes.\textsuperscript{23} The optimal target contains an unfunctionalized $\beta$-amino amide. A strategy was sought to install this moiety directly by asymmetric hydrogenation of unsubstituted $\beta$-enamino ester and amide derivatives\textsuperscript{24} (e.g., \textbf{36}). A traditional hydrogenation route for the production of amino acids is a proven, cost-effective method for the synthesis of chiral building blocks. The industrial infrastructure is already in place to realize this goal; however, in this case, the reduction of unprotected $\beta$-enamino acids was not effective with existing chiral catalysts. A crucial component in addressing such limitations was Merck’s high-throughput screening facility, which allowed rapid
screening of catalyst structures and reaction conditions (an essential component for the
success of any asymmetric catalytic process). One potential complication for this
hydrogenation strategy was avoided when it was observed that the preparation of the
\(\beta\)-enamino ester and amide substrates (e.g., \(35 \rightarrow 36\)) proceeded with complete
selectivity for the \(Z\)-isomer, presumably owing to hydrogen bonding in the products.

\[\text{Scheme 1.3.1. Enantioselective hydrogenation of a } \beta\text{-enamino amide toward the synthesis of Januvia}\]

During the screening, a survey of transition metals and ligands revealed that rhodium
complexes of the Josiphos (e.g., \(37\), Scheme 1.3.1) family of ligands efficiently catalyze
the hydrogenation of a variety of substrates to give high yields with excellent
enantioselectivities. The remarkable functional-group tolerance of this catalyst allowed
the strategic implementation of this asymmetric transformation as the penultimate step of the synthesis, thereby maximizing the usefulness of the process and materials. Thus, phenylacetic acid derivative 32 was converted into β-ketoamide 35 in a one-pot procedure via acylation of Meldrum’s acid (33), followed by treatment with triazole salt 34. Exposure to ammonium acetate converted this into β-enamino amide 36 as a single enamine isomer. Hydrogenation of amide 36 in the presence of 0.30 mol % of rhodium(I) and ligand 37 provided β-amino amide 39 in >95% conversion and 95% enantiomeric excess. Subsequent recrystallization and salt formation with phosphoric acid gave Januvia (40). Efforts to optimize efficiency and examine the mechanism of the asymmetric process revealed that reactivity and selectivity were dependent on the pH of the reaction solution. It was found that ~1 mol % of a mild acid (i.e., ammonium chloride) was essential for the reaction to proceed reproducibly on a large scale. In addition, it was observed that hydrogenation of a related substrate under identical conditions with a deuterium gas atmosphere resulted in deuterium incorporation at the β-position only, suggesting that an imine is an intermediate (38) and that an enamine–imine tautomerization process plays an important part in the mechanism. Interestingly, intermediates such as 38 have a striking similarity to asymmetric β-carbonyl hydrogenations pioneered by Noyori and co-workers.

This example demonstrates the development of asymmetric catalysis into a state-of-the-art science through maximizing the efficiency by minimizing unnecessary functionality, by using atom economy, and by using extremely active catalysts. Moreover, the development of the catalyst system for the synthesis of Januvia exemplifies the continued need for subtly different catalysts to meet new synthetic
demands. Building on the experience obtained during the development of a highly efficient enamide reduction toward α-amino acids, such large-scale industrial synthesis of important β-amino acids has been a relatively rapid process.

1.3.2 \( \text{C}(sp^3)-\text{C}(sp^3) \text{ CROSS-COUPINGS} — \text{FLUVIRUCININE A}_1 \)

Transition metal-catalyzed cross-coupling reactions have been used extensively for constructing C–C bonds and, consequently, have had a substantial effect on the field of complex molecule synthesis. The predominance of palladium and nickel catalysts in cross-coupling technologies and their extraordinary functional-group tolerance increases the efficiency of this process by allowing a large degree of functionalization before coupling. Moreover, the efficacy of this cross-coupling strategy for streamlining synthesis has allowed retrosynthetic analyses that had been thought impossible with standard, nonmetal reactions. Until recently, however, most cross-coupling methods involved C(sp\(^2\))–C(sp\(^2\)) or C(sp\(^2\))–C(sp) centers, limiting the application potential. Two crucial issues associated with expanding the substrate scope to include C(sp\(^3\))–C(sp\(^3\)) couplings are the relatively low reactivity of alkyl halides toward oxidative addition and the propensity of \(\sigma\)-alkyl organometallic complexes to undergo rapid \(\beta\)-hydrogen elimination reactions. Practical solutions to this problem were first presented by Suzuki and Knochel, followed more recently by Fu. In general, the reaction scope now encompasses a variety of primary and secondary halides and pseudohalides as the electrophilic component, with organoboranes, boronic acids, alkylmagnesium halides and alkylzinc halides as the nucleophilic component. Although perhaps not developed in the context of a particular target molecule, progress in these cross-coupling methods has
allowed retrosynthetic disconnections that were not practical previously. Asymmetric cross-coupling protocols could, in turn, allow the direct formation of remote stereocenters in relatively unfunctionalized molecules.

Early examples of catalytic asymmetric cross-coupling reactions involving C(sp^3)–C(sp^2) centers were explored by Kumada and co-workers in the late 1970s and produced moderate enantioselectivities. Despite these initial reports and the subsequent evolution of cross-coupling methods and asymmetric catalysis, a deficiency in the development of catalytic asymmetric methods for C(sp^3)–C(sp^3) couplings existed until Fu and co-workers reported an asymmetric Negishi coupling in 2005. Before this report, researchers in the Fu laboratory observed the proficiency of tridentate pybox ligands (e.g., Scheme 1.3.2) at enabling the room temperature nickel-catalyzed Negishi coupling of symmetric secondary alkyl bromides and iodides. It was postulated that the tridentate nature of pybox ligands prevented the undesired β-hydrogen-elimination pathway, which would require a vacant coordination site. Reaction optimization facilitated the development of several asymmetric variations that generate challenging stereocenters applicable to complex molecule synthesis, as demonstrated in Fu’s formal total synthesis of fluvirucine A_1 (49), the aglycon of the macrolactam antibiotic fluvirucin A_1 (50). A key nickel(II)-catalyzed asymmetric cross-coupling of racemic allylic chloride 41 and alkylzinc reagent 42 in the presence of (S,S)-48 generated γ-disubstituted enone 43 in an excellent yield and 96% enantiomeric excess. Elaboration over two steps to a bromide (44), followed by conversion to the alkylzinc form and a second nickel(II)-catalyzed asymmetric Negishi cross-coupling with racemic allylic chloride 45, provided the ester 46 in a good yield and with >98% enantiomeric excess
and a 15:1 ratio of diastereomers. A subsequent two-step conversion to the aldehyde intersected Suh’s synthesis of fluvirucinine A₁ (49). This method exemplifies the efficiency of the C(sp³)–C(sp³) cross-coupling and presents a creative solution to the particularly difficult challenge of remote stereochemical control.

Scheme 1.3.2 Enantioselective C(sp³)–C(sp³) cross-couplings toward fluvirucinine A₁

At present, most examples of this technology require a stabilizing group adjacent to the site of the putative carbon-centered radical. Eliminating this condition would further improve the utility of this asymmetric cross-coupling method. In addition, stereogenic organometallic coupling partners (e.g., secondary alkylzinc reagents) have not yet been reported in this asymmetric transformation. A potential goal for this synthetic method would be the combination of a racemic secondary alkyl halide and a racemic secondary
alkylmetal reagent to form vicinal stereocenters along an alkyl chain with high levels of enantioselectivity and diastereoselectivity.

1.3.3 INTRAMOLECULAR HECK CYCLIZATIONS — MINFIENSINE

The enantioselective generation of all-carbon quaternary stereocenters is a considerable challenge for synthetic chemists. As quaternary stereocenters are found in many natural product structures, convenient enantioselective methods for their formation would be useful. One such method is the Heck reaction, in which a palladium(0) catalyst promotes the vinylation of an aryl halide, vinyl halide, or trifluoromethane sulfonate. The large body of literature on palladium catalysis and mechanisms, as well as an ever-growing collection of chiral ligands for transition-metal catalysis, greatly increased the potential of using this method to carry out asymmetric catalysis. In addition, many synthetic endeavors using diastereoselective or nonstereoselective intramolecular Heck reactions have been reported, increasing the significance of an enantioselective process. In 1989, the laboratories of Shibasaki and Overman independently reported the first variants of an intramolecular catalytic asymmetric Heck reaction. Initial levels of enantioselectivity were moderate; however, subsequent optimizations realized good-to-excellent selectivities in the generation of tertiary and all-carbon quaternary stereocenters.

Indole alkaloids encompass a large number of natural and pharmaceutical substances with a wide range of biological activities. The plant alkaloid minfiensine is a compelling example of the all-carbon quaternary stereocenter motif in biologically active natural products. Minfiensine and related alkaloids have been used in
traditional medicines and have promising anticancer activity.\textsuperscript{44} The intriguing polycyclic structure and biological relevance of minfiensine prompted the Overman laboratory\textsuperscript{45} to explore a catalytic enantioselective Heck reaction to generate the sole quaternary stereocenter at C(9a). It was discovered that the palladium-catalyzed intramolecular Heck reaction of dienyl aryl trifluoromethane sulfonate \textbf{51} in the presence of the phosphinoaxazoline ligand (\textit{S})-\textbf{55} under microwave conditions produced indoline \textbf{52} in good yield and with 99\% enantiomeric excess. Subsequent acid-promoted carbamate cyclization produced the tricyclic core of minfiensine (\textbf{53}), which was then converted to the natural product. The efficiency and selectivity of the catalytic asymmetric Heck reaction facilitated completion of the target, where the remaining stereocenters are derived from this initial transformation.

\textit{Scheme 1.3.3. Enantioselective intramolecular Heck reaction toward minfiensine}

Despite numerous examples of the asymmetric Heck reaction in total synthesis,\textsuperscript{42} there are several features that could be improved. Reactions typically require high temperatures and relatively high catalyst loadings, and the development of chiral ligands
that greatly increase the reactivity of the transition metal while maintaining an adequate asymmetric environment would be greatly beneficial.

As most enantioselective Heck reactions use an sp²-hybridized organohalide component, another frontier lies in the application of unactivated alkyl carbon electrophiles that have β-hydrogens in both intramolecular and intermolecular cases, an area currently in its infancy.46

1.3.4 **INDOLE FRIEDEL–CRAFTS ALKYLATIONS — FLUSTRAMINE B**

Numerous methods have been developed for the generation of substituted indoles;47 however, enantioselective indole functionalization has been far less explored. To address the deficiencies in the indole functionalization literature, Jørgensen48 and MacMillan49 independently developed strategies for asymmetric Friedel–Crafts alkylation of conjugate acceptors with electron-rich heteroaromatics. MacMillan’s method uses a secondary amine catalyst (61, Scheme 1.3.4) that facilitates the LUMO-lowering activation of α,β-unsaturated aldehydes for a variety of transformations.50 Although imidazolidinone 61 was a sufficient catalyst for the Friedel–Crafts alkylation of pyrroles, generating good yields and excellent enantioselectivities,49 application of less-activated indole substrates resulted in sluggish reactivity with considerably diminished selectivities.51 Kinetic investigations of iminium-catalyzed reactions revealed that the overall reaction rate was influenced by the efficiency of formation for both the iminium ion and the C–C bond, prompting the development of a modified imidazolidinone catalyst (62). This refinement minimized the steric bulk around one face of the catalyst, thereby exposing the lone pair of electrons on the secondary amine nitrogen. This structural change translated into
increased reactivity that enabled the asymmetric Friedel–Crafts alkylation of a variety of indoles with good-to-excellent yields and very high enantioselectivities.\textsuperscript{51}

Scheme 1.3.4. Enantioselective Friedel–Crafts alkylation toward flustramine B

Pyrroloindoline alkaloids are a family of polyindole alkaloids of diverse structural complexity and biological relevance.\textsuperscript{52} Diastereoselective syntheses of the core of these compounds have focused on the control of the C(3a) all-carbon quaternary stereocenter as a key design element.\textsuperscript{53} With a powerful and mild indole alkylation method in hand, MacMillan and co-workers\textsuperscript{54} devised a cascade strategy for the catalytic asymmetric preparation of the C(3a) stereocenter and the pyrroloindoline core of the potassium-channel blocker (–)-flustramine B (60, Scheme 1.3.4) in one step. In this key transformation, tryptamine derivative 56 and 2-propenal (acrolein, 57), in the presence of catalyst 62, underwent the asymmetric Friedel–Crafts alkylation to provide iminium intermediate 58. Subsequent carbamate cyclization and hydrolysis to regenerate the catalyst provided the core (59) with a good yield and 90% enantiomeric excess.
Importantly, this allowed completion of (−)-flustramine B (60) in just six steps and with good overall yield, highlighting the efficiency of this cascade approach. It is noteworthy that this strategy also has the potential to be applied to the synthesis of various polycyclic indolines such as the diazomamide family of cytotoxic alkaloids.\textsuperscript{54} It is also interesting to note that both the intramolecular Heck reaction (see subsection 1.3.3) and the indole Friedel–Crafts alkylation can generate similar indoline structural motifs despite the markedly different bond-connecting strategies of these reactions. The success of these dissimilar strategies allows a great deal of flexibility in the planning of syntheses.

Iminium-activation methods with chiral amine catalysts have been successful for numerous transformations, but catalyst loading, turnover frequency, and excesses of certain reagents limit the large-scale industrial application of these methods. In addition, in some cases, the organic catalyst may be more difficult to remove from the reaction products than a metal catalyst. However, the typically air- and moisture-stable reaction conditions, low cost of some catalysts, and often metal-free conditions are attractive. The variety of asymmetric transformations (some proceeding through substantially different reaction pathways) that have been realized with chiral amine catalysts so far indicates a burgeoning field in which there are many useful enantioselective catalysts.

1.3.5 PICTET–SPENGLER CYCLIZATIONS — HARMICINE

Since Pictet and Spengler reported the intramolecular cyclization of an aromatic ring onto an iminium species in 1911,\textsuperscript{55} this transformation has been of great use in the synthesis of many important alkaloid natural products.\textsuperscript{56} Indeed, the need for asymmetric variants of this reaction was recognized, and several diastereoselective protocols have
been devised.\textsuperscript{56} A common approach to diastereoselective Pictet–Spengler cyclization has been to use tryptophan derivatives to control the stereochemistry of the cyclization. However, using this type of technique for the synthesis of a natural product such as harmicine (\textsuperscript{68}, Scheme 1.3.5), which is active against the disease leishmaniasis, necessitates the removal of the stereocontrol element at C(5), following the diastereoselective cyclization. Nonetheless, Allin and co-workers\textsuperscript{57} proved this to be a viable method in 2007. This particular structure, however, highlighted a challenge for enantioselective catalysis and an opportunity to improve synthetic efficiency.

\textit{Scheme 1.3.5. Enantioselective Pictet–Spengler cyclization toward harmicine}

When considering prospects for asymmetric induction, Jacobsen and Taylor considered activated \textit{N}-acyl-iminium ions as a template and reasoned that a chiral thiourea derivative might be effective in promoting cyclization.\textsuperscript{58} In practice, these Brønsted acids,\textsuperscript{58} as well as other Brønsted acids investigated later by other groups,\textsuperscript{59} proved to be excellent catalysts for enantioselective indole annulations with in situ-
generated N-acyl-iminium species (e.g., 66, Scheme 1.3.5). In later studies by Jacobsen and co-workers, it was found that hydroxylactams (e.g., 64) are convenient precursors to N-acyl-iminium ions, which in turn enable access to various polycyclic structures.\textsuperscript{60} Given this effective protocol, an efficient catalytic asymmetric synthesis of harmicine (68) was realized in four steps from tryptamine (63). Several mechanistic experiments have suggested that asymmetric induction is controlled by a complex of the Brønsted acid catalyst (65) and a chloride counterion closely associated with the iminium ion (e.g., 66) that effectively blocks approach to one face of the electrophile, providing annulated products (e.g., 67) with excellent enantiomeric excesses. This insight into the remarkable mechanism of this transformation has led to a related C–C bond-forming process using oxocarbenium ions.\textsuperscript{61} Further exploitation of this unusual proposed catalyst–anion interaction could lead to a variety of other asymmetric addition reactions, such as intermolecular alkylation of N-acyl-iminium ions. In common with the history of the Diels–Alder reaction (see section 1.2), the exploration of the Pictet–Spengler cyclization has provided a useful method to access many heterocyclic structures embedded in alkaloid natural products using a classical reaction with well-established synthetic applications.

1.3.6 \textit{PHASE TRANSFER ALKYLATIONS — INDACRINONE}

Enolate alkylation exemplify the fundamental usefulness of the carbonyl group for C–C bond formation. Strategies to induce asymmetry in these reactions have included chiral auxiliaries and chiral ligands, although few examples are catalytic. A particularly challenging class of product targets is all-carbon quaternary stereocenters adjacent to
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carbonyl groups. One example of an important target bearing this motif is the diuretic
drug candidate indacrinone (73, Scheme 1.3.6).62 Given the lack of efficient methods for
synthesizing this structure, researchers at Merck envisaged an enantioselective phase-
transfer alkylation method based on a quaternary ammonium salt derived from a naturally
occurring cinchona alkaloid (e.g., 70). In the event, readily prepared indanone 69 was
methylated, producing ketone 72 with 95% yield and 92% enantiomeric excess, and 72
was then converted to indacrinone (73) in three additional steps.

Scheme 1.3.6. Phase-transfer alkylation toward indacrinone

Although successful in achieving enantioselective enolate alkylation, the mechanism
for this process seems to be complex;63 however, enantiofacial selectivity in the
alkylation event may be rationalized through the hypothetical transition state 71 (Scheme
1.3.6). Three key interactions are thought to control selectivity: a hydrogen bond
between the enolate oxygen and the catalyst hydroxyl group, and two π-system stacking
interactions between the four aromatic rings. Perhaps as a consequence of the complex
mechanism, the range of substrates for enolate alkylation is limited, and other solutions to this problem are still needed. However, these initial results have led to several related catalytic enantioselective reactions using cinchoninium salts or related organic ammonium complexes as catalysts. The discovery of these useful catalysts has provided not only an alternative to related transformations using metal catalysts but also a means of accessing chiral environments that are simply not possible with metal-based catalysts. Moreover, eliminating metal waste materials is attractive from an industrial and environmental standpoint. Ultimately, the studies directed toward an enantioselective synthesis of indacrinone demonstrate the versatility of privileged catalysts developed for the synthesis of target molecules for a range of other applications.

1.3.7 Pd-CATALYZED ENOLATE ALKYLATION — CYANTHIWIGIN F

A recent case of enantioselective enolate alkylation is the synthesis of cyanthiwigin F (83, Scheme 1.3.7), a cytotoxic natural product from a sea sponge. The cyanthiwigin family is composed of more than 30 diterpenoids, most of which bear two quaternary stereocenters, at C(6) and C(9), and a syn relationship of the methyl groups in the central ring. These core stereochemical elements are a complicating factor for a convergent strategy that might seek to couple the five- and seven-membered ring portions and subsequently form the six-membered ring. To avoid this difficulty, Enquist and Stoltz chose instead to address these two central stereocenters at an early stage and append the five- and seven-membered rings to the assembled cyclohexane. Accordingly, a synthetic strategy was devised that involved a one-pot double-enantioselective enolate alkylation reaction to form both quaternary stereocenters simultaneously. Although such
enantioselective alkylation have proved difficult, recent studies have identified palladium catalysts that might provide a solution to this problem and enable the synthesis of a variety of targets containing quaternary carbon stereocenters, including the cyanthiwigins.\textsuperscript{66}

**Scheme 1.3.7. Pd-catalyzed enolate alkylation toward cyanthiwigin F**

The implementation of this retrosynthetic strategy began with a Claisen–Dieckmann sequence that converted diallyl succinate (74, Scheme 1.3.7) to bis(β-ketoester) 75 as a 1:1 mixture of racemic and meso diastereomers. On exposure to the catalyst derived from Pd(dmdba)\textsubscript{2} and phosphinooxazoline ligand (S)-55,\textsuperscript{66} each stereoisomer of 75 was
transformed to bis(allylated) ketone 76 with 75% yield and 99% enantiomeric excess as a 4.4:1 mixture of diastereomers. With both quaternary centers in place, elaboration of this stereochemically rich core structure to the natural product was achieved in six further steps. Enol triflate formation and Negishi coupling (76 + 77 \rightarrow 78) preceded a tandem ring-closing metathesis–cross-metathesis sequence with Grubbs’ ruthenium catalyst 79. Aldehyde–alkene radical cyclization generated the final ring of the cyanthiwigin core (81 \rightarrow 82), and enol triflate formation and palladium-catalyzed cross-coupling formed (−)-cyanthiwigin F (83), together with reduction product 84. Choosing to confront the difficult stereochemical elements of the cyanthiwigin structure at an early stage led to a direct synthetic route proceeding in nine steps from diallyl succinate. This strategy was made possible by the intriguing reaction mechanism of the enantioselective decarboxylative allylation, in which all three stereoisomers of bis(β-ketoester) 75 were converted to a specific stereoisomer of product (76) with high selectivity, through a stereoablative process. In addition, of the nine steps required for the synthesis, seven form C–C bonds, and four form multiple C–C bonds. Directly addressing the carbon framework of the target molecule and the stereochemical challenges embedded within ultimately led to an efficient synthetic sequence for this important molecule.

Recently, the proposed chiral palladium enolate was shown to be intercepted by allyl or proton electrophiles. Although the synthesis of cyanthiwigin F demonstrates the versatility of allyl moieties for further derivatization, the direct use of alternative electrophiles would provide a more general and direct method for transition metal-mediated enolate functionalization.
Of the many fundamental approaches to the formation of five-membered rings from acyclic precursors, the [3 + 2] cycloaddition is among the most convergent strategies. A useful method of achieving such a cyclization is via a trimethylenemethane (TMM) intermediate. This interesting non-Kekulé molecule was first prepared and studied through photolytic decomposition of a cyclic diazene precursor. However, the free diyl is prone to several undesired reaction pathways and does not lend itself to asymmetric catalysis. Despite this, intramolecular diyl-trapping reactions are valuable methods of cyclopentane formation. Recognizing the synthetic utility of TMM, Trost and co-workers developed an array of 2-(trimethylsilyl)-2-propenyl acetate reagents that generate a metal•TMM complex when exposed to a palladium catalyst. A recent application of this transformation in total synthesis is the approach to marcfortine B (90, Scheme 1.3.8a), a member of a family of antiparasitic agents. The strategy used sought to forge the [2.2.2]bicycle via an intramolecular radical cyclization and install the spiro all-carbon quaternary stereocenter by the cycloaddition of oxindole 85 with TMM precursor 86. In the event, an excellent yield was observed for the annulation reaction yielding spirooxindole 87 as a 1:1 mixture of diastereomers. Over the course of nine additional steps, spirocycle 87 was transformed into amide 88. Preparation of the xanthate derivative of alcohol 88 allowed radical cyclization, generating the challenging [2.2.2]bicycle 89. Seven further steps produced (±)-marcfortine B (90).
Although this strategy demonstrated several intriguing ring-forming reactions, an asymmetric synthesis of 90 would require an enantioselective variant of the key TMM-[3 + 2] cycloaddition, a goal that has remained elusive.\textsuperscript{74} The first asymmetric palladium-catalyzed [3 + 2] cycloaddition with various bis(phosphine) ligands was reported by Ito and co-workers,\textsuperscript{75} but with only moderate enantiomeric excess (up to 78%) and diastereomeric ratio (up to 4:1 trans:cis). Thereafter, Trost and co-workers explored bulky monodentate phosphoramidite ligands (e.g., (R,R,R)-94, Scheme 1.3.8b) for the transformation and observed very high enantioselectivity for the first time.\textsuperscript{76} Of particular interest is the enantioselective addition of substituted TMM reagents to
functionalized oxindole derivatives. The use of oxindole 91 and TMM-precursor 92 in the palladium-catalyzed cyclization with ligand \((R,R,R)\)-94 yielded spirooxindole 93 with 14:1 diastereomeric ratio and 96% enantiomeric excess for the major diastereomer. Although a completed asymmetric synthesis of marcfortine B (90) from intermediate 93 has not been reported, many of the key functional groups are in place and the challenging spiroquaternary stereocenter has been installed (cf. 87 and 93). The development of this valuable asymmetric transformation highlights the ongoing efforts to devise new and useful techniques for the construction of important molecules.

1.4 OUTLOOK

The representative synthetic efforts presented here demonstrate the crucial interplay between target-directed synthesis and the development of novel reaction methods. Although many useful asymmetric technologies are currently available, the specific challenges posed by important natural products and pharmaceutical compounds highlight deficiencies in the current technology. Envisaging strategies to construct these relevant molecules through means beyond the current arsenal of enantioselective transformations will aid the evolution of both synthetic planning and reaction development. The symbiotic relationship between total synthesis and method development can continue to expand the understanding of synthetic strategy and catalysis on both fundamental and practical levels.

Despite the substantial advances that have been made so far, significant challenges remain for both multistep synthesis and catalysis. In addition to improvements to efficiency and selectivity, better reactivity and handling stability are constantly required
to implement and improve industrial processes for existing methods. Exceptionally reliable methods will aid in the discovery of new biologically active compounds by using high-throughput combinatorial screening techniques that are well established in the pharmaceutical industry, although these techniques are limited by the number of readily accessible chiral building blocks. Existing methods may be improved by identifying systems with better functional-group tolerances that might obviate the need for protecting and masking groups. Similarly, known privileged chiral frameworks may be modified to control chiral space more effectively for especially challenging transformations, a technique conspicuously successful for Trost’s TMM cyclizations (see subsection 1.3.8).

Overall, creative solutions are required to address specific organic transformations that remain significant impediments to efficient syntheses, namely forming multiple stereocenters and rings, forming multiple C–C bonds, generating vicinal quaternary stereocenters, and achieving C–H and C–C functionalization reactions. Cyclic structures often present particular challenges owing to the unique strain and steric elements imparted by their connectivity. As a result, many highly strained or complex polycyclic structures are daunting targets for synthesis. Finally, the discovery of new natural products will undoubtedly result in new challenges for synthetic chemistry and catalysis. In this thesis, examples of the development of useful enantioselective transformations for the synthesis of natural products will be presented. These reactions were initially conceived as solutions to synthetic problems in the context of total synthesis efforts and have led to various derivative applications and methodologies with broad utility.
1.5 NOTES AND REFERENCES


(8) For examples, see: (a) Hayashi, Y. Catalytic Asymmetric Diels–Alder Reactions. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K.


    (b) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.;


(64) Asymmetric Phase Transfer Catalysis; Maruoka, K., Ed.; Wiley-VCH: Weinheim, 2008.


CHAPTER 2

The Variecolin Family of Sesterterpenoids

2.1 INTRODUCTION AND BACKGROUND

The variecolin family of sesterterpenoids has emerged as an intriguing class of biologically relevant natural products. Members of this family possess an array of biological activities including anti-HIV, antihypertensive, and immunosuppressant properties. Structurally, the variecolin-type sesterterpenoids are defined by their complex molecular architecture including a central eight-membered ring, a high degree of stereocomplexity, and a low degree of oxidation. Thus, this important class of natural products constitutes a formidable challenge for chemical synthesis.

2.1.1 ISOLATION AND STRUCTURAL ELUCIDATION

Hensens and co-workers at Merck first isolated variecolin (95) in 1991 as a bioactive component of the fungi imperfecti Aspergillus variecolor.\(^1\) Extensive structural elucidation via 2D NMR spectroscopy and \(^1\)H–\(^1\)H coupling constant analysis revealed a sesterterpenoid with a novel tetracyclic ring skeleton possessing the relative
stereochemistry as shown in Figure 2.1.1. The absolute stereochemistry was proposed as *ent*-95 due to biosynthetic considerations and structural similarity to the ceriferene class of sesterterpenoids (e.g., Flocerol (96)), which contains an analogous CD ring system.2

Figure 2.1.1. Proposed structure of variecolin.†

Variecolin (95) was later identified from the fungus *Emericella aurantiobrunnea* nine years after its first isolation.3,4 Although direct confirmation of the absolute configuration was not feasible, Fujimoto and co-workers obtained structural verification through derivatization. Functionalization of 95 with (2R,3R)-(−)-butane-2,3-diol (97) generated chiral polycyclic acetal 98, which, upon structural analysis, revealed four possible conformations—two derived from each enantiomer of 95—that could be distinguished by NOESY correlation (Scheme 2.1.1). In a key NOE experiment a sole interaction of 6–9% was observed between H6 and H3’, indicating that variecolin possesses a C(6) R-configuration, opposite to that of the biosynthetic proposal by Hensens. Butler provided further validation of the relative stereochemistry by X-ray crystal analysis of 95, although the absolute configuration could not be determined.5

In subsequent reports, variecolin (95) has been isolated from the related fungi *Emericella purpurea* and *Phoma* sp. Several variecolin congeners (99–107, Figure 2.1.2) have also been identified from the aforementioned fungi extracts and share a common ABCD ring system with identical CD rings and subtle oxidation state variations in the A and B rings. In addition to the structural data of 95, the absolute stereochemistry of variecolol (99) has been confirmed by semisynthesis and the relative stereochemistry of variecolactone (100) has been verified by X-ray crystal analysis. The structural information and origin of isolation for the members of this family suggests the absolute stereochemistry of all related members is that depicted in Figure 2.1.2, and thus based on the revised assignment of variecolin.
2.1.2 BIOSYNTHETIC PROPOSAL

A detailed study of the variecolin family sesterterpenoid\(^2\) biosynthesis has not been reported. The authors from the original isolation work surmised that a potential biogenetic link existed between the ophiobolin and ceriferene class of sesterterpenoids, of which variecolin is thought to be descended.\(^1\) Utilizing the reported biosynthetic studies of the ophiobolins\(^2\) and triterpenoids\(^9\) as a premise, Hensens proposed that the variecolin sesterterpenoids arise from geranylfarnesyl diphosphate (108) of the mevalonate biosynthetic pathway. An initial cyclization cascade with displacement of pyrophosphate generates intermediate 109, which is perceived as a divergent intermediate (Scheme
2.1.2. One potential fate of this intermediate is cyclization concomitant with a hydride shift (path a) and oxidation to generate the ring system of the ophiobolanes ceroplasteric acid (110) or ophiobolin C (111). Alternatively, a ring-expanding C–C migration (path b) affords ceriferene intermediate 112 that can undergo a cyclization (path c) to afford the flocerol (96), or cyclization followed by a H-shift cyclization (paths c and d) to give variecolin (95). This unified scheme effectively links all three classes to this divergent intermediate (109).  

Scheme 2.1.2. Hensens’ biosynthetic proposal for variecolin
2.2 BIOLOGICAL ACTIVITY

Variecolin and related sesterterpenes exhibit diverse biological activities. Numerous studies describe the general activity of this family toward a distinct biological target; however, details regarding specificity and mode of action are nonexistent at this time.

2.2.1 ANTIHYPERTENSIVE PROPERTIES

The initial isolation by Hensens indicated variecolin (95) as an angiotensin II antagonist that was shown to inhibit $^{125}$I-labeled angiotensin II binding in rabbit aortic or bovine adrenal cortical membranes ($IC_{50} = 3.6 \pm 1 \, \mu M$). Angiotensin II is a blood hormone that acts as a vasoconstrictor that contributes to the pathogenesis of hypertension, cardiovascular disease, and affects water and ion homeostasis in the kidneys. Angiotensin II antagonists have been shown to be effective toward treating hypertension as well as for the prevention of congestive heart failure. Although variecolin has shown modest antagonist activity, inhibition of carbachol-induced inositol phosphate accumulation indicates a possible nonspecific inhibition of the angiotensin response.

Several years later, a Japanese patent claimed variecolactone (100) to be an effective endothelin antagonist that inhibits binding to endothelin A ($ET_A$, $IC_{50} = 0.765 \, \mu M$) and endothelin B ($ET_B$, $IC_{50} = 0.683 \, \mu M$) receptors. Endothelin is a potent vasoconstrictor peptide that has similar physiological effects as the angiotensin II peptide. This finding suggests 100 as a potential therapy for hypertension, cardiovascular diseases, cerebrovascular diseases, renal disease, asthma, and pulmonary hypertension.
Variecolin and related sesterterpenes have been shown to possess immunosuppressive properties against both humoral (B-cell, LPS-induced) and cell-mediated (T-cell, Con A-induced) proliferations of splenic lymphocytes (Table 2.2.1). Of those examined, variecolin was the most active at suppressing the immune responses, suggesting an important role of the ketone and aldehyde functionalities. The activity compared to other classic immunosuppressants shows comparable data up to the strong binder FK506 (115).

Table 2.2.1. Immunosuppressant activity of the variecolin sesterterpenes

<table>
<thead>
<tr>
<th>compound</th>
<th>Con A-induced IC₅₀ (µg/mL)</th>
<th>LPS-induced IC₅₀ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variecolin (95)</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Variecolactone (100)</td>
<td>8.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Variecoacetal A (102)</td>
<td>4.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Variecoacetal B (103)</td>
<td>6.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Variecolol (99)</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Azathioprine (114)</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Cyclosporin A (113)</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>FK506 (115)</td>
<td>1.5 x 10⁻⁵</td>
<td>1.6 x 10⁻³</td>
</tr>
</tbody>
</table>

Cyclosporin A (113) Azathioprine (114) FK506 (115)
2.2.3 **CCR5 ANTAGONIST**

Butler and co-workers showed in 2004 that variecolin (95) and variecolol (99) both compete with macrophage inflammatory protein (MIP)-1α for binding to human CCR5 receptor (IC$_{50}$ = 9 and 32 µM, respectively).\(^5\) Chemokine receptor CCR5 is a key coreceptor involved in the uptake of HIV-1 into target cells.\(^13\) As a result, CCR5 plays a major role in the early transmission of HIV-1, the major cause of AIDS. Observation that the inhibition of CCR5 retards viral uptake while maintaining immune competence suggests this receptor as an emerging target for anti-HIV therapeutics. It should be noted that emericolin A–D (104–107) showed no activity toward CCR5, further indicating an important role for the ketone and aldehyde functionalities present in 95.

2.2.4 **ANTIBIOTIC AND ANTIFUNGAL PROPERTIES**

A 1998 Japanese patent disclosed the potential antibacterial and antifungal properties of variecolin (95), variecolactone (100), and AB5362-A (101).\(^7\) It was observed that 100 displays 100% antifungal activity at 10 ppm against *Pseudoperonospora cubensis* without damaging a cucumber, highlighting its potential as a herbicide.

2.3 **SYNTHETIC STUDIES TOWARD VARIECOLIN**

The variecolin family of sesterterpenes has received only modest attention from the synthetic community in the 18 years since the first discovery of variecolin despite their intriguing structure and biological relevance. At the onset of our studies toward variecolin (95), two laboratories have disclosed synthetic efforts en route to this
sesterterpenoid. Despite significant progress in this area, these distinct approaches have not yet culminated in the completion of variecolin or any member of this class (Figure 2.1.2).

2.3.1  **PIERS’ APPROACH TO THE CD RING SYSTEM**

In the first report of a synthetic approach toward variecolin, Piers and Boulet demonstrated their key method for the stereoselective generation of the CD ring system.\textsuperscript{14} Starting racemic enone 118 was prepared in two steps from 3-methylcyclohexenone (116), followed by a diastereoselective conjugate addition of a higher-order 2-propenyl cuprate to afford a mixture of C(15)\textsuperscript{15} epimers 120 and 121 (11:1) in 86% yield (Scheme 2.3.1). An important feature of this transformation is the generation of the relative anti stereochemistry of the all-carbon quaternary stereocenter and the newly installed 2-propenyl group. However, the cis stereochemistry of the ring juncture is opposite to that required for variecolin. Thus, a thermodynamic equilibration with NaOMe in methanol facilitated a C(15) epimerization to favor the desired *trans*-fused isomer, 121 (14:1 of 121:120), the bicyclic CD system of which maps on to 95 as well as several other diterpenoids.\textsuperscript{14}
With an effective preparation of this key bicyclic intermediate (121), graduate student Shawn Walker explored its utility toward the total synthesis of variecolin.\textsuperscript{16} Their devised synthetic strategy employing this intermediate involved the linear, stepwise annulation of the B and A rings on to this key CD ring fragment. Accordingly, sequential alkylation of intermediate (±)-121 provided ketone 123 as a single diastereomer, possessing the correct relative quaternary stereochemistry at C(11) (Scheme 2.3.2). Functional group interconversion to a vinyl iodide, followed by lithium–halogen exchange with carbonyl addition, then a PCC-mediated allylic alcohol transposition with oxidation afforded the annulated tricycle 124. The stereochemistry at C(10) was achieved via Birch reduction of this cycloheptenone (124) using potassium in ammonia, moderately favoring the desired C(10) epimer 125 as a 2.2:1 mixture of inseparable isomers (125:126). Further transformation via $\alpha$-functionalization of the carbonyl with diphenyldisulfide afforded separable compounds at the C(10) stereocenter to provide 127 in modest yield.
Carbonyl transposition of 127 over four steps provided ketone 128 which was then utilized for a one-carbon ring expansion via a cyclopropanation–cleavage sequence (Scheme 2.3.3). Ketone enolization and cyclopropanation afforded 129, which upon FeCl₃-mediated radical cleavage followed by β-chloro elimination completed the B-ring expansion to generate cyclooctenone 130 in 64% yield over four steps. With the BCD carbocyclic skeleton in place, annulation of the final A ring was accomplished utilizing a bifunctional cuprate reagent (131), first to achieve the conjugate 1,4-addition, succeeded by an alkylation event (i.e., 130 → 132). The C(6) stereocenter readily epimerized during the final alkylation event and, consequently, modest conversions employing LiOtf-Bu were necessary to overcome this difficulty. Importantly, the preparation of tetracycle 132 comprised the complete ABCD ring structure of variecolin.
The remaining transformations toward completion of variecolin involved the functionalization of the A and B rings. Accordingly, conversion of ketone 132 to an enol triflate and palladium-catalyzed carbonylation generated ester 133 (Scheme 2.3.4). This trisolefin intermediate was then chemo- and stereoselectively hydrogenated at C(3), followed by ester reduction to form (±)-5-deoxyemericolin B (134). Allylic oxidation using MnO₂ provided (±)-deoxyemericolin A (135), whereas oxidation using Pb(OAc)₄ afforded (±)-5-deoxyvariecolol (136). Further oxidation using Collins reagent gave (±)-5-deoxyvariecolactone (137).
The preparation of highly advanced deoxy analogues of variecolin and related sesterterpenes set the stage for further C(5) oxidation and completion of the targets, although “material constraints” have hindered this progress. Indeed, this synthetic sequence is highly linear, requiring 28 steps for the longest linear sequence. The incorporation of the central eight-membered B ring is tedious, requiring 12 steps to achieve a one-carbon ring expansion. An issue yet to be addressed is the incorporation of asymmetry, which would have to occur at the beginning of the synthesis due to linearity.\textsuperscript{17} Nonetheless, Piers’ impressive synthetic effort has highlighted various reactivity and selectivity features of this system and enabled the preparation of highly advanced intermediates.
2.3.2 MOLANDER’S APPROACH TO THE B RING

The Molander laboratory disclosed a samarium(II) iodide-promoted annulative approach toward variecolin in 2001. This strategy was derived from previous work in their laboratory delineating SmI$_2$-promoted sequential reactions for the rapid and stereoselective construction of medium-sized carbocycles. A model system was devised to rapidly explore a carbonyl addition–nucleophilic acyl substitution reaction en route to the carbocyclic core of variecolin. The samarium(II) iodide-promoted intermolecular Barbier reaction of ketochloride 139 and alkyl iodide 138 furnished chloroalcohol 140 (Scheme 2.3.5). Oxidation of the methyl ether moiety with concomitant lactonization gave spirocyclic lactone 141, a substrate for the intramolecular nucleophilic acyl substitution reaction studies. The samarium(II) iodide-promoted reductive cyclization occurred under photochemical conditions to generate 142, which possesses the ABC carbocyclic core of variecolin.

Scheme 2.3.5. Samarium(II) iodide-promoted medium ring synthesis
With a viable strategy in hand, Molander and co-workers pursued enantioselective syntheses of suitable A- and CD ring fragments to explore their key sequential samarium-promoted coupling toward ent-95. Accordingly, the A-ring fragment was asymmetrically synthesized from meso-diol 146, which was prepared in eight steps from tetrahydrophthalic anhydride (143, Scheme 2.3.6). Acidic methanolysis of 143, oxidative olefin cleavage and intramolecular Dieckmann cyclization with decarboxylation generated meso-cyclopentanone 144. Ketone protection, ester reduction and exposure to \( \text{Ac}_2\text{O} \) afforded protected meso-bisacetate 145, upon which all protecting groups were cleaved to form meso-diol 146 (50% yield over eight steps). Enzymatic desymmetrization via acylation produced monoacetate 148 in 47% yield and 96% ee, which was elaborated to \( \beta \)-ketolactone 149 over five steps. Advancement of this material toward an intermediate analogous to 150, what would be suitable for the key samarium coupling, was not described.

Scheme 2.3.6. Molander’s first-generation synthesis of A-ring fragment
The targeted CD ring fragment was prepared from Hajos–Parrish ketone (R)-19, which is readily available in >99% ee (Scheme 2.3.7). Stereoselective ketone reduction and protection as a pivalate ester generated 151. α-Alkylation of this intermediate with iodide 152 was achieved from the thermodynamic enolate of enone 151 using sodium dimysylate, and subsequent stereoselective 1,4-reduction and benzyl cleavage steps provided acetal 153. This material was advanced to enone 155 in four steps to set the stage for a diastereoselective 2-propenyl cuprate (119) addition followed a Wolff–Kishner reduction to afford acetal (+)-155, albeit in modest yield with the undesired C(16) stereochemistry.\textsuperscript{15} This was rectified with a three-step ozonolysis, epimerization, and Wittig olefination sequence to provide thermodynamic product (+)-156. Acetal cleavage and conversion to an alkyl chloride gave desired intermediate 157. These efforts have demonstrated enantioselective approaches to A-ring fragment 149 and CD ring fragment 157, although details of the potential samarium-promoted coupling and further functionalization toward variecolin were not described.
2.3.3 MOLANDER’S SECOND-GENERATION APPROACH

Graduate student Kelly George of the Molander laboratory disclosed a second-generation approach to variecolin in 2005.21 The overall synthetic strategy incorporating the key sequential samarium coupling remained the same. However, the synthetic sequences to the A- and CD ring fragments were improved and coupling studies were explored.

The revised stereoselective synthesis of a viable A-ring fragment began with the asymmetric desymmetrization of meso-anhydride 143 with quinidine to produce monoacid 158 in 99% yield (Scheme 2.3.8). Chemoselective ester reduction and cyclization provided γ-lactone 159 in 98% ee and 87% yield over two steps. Lactone functionalization and olefin oxidative cleavage over four steps afforded acyclic diacid
160 which was transformed into iodides 161 and 162 in good overall yield (four steps).

This reaction sequence provided the A-ring intermediates in 11 steps, a marked improvement over the previous generation synthesis (>14 steps).²²

Scheme 2.3.8. Molander’s revised A-ring synthesis

Molander’s revised approach to the CD ring proceeded from the correct enantiomer of the Hajos–Parrish ketone ((S)-19) (Scheme 2.3.9). Enone reduction with copper hydride and diastereoselective allylation of the resulting enolate furnished allyl ketone 163. Oxidative cleavage of the allyl group, aldehyde reduction and acetylation gave acetal 164. Typical D-ring functionalization installed the C(16) 2-propenyl moiety in the wrong configuration ((−)-155). This was advanced to acetal (−)-156 by a similar three-step sequence as above (cf. Scheme 2.3.7) to achieve the correct C(16) stereochemistry, and acetal cleavage with alcohol protection provided a suitable coupling partner (165). The revised CD ring fragment synthesis was accomplished in 14 steps, a modest improvement over the previous 16-step sequence.
The development of scalable asymmetric syntheses of both the A- and CD ring fragments enabled the exploration of the samarium-promoted coupling strategy. In the event, the intermolecular samarium-promoted Barbier coupling of iodide 161 and chloroketone 165 generated intermediate 166 in variable yields (Scheme 2.3.10). This material was advanced to β-ketolactone 167 over three steps. Silyl cleavage and alcohol conversion to an alkyl iodide afforded 168; however, the β-ketoester moiety existed in the enolized form removing the C(6) stereochemistry. Ketone reduction and protection as a pivalate under various conditions provided iodolactone 169 in low yields. In the key reaction, it was found that the samarium-promoted intramolecular nucleophilic acyl substitution of this iodolactone proceeded efficiently, constructing 170 in 82% yield. While this method successfully generated the ABCD carbocyclic core of variecolin, low and variable yields as well as C(5) stereochemical issues hampered further progress.
To overcome these difficulties, Molander and co-workers investigated a revised reaction sequence altering the order of operations. The new route involved the samarium-promoted coupling of iodide 162 and ketone 165 over four steps to produce β-ketoester 167 in 48% yield (Scheme 2.3.11). Importantly, the revised A-ring ketone protecting group and modified reaction conditions improved yields and minimized the troublesome C(6) enolization. Diastereoselective ketone reduction with super hydride produced β-hydroxyketone 171 and subsequent fluoride-mediated silyl cleavage resulted in β-hydroxy elimination to form α,β-unsaturated lactone 172, removing the C(5) and C(6) stereocenters. Efforts to circumvent this problem have not been described.
The progress of Molander and co-workers toward variecolin appears to have stalled at this intermediate (172). The apparent difficulties observed with this sequential samarium-promoted coupling strategy seem to be involved with the order of chemical operations on sensitive intermediates as well as lengthy preparations of these intermediates. In addition to these issues, the strategy necessitates the late installation of the C(11) all-carbon quaternary stereocenter after the final intramolecular nucleophilic acyl substitution reaction. However, model system studies to forge this bond by reported methods\textsuperscript{23} resulted with intractable mixtures and no quaternary stereocenter formation (Scheme 2.3.12). Thus, the strategy must be further revised to incorporate this stereocenter at an earlier intermediate via a separate method, which would obviate the designed sequential samarium couplings.
2.4 CONCLUSION

The variecolin sesterterpenes are a structurally complex and biologically active class of natural products isolated from various fungal sources. Biological investigations of this family have indicated anti-HIV, antihypertension, immunomodulatory, and antibacterial properties. The extraordinary tetracyclic core defined by a central eight-membered ring with a high degree of stereocomplexity has inspired valiant synthetic efforts from the Piers and Molander laboratories. These unique approaches to variecolin highlight various stereochemical and functional group attributes for this unusual system. Despite significant progress in this area, completion of variecolin or any of its congeners has yet to be reported.
2.5  NOTES AND REFERENCES


(4) The ascomycetes Emericella sp. reproduce sexually and are the sexual (perfect) state of the hyphomycetes Aspergillus sp.


(8) For a separate reported isolation of variecolactone (100) from E. aurantiobrunnea, see: Sato, A.; Morishita, T.; Hosoya, T. S-19777 as Endothelin


(10) At the time of this biosynthetic proposal, the hypothesized configuration of variecolin adequately linked to this divergent scheme. The revised stereochemical assignment of variecolin, however, would necessitate the enantiomer of divergent intermediate 109 (i.e., *ent-109*), as would ophiobolin C (111).


(15) Atom numbering follows that of variecolin (see ref 1).

(16) Walker, S. D. A Synthetic Approach to the Variecolin Class of Sesterterpenoids: Total Synthesis of (±)-5-Deoxyvariecolin, (±)-5-Deoxyvariecolol and (±)-5-


(20) At the time of Molander and co-workers’ initial synthetic efforts, the absolute configuration of variecolin had not yet been determined. Consequently, their plans toward an asymmetric route were dependent upon the original (and incorrect) biosynthetic proposal by Hensens; see ref 1.


(22) Molander’s first-generation synthesis of an A-ring fragment required 14 steps and does not include the additional transformations necessary to produce a viable coupling fragment.
CHAPTER 3

Progress toward the Asymmetric Total Synthesis of Variecolin†

3.1 INTRODUCTION AND SYNTHETIC STRATEGY

3.1.1 INTRODUCTION

Variecolin (95) is a complex sesterterpenoid isolated from extracts of the fungi Asperigillus sp. and Emericella sp. It belongs to a growing class of sesterterpene natural products defined by a tetracyclic core possessing a central eight-membered ring, comprising variecolol (99), variecolactone (100), AB5362-A (101), and emericolins A–D (104–107) (Figure 3.1.1). This family exhibits an array of biological activities, including antihypertensive, anti-HIV, immunosuppressive, and antifungal properties. Our interest in the pursuit of an effective and general synthetic strategy toward these bioactive natural products focused on variecolin, as it represents the most widely studied and biologically relevant member. The inherent synthetic challenges

† This work was performed in collaboration with Thomas Jensen, a visiting scholar from the Technical University of Denmark, and Dr. Chris Henry, a postdoctoral scholar in the Stoltz group.
posed by the complex tetracyclic core representative of this sesterterpene family provide inspiration to utilize and expand the state of the art in catalysis and synthetic methodology.

Figure 3.1.1. Variecolin family of sesterterpenes.

The 25-carbon tetracyclic core of variecolin (95) consists of a central eight-membered ring and possesses eight stereocenters, including two all-carbon quaternary stereocenters at C(11) and C(14) of the B–C and C–D ring fusions, respectively. Synthetic control of the relative and absolute stereochemistry of these trans-fused rings poses a significant challenge for the design of critical bond-forming reactions. Herein we present a convergent approach to variecolin that harnesses methods developed in our laboratories to construct these key structural features and provides opportunities to explore new reactivity. At the outset of our investigations, two laboratories had published efforts
Chapter 3—Progress toward the Asymmetric Total Synthesis of Variecolin

toward variecolin, although all members of this family have thus far continued to elude chemical synthesis.4

3.1.2 RETROSYNTHETIC ANALYSIS

Our retrosynthetic approach toward variecolin (95) focused on the construction of the central eight-membered ring and two all-carbon quaternary stereocenters,5 with the intention of improving synthetic efficiency through the coupling of two highly substituted fragments. We envisioned a critical C-ring disconnection, through bisketone 175, to AB ring fragment 176 and D-ring fragment 179 (Scheme 3.1.1). Our laboratory recently developed a powerful tandem Wolff/Cope rearrangement for the facile generation of functionalized fused bicyclic cycloheptadienones from vinyl cyclopropyl diazo ketones.6 Using this technology, we anticipated that AB ring synthon 176 could be accessed through a Wolff/Cope rearrangement of highly functionalized cyclobutane 177, which may in turn be assembled via a tethered cycloaddition of alcohol 178. We surmised that the crucial all-carbon quaternary stereocenter of D-ring synthon 179 could be installed through an enantioselective Pd-catalyzed alkylation of in situ-generated cyclic enolates recently developed in our laboratories.7 Accordingly, 179 could originate from a ring contraction of cycloheptenone 180, which itself would arise from the asymmetric palladium-catalyzed alkylation of racemic vinylogous β-ketoester (±)-181.
3.2 A WOLFF/COPE APPROACH TO THE AB RING SYSTEM

Eight-membered rings are common structural motifs that occur in widely diverse terrestrial plants, insects, marine organisms, and fungi. The theoretical and synthetic intrigue of these medium-sized carbocyclic structures has stimulated the development of various strategies for their preparation, many of which have been applied toward the synthesis of complex molecular targets. Inasmuch as we are restricted by the limitations of reaction scope in the state of the art, the selective preparation of eight-membered rings remains a noteworthy and continuing challenge to modern chemical methods.

The design of tandem reaction sequences for the rapid generation of molecular complexity is an area of constant investigation in our laboratory. We have recently developed a tandem Wolff/Cope rearrangement for the facile construction of functionalized seven-membered rings. A critical component to the success of this method was the identification of photochemical or silver-catalyzed sonochemical
conditions to allow direct access to a variety of \([n-7]\) fused bicyclic systems in excellent yields. In drawing inspiration from this efficient process, a primary objective of the devised synthetic plan toward variecolin (95) is the development of a tandem Wolff/Cope rearrangement to forge fused carbocyclic eight-membered ring systems. Application of this key transformation for the construction of the central B ring of 95 would expand the reaction scope, and furthermore, could provide new tools and strategies for the general preparation of natural and nonnatural substances containing this eight-membered ring motif.

### 3.2.1 Model Studies of the Wolff/Cope Rearrangement Toward Construction of the Eight-Membered AB Ring

In order to investigate the tandem Wolff/Cope rearrangement toward eight-membered AB ring fragment (176), we sought an expedient, stereoselective synthesis of a highly substituted cyclobutane substrate (e.g., 177). During the course of our efforts, we elected to use an exceedingly effective cyclobutadiene–olefin cycloaddition for the rapid construction of this cyclobutane moiety.\(^{11}\) Model studies pursued toward this goal provided insight into the physical properties and identification of reaction intermediates using a readily available cyclopentenol analogue.

#### 3.2.1.1 Model Wolff/Cope Substrate Synthesis

We initiated investigations toward an AB ring model system by preparing a suitable tricarbonyliron-cyclobutadiene derivative with sufficient electrophilicity to enable
alcohol alkylations under mild conditions. Conversion of pyrone 182 into tricarbonyliron-cyclobutadiene complex 183, followed by ester reduction produced alcohol 184 (Scheme 3.2.1). Alkoxide generation using KH and exposure to trichloroacetonitrile effectively formed trichloroacetimidate 185 in quantitative yield.

Scheme 3.2.1. Preparation of trichloroacetimidate 185

The stereoselective synthesis of a chiral cyclopentenol was achieved utilizing precedent cuprate chemistry. Readily available anti-cyclopentenol (±)-187 was prepared from monoacetate (±)-186 by a copper(I) cyanide-catalyzed S_N2 displacement using p-tolylmagnesium bromide (Scheme 3.2.2). Zinc(II)-catalyzed alkylation of anti-cyclopentenol 187 with trichloroacetimidate 185 afforded the requisite intramolecular cycloaddition substrate 188 in 76% yield. Oxidative liberation of cyclobutadiene promoted by ceric ammonium nitrate (CAN), with subsequent olefin cycloaddition rapidly assembled the desired cyclobutene 189 in 76% yield, establishing the stereoselective preparation of a model for our highly substituted cyclobutane intermediate.
We next considered regioselective functionalization of the cyclobutene moiety via construction of cycloadduct 189 en route to a Wolff/Cope substrate. To this end, we explored a method for the ozonolytic cleavage of olefins to terminally differentiated products in CH₂Cl₂ and methanol popularized by Schreiber.¹⁷,¹⁸ Exposure of cycloadduct 189 to typical reaction conditions provided a mixture of compounds including undesired acetal 190 in 13% yield and an inseparable 9:1 mixture of acetal 191 and desired aldehyde 192 in 68% yield (Scheme 3.2.3). Direct Wittig methylation of the mixture afforded pure acetal 191 in addition to minor quantities of desired olefin 193.
The production of acetals 190 and 191 from this unsymmetrical ozonolysis indicates diverging reaction pathways (Scheme 3.2.4). Cycloaddition of ozone to cyclobutene 189 generates primary ozonide 194, which fragments in one of two ways. Cleavage of the primary ozonide to 195 (path a) positions the carbonyl oxide on the fully substituted carbon. Subsequent addition of methanol to this intermediate and dehydration with Ac₂O/Et₃N generates acetal 190. Conversely, primary ozonide cleavage in the opposite manner produces 196 (path b) with the carbonyl oxide positioned on the less-substituted carbon. This intermediate further reacts by another of two possible pathways: (1) addition of methanol from the reaction medium (path c) and dehydration to generate acetal 191, or (2) methanol addition to the carbonyl oxide (path d) and dehydration to furnish aldehyde 192. Although desired aldehyde 192 is a minor component of this reaction, the selectivity for the cleavage of primary ozonide 194 via the desired path b is favored in an approximate 3:1 ratio, and is presumably the result of steric influences of the cyclobutene moiety.¹⁹
The isolation of aldehyde 192 as a minor product from the unsymmetrical ozonolysis of cyclobutene 189 hindered progress toward a model Wolff/Cope substrate. Fortuitously, we recognized that acetal 191 and aldehyde 192 arise from the same fragmentation pathway (path b, Scheme 3.2.4) and thus possess the same aldehyde oxidation state at C(8) (cf. Scheme 3.2.3). To exploit this result, we explored potential equilibration conditions to determine the propensity for formation of aldehyde 192 from the isomeric aldehyde/acetal mixture (Table 3.2.1). Our primary investigations revealed that solvation of pure acetal 191 in methanol effected the equilibration to favor aldehyde 192 and produced minor quantities of acetal diastereomer 197 (entries 1 and 2). A survey of various Lewis acids identified the proficiency of divalent triflate salts in shifting the equilibrium to further favor 192 (entries 3–6). Similarly, molecular sieves and combinations thereof with Lewis acids proved to be efficient for the conversion to 192 (entries 7–10). As a result of this screen of conditions, we elected to proceed in the
synthesis using 4 Å MS in our optimal conditions because they provide a nearly 3:1 ratio of \( 192:191 + 197 \) and enhanced operational efficiency.\(^{21}\)

**Table 3.2.1. Equilibration of acetal 191**

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>additive(^b)</th>
<th>( 191 + 197 : 192 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>66 : 34</td>
</tr>
<tr>
<td>2</td>
<td>——(^d)</td>
<td>39 : 61</td>
</tr>
<tr>
<td>3</td>
<td>CuCl(_2)</td>
<td>75 : 25</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl(_2)</td>
<td>41 : 59</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)(_2)</td>
<td>36 : 64</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)(_2)</td>
<td>30 : 70</td>
</tr>
<tr>
<td>7</td>
<td>3 Å MS</td>
<td>32 : 68</td>
</tr>
<tr>
<td>8</td>
<td>4 Å MS</td>
<td>29 : 71</td>
</tr>
<tr>
<td>9</td>
<td>4 Å MS/Zn(OTf)(_2)</td>
<td>27 : 73</td>
</tr>
<tr>
<td>10</td>
<td>4 Å MS/Cu(OTf)(_2)</td>
<td>28 : 72</td>
</tr>
</tbody>
</table>

\(^a\) Each entry started from pure acetal 191. \(^b\) Lewis acids were used in 20 mol %; molecular sieves were used in 0.5 g/ml. \(^c\) Ratio determined by \(^1\)H NMR analysis of crude reaction filtrate after 20–24 h. \(^d\) At 50 °C.

The equilibration of acetal 191 to desired aldehyde 192 considerably improved the overall reaction sequence for the preparation of a Wolff/Cope \( \alpha \)-diazoketone substrate (e.g., 177). In the event, the unsymmetrical ozonolysis of cyclobutene 189 followed by equilibration with 4 Å MS in methanol afforded a ~1:3 ratio of acetals 191 + 197 and aldehyde 192 (Scheme 3.2.5). Wittig methylenation of this mixture produced the desired olefin 193 in 40% yield over three steps, while the recovery of acetals 191 and 197 in 14% yield enabled recycling of material.\(^{22}\) Hydrolysis of ester 193 with KOTMS and
conversion to $\alpha$-diazoketone $200$ by way of an acid chloride and diazomethane (199) proceeded in excellent yield.

Scheme 3.2.5. Optimized synthesis of $\alpha$-diazoketone $200$

3.2.1.2 MODEL WOLFF/COPE REARRANGEMENT INVESTIGATIONS

The synthesis of $\alpha$-diazoketone $200$ enabled the examination of our key Wolff/Cope rearrangement toward the eight-membered B ring of variecolin. Thorough investigations of this transformation utilizing various photochemical or silver(I)-catalyzed sonochemical conditions afforded only intractable mixtures (Scheme 3.2.6). The lack of useful information acquired from these initial experiments required us to examine the tandem process in a stepwise manner. Accordingly, irradiation of $\alpha$-diazoketone $200$ in methanol with a 350 nm light induced the photochemical Wolff rearrangement to form homologated ester $203$ as the sole product, confirming the intermediacy of ketene $202$. We were thus able to conclude that the ketene vinyl cyclobutane rearrangement does not readily occur under the conditions surveyed.
Scheme 3.2.6. Initial Wolff/Cope studies on α-diazoketone 200

To rationalize the difficulty of the cis-ketene vinyl cyclobutane rearrangement of 202, we considered the analogous cis-divinyl cyclobutane rearrangement. A comparison of the experimental activation energy ($E_A$) for a strain-releasing Cope rearrangement of cis-divinyl cyclopropane (204) to that of cis-divinyl cyclobutane (206) reveals a higher activation barrier of the latter by roughly 4–5 kcal/mol (Figure 3.2.1). The related decrease in reaction rate constant is consistent with the slightly elevated reaction temperatures known to be required for cis-divinyl cyclobutane rearrangements. This difference, when coupled with our observations that the ketene vinyl cyclopropane rearrangement to afford substituted cycloheptadienones occurs under mild conditions, suggested that thermolysis of the intermediate ketene should facilitate the rearrangement. In the event, a photochemical Wolff rearrangement with subsequent thermolysis at 80 °C provided cyclooctenone 201 in 59% yield (Scheme 3.2.7).

With the success of this tandem reaction, we recognized that the high reactivity of a ketene intermediate and the time between photolysis/thermolysis could account for the
moderate yield of 201 and furthermore might hinder material throughput. In our search for alternative conditions, we investigated reports harnessing microwave irradiation to promote Wolff rearrangements, where we anticipated that the surplus energy could facilitate the Cope rearrangement. Indeed, microwave irradiation for 20 minutes at 140 °C in toluene afforded cyclooctadienone 201 in 95% yield. These model system results thereby confirm the Wolff/Cope strategy for the synthesis of the AB fragment of variecolin (95), and provide new tools for the construction of substituted eight-membered rings.

**Figure 3.2.1 Comparison of the strain-releasing Cope rearrangements of 204 and 206.**

**Scheme 3.2.7. Successful Wolff/Cope rearrangement of α-diazoketone 200**

*Photochemical/Thermal:*

\[ \text{hv (310 nm), PhH, 23 °C; then 80 °C} \]

59% yield

*Thermal (Microwave):*

H\text{waves, PhMe, 140 °C} 20 min

95% yield
3.2.2 ASYMMETRIC SYNTHESIS OF THE AB RING FRAGMENT OF VARIECOLIN EMPLOYING THE WOLFF/COPE REARRANGEMENT

Having established a viable route toward the AB ring system of variecolin through model system studies, we then pursued an asymmetric synthesis of this fragment.

3.2.2.1 ASYMMETRIC SYNTHESIS OF WOLFF/COPE SUBSTRATE TOWARD VARIECOLIN

The application of our proven intramolecular cycloaddition strategy for an asymmetric synthesis of the AB ring fragment (i.e., 176, Scheme 3.1.1) originated from a chiral cyclopentenol possessing syn stereochemistry. An enzymatic desymmetrization of meso-bisacetate 208 provided monoacetate (+)-186 in excellent yield and 99% ee (Scheme 3.2.8). Copper(I) cyanide-catalyzed $S_N2$ displacement using methylmagnesium chloride with monoacetate 186 afforded a 95:5 mixture of alcohols 209 and 210 in 91% yield.\(^{14a}\) Mitsunobu inversion of this alcohol mixture using benzoic acid produced allylic benzoate 211, possessing the desired syn stereochemistry between C(3) and C(5).\(^{3,28}\) Benzoate methanolysis and zinc(II)-catalyzed coupling\(^{16}\) with tricarbonyliron-cyclobutadiene trichloroacetimidate 185 gave the requisite intramolecular cycloaddition substrate (212).
Efforts toward the intramolecular cyclobutadiene–olefin cycloaddition of 212 promoted by CAN resulted in low yields and complex mixtures of products, presumably the result of competing intermolecular dimerization reactions. Snapper has established that the rapid oxidative decomplexation of tricarbonyliron-cyclobutadiene complexes using CAN provides sufficient access to cycloadducts of substrates predisposed for the intramolecular cycloaddition (e.g., 188).\textsuperscript{11f} Oxidations using trimethylamine-N-oxide, however, enact a slow release of cyclobutadiene to enable access to cycloadducts of substrates with a lower reactivity for this process (e.g., 212). The gradual liberation of the highly reactive intermediate favors an intramolecular cycloaddition process by disfavoring intermolecular reaction pathways. Application of trimethylamine-N-oxide to facilitate the oxidative decomplexation of 212 in refluxing acetone smoothly generated cycloadduct 213 (Scheme 3.2.9).\textsuperscript{29,30} Subsequent unsymmetrical ozonolysis of 213, acetal equilibration promoted by 4 Å MS in refluxing methanol and Wittig methylenation afforded a 2.7:1 ratio olefins 216 and 217, in addition to acetals 214 and 215. This reaction sequence provided desired olefin 216 in 16% yield over four steps, together with
17% yield of recyclable acetal 214. Critically, acetal 215 was sufficiently crystalline to enable X-ray analysis, providing further confirmation of the desired relative stereochemistry of this polycyclic fragment (Figure 3.2.2).

Scheme 3.2.9. Cycloaddition, ozonolysis, and olefination toward an asymmetric Wolff/Cope substrate

Figure 3.2.2. X-ray crystal structure of acetal 215. The molecular structure is shown with 50% probability ellipsoids. a) Side view. b) Top view.
3.2.2.2  α-DIAZOKETONE SYNTHESIS AND WOLFF/COPE STUDIES

In the synthesis of our asymmetric AB ring fragment, we desired cyclooctadienone products 176 where R = H, Me, or alkyl (Scheme 3.1.1). Model studies have demonstrated the tandem rearrangement where R = H (i.e., 200 → 201, see subsection 3.2.1.2). However, alkyl substitution had not yet been explored for the Wolff/Cope rearrangement and thus represented an unprecedented extension of the methodology.

Advancing to the target α-diazoketones, hydrolysis of ester 216 to acid 218 and conversion to the acid chloride and treatment with either diazomethane (199, R = H) or diazoethane (219, R = Me) produced α-diazoketones 220 and 221, respectively (Scheme 3.2.10). Although diazomethane generated 220 in 91% yield, we were surprised by the inconsistent and lower-yielding results obtained using diazoethane. Despite extensive efforts toward optimization, however, improvements in yield could not be realized. Nonetheless, the microwave-promoted tandem Wolff/Cope rearrangement of both substrates resulted in the successful construction of their respective cyclooctadienones (222 and 223).

Scheme 3.2.10. α-Diazoketone synthesis and Wolff/Cope rearrangement
The notably low yield of \( \alpha \)-substituted cyclooctadienone 223 using microwave irradiation is a direct result of the formation of numerous byproducts.\(^{35}\) Inspection of these various compounds revealed that cyclopropane 224 is a major side product (~1:1 ratio of 223:224) of this reaction, formed through a carbene intermediate. Two mechanisms have been proposed for the Wolff rearrangement: 1) a concerted group migration with nitrogen expulsion to a ketene or 2) the stepwise loss of nitrogen to generate an \( \alpha \)-carbonyl carbene intermediate that can either undergo the desired Wolff rearrangement to a ketene or participate in other intra- or intermolecular reactions.\(^{36}\) A complicating factor in our analysis of the rearrangement of 221 is that the two mechanisms often operate competitively with high substrate dependence. However, we noted the influence of solvent toward substrate conformation (224) and its impact on the mechanistic pathway,\(^{37}\) and thus posited that solvent variation might facilitate an increase in the production of our targeted cyclooctadienone 223 (Table 3.2).\(^{38}\) We observed that high-polarity solvents such as acetonitrile or 1,2-dichloroethane favored cyclopropane formation decidedly over the Wolff rearrangement (entries 1 and 2). Less-polar solvents, such as THF, ethyl acetate, and toluene, reversed the selectivity and improved the formation of desired product 223 (entries 3–6). Furthermore, the nonpolar solvents methylcyclohexane and heptane reversed the reaction selectivity to favor the desired 223 as a major product, in a 3:1 ratio (entries 7 and 8). Although solvent polarity roughly reflects product selectivity, in which less-polar solvents favor the Wolff rearrangement, the complex reaction profile makes it difficult to conclusively correlate solvent polarity to reaction pathway.
Table 3.2.2. Wolff/Cope solvent studies of α-diazoketone 221

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>dielectric constant (r)</th>
<th>223 : 224&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetonitrile</td>
<td>37.5</td>
<td>1 : 4</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>10.4</td>
<td>1 : 2.8</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>7.58</td>
<td>1 : 1.1</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>6.02</td>
<td>1 : 1.3</td>
</tr>
<tr>
<td>5</td>
<td>toluene</td>
<td>2.38</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>6</td>
<td>1,4-dioxane</td>
<td>2.21</td>
<td>1 : 1.7</td>
</tr>
<tr>
<td>7</td>
<td>methylcyclohexane</td>
<td>2.02</td>
<td>3 : 1</td>
</tr>
<tr>
<td>8</td>
<td>heptane</td>
<td>1.92</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Starting material was consumed in all reactions. <sup>b</sup> Ratios determined by 1H NMR analysis of crude reaction mixtures.

The application of these optimized reaction conditions with heptane enabled the microwave-promoted rearrangement of 221 to produce α-methyl cyclooctadienone 223 in 42% isolated yield (Scheme 3.2.11). The success of this rearrangement is significant as it represents the first example of the tandem Wolff/Cope rearrangement of a substrate possessing α-alkyl functionality. Moreover, the combined results from all substrates in this study (i.e., 200, 220, and 221) highlight the utility of microwave energy to facilitate tandem rearrangements and expand the collection of eight-membered rings available by this method. This Wolff/Cope approach to variecolin AB ring systems 222 and 223 provided advanced material to support fragment coupling studies toward completion of the natural product.
Scheme 3.2.11. Optimized rearrangement of $\alpha$-diazoketone 221 to $\alpha$-methyl cyclooctadienone 223

![Optimized rearrangement of $\alpha$-diazoketone to $\alpha$-methyl cyclooctadienone](image)

3.3 CATALYTIC ASYMMETRIC SYNTHESIS OF A D-RING FRAGMENT

D-ring fragment 179 presents an all-carbon quaternary stereocenter contained within the cyclopentene core as the key synthetic challenge. Literature reports of approaches to similar quaternary acylcyclopentenones are remarkably limited, and thus we sought a novel route to construct these potentially useful substances. Structures analogous to 179 have been assembled both from five-membered rings and as the products of six-membered ring contractions. In our design of a synthetic route to D-ring fragment 225 we envisioned the contraction of cycloheptenone 180 via a retro-aldol/aldol sequence to enable the direct formation of a cyclopentene intermediate (Scheme 3.3.1).

Scheme 3.3.1. Proposed ring contraction approach to acylcyclopentene 225

![Proposed ring contraction approach to acylcyclopentene](image)
The palladium-catalyzed enantioselective alkylation of unstabilized, prochiral ketone enolates has been an area of intense investigation in our laboratory.\(^7\) This technology has enabled the preparation of a wide variety of cyclic carbonyl compounds possessing adjacent quaternary stereocenters with high levels of selectivity and excellent yields. To explore this ring contraction pathway, we pursued the enantioselective construction of the C(14) quaternary stereocenter via the asymmetric alkylation of racemic vinylogous\(^{44}\) β-ketoester (±)-181.

### 3.3.1 OPTIMIZATION OF THE Pd-CATALYZED ASYMMETRIC ALKYLATION OF CYCLIC SEVEN-MEMBERED VINYLOGOUS β-KETOESTERS

The synthesis of a suitable β-ketoester substrate initiated with the production of vinylogous ester 228 from cycloheptane-1,3-dione (227)
\(^{45}\) (Scheme 3.3.2). Ketone enolization and acylation with allyl chloroformate formed an intermediate β-ketoester that was subsequently alkylated with methyl iodide to produce racemic β-ketoester (±)-181. In the presence of our standard alkylation conditions employing a catalyst complex generated in situ from Pd\(_2\)(pmdba)\(_3\) and (S)-r-Bu-PHOX ((S)-55) in THF at 30 °C, vinylogous β-ketoester was transformed to α-quaternary ketone (−)-229 in 94% yield and 84% ee.
Although allyl ketone 229 was produced in excellent yield, we sought to improve the enantioselectivity of the process. A survey of common solvents afforded similar yields of allyl ketone 229 with a distinct enhancement of enantioselectivity (Table 3.3.1). Ethereal solvents enabled a modest selectivity increase to 86% ee in Et₂O (entries 1–3), while aromatic solvents provided a more substantial improvement to 88% ee in toluene (entries 4 and 5). In addition, we altered the electronics of our ligand, using fluorinated derivative 230⁴⁶ to produce allyl ketone 229 in 90% ee, albeit with diminished yield at higher catalyst loading (entry 6). Since the diminished reactivity⁴⁷ of the electronically deficient palladium complex derived from 230 required increased catalyst loadings and resulted in lower yields, we elected to use the standard t-Bu-PHOS ligand (55) in toluene to carry out our asymmetric alkylation. The large-scale application of this method was facilitated by lower catalyst loadings (2.4 mol %) and increased reaction concentrations (0.2 M) to smoothly form allyl ketone 229 in 98% yield and 88% ee, a critical result that enhanced the practicality of the transformation (Scheme 3.3.3). Moreover, the optimal conditions for this class of cyclic vinylogous esters provide us with a new variety of
substrates for our asymmetric alkylation methodology as we continue to seek new synthetic applications for this chemistry.

**Table 3.3.1. Asymmetric alkylation screen of vinylogous β-ketoester (±)-**181

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ligand</th>
<th>solvent</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55 (R = H, Ar = Ph)</td>
<td>THF</td>
<td>94</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>55 (R = H, Ar = Ph)</td>
<td>TBME</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>55 (R = H, Ar = Ph)</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>55 (R = H, Ar = Ph)</td>
<td>benzene</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>55 (R = H, Ar = Ph)</td>
<td>toluene</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>230 (R = CF&lt;sub&gt;3&lt;/sub&gt;, Ar = 4-CF&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>benzene</td>
<td>57</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup> pmdba = bis(4-methoxybenzylidene)acetone. <sup>b</sup> Isolated yield. <sup>c</sup> Enantiomeric excess determined by chiral HPLC. <sup>d</sup> 5 mol % Pd<sub>2</sub>(pmdba)<sub>3</sub> and 12.5 mol % 230 were used to reach complete conversion.

**Scheme 3.3.3. Large-scale enantioselective alkylation of β-ketoester (±)-**181

**3.3.2 RING CONTRACTION INVESTIGATIONS AND DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY**

A scalable and efficient asymmetric preparation of allyl ketone 229 enabled our pursuit of the targeted D-ring fragment 179. Reduction of vinylogous ester 229 with
acidic workup furnished a 10:1 mixture of β-hydroxyketone 231 and enone 180 in 99% overall yield (Scheme 3.3.4). Exposure of this crude mixture to aldol conditions using LiOr-Bu in t-BuOH produced the desired ring-contracted acylcyclopentene 225 in 53% yield. Our isolation of the desired product in greater than 10% yield indicated to us that β-hydroxyketone 231 is readily converted to 225, whereas the minor cycloheptenone 180 remained in the reaction after consumption of 231. Since β-hydroxyketone 231 is equivalent to the first step of the retro-aldol/aldol sequence (through water addition to the enone) and is available as the major product from the reduction of 229, it thus provided us with an ideal substrate on which to pursue further studies.\(^{48}\)

Scheme 3.3.4. Reduction of ketone 229 and preliminary ring contraction

Our subsequent efforts to maximize the efficiency of this transformation focused on the ring contraction of the major reduction product, β-hydroxyketone 231. Given our early result using LiOr-Bu (Scheme 3.3.4), we examined numerous aldol conditions that consisted of a variety of non-nucleophilic bases (Table 3.3.2).\(^{49}\) We observed that several t-butoxides in t-BuOH and THF effected substrate conversion to the desired product (225) in good yields (entries 1–4), noting that the rate of product formation was comparatively slower with LiOr-Bu than that of Na- and KOt-Bu. The use of various hydroxides revealed a similar trend, where NaOH and KOH generated 225 in 4 hours.
with improved yields over their respective \(t\)-butoxides (entries 5 and 6). In contrast, the reactivity of LiOH was comparatively sluggish, providing 225 in low yield with the formation of various intermediates (entry 7).\(^{50}\) To harness the mild reactivity of LiOH while improving the yield of 225, we investigated the effect of alcohol additives to modulate the efficacy of the transformation. The combination of \(t\)-BuOH and LiOH in THF increased the yield of 225 to a similar level as that observed with LiOr-Bu, although the reaction continued to proceed at a slow rate (entry 8). Application of more acidic, non-nucleophilic alcohols such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP)\(^{51}\) demonstrated exceptional reactivity with LiOH to efficiently produce 225 in high yields (entries 9 and 10).\(^{52}\) This is reflective of the recently reported use of fluorinated lithium alkoxides to promote Horner–Wadsworth–Emmons olefinations of sensitive substrates and underscores their mild reactivity and efficacy.\(^{53}\) The data from our study further recognize the unique properties of these mild bases and suggest their application may be examined in a broader context. While a number of bases are effective in the production of 225 in good yields, we selected the combination of LiOH and TFE as our optimal conditions for scale-up efforts. Importantly, none of the conditions surveyed for the ring contraction studies generated the \(\beta\)-elimination product, cycloheptenone 180, providing further validation that \(\beta\)-hydroxyketone 231 is an ideal substrate for this transformation.\(^{54}\)
Further functionalization of semicarbazone \( \textit{232} \) with 4-iodobenzyl amine furnished \( \textit{233} \),

The reduction of allyl ketone \( \textit{229} \) with acidic workup furnished \( \beta \)-hydroxyketone \( \textit{231} \) in 90% yield and 1:1.5 dr (Scheme 3.3.5). Application of the devised ring contraction conditions consisting of LiOH and TFE in THF at 60 °C facilitated the preparation of desired acylcyclopentene \( \textit{225} \) in 96% yield, and enabled access to multigram quantities of this important intermediate. The production of allyl ketone \( \textit{229} \) in 88% ee from the asymmetric allylic alkylation reaction was satisfactory for our synthetic efforts, but we were interested in identifying an appropriate crystalline derivative to enhance the optical purity of our material. We thus pursued the derivatization of acylcyclopentene \( \textit{225} \) by conversion to semicarbazone \( \textit{232} \) in 92% yield and with a marginal increase in ee to 91%. Recrystallization of this material provided semicarbazone \( \textit{232} \) in 98% ee, which was readily cleaved under acidic conditions to reveal the desired acylcyclopentene (\( \textit{225} \)).

### Table 3.3.2. Ring contraction investigations of \( \textit{231} \)

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>additive</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>t (h)</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOT-Bu</td>
<td>–</td>
<td>t-BuOH</td>
<td>40</td>
<td>9</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>LiOT-Bu</td>
<td>–</td>
<td>THF</td>
<td>40</td>
<td>8</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>NaOT-Bu</td>
<td>–</td>
<td>THF</td>
<td>40</td>
<td>5</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>KOI-Bu</td>
<td>–</td>
<td>THF</td>
<td>40</td>
<td>5</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>NaOH</td>
<td>–</td>
<td>THF</td>
<td>60</td>
<td>4</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>KOH</td>
<td>–</td>
<td>THF</td>
<td>60</td>
<td>4</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>LiOH</td>
<td>–</td>
<td>THF</td>
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<td>24</td>
<td>78</td>
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<tr>
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<td>t-BuOH</td>
<td>THF</td>
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<td>9</td>
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<td>TFE</td>
<td>THF</td>
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<td>12.5</td>
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<tr>
<td>10</td>
<td>LiOH</td>
<td>HFIP</td>
<td>THF</td>
<td>60</td>
<td>12.5</td>
<td>99</td>
<td>87</td>
</tr>
</tbody>
</table>

* a TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoro-2-propanol. b Reactions performed with 1.5 equiv each of base and additive at 0.1 M in solvent. c Determined by GC analysis using an internal standard. d Several intermediates observed by TLC and GC analysis.
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and enabled X-ray crystal structure analysis to confirm the absolute stereochemistry of the asymmetric alkylation (Figure 3.3.1).56

Scheme 3.3.5. Scale-up, derivatization, and enantioenrichment of aclyclopentene 225
3.3.3 COMPLETION OF THE D-RING FRAGMENT

The completion of a viable D-ring fragment required protection of the carbonyl as acetal 235 (Scheme 3.3.6). Oxidative cleavage of the allyl group using modified Lemieux–Johnson conditions with reduction of the resulting aldehyde generated alcohol 236, a useful intermediate for further derivatization. Conversion to iodide 237 was readily achieved with iodine/Ph₃P, completing the synthesis of the devised D-ring component to enable fragment-coupling studies with AB ring intermediates 222 and 223 toward the synthesis of variecolin (95).
3.4 STUDIES TOWARD THE FRAGMENT COUPLING OF THE AB AND D-RING FRAGMENTS TOWARD VARIECOLIN

The asymmetric syntheses of AB ring fragments 222 and 223 and D-ring fragment 237 allowed the evaluation of C-ring annulation strategies toward completion of the target. We envisioned that construction of the final two bonds of the tetracyclic core of variecolin could be achieved by a convergent, strategic operation from these advanced intermediates. An important characteristic of the cyclooctadienones generated by the Wolff/Cope rearrangement is the ability of the enone functionality to provide regiocontrol for the reductive generation of nonsymmetrical ketone enolates.\(^{59}\) We planned to harness this regiospecific enolate generation to carry out a diastereoselective C(11)\(^3\) alkylation of D-ring iodide 237 to produce a derivative of coupled diketone 175 (Scheme 3.1.1). With the fusion of fragments 223 and 237 to produce a derivative of diketone 175, we envisioned that the final C-ring closure would occur via radical addition.
to the conjugated enone. Toward this end, we examined model compounds to determine the feasibility of this convergent approach for the construction of the C ring.

### 3.4.1 MODEL STUDIES FOR FRAGMENT COUPLING AND C-RING ANNULATION

#### 3.4.1.1 MODEL REDUCTIVE ENONE ALKYLATION AND HYDROSILYLATION/ALKYLATION

The availability of 2-methyl cyclooctenone (238) as a model α-substituted eight-membered enone allowed us to evaluate various reductive methods to install the C(11) all-carbon quaternary stereocenter of variecolin (95). This can be readily accomplished with 238 in a one-pot dissolving metal (Li/NH₃) reductive alkylation procedure⁶⁰ to generate an intermediate lithium enolate that was subsequently alkylated with D-ring iodide 237 to construct ketone 239 in 75% yield as a mixture of diastereomers (Scheme 3.4.1). An alternative two-step method used a rhodium(I)-catalyzed hydrosilylation of enone 238 with PhMe₂SiH to produce isolable enol silane 240.⁶¹ This was next exposed to Noyori’s⁶² alkylation conditions with D-ring iodide 237 to furnish the desired quaternary ketone (239) in 61% yield over two steps. The results of this model study establish a reasonable precedent for the construction of the C(11) quaternary stereocenter via alkylation, and importantly underscore the reactivity of D-ring iodide 237 with a congested lithium enolate (derived from 238).
3.4.1.2 MODEL C-RING RADICAL CYCLIZATION

With a plausible unification of the model fragments to form BD ring ketone 239 established, we pursued a radical-mediated formation of the final C–C bond to complete the C-ring annulation. The requisite substrate was prepared from LiAlH₄ reduction of ketone 239 with acidic workup to effect protecting group cleavage and reveal cyclopentene 241 as a mixture of four diastereomers (Scheme 3.4.2). Conversion of the alcohol into imidazoyl thiocarbonate 242 followed by the AIBN-initiated radical cyclization with slow addition of tri-n-butyltin hydride formed the final C–C bond of our model BCD ring core (i.e., 243) for the variecolin sesterterpenes. This significant result provides firm precedent for the C-ring annulation approach for completion of the tetracyclic core of this family, although information concerning the stereochemistry of our model cyclization product could not be conclusively discerned from this system owing to the number of diastereomers present in the starting material and product mixtures.
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Scheme 3.4.2. Model radical cyclization for annulation of the C ring

3.4.2 COUPLING STUDIES REGARDING THE ASYMMETRIC AB RING FRAGMENT OF VARIECOLIN

3.4.2.1 ENONE REDUCTIVEALKYLATION OF THE ASYMMETRIC AB RING FRAGMENT

The confirmation of our model alkylation/radical cyclization sequence to form the C ring of variecolin prompted application toward the total synthesis. The direct formation of the C(11) quaternary stereocenter was initially examined using the one-pot reductive alkylation procedure. In the event, dissolving metal reduction of \( \alpha \)-substituted cyclooctadienone intermediate 223 and exposure to an excess of D-ring iodide 237 resulted in a number of products, with saturated ketone 244—the 1,4-reduction product of 223—as the major component (Scheme 3.4.3). Unfortunately, the desired \( \alpha \)-quaternary ketone 246 was not observed. Further investigation of this direct reductive alkylation of...
AB ring fragment 222 yielded similar results, thus indicating that D-ring iodide 237 is not sufficiently reactive toward enolates derived from 222 and 223.

To understand the reactivity difference of the alkylation model system (238) and AB ring nucleophiles (222 and 223) toward the D-ring iodide (237), we explored more reactive electrophiles. Interestingly, the reductive alkylation of enone 222 using either methyl iodide or allyl bromide produced the desired α-tertiary ketones 244 and 248 in good yield and diastereoselectivity with only minor quantities of reduced ketone 245 (Scheme 3.4.4). These observations provide further evidence that D-ring iodide 237 is not sufficiently reactive toward AB ring nucleophiles derived from 222 and 223. Due to limited quantities of α-substituted cyclooctadienone 223, we are currently unable to assess the potential of a direct reductive alkylation with reactive electrophiles (e.g., allyl bromide) to generate the C(11) quaternary stereocenter.
Although we are currently unable to construct the C(11) quaternary stereocenter using a direct reductive alkylation of D-ring iodide \(237\), the availability of saturated \(\alpha\)-substituted ketones \(244\) and \(248\) encouraged us to determine the plausibility for regioselective enolate formation for this alkylative step. Soft enolization conditions employing TMSI/Et\(_3\)N\(^6\) smoothly transformed ketones \(244\) and \(248\) to tetrasubstituted enol silanes \(249\) and \(250\), respectively, as the exclusive reaction products (Scheme 3.4.5).

The preparation of various latent enolate equivalents thus expands our investigations to include a host of enolate alkylation conditions that will promote the formation of the C(11) all-carbon quaternary stereocenter.

\[ \text{Scheme 3.4.5. Soft enolization of ketones} \ 244 \ \text{and} \ 248 \]
3.4.2.2 ENONE HYDROSILYLATION OF THE ASYMMETRIC AB RING FRAGMENT

After identifying an effective two-step procedure to generate substituted enol silanes in model studies (see subsection 3.4.1.1), we explored a potential one-step transformation using a transition-metal catalyzed hydrosilylation reaction. We applied conditions optimized using model studies to α-substituted enone 223 that provided a number of compounds by TLC analysis, including saturated ketone 244 (Scheme 3.4.6). We were unable to determine if any of the remaining products were the desired silyl enol ether due to difficulties encountered during purification of the side products. Purification of 244 and exposure of the mass balance to TBAF provided 244, suggesting that some of the products formed under the reaction conditions are isomeric to the desired enol silane. The use of enone 222, which does not possess α-substitution, yielded similar results, demonstrating a unique conformational preference for the fused [5–5–8] system that inhibits the desired reactivity observed in the model system. The inability to generate a pure enol silane product and isolation difficulties halted further hydrosilylation efforts.

Scheme 3.4.6. Hydrosilylation investigations of enones 222 and 223
3.5 PROPOSED COMPLETION OF VARIECOLIN

The regioselective preparation of enol silane 249 provides optimism for advancing the AB and D-ring fragments toward variecolin (95). Potential access to a variety of D-ring derivatives through our synthetic route, and the observed stereoselective alkylation (222 → 244, Scheme 3.4.4) are key elements that predict the success of this strategy. In the event of the desired C(11) alkylation with a suitable D-ring fragment to form ketone 246, we anticipate that the following transformations will enable the rapid completion of the total synthesis (Scheme 3.5.1). Reduction of ketone 246 and acylation with thiocarbonyldiimidazole (TCDI) should form the imidazoyl thiocarbonate 251. Radical generation and diastereoselective cyclization should accomplish the C(10)–C(15) ring closure to complete the tetracyclic core of variecolin (i.e., 252). Carbonyl methylenation, allylic ether oxidation with PCC/pyridine,4b,13 and lactone reduction with i-Bu₂AlH will produce emericolin B (105). Diol oxidation using Dess–Martin periodinane57 will then furnish variecolin (95).
3.6 CONCLUSION

In summary, we have achieved significant progress toward a general, convergent asymmetric approach for the total synthesis of the variecolin sesterterpenoids. Our critical disconnection bisected variecolin into two highly substituted fragments containing the central eight-membered ring and an important all-carbon quaternary stereocenter. The AB ring preparation features an intriguing regioselective cleavage of a fused cyclobutene to terminally differentiated products en route to several advanced α-diazoketones, and set the stage for a key tandem Wolff/Cope rearrangement to construct the eight-membered ring. Importantly, our investigations revealed the proficiency of microwave energy to promote this tandem process, and provided first examples of α-substituted cyclooctadienones to further expand the collection of eight-membered rings available by this method. Our synthetic route to the D ring features a
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Palladium-catalyzed enantioselective alkylation of racemic vinylogous $\beta$-ketoester (±)-181 for the construction of the C(14) quaternary stereocenter. The efficient, large-scale preparation of ketone 229 enabled our development of a new strategy for the synthesis of enantioenriched quaternary cyclopentenes that harnesses the exceptional reactivity of fluorinated lithium alkoxides, and moreover, provides a new variety of substrates for our Pd-catalyzed asymmetric alkylation methodology. We believe that the results achieved from this synthetic endeavor highlight intriguing reactivity and expand synthetic methods that can be of general use for the preparation of natural and non-natural substances. Studies directed toward the coupling of these highly substituted AB and D-ring fragments for the final C-ring annulation and completion of the synthesis are ongoing.
3.7 EXPERIMENTAL SECTION

3.7.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Reagent grade acetone was used as received. Water (18 MΩ) used as reaction medium was obtained from a Millipore MiliQ water purification system. All starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Brine solutions refer to saturated aqueous sodium chloride solutions. Diiron nonacarbonyl was stored and handled in a glove box. Triethylamine, diisopropylamine, and t-BuOH were distilled from CaH₂ prior to use. The following liquids were purified by distillation and stored in a Schlenk tube under nitrogen: acetic acid (from CrO₃), hexamethylphosphoramide (from CaH₂), and oxalyl chloride. Zinc dust was activated over 1% HCl. Solutions of n-BuLi, MeLi, p-TolMgBr, and MeMgCl were titrated prior to use. Molecular sieves were dried and stored in a 115 °C oven. Anhydrous granular LiOH was pulverized using a mortar and pestle. Lithium wire was stored over mineral oil and washed with hexanes, then methanol, then hexanes prior to use. Previously reported methods were used to prepare Pd₂(pmdba)₃,₆₈ (S)-t-Bu-PHOX ((S)-55),₆₉ fluorinated PHOX ligand 230,₄₆ and RhH(Ph₃P)₄.₇₀ Diazomethane (199) was freshly prepared from N-methyl-N-nitroso-p-toluene sulfonamide (Diazald) as a solution in Et₂O using a Diazald kit. Diazaoethane (219) was freshly prepared from N-ethyl-N-nitrosourea₇¹ as a solution in Et₂O using a
Diazald kit. Diazoalkane solutions were dried over KOH pellets for ca. 30 min at or below 0 °C and cannula (Teflon) transferred under nitrogen to a dry Erlenmeyer flask prior to use. Reaction temperatures were controlled by an IKAmag temperature modulator. Ozonolysis reactions were performed with an OzoneLab OL80 Desktop ozone generator. Photochemical irradiation was performed in septum sealed quartz tubes with a Luzchem Photochemical reactor or with a water-cooled Hanovia 450 W medium pressure mercury-vapor immersion lamp. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, p-anisaldehyde, potassium permanganate, or ceric ammonium molybdate staining. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min mobile phase and visualization at 254 nm. Analytical achiral GC was performed on an Agilent 6850 GC with FID detector using an Agilent DB-WAX (30.0 m x 0.25 mm) column at 1.0 mL/min He carrier gas flow. Chiral GC was performed on an Agilent 6850 GC with FID detector using a Chiraldex GTA column (30.0 m x 0.25 mm, purchased from Bodman Industries) at 1.0 mL/min He carrier gas flow. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using spectrophotometric grade solvents. 1H and 13C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Inova 500 (at 500 MHz and 126 MHz, respectively) or Varian Inova 600 (at 600 MHz), and are reported relative to Me₄Si (δ 0.0
Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm$^{-1}$). Melting points were acquired using a Buchi Melting Point B-545 instrument and the values are uncorrected. High-resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in ESI, APCI, or MM (ESI/APCI) ionization mode, in addition to the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.
3.7.2 PREPARATIVE PROCEDURES

3.7.2.1 TRICARBONYLIRON-CYCLOBUTADIENE FRAGMENTS

Tricarbonyliron-cyclobutadiene methyl ester 183.13b Pyrone 182 (5.086 g, 33.00 mmol, 1.0 equiv) was dissolved in spectrophotometric grade benzene (1 L, 0.033 M) in a flame-dried 1 L photochemical reactor containing a stir bar, the reactor and lamp were assembled and the solution was sparged with N₂ for 30 min. The resulting degassed solution was irradiated with a Hanovia medium-pressure mercury-vapor lamp affixed with a pyrex filter until consumption of pyrone 182 by TLC (5:1 CH₂Cl₂/EtOAc, typically requires 20 h to 5 d; T\textsubscript{internal} = 25–35 °C). The lamp was removed from the reactor and the solution was transferred to a dry 3 L flask containing a stir bar, washing the photoreaction with excess benzene (2 x 30 mL). Fe₂(CO)₉ (14.4 g, 39.6 mmol, 1.2 equiv) was weighed into a glass jar in a glove box, transferred out of the box, and added to the reaction. The resulting suspension was warmed to 50 °C (internal) in an oil bath (T = 55–60 °C) and after 2 h at 50 °C, a second portion of Fe₂(CO)₉ (2.40 g, 6.60 mmol, 0.2 equiv) was added to the reaction. After another 1 h, the turbid reaction was cooled to room temperature and filtered through a plug of basic alumina (5 x 8 cm) capped with Celite (5 x 16 cm) washing with excess Et₂O (ca. 400 mL) until the eluent was colorless. The dark yellow solution was concentrated under reduced pressure to a turbid, yellow/brown oil. The crude material was purified by flash chromatography on SiO₂ (2.5
x 24 cm, 15:1 → 9:1 → 4:1 hexanes/Et₂O) to afford tricarbonyliron-cyclobutadiene methyl ester 183 (4.2585 g, 17.03 mmol, 52% yield) as a dark yellow/brown oil that solidified in a –20 °C freezer. \( R_f = 0.54 \) (2:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz, C₆D₆) \( \delta \) 3.84 (s, 2H), 3.22 (s, 3H), 3.20 (s, 1H). All other spectral data are consistent with reported values.

**Hydroxymethyl cyclobutadiene 184.** To a solution of cyclobutadiene ester 183 (9.066 g, 36.27 mmol, 1.0 equiv) in PhMe (120 mL, 0.3 M) at –78 °C was added neat \( i-\text{Bu}_2\text{AlH} \) (14.54 mL, 81.60 mmol, 2.25 equiv) dropwise over 15 min with vigorous stirring. Upon consumption of 183 by TLC analysis (typically as last of \( i-\text{Bu}_2\text{AlH} \) is added), EtOAc (3.54 mL, dried over MgSO₄, 1.0 equiv) was added and after 5 min the reaction was placed in a 0 °C ice bath. After 30 min the reaction was slowly quenched with a 1 M solution of Na/K tartrate (100 mL) with vigorous stirring. After 5 min, the cooling bath was removed and EtOAc (50 mL) was added to the thick suspension. When the layers became homogeneous (typically 5–8 h), the layers were separated and the aq phase was extracted with Et₂O (2 x 50 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. The thick oil was dried under high vacuum until a constant mass was achieved to afford hydroxymethyl cyclobutadiene 184 (8.105 g, 36.51 mmol, 100% yield) as a pale brown solid. \( R_f = 0.29 \) (2:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz, C₆D₆) \( \delta \) 3.37 (s, 3H), 3.34 (s, 1H), 3.26 (s, 1H), 0.62 (t, \( J = 5.9 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, C₆D₆) \( \delta \) 214.9, 85.0, 63.9, 62.2, 58.0; IR
(Neat Film NaCl) 3326 (br), 2932, 2872, 2046, 1963, 1448, 1297, 1070, 997, 822, 613 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_8$H$_6$O$_4$Fe [M$^+$]: 221.9616, found 221.9615.

**Cyclobutadiene trichloroacetimidate 185.** To a round-bottom flask charged with KH (41 mg, 1.0 mmol, 0.057 equiv) and Et$_2$O (43 mL) at 0 °C was added a solution of hydroxymethyl cyclobutadiene 184 (3.86 g, 17.4 mmol, 1.0 equiv) in Et$_2$O (43 mL, 0.2 M total) by cannula. After 10 min, trichloroacetonitrile (8.7 mL, 87 mmol, 5.0 equiv) was added to the light orange solution dropwise by syringe. Over the course of the addition, the reaction turned dark brown. After 15 min, the ice bath was removed and the reaction was allowed to warm to room temperature. Upon reaching ambient temperature the volatiles were removed in vacuo and the remaining dark brown oil was taken up in hexane (20 mL, from solvent column) with vigorous shaking. This solution was filtered through a pad of Celite, and the reaction flask was washed with an additional portion of hexane (20 mL) and filtered. The combined filtrate was concentrated in vacuo to afford trichloroacetimidate 185 (6.38 g, 17.4 mmol, 100% yield) as a clear, pale red oil. This oil was immediately used in the next step without further purification and is not stable to prolonged storage. $R_f = \text{unstable to SiO}_2$; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 8.22 (br s, 1H), 4.25 (s, 2H), 3.49 (s, 2H), 3.30 (s, 1H); $^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$ 214.5, 162.6, 92.0, 76.8, 65.7, 64.9, 64.5; IR (Neat Film NaCl) 3344, 2049, 1971, 1666, 1449, 1368, 1304,
1288 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for \(C_9H_6Cl_3FeNO_3\) [M – CO]: 336.8763, found 336.8769.

### 3.7.2.2 AB RING MODEL SYSTEM FRAGMENTS

**Monoacetate 186.\(^{15}\)** A 1 L 3-neck flask fitted with an addition funnel was charged with \(\text{Pd}(\text{Ph}_3\text{P})_4\) (595 mg, 0.515 mmol, 0.001 equiv) and dissolved in THF (258 mL, 2 M). The catalyst solution was cooled to 0 °C and a solution of epoxide 252 (42.29 g corrected, 515.1 mmol, 1.0 equiv) in THF (86 mL) was transferred to the addition funnel via cannulation. To the catalyst solution was added AcOH (29.5 mL, 515.1 mmol, 1.0 equiv) via syringe, followed by the solution of 252 via addition funnel over 20 min. Upon consumption by TLC (reaction turns orange in color when complete) the solution was transferred to a flask washing with EtOAc and concentrated in vacuo. The crude material was purified by flash chromatography on SiO\(_2\) (7 x 5 cm, dry load onto SiO\(_2\), flush with Et\(_2\)O until product elutes by TLC) to afford monoacetate (±)-186 as a yellow semisolid. This was diluted with heptane (100 mL), concentrated and dried under high vacuum to afford a pale yellow semisolid (62.30 g, 438.3 mmol, 85.1% yield) that completely solidified in a –20 °C freezer. \(R_f = 0.33\) (1:1 hexanes/EtOAc); \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 6.12 (ddd, \(J = 5.61, 2.07, 1.30\) Hz, 1H), 5.99 (ddd, \(J = 5.57, 2.04, 1.06\) Hz, 1H), 5.52–5.47 (m, 1H), 4.76–4.69 (m, 1H), 2.81 (app dt, \(J = 14.7, 7.4\) Hz, 1H),
2.06 (s, 3H), 1.72 (br s, 1H), 1.66 (app dt, $J = 14.6, 3.8$ Hz, 1H). All other spectral data are consistent with reported values.

**Aryl cyclopentenol 187.**\(^{14b}\) A flask was charged with LiCl (896.4 mg, 21.1 mmol, 4.0 equiv), flame-dried under vacuum and cooled under nitrogen. To this was added CuCN (142 mg, 1.59 mmol, 0.3 equiv) and the solids were partially dissolved in THF (20 mL) and cooled to 0 °C. To this suspension was added a solution $p$-TolMgBr (15.9 mL, 15.9 mmol, 1 M in Et\(_2\)O). After 5 min, a solution of monoacetate (±)-186 (751.5 mg, 5.29 mmol, 1.0 equiv) in THF (15 mL) over 5 min via cannulation and the flask was washed with additional THF (2 x 1 mL) for a quantitative transfer. Upon consumption of 186 by TLC (ca. 1.5 h), the reaction was slowly quenched with sat aq NH\(_4\)Cl (10 mL) and water (5 mL) and stirred vigorously for 30 min. The homogeneous phases were separated, the aq layer was extracted with EtOAc (3 x 30 mL), and the combined organics were dried over MgSO\(_4\), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO\(_2\) (6:1 → 3:1 → 1:1 hexanes/Et\(_2\)O) to afford aryl cyclopentenol 187 (829.7 mg, 4.76 mmol, 90% yield) as a pale yellow oil. $R_f = 0.63$ (1:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) $\delta$ 7.10 (d, $J = 7.83$, 2H), 7.03 (d, $J = 8.0$ Hz, 2H), 6.04–6.01 (comp m, 2H), 5.05 (d, $J = 5.1$ Hz, 1H), 4.13–4.10 (m, 1H), 2.32 (s, 3H), 2.27 (ddd, $J = 14.1, 8.0, 2.7$ Hz, 1H), 2.09 (ddd, $J = 14.1, 7.0, 5.5$, 1H). All other spectral data are consistent with reported values.
Aryl cyclopentenol ether 188. To a round-bottom flask charged with zinc(II) triflate (14.9 mg, 0.041 mmol, 5 mol %) and PhMe (0.2 mL) at 0 °C was added aryl cyclopentenol 187 (151.3 mg, 0.868 mmol, 1.0 equiv) by syringe. To this suspension was added a solution of cyclobutadiene trichloroacetimidate 185 (370 mg, 1.01 mmol, 1.2 equiv) in PhMe (0.2 mL) by cannula transfer, with further washing by additional PhMe (0.2 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a thick slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 6 h at ambient temperature. The crude reaction mixture was transferred directly onto a 5 g silica gel loading cartridge and purified with a Teledyne ISCO CombiFlash system using a 40 g silica column (1:0 → 9:1 hexanes/EtOAc) to afford ether 188 (250.8 mg, 0.663 mmol, 76% yield) as a pale yellow oil. $R_f = 0.56$ (4:1 hexanes/EtOAc); $^1$H NMR (300 MHz, C$_6$D$_6$) δ 7.00 (d, $J = 7.8$ Hz, 2H), 6.94 (d, $J = 7.9$ Hz, 2H), 5.88–5.85 (m, 1H), 4.45–4.44 (m, 1H), 3.96–3.94 (m, 1H), 3.55 (d, $J = 1.2$ Hz, 2H), 3.46 (s, 2H), 3.33 (s, 1H), 2.28 (ddd, $J = 13.8$, 6.9, 5.4 Hz, 1H), 2.14 (s, 3H), 1.86 (ddd, $J = 13.7$, 6.9, 5.4 Hz, 1H); $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ 215.0, 142.3, 140.1, 135.9, 131.6, 129.5, 127.4, 84.9, 82.5, 64.6 (two lines), 64.0, 62.3, 50.1, 41.2, 21.0; IR (Neat Film NaCl) 2863, 2044, 1959, 1513, 1075, 1048, 613 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{20}$H$_{18}$O$_4$Fe [M$^+$]: 378.0554, found 378.0551.
**Aryl cyclobutene 189.** To a vigorously stirring solution of aryl cyclopentenol ether 188 (683 mg, 1.806 mmol, 1.0 equiv) in acetone (1.81 mL, 1 mM) was added CAN (1.98 g, 3.61 mmol, 2.0 equiv) under ambient atmosphere. After 15 min, a second portion of CAN (1.98 g, 3.61 mmol, 2.0 equiv) was added. After 5 min, TLC showed consumption of 188 (4:1 hexanes/Et₂O, developed twice) and the reaction was quenched by addition of sat aq NaHCO₃ (50 mL). After 15 min, stirring was ceased, the solids were allowed to settle and the supernatant was decanted into a flask (to prevent bumping) and concentrated in vacuo to ca. 50 mL. This slurry and the remnants of the flask were transferred to a separatory funnel with minimal acetone, diluted with brine (10 mL) and pentane (200 mL). The layers were separated, the organic phase was washed with water (2 x 100 mL), and the combined aq layers were extracted with 1:1 hexanes/Et₂O (200 mL). The combined organic layers were concentrated to ca. 25 mL, transferred to a sep funnel and diluted with CH₂Cl₂ (30 mL) and brine (25 mL). The layers were separated, the aq was extracted with CH₂Cl₂ (2 x 30 mL), the organics were dried over MgSO₄, filtered, and concentrated to a dark orange oil. The crude material was purified by flash chromatography on SiO₂ (2.5 x 21 cm, 15:1 → 9:1 hexanes/Et₂O, slow gradient) to afford aryl cyclobutene 189 (326.2 mg, 1.37 mmol, 76% yield) as a colorless oil that solidified in a −20 °C freezer. \( R_f = 0.54 \) (4:1 hexanes/Et₂O, developed twice); \(^1\)H NMR (500 MHz, CDCl₃) δ 7.11 (d, \( J = 8.2 \) Hz, 2H), 7.08 (d, \( J = 8.2 \) Hz, 2H), 6.35 (d, \( J = 2.1 \) Hz, 2H).
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Hz, 1H), 6.31 (d, \( J = 2.3 \) Hz, 1H), 4.71–4.69 (m, 1H), 3.91 (d, \( J = 9.8 \) Hz, 1H), 3.87 (d, \( J = 9.8 \) Hz, 1H), 3.27 (ddd, \( J = 8.6, 8.6, 3.9 \) Hz, 1H), 3.06 (app t, \( J = 3.1 \) Hz, 1H), 2.94 (s, 1H), 2.46 (ddd, \( J = 13.8, 7.0, 2.3 \) Hz, 1H), 2.35 (app t, \( J = 4.8 \) Hz, 1H), 2.32 (s, 3H), 2.03 (ddd, \( J = 13.8, 8.8, 4.9 \) Hz, 1H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 142.9, 140.3, 138.4, 135.6, 129.3, 127.2, 84.1, 71.2, 59.6, 54.9, 52.6, 50.3, 46.5, 44.6, 21.1; IR (Neat Film NaCl) 3025, 2949, 1514, 1074, 1041, 1025, 811, 744 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for C\(_{17}\)H\(_{17}\)O \([\text{M + H} - \text{H}_2]^+\): 237.1279, found 237.1271.

**Diol 253.** To a solution of aryl cyclobutene 189 (18.0 mg, 75.5 \( \mu \)mol, 1.0 equiv) in a 2:1 mixture of CH\(_2\)Cl\(_2\) (1.0 mL) and MeOH (0.5 mL) was added a solution of Sudan Red 7b (25 \( \mu \)L of a 0.05 wt % in MeOH) and cooled to \(-78^\circ\)C. The resulting pink solution was sparged with a gentle stream of oxygen for \( \sim 1 \) min, then ozonolyzed until consumption of 189 by TLC (indicator typically turned colorless just prior to completion). The solution was sparged with oxygen for another 1 min, and NaBH\(_4\) (28.8 mg, 0.76 mmol, 10 equiv) was added and the bath was removed. When the reaction reached room temperature, CH\(_2\)Cl\(_2\) (2 mL) was added followed by quenching with 10% HCl (1 mL). The layers were separated, the aq extracted with CH\(_2\)Cl\(_2\) (3 x 2 mL), the organics were dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO\(_2\) to afford diol 253 (18.2 mg, 66.3 \( \mu \)mol, 88% yield) as a colorless oil. \( R_f = 0.31 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz,
CDCl$_3$ $\delta$ 7.09 (d, $J = 8.1$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 4.60 (app t, $J = 4.3$ Hz, 1H), 4.24 (d, $J = 11.5$ Hz, 1H), 4.10 (d, $J = 9.2$ Hz, 1H), 3.88–3.78 (comp m, 2H), 3.69 (d, $J = 9.2$ Hz, 1H), 3.55 (d, $J = 11.5$ Hz, 1H), 3.42 (ddd, $J = 10.6$, 7.1, 3.8 Hz, 1H), 2.82 (dd, $J = 8.5$, 5.3 Hz, 1H), 2.58 (dd, $J = 14.0$, 7.2 Hz, 1H), 2.36 (dd, $J = 11.0$, 5.4 Hz, 1H), 2.31 (s, 3H), 1.99 (app dt, $J = 8.7$, 4.4 Hz, 1H), 1.73 (ddd, $J = 13.9$, 10.5, 3.4 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.1, 135.7, 129.3, 127.0, 86.2, 80.6, 63.5, 63.4, 51.4, 50.8, 49.1, 44.8, 42.2, 21.1; IR (Neat Film NaCl) 3332 (br), 2922, 1514, 1436, 1100, 1037, 811 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{17}$H$_{21}$O$_3$ [M + H – H$_2$]$^+$: 273.1491, found 273.1485.

Ozonolysis of cyclobutene 189 to form acetals 190 and 191, along with aldehyde 192. To a solution of aryl cyclobutene 189 (49.6 mg, 0.208 mmol, 1.0 equiv) in a 5:1 mixture of CH$_2$Cl$_2$ (1.75 mL) and MeOH (0.35 mL, 0.1 M total) was added NaHCO$_3$ (5.2 mg, 63 µmol, 0.3 equiv) and a solution of Sudan Red 7b (75 µL of a 0.05 wt % solution in MeOH). The resulting pink-colored solution was cooled to $–78$ °C, sparged with a stream of oxygen for 1 min, then ozonolyzed until consumption of 189 by TLC (typically just as indicator turns colorless). The solution was sparged with oxygen for 1 min, the gas inlet was removed and the flask was fitted with a drying tube and warmed to room temperature. The crude reaction was filtered through a cotton plug with CH$_2$Cl$_2$ (2 x 1 mL) and benzene (1 mL). The filtrate was concentrated to ca. 0.5 mL in vacuo,
diluted with 5 mL of benzene, and further concentrated to ca. 0.5 mL. This crude was dissolved in CH$_2$Cl$_2$ (2.1 mL), cooled to 0 °C, and Ac$_2$O (58.5 µL, 0.624 mmol, 3 equiv) and Et$_3$N (37.7 µL, 0.270 mmol, 1.3 equiv) were added. After 5 min the bath was removed and the reaction was stirred at room temperature for 5 h, at which point the reaction was diluted with CH$_2$Cl$_2$ (25 mL), washed with 5% H$_2$SO$_4$ (3 x 5 mL), sat aq NaHCO$_3$ (3 x 5 mL), brine, and dried over Na$_2$SO$_4$. The crude pale yellow oil was purified by flash chromatography on SiO$_2$ (4:1 → 3:1 → 1:1 hexanes/EtOAc) to furnish acetal 190 (8.3 mg, 27.6 µmol, 13% yield) as a colorless oil and an inseparable 9:1 mixture of acetal 191 and aldehyde 192 (42.6 mg, 0.142 mmol, 68% yield) as a pale yellow oil.

**Acetal 190.** $R_f = 0.52$ (1:2 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.13 (d, $J = 7.8$ Hz, 2H), 7.05 (d, $J = 8.1$ Hz, 2H), 5.36 (s, 1H), 4.75 (dd, $J = 5.2$, 4.0 Hz, 1H), 4.13 (d, $J = 9.7$ Hz, 1H), 4.01 (d, $J = 9.7$ Hz, 1H), 3.56 (app t, $J = 6.3$ Hz, 1H), 3.49 (s, 3H), 3.48–3.45 (m, 1H), 2.58–2.52 (comp m, 3H), 2.33 (s, 3H), 1.80 (ddd, $J = 14.4$, 10.9, 3.7 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.5, 141.3, 136.3, 129.5, 127.2, 109.0, 85.9, 73.0, 56.8, 55.5, 51.9, 51.3, 51.2, 44.5, 44.2, 21.1; IR (Neat Film NaCl) 2927, 1773, 1515, 1353, 1182, 1143, 1118, 1018, 990, 930, 814 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{18}$H$_{21}$O$_4$ [M + H]$^+$: 301.1440, found 301.1448. Relative stereochemistry determined by NOE interactions shown below.
Mix of acetal 191 and aldehyde 192. Aldehyde 192 was difficult to isolate as a pure compound, as it usually contained varying quantities of acetal 191. It has the following spectrum: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.76 (s, 1H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.04 (d, $J = 8.2$ Hz, 2H), 4.69 (dd, $J = 4.5$, 3.9 Hz, 1H), 4.10 (d, $J = 9.6$ Hz, 1H), 3.91 (d, $J = 9.7$ Hz, 1H), 3.70 (s, 3H), 3.59 (dd, $J = 8.3$, 5.3 Hz, 1H), 3.45 (ddd, $J = 10.7$, 7.1, 3.7 Hz, 1H), 3.06–2.97 (comp m, 2H), 2.63 (dd, $J = 14.2$, 7.3 Hz, 1H), 2.31 (s, 3H), 1.81 (ddd, $J = 14.1$, 10.6, 3.4 Hz, 1H).

Wittig methylenation to form olefin 193 and recover acetal 191. To a suspension of methyltriphenylphosphonium bromide (23.6 mg, 66 µmol, 0.58 equiv) in THF (0.4 mL) at 0 °C was added KOt-Bu (6.4 mg, 57 µmol, 0.5 equiv) in one portion. The white suspension immediately turned bright yellow in color and was stirred for 15 min, at which point a solution of a ~9:1 mixture acetal 191 and aldehyde 192 (34.2 mg, 114 µmol, 1.0 equiv) in THF (0.2 mL) was quantitatively transferred via cannulation. After 30 min, the reaction was quenched with 0.5 mL water and diluted with CH$_2$Cl$_2$ (3 mL). The layers were separated, the aq layer was extracted with CH$_2$Cl$_2$ (3 x 2 mL), the organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by preparative TLC on SiO$_2$ (2:1 hexanes/EtOAc) to give olefin 193 (1.8 mg, 6.0 µmol, 5% yield) as a colorless oil and recovered acetal 191 (27.1 mg, 90.2 µmol, 79% yield) as a colorless oil.
**Olefin 193.** $R_f = 0.62$ (2:1 hexanes/EtOAc); $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.09 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.2$ Hz, 2H), 5.94 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.18 (dd, $J = 10.8$, 1.1 Hz, 1H), 5.14 (dd, $J = 17.5$, 1.1 Hz, 1H), 4.64 (app t, $J = 4.3$ Hz, 1H), 4.03 (d, $J = 9.2$ Hz, 1H), 3.62 (s, 3H), 3.57 (d, $J = 9.2$ Hz, 1H), 3.40 (ddd, $J = 17.5$, 10.8 Hz, 1H). $^13C$ NMR (126 MHz, CDCl$_3$) $\delta$ 173.3, 142.6, 135.6, 134.7, 129.2, 127.1, 116.3, 86.5, 78.9, 55.2, 53.0, 51.6, 51.2, 51.1, 45.0, 40.8, 21.1; IR (Neat Film NaCl) 2952, 2922, 1733, 1515, 1435, 1210, 1158, 1055, 1037, 919, 812 cm$^{-1}$; HRMS (EI+) $m/z$ calc’$d$ for C$_{19}$H$_{22}$O$_3$ [M]$^+$: 298.1569, found 298.1580.

**Acetal 191.** $R_f = 0.33$ (1:2 hexanes/Et$_2$O); $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.09 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 8.1$ Hz, 2H), 5.40 (s, 1H), 4.71 (dd, $J = 5.4$, 3.1 Hz, 1H), 4.08 (d, $J = 10.5$ Hz, 1H), 3.78 (d, $J = 10.5$ Hz, 1H), 3.55 (app pentet, $J = 6.1$ Hz, 1H), 3.48 (s, 3H), 3.31 (dd, $J = 7.4$, 5.7 Hz, 1H), 2.89 (d, $J = 2.4$ Hz, 1H), 2.66 (ddd, $J = 7.6$, 5.2, 2.4 Hz, 1H), 2.53 (dd, $J = 13.8$, 6.7 Hz, 1H), 2.31 (s, 3H), 1.76 (ddd, $J = 13.9$, 11.7, 3.2 Hz, 1H); $^{13}C$ NMR (126 MHz, CDCl$_3$) $\delta$ 177.7, 140.1, 136.1, 129.4, 127.1, 106.3, 85.7, 71.8, 56.8, 55.0, 51.1, 50.0, 47.9, 46.2, 43.9, 21.1; IR (Neat Film NaCl) 2925, 2847, 1772, 1516, 1352, 1207, 1168, 1144, 1108, 1042, 943, 814, 729, 705 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’$d$ for C$_{18}$C$_{21}$O$_4$ [M + H]$^+$: 301.1440, found 301.1444. Relative stereochemistry determined by NOE interactions shown below.
Equilibration of acetal 191. To a solution of pure acetal 191 in MeOH (25 mM) added the appropriate additive (MS = 0.5 mg/µmol; Lewis acid = 20 mol %). The reaction atmosphere was purged with nitrogen, capped and stirred at ambient temperature. After 20–24 h the reaction was diluted with Et₂O, filtered through a small plug of SiO₂ and concentrated in vacuo. The crude filtrate was then analyzed by ¹H NMR analysis. In addition to acetal 191 and aldehyde 192, acetal diastereomer 197 was identified as a minor product.

Acetal 197. \( R_f = 0.19 \) (1:2 hexanes/Et₂O); ¹H NMR (500 MHz, CDCl₃) \( \delta \) 7.1 (d, \( J = 8.0 \) Hz, 2H), 7.06 (d, \( J = 8.1 \) Hz, 2H), 5.30 (s, 1H), 4.68 (dd, \( J = 5.6, 3.3 \) Hz, 1H), 4.07 (d, \( J = 9.5 \) Hz, 1H), 3.72 (dd, 7.2, 6.2 Hz, 1H), 3.69 (d, \( J = 9.5 \) Hz, 1H), 3.63 (s, 3H), 3.52–3.47 (m, 1H), 2.85 (d, \( J = 2.7 \) Hz, 1H), 2.66 (ddd, \( J = 7.7, 5.0, 2.7 \) Hz, 1H), 2.54 (dd, \( J = 13.9, 6.8 \) Hz, 1H), 2.31 (s, 3H), 1.79 (ddd, \( J = 14.0, 11.5, 3.3 \) Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) \( \delta \) 175.8, 140.8, 136.1, 129.4, 127.1, 104.0, 86.0, 72.7, 58.7, 54.5, 50.2 (two lines), 47.7, 44.8, 44.0, 21.1; IR (Neat Film NaCl) 2922, 1770, 1515, 1450, 1386, 1209, 1170, 1106, 1041, 995, 942, 813 cm⁻¹; HRMS (MM: ESI/APCI) \( m/z \) calc’d for
C_{18}H_{21}O_{4} [M + H]^+: 301.1434, found 301.1432. Relative stereochemistry determined by NOE analysis as shown below.

**Dimethyl acetal 254.** To a solution of acetal 191 (1.0 equiv) in MeOH (25 mM) was added either La(OTf)_{3} or Sm(OTf)_{3} (20 mol %). The reaction was stirred until complete conversion by TLC, diluted with Et_{2}O, filtered through a plug of Celite, and concentrated in vacuo. The crude ^{1}H NMR showed dimethyl acetal 254 as the exclusive product. R_{f} = 0.36 (1:2 hexanes/Et_{2}O); ^{1}H NMR (600 MHz, CDCl_{3}) δ 7.08 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.1 Hz, 2H), 4.69 (s, 1H), 4.58 (dd, J = 4.8, 3.8 Hz, 1H), 3.88 (d, J = 9.2 Hz, 1H), 3.86 (d, J = 9.2 Hz, 1H), 3.67 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 3.36 (ddd, J = 10.7, 7.4, 3.8 Hz, 1H), 3.23 (dd, J = 8.7, 5.3 Hz, 1H), 2.93 (ddd, J = 9.1, 5.6, 3.8 Hz, 1H), 2.82 (d, J = 5.7 Hz, 1H), 2.60 (dd, J = 14.1, 7.4 Hz, 1H), 2.30 (s, 3H), 1.75 (ddd, J = 14.0, 10.3, 3.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_{3}) δ 174.1, 142.7, 135.6, 129.2, 127.1, 105.0, 85.8, 75.0, 58.3, 56.6, 54.5, 52.1, 51.7, 51.4, 49.4, 45.0, 42.4, 21.1; IR (Neat Film NaCl) 2952, 1727, 1515, 1435, 1362, 1069, 1042, 977, 813 cm^{-1}; HRMS (FAB+) m/z calc’d for C_{20}H_{23}O_{5} [M + H – H_{2}]^+: 345.1702, found 345.1701.
Conversion of cyclobutene 189 over three steps to olefin 193 and acetals 191 and 197. A solution of cyclobutene 189 (326.2 mg, 1.369 mmol, 1.0 equiv) in CH₂Cl₂/MeOH (5:1, 27.4 mL, 0.05 M) containing NaHCO₃ (34.5 mg, 0.411 mmol, 0.3 equiv) and Sudan Red 7b (150 µL of a 0.05 wt% solution in MeOH) at −78 °C was sparged with a stream of oxygen for ~1 min and ozonolyzed until consumption by TLC analysis (typically as indicator turned colorless). After sparging with oxygen for an additional 3 min, the reaction was capped with a drying tube and warmed to room temperature. The solution was filtered through a cotton plug, washing with benzene (3 mL). The reaction was concentrated in vacuo to ~2 mL, and to this flask was added a stir bar, septum, and the flask was evacuated/purged briefly (3x). To the crude was added CH₂Cl₂ (13.7 mL), the solution was cooled to 0 °C, and to this was added Ac₂O (387 µL, 4.11 mmol, 3.0 equiv) and Et₃N (286 µL, 2.05 mmol, 1.5 equiv). The bath was removed and the reaction was stirred at room temperature for 8 h, diluted with CH₂Cl₂ (25 mL), washed with 2% HCl (10 mL), then 10% NaOH (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo to a pale yellow oil. The crude oil was purified by flash chromatography on SiO₂ (2.5 x 8 cm, 4:1 → 1:1 hexanes/Et₂O) to afford acetal 190 (61.5 g, 0.205 mmol, 15%
yield) and a mixture of aldehyde 192 and acetals 191 and 197 (293.5 mg, 0.977 mmol, 71% yield).

The mixture of desired isomers (293.5 mg) was dissolved in MeOH (19.5 mL, 0.05 M) and to this was added oven-dried 4 Å MS (489 mg, 0.5 g/mmols). After 24 h at room temperature, the reaction was diluted with EtOAc (20 mL), filtered through a plug of Celite, and concentrated to a turbid yellow oil. This was dissolved in CH₂Cl₂ and passed through a small SiO₂ plug and concentrated in vacuo to afford a pale yellow oil (312.1 mg).

To a solution of methyltriphenylphosphonium bromide (390 mg, 1.09 mmol, 1.05 equiv) at 0 °C was added KOt-Bu (105 mg, 0.935 mmol, 0.9 equiv). The resulting bright yellow solution was stirred for 1 h, and a solution of aldehyde 192 and acetals 191 and 197 (312.1 mg) in THF (2 mL) was quantitatively transferred via cannulation. After 10 min, the bath was removed and at 5 h the reaction was quenched with water (5 mL) and diluted with Et₂O (5 mL). The layers were separated, the aq was extracted with Et₂O (2 x 10 mL), the combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo to a pale yellow oil. The crude material was purified by flash chromatography on SiO₂ (2.5 x 15 cm, 9:1 → 1:1 hexanes/Et₂O) to afford olefin 193 (162.2 mg, 0.544 mmol, 40% yield over three steps) and a ~7:3 mixture of acetals 191 and 197 (59.5 mg, 0.198 mmol, 14% yield over three steps).
Recycling of acetals 191 and 197. A ~7:3 mixture of acetals 191 and 197 (60.7 mg, 0.202 mmol) were equilibrated in MeOH with 4 Å MS to ~3:1 mixture of aldehyde 192 and acetals 191 and 197, and the resulting crude was olefinated as detailed above with methyltriphenylphosphonium bromide (1.5 equiv) and KOt-Bu (1.25 equiv) and purified by flash chromatography on SiO$_2$ to provide olefin 193 (46.2 mg, 0.155 mmol, 76% yield over two steps) and acetal 191 (13.0 mg, 0.432 mmol, 21% yield over two steps).

Acid 198. To a solution of olefin 193 (162.2 mg, 0.544 mmol, 1.0 equiv) in THF (10.9 mL, 0.05 M) at 0 °C was added KOTMS (698 mg, 5.44 mmol, 10 equiv) in one portion. The cooling bath was removed and the reaction was stirred until consumption of 193 by TLC analysis (typically 5–6 h). The reaction was cooled to 0 °C and slowly quenched with 1 N HCl (10 mL), diluted with EtOAc (20 mL) and brine (5 mL). The layers were separated, the aq was extracted with EtOAc (3 x 20 mL), the combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated to a pale yellow semisolid. The crude material was purified by flash chromatography on SiO$_2$ (1:1 hexanes/EtOAc) to give acid 198 (148.7 mg, 0.523 mmol, 96% yield) as a white solid. $R_f = 0.23$ (2:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.09 (d, $J = 8.0$ Hz, 2H), 7.04 (d, $J = 8.1$ Hz, 2H), 6.00 (dd, $J = 17.4$, 10.8 Hz, 1H), 5.21 (dd, $J = 10.8$, 1.1 Hz, 1H), 5.17 (dd, $J = 17.6$, 1.2 Hz, 1H), 3.64 (dd, $J = 4.7$, 3.7 Hz, 1H), 4.04 (d, $J = 9.3$ Hz, 1H), 3.57 (d, $J = 9.3$ Hz, 1H).
Hz, 1H), 3.40 (ddd, J = 10.6, 7.3, 3.6 Hz, 1H), 3.26 (dd, J = 8.2, 5.2 Hz, 1H), 3.00–2.95 (comp m, 2H), 2.64 (d, J = 14.2, 7.3 Hz, 1H), 2.31 (s, 3H), 1.78 (ddd, J = 14.0, 10.5, 3.3 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.7, 142.6, 135.7, 134.4, 139.3, 127.7, 116.6, 86.6, 79.0, 54.9, 53.2, 51.1 (two lines), 44.9, 40.8, 21.1; IR (Neat Film NaCl) 2923, 1729, 1700, 1515, 1418, 1223, 1053, 992, 918, 812 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_{18}$H$_{21}$O$_3$ [M + H]$^+$: 285.1491, found 285.1495.

**α-Diazoketone 200.** To a solution of acid 198 (14.7 mg, 51.7 µmol, 1.0 equiv) in CH$_2$Cl$_2$ (2 mL, 0.025 M) at 0 °C was added a solution of oxalyl chloride (107 µL of a 1.45 M solution in CH$_2$Cl$_2$, 155 µmol, 3.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 1 h, at which point the stir bar was removed and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in CH$_2$Cl$_2$ (1 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (199, 5–8 mL) at 0 °C. After 30 min the cooling bath was removed, and after a further hour the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small SiO$_2$ plug (Et$_2$O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO$_2$ (9:1 → 3:1 hexanes/EtOAc) to afford α-diazoketone 200 (13.2 mg, 42.8 µmol, 83% yield) as a bright yellow oil that solidified
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in a −20 °C freezer. \( R_f = 0.31 \) (2:1 hexanes/EtOAc); \(^1^H\) NMR (500 MHz, CDCl\(_3\))
\( \delta \) 7.07 (d, \( J = 7.9 \) Hz, 2H), 7.03 (d, \( J = 7.9 \) Hz, 2H), 6.01 (dd, 17.5, 10.8 Hz, 1H), 5.17 (d, \( J = 10.8 \) Hz, 1H), 5.11–5.06 (br m, 2H), 4.64 (app t, \( J = 4.0 \) Hz, 1H), 3.97 (br d, \( J = 9.1 \) Hz, 1H), 3.66 (br d, \( J = 8.6 \) Hz, 1H), 3.36 (dd, \( J = 7.7 \) Hz, 1H), 3.19 (br s, 1H), 3.11 (br s, 1H), 2.92 (br s, 1H), 2.64 (dd, \( J = 14.2 \) Hz, 1H), 2.30 (s, 3H), 1.78 (ddd, \( J = 13.7 \) Hz, 10.5 Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 193.6, 142.5, 135.7, 134.9, 129.3, 127.1, 116.0, 86.5, 78.6, 60.8, 55.3, 53.6, 51.4, 44.9, 40.5, 30.4, 21.1; IR (Neat Film NaCl) 2955, 2921, 2100, 1633, 1514, 1370, 1352, 1048, 812 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for C\(_{19}\)H\(_{21}\)O\(_2\)N\(_2\) [M + H]\(^+\): 309.1603, found 309.1619.

**Homologated ester 203.** A solution of \( \alpha \)-diazoketone 200 (3.2 mg, 104 \( \mu \)mol) in MeOH (5.2 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem rayonette (\( \lambda = 350 \) nm) for 1.5 h. The solution was concentrated in vacuo and revealed homologated ester 203 as the sole product by crude \(^1^H\) NMR. An analytical sample was obtained from purification by preparative TLC on SiO\(_2\) (2:1 hexanes/EtOAc) to give 203 (2.4 mg, 7.7 \( \mu \)mol, 74% yield) as a colorless oil. \( R_f = 0.43 \) (2:1 hexanes/EtOAc); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.07 (d, \( J = 7.5 \) Hz, 2H), 7.02 (d, \( J = 7.5 \) Hz, 2H), 5.89 (dd, \( J = 16.9 \), 10.2 Hz, 1H), 5.22 (d, \( J = 10.7 \) Hz, 1H), 5.13 (d, \( J = 17.5 \) Hz, 1H), 4.64 (app t, \( J = 3.9 \) Hz, 1H), 3.97 (d, \( J = 8.7 \) Hz, 1H), 3.51 (s, 3H), 3.50 (d, \( J = 8.7 \) Hz, 1H), 3.46–3.42 (m, 1H), 3.23 (dd, \( J = 7.9 \) Hz, 1H), 2.61 (dd, \( J = 14.1 \), 7.3 Hz, 1H), 2.54–2.36 (comp
m, 3H), 2.30 (s, 3H), 2.11 (app dt, \( J = 7.7, 3.8 \) Hz, 1H), 1.78 (ddd, \( J = 12.7, 10.4, 2.1 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 173.1, 143.6, 135.5, 135.3, 129.2, 127.1, 116.4, 86.7, 79.2, 52.4, 51.9, 51.6, 50.1, 47.0, 46.9, 45.0, 37.2, 21.1; IR (Neat Film NaCl) 2951, 2922, 1736, 1514, 1435, 1207, 1163, 1041, 916, 808 cm\(^{-1}\); HRMS (EI+) \( m/z \) calc’d for C\(_{20}\)H\(_{24}\)O\(_3\) [M\(^+\)]: 312.1726, found 312.1725.

Cyclooctadienone 201. Photochemical/Thermal: A solution of \( \alpha \)-diazoketone 200 (3.5 mg, 11.4 \( \mu \)mol) in PhH (5.7 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem photochemical reactor (\( \lambda = 310 \) nm) for 10 min, and then the lamp was turned off and the quartz tube was placed in an 80 °C oil bath for 2 h. The reaction was concentrated in vacuo and purified by preparative TLC on SiO\(_2\) (1:1 hexanes/Et\(_2\)O, developed twice) to give cyclooctadienone 201 (1.9 mg, 6.8 \( \mu \)mol, 59% yield) as a colorless oil.

Microwave (thermal): A solution of \( \alpha \)-diazoketone 200 (2.3 mg, 7.5 \( \mu \)mol) in PhMe (1.5 mL, 5 mM) was prepared in a nondried microwave vial containing a stir bar under ambient atmosphere. The vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 140 °C, and the temperature was maintained for 20 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by crude \(^1\)H NMR analysis (C\(_6\)D\(_6\)). The crude material was purified by preparative TLC on
SiO₂ (2:1 hexanes/EtOAc) to give 201 (2.0 mg, 7.1 µmol, 95% yield) as a colorless oil that solidified in a −20 °C freezer.  

\[ R_f = 0.32 \] (3:1 hexanes/EtOAc); \[ \text{H NMR (CDCl₃, 500 MHz)} \] δ 7.17–7.13 (comp m, 4H), 5.80–5.73 (comp m, 2H), 5.63–5.59 (m, 1H), 4.76 (d, \( J = 5.2 \text{ Hz, 1H} \)), 3.66 (dd, \( J = 10.8, 5.9 \text{ Hz, 1H} \)), 3.41 (dd, \( J = 14.7, 8.1 \text{ Hz, 1H} \)), 3.23 (app t, \( J = 11.3 \text{ Hz, 1H} \)), 3.13–3.05 (comp m, 2H), 2.34 (s, 3H), 2.30 (dd, \( J = 13.8, 5.9 \text{ Hz, 1H} \)), 1.93 (ddd, \( J = 13.8, 12.1, 4.6 \text{ Hz, 1H} \)); \[ \text{C NMR (126 MHz, CDCl₃) δ 203.3, 146.8, 139.7, 138.4, 136.9, 129.7, 129.2, 127.9, 144.2, 85.3, 72.2, 53.9, 50.6, 48.1, 45.4, 41.4, 21.2 \); \[ \text{H NMR (500 MHz, C₆D₆)} \] δ 6.99 (d, \( J = 7.7 \text{ Hz, 2H} \)), 6.86 (d, \( J = 6.9 \text{ Hz, 2H} \)), 5.78–5.75 (m, 1H), 5.55 (d, \( J = 13.6 \text{ Hz, 1H} \)), 5.11–5.08 (m, 1H), 4.35 (app t, \( J = 5.13 \text{ Hz, 1H} \)), 4.24 (d, \( J = 13.1 \text{ Hz, 1H} \)), 4.11 (d, \( J = 13.2 \text{ Hz, 1H} \)), 3.04–2.89 (comp m, 4H), 2.70 (app t, \( J = 11.3 \text{ Hz, 1H} \)), 2.20 (dd, \( J = 13.6, 5.9 \text{ Hz, 1H} \)), 2.15 (s, 3H), 1.53–1.46 (m, 1H); \[ \text{C NMR (126 MHz, C₆D₆) δ 201.9, 147.2, 139.2, 138.6, 136.8, 130.1, 130.0, 128.7, 114.4, 85.5, 72.5, 53.8, 51.2, 48.3, 45.9, 41.9, 21.3 \); IR (Neat Film NaCl) 3015, 2922, 1693, 1661, 1516, 1435, 1318, 1208, 1062, 1030, 817 cm⁻¹; HRMS (MM: ESI/APCI) m/z calc’d for C₁₉H₁₉O₂ [M – H]⁺: 279.1319, found 279.1384.

### 3.7.2.3 AB RING ASYMMETRIC FRAGMENTS

![Diagram of AB ring asymmetric fragments](image-url)
**Monoacetate (+)-186.** To a solution of monoacetate (±)-186 (40.43 g, 284.4 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (47 mL, 6 M) was added imidazole (21.11 g, 310 mmol, 1.09 equiv), and after the contents were completely dissolved, the solution was cooled to 0 °C and Ac$_2$O (29.3 mL, 310 mmol, 1.09 equiv) was added over 5–7 min via syringe. After 10 min, the bath was removed and the solution was stirred for 22 h at room temperature, at which EtOAc (150 mL) was added and the contents were poured into ice-cold 1 N HCl (150 mL). The layers were separated and the aq layer was saturated with NaCl (s) and extracted with Et$_2$O (2 x 100 mL, 1 x 50 mL). The combined organics were washed with sat. aq NaHCO$_3$ (100 mL), this aq layer was saturated with NaCl (s) and extracted with Et$_2$O (2 x 100 mL). The combined organics were dried over MgSO$_4$, filtered, concentrated, and dried under high vacuum to afford meso-bisacetate 208 (50.88 g, 276.2 mmol, 97% yield) as a pale yellow oil. This material could be used in subsequent reactions as is, or can be purified by short-path distillation (bp = 74–98 °C, ~0.8 torr) to give 208 as a colorless oil in 89% yield. $R_f = 0.75$ (Et$_2$O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.09 (d, $J = 0.9$ Hz, 2H), 5.54 (ddd, $J = 7.6$, 3.8, 0.9 Hz, 2H), 2.88 (app dt, $J = 15.1$, 7.6 Hz, 1H), 2.06 (s, 6H), 1.74 (app dt, $J = 15.0$, 3.8 Hz, 1H). All other spectral data are consistent with reported values.$^{27c}$

**meso-Bisacetate 208** (33.15 g, 180.0 mmol, 1.0 equiv) was added to a purified water triple-rinsed 1 L Erlenmeyer flask containing a stir bar and partially dissolved in aq NaH$_2$PO$_4$/K$_2$HPO$_4$ buffer (0.05 M, pH = 8.0). To this solution was added Novozym 435 (4.0 g), the flask was covered with parafilm and stirred gently to at room temperature until consumption of 208 by TLC analysis (5–8 h). The contents were vacuum filtered and the supported enzyme was washed with water (150 mL) and EtOAc (2 x 150 mL).
The filtrate layers were separated and the aq layer was saturated with NaCl (200 g), extracted with EtOAc (5 x 200 mL, follow by TLC), and the combined organics were dried over MgSO₄, filtered, and concentrated in vacuo. The crude oil was dissolved in Et₂O (150 mL) and heptane was added (150 mL), followed by concentration in vacuo to afford a white semisolid. This was repeated one more time and the solid was dried under high vacuum to provide monoacetate (+)-186 (24.36 g, 171 mmol, 95% yield) as a white semisolid. The crude material is >95% pure by ¹H NMR, but can be purified by flash chromatography on SiO₂ (1:2 hexanes/Et₂O, dry load onto SiO₂) to provide 186 in 89% yield. The material displayed the same spectral properties as above;²⁷ᵃᵇ [α]D₂₂.₅ +61.2° (c 1.28, CHCl₃, 99% ee). GC conditions: 100 °C isothermal, GTA column, tR (min): major = 30.5, minor = 27.6. We have reused the recovered Novozym 435 up to four times and observed slightly lower activity for each subsequent use with identical selectivities.

**anti-Cyclopentenols 209 and 210.** A 2 L 3-neck flask was charged with CuCN (2.01 g, 112.2 mmol, 0.2 equiv) and THF (280 mL), and the suspension was cooled to ca. −20 °C (internal) using a cryocool. To this was added a solution of MeMgCl (109 mL, 337 mmol of a 3.1 M solution in THF) and the internal temperature warmed to −14 °C. After 30 min at −20 °C, a solution of monoacetate (+)-186 (15.95 g, 112.2 mmol, 1.0 equiv) in THF (40 mL) was slowly transferred (quantitative) via cannulation at such a
rate that the temperature does not rise above −10 °C (requires ~1 h). After 30 min the reaction was slowly quenched with sat. aq NH₄Cl (100 mL), 50% sat. brine (100 mL), the cooling bath was removed and the viscous suspension was stirred vigorously for several hours. Additional water (200 mL) and 3% HCl (100 mL) was added and the layers were separated. The aq layer was extracted with Et₂O (3 x 200 mL), the combined organics were dried over MgSO₄, filtered, and concentrated carefully (water bath = 5 °C, down to 30 torr) to a pale yellow oil. The crude material was purified by short path distillation (bp = 88–92 °C, 40 torr) to afford a 95:5 mixture of anti-cyclopentenols 209 and 210 (8.847 g, 90.2 mmol, 80% yield). The early distillation fractions and washing from the apparatus were combined and purified by flash chromatography on SiO₂ (2.5 x 27 cm, 6:1 → 1:1 pentane/Et₂O) to provide another 1.049 g of 209 and 210. The combined yield obtained was 9.996 g, 101.9 mmol, 91% yield. \( R_f (210) = 0.35 \) (1:1 hexanes/EtOAc); \( R_f (209) = 0.29 \) (1:1 hexanes/EtOAc); bp = 88–92 °C (40 torr).

An analytical sample of 209 was obtained from the column conditions above. \(^1\)H NMR (500 MHz, CDCl₃) δ 5.89 (dd, \( J = 5.5, 1.9 \) Hz, 1H), 5.79 (ddd, \( J = 4.6, 2.2, 2.2 \) Hz, 1H), 4.88–4.86 (m, 1H), 2.99–2.91 (m, 1H), 1.96 (ddd, \( J = 14.0, 7.5, 2.6 \) Hz, 1H), 1.71 (ddd, \( J = 14.0, 7.1, 5.2 \) Hz, 1H), 1.48 (br s, 1H), 1.03 (d, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl₃) δ 142.0, 132.1, 77.6, 42.7, 38.5, 21.0; IR (Neat Film NaCl) 3338 (br), 2956, 2870, 1354, 1088, 1017, 982, 742 cm⁻¹; HRMS (EI⁺) \( m/z \) calc’d for C₆H₁₀O [M]+: 98.07317, found 98.07171; \([\alpha]_D^{21} = -272.2^\circ \) (c 0.39, CHCl₃, 99% ee). GC conditions: 45 °C isothermal, GTA column, \( t_R \) (min): major = 37.7, minor = 36.7.
**syn-Benzanoate 211.** To a suspension of Ph₃P (13.41 g, 51.12 mmol, 1.2 equiv) and benzoic acid (6.243 g, 51.12 mmol, 1.2 equiv) in PhMe (237 mL) at −75 °C (internal) was added DIAD (10.1 mL, 51.12 mmol, 1.2 equiv) dropwise, neat over 15 min. The resulting yellow suspension was stirred vigorously for 30 min, at which point a solution of 209 and 210 (4.1806 g, 42.60 mmol, 1.0 equiv) in PhMe (47 mL, 0.15 M total) was transferred via cannula quantitatively over 30 min (observed maximum temperature increase to −70 °C). When ~1/3 of this solution was added, the reaction mixture turned homogeneous. After complete addition of 209 and 210, the reaction was stirred for an additional 30 min (white precipitate has formed) and quenched with sat. aq NaHCO₃ (100 mL) and water (100 mL) and the contents were warmed to room temperature. The layers were separated, the aq was extracted with Et₂O (2 x 50 mL), and the combined organics were shaken with 3% aq H₂O₂ until TLC showed disappearance of Ph₃P. The layers were separated, the aq was extracted with Et₂O (1 x 50 mL), and the combined organics were dried over MgSO₄, filtered, and concentrated to a pale yellow solid. The crude material was purified by flash chromatography on SiO₂ (7 x 7.5 cm, 1:0 → 24:1 hexanes/Et₂O, dry loaded onto SiO₂) to give syn-benzoate 211 (7.792 g, 38.53 mmol, 90% yield) as a pale yellow oil. \( R_f = 0.57 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl₃) δ 8.04 (dd, \( J = 8.2, 1.2 \) Hz, 2H), 7.56–7.53 (m, 1H), 7.43 (app t, \( J = 7.8 \) Hz, 2H), 6.03 (dd, \( J = 4.4, 2.0 \) Hz, 1H), 5.90–5.86 (comp m, 2H), 2.80–2.73 (m, 1H), 2.65 (ddd, \( J = 14.0, 7.8, 7.8 \) Hz, 1H), 1.51 (ddd, \( J = 14.0, 4.4, 4.4 \) Hz, 1H), 1.16 (d, \( J = 7.0 \) Hz, 3H);
13C NMR (126 MHz, CDCl$_3$) $\delta$ 166.6, 142.9, 132.9, 130.8, 129.7, 128.6, 128.4, 80.9, 38.9, 38.7, 21.7; IR (Neat Film NaCl) 2961, 1716, 1451, 1340, 1315, 1272, 1110, 711 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{13}$H$_{14}$O$_2$ [M]$^+$: 202.0994, found 202.0957; $[\alpha]_D^{25.7} +123.8^\circ$ (c 1.175, CHCl$_3$, 98–99% ee). For a chiral analytical assay, see syn-diol 178.

**syn-Cyclopentenol 178.** To a solution of benzoate 211 (6.255 g, 30.93 mmol, 1.0 equiv) in MeOH (62 mL, 0.5 M) was added K$_2$CO$_3$ (8.549 g, 61.85 mmol, 2.0 equiv) in one portion. After completion as judged by TLC analysis (3 h, 3:1 hexanes/EtOAc), the reaction was concentrated carefully in vacuo to a slurry (~5–10 mL). The white slurry was diluted with brine (25 mL) and extracted with Et$_2$O (4 x 25 mL, follow by TLC), the organics were dried over MgSO$_4$, filtered, and concentrated carefully in vacuo. The crude material was purified by flash chromatography on SiO$_2$ (5 x 12 cm, 6:1 $\rightarrow$ 1:1 pentane/Et$_2$O) and concentrated down to 100 torr until $^1$H NMR analysis revealed the absence of solvent to afford *syn*-cyclopentenol 178 (2.728 g, 27.79 mmol, 90% yield) as a colorless oil. $R_f = 0.25$ (3:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.82 (app dt, $J = 5.5$, 1.5 Hz, 1H), 5.73 (app dt, $J = 5.5$, 2.0 Hz, 1H), 4.79 (br s, 1H), 2.66–2.59 (m, 1H), 2.52 (ddd, $J = 13.4$, 7.6, 7.6 Hz, 1H), 1.79 (br s, 1H), 1.17 (app dt, 13.4, 5.4 Hz, 1H), 1.09 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 140.4, 132.8, 77.8, 42.6, 39.0, 22.0; IR (Neat Film NaCl) 3338 (br), 3048, 2959, 2870, 1456, 1356, 1322, 1115,
1051, 755 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc’d for C\(_6\)H\(_{10}\)O [M]\(^+\): 98.07317, found 98.06857; \([\alpha]\)\(_D\)\(^{27}\) = \(-23.0^\circ\) (c 0.475, CHCl\(_3\), 98.2% ee). GC conditions: 50 °C isothermal, GTA column, \(t_R\) (min): major = 21.2, minor = 20.7.

**Cyclobutadiene-iron ether complex 212.** To a round-bottom flask containing zinc(II) triflate (271 mg, 0.745 mmol, 5 mol\%) and PhMe (3.7 mL) at 0 °C was added cyclopentenol 178 (1.45 g, 14.8 mmol, 1.0 equiv) by syringe. To this suspension was added a solution of cyclobutadiene trichloroacetimidate 185 (6.38 g, 17.4 mmol, 1.2 equiv) in PhMe (2.0 mL) by cannula transfer, with further washing by PhMe (1.7 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a viscous slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 0.5 h at ambient temperature. The crude reaction mixture was transferred directly onto a 25 g silica gel loading cartridge and purified with a Teledyne ISCO CombiFlash system using a 125 g silica column (1:0 → 19:1 hexanes/EtOAc) to afford cyclobutadiene-ether complex 212 (3.65 g, 12.2 mmol, 82% yield) as a pale yellow oil. \(R_f = 0.73\) (4:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.72 (app dt, \(J = 5.6, 1.9\) Hz, 1H), 5.66 (app dt, \(J = 5.6, 1.6\) Hz, 1H), 4.27–4.24 (m, 1H), 3.54 (d, \(J = 9.1\) Hz, 1H), 3.52 (d, \(J = 9.1\) Hz, 1H), 3.48 (s, 2H), 3.32 (s, 1H), 2.43–2.39 (m, 1H), 2.15 (app dt, \(J = 13.3, 7.6\) Hz, 1H), 1.26 (ddd, \(J = 17.0, 11.2, 6.9\) Hz, 1H), 0.98 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 215.0, 140.5, 130.5,
85.2, 82.6, 64.6 (two lines), 64.0, 62.2, 39.1, 38.9, 21.6; IR (Neat Film NaCl) 2961, 2871, 1965, 1359, 1076, 1055, 757 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for $\text{C}_{14}\text{H}_{14}\text{FeO}_{4}$ [M]$^+$: 302.0242, found 302.0244; $[\alpha]_D^{25} +22.7^\circ$ (c 0.86, hexane, 98% ee).

Cycloaddition to cyclobutene 213. A solution of ether 212 (2.3582 g, 7.806 mmol, 1.0 equiv) dissolved in acetone (780 mL, 10 mM) in a 1 L round-bottom flask fitted with a reflux condenser was warmed in a 70 °C oil bath. When the solution approached reflux, the condenser was momentarily removed and Me$_3$NO•2H$_2$O (8.77 g, 78.9 mmol, 10 equiv) was added in a single portion. The solution was allowed to reflux and within 10 min the reaction vessel was filled with a rust colored precipitate. After 4 h a second portion of Me$_3$NO•2H$_2$O (4.35 g, 45.9 mmol, 5.8 equiv) was added. The solution was heated at reflux for an additional 17 h after which the reaction was judged to be complete by TLC analysis (4:1 hexanes/EtOAc). The solution was cooled to room temperature and poured directly onto a SiO$_2$ column (25 x 5 cm) packed in pentane. The column was washed with 0 $\rightarrow$ 10% Et$_2$O in pentane, and all fractions containing cyclobutene 213 were combined and concentrated carefully to a volume of ~30 mL by atmospheric
pressure distillation. This solution was purified by flash chromatography on SiO\(_2\) (pack with pentane, elute with 20:1 pentane/Et\(_2\)O). The fractions containing product were combined and concentrated to a volume of ~10 mL by atmospheric pressure distillation. This pale yellow cyclobutene solution in pentane was used directly in the following reaction. An analytical sample of cyclobutene 213 could be prepared by further chromatography and exhaustive distillation of solvent. \(R_f = 0.39\) (3:1 hexanes/Et\(_2\)O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.27 (d, \(J = 2.2\) Hz, 1H), 6.22 (s, 1H), 4.84 (dd, \(J = 14.4, 7.1\) Hz, 1H), 4.04 (d, \(J = 9.1\) Hz, 1H), 3.94 (d, \(J = 8.6\) Hz, 1H), 3.00 (s, 1H), 2.89 (dd, \(J = 19.7, 13.8\) Hz, 1H), 2.27–2.18 (m, 1H), 2.10–2.05 (comp m, 2H), 1.37 (ddd, \(J = 13.0, 13.0, 7.0\) Hz, 1H), 0.97 (d, \(J = 6.7\) Hz, 3H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 140.2, 138.4, 84.7, 70.3, 57.9, 52.0, 47.8, 44.8, 39.0, 37.3, 14.3; IR (Neat Film NaCl) 2955, 2865, 1458, 1334, 1089, 1075, 1057, 1032, 931, 740 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc’d for C\(_{11}\)H\(_{14}\)O \([\text{M}]^+\): 162.1045, found 162.1026; an optical rotation was not obtained due to the volatility of this compound. Cyclobutene 213 was found to possess an optical purity (ee) of 98% by chiral GC analysis; GC conditions: 110 °C isothermal, GTA column, \(t_R\) (min): major = 13.6, minor = 13.3.

**Ozonolysis, equilibration, and methylenation to olefins 216 and 217, and acetals 214 and 215.** In a 250 mL round-bottom flask, the cyclobutene solution prepared above was diluted with CH\(_2\)Cl\(_2\) (130 mL) and methanol (26 mL, 5:1, 0.05 M total). To this was added NaHCO\(_3\) (205.2 mg, 2.44 mmol, 0.3 equiv) and a few drops of Sudan Red (0.05 wt % in MeOH) until the solution became a persistent pink color (ca. 10 drops). The reaction vessel was cooled to \(-78\) °C and the solution was sparged with O\(_2\) gas (0.5 L/min) for 2 min. The reaction was then ozonolyzed (setting the ozone generator to
“5” with an O$_2$ flow rate of 0.5 L/min) for 60 min, at which point the pink color of the solution had disappeared and the reaction was judged to be complete by TLC analysis. The ozone was sparged with O$_2$ gas (1 L/min) through the solution for 2 min, and the pale yellow solution was warmed to room temperature and filtered through a cotton plug to remove the solid NaHCO$_3$. The cotton plug was washed with PhH (10 mL) and the filtrate was concentrated to a small volume (ca. 3–4 mL). The resulting crude yellow oil was dissolved in CH$_2$Cl$_2$ (78 mL), cooled to 0 °C, and to this was added Et$_3$N (1.63 mL, 11.7 mmol, 1.5 equiv) and Ac$_2$O (2.21 mL, 23.4 mmol, 3.0 equiv) dropwise via syringe. After 6 h, the reaction was quenched by the addition of 2 M HCl (25 mL), the organic layer was separated and washed with 2 M NaOH (25 mL), and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (5 x 25 mL). The organics were dried over MgSO$_4$, filtered, and concentrated to afford a pale brown oil which was passed through a SiO$_2$ plug eluting with EtOAc, and concentrated to afford a pale yellow oil (0.8504 g, 3.8 mmol, three steps, 48% crude yield) containing mostly acetals \text{214 and 215.}

The crude pale yellow oil prepared above was azeotroped from PhH (2 x 10 mL) in a 250 mL round-bottom flask and dissolved in MeOH (76 mL, 0.05 M). To this was added oven dried 4 Å MS (1.90 g, 0.5 g/mmol) and the flask was fitted with a reflux condenser and heated to reflux using an 80 °C oil bath. After 6 h, a reaction aliquot was judged complete by $^1$H NMR analysis and the reaction was cooled to room temperature. Most of the 4 Å MS were removed by filtration through Celite eluting with EtOAc. The filtrate was concentrated and the resultant turbid oil was further purified by filtration through a SiO$_2$ plug with EtOAc. This filtrate was concentrated to afford a yellow oil (0.8420 g)
containing mostly aldehydes derived from 214 and 215 with acetals 214 and 215.

This was used directly in the following reaction.

A flask containing Ph₃PCH₃Br (1.62 g, 4.54 mmol, 1.2 equiv) was partially dissolved with THF (15 mL) and cooled to 0 °C. To this was added KOt-Bu (423 mg, 3.77 mmol, 1.0 equiv) in one portion, and the solution immediately displayed a bright yellow color. The crude yellow oil of aldehydes/acetals (0.8420 g, ~3.7 mmol) prepared above was azeotroped from PhH (2 x 10 mL), dissolved in THF (7.5 mL), cooled to 0 °C, and transferred dropwise via positive pressure cannulation into the solution of phosphorane over ca. 10 min. The flask was then washed with a second portion of THF (7.5 mL) to ensure quantitative transfer. The reaction was gradually allowed to warm to room temperature. After 18 h the reaction was quenched by the addition of H₂O (25 mL) and extracted with Et₂O (4 x 20 mL) then EtOAc (2 x 20 mL). The combined organics were dried with MgSO₄, filtered and concentrated in vacuo. The crude yellow residue was purified flash chromatography on SiO₂ (15 x 2 cm, 20:1 → 4:1 hexanes/EtOAc) to afford olefins 216 and 217 (384.4 mg, 1.729 mmol, 2.7:1 ratio, 22.2% yield over four steps from ether 212) as a colorless oil and acetals 214 and 215 (400.5 mg, 1.786 mmol; 2.7:1 ratio, 22.9% yield over four steps from ether 212) as pale yellow oil. Olefins 216 and 217 could be separated by further flash chromatography on SiO₂ (20:1 → 9:1 hexanes/EtOAc), and acetals 214 and 215 could be separated by further flash chromatography on SiO₂ (3:1 → 1:1 hexanes/EtOAc).

Olefin 216. \( R_f = 0.46 \) (9:1 hexanes/EtOAc, developed thrice); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 5.95 (dd, \( J = 17.5, 10.8 \) Hz, 1H), 5.15 (dd, \( J = 10.8, 1.2 \) Hz, 1H), 5.11 (dd, \( J = 17.5, 1.2 \) Hz, 1H), 4.59 (ddd, \( J = 6.3, 6.3, 1.5 \) Hz, 1H), 3.99 (d, \( J = 9.0 \) Hz, 1H), 3.64 (s,
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3H), 3.54 (d, \( J = 9.0 \) Hz, 1H), 3.16 (d, \( J = 7.1 \) Hz, 1H), 3.02 (app t, 7.1 Hz, 1H), 2.95 (dd, \( J = 7.5, 7.4 \) Hz, 1H). 2.43–2.34 (m, 1H), 2.18 (ddd, \( J = 14.7, 10.4, 5.7 \) Hz, 1H), 1.71 (ddd, \( J = 14.6, 6.3, 1.7 \) Hz, 1H), 1.02 (d, \( J = 7.0 \) Hz, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 173.6, 134.9, 115.9, 87.1, 78.7, 52.6, 51.6, 51.4, 44.8, 42.5, 38.9, 37.2, 17.2; IR (Neat Film NaCl) 2954, 1736, 1436, 1363, 1236, 1206, 1162, 1042, 920 cm\textsuperscript{-1}; HRMS (MM: ESI/APCI) \( m/z \) calc’d for C\textsubscript{13}H\textsubscript{18}O\textsubscript{3} [M + H]\textsuperscript{+}: 223.13287, found 223.13255; \([\alpha]_D^{16.8} = -4.73^\circ \) (c 1.18, CH\textsubscript{2}Cl\textsubscript{2}, 98% ee).

Olefin 217. \( R_f = 0.39 \) (9:1 hexanes/EtOAc, developed thrice); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.86 (ddd, \( J = 17.0, 10.3, 7.8 \) Hz, 1H), 5.05 (ddd, \( J = 17.1, 1.5, 1.5 \) Hz, 1H), 5.02 (ddd, \( J = 10.3, 1.4, 1.4 \) Hz, 1H), 4.67 (ddd, \( J = 6.6, 6.6, 2.8 \) Hz, 1H), 4.02 (d, \( J = 9.4 \) Hz, 1H), 3.88 (d, \( J = 9.4 \) Hz, 1H), 3.68 (s, 3H), 3.30 (app t, \( J = 7.2 \) Hz, 1H), 3.00 (app t, \( J = 7.2 \) Hz, 1H), 2.54 (app q, 7.16 Hz, 1H), 2.35 (d septuplets, \( J = 9.6, 7.1 \) Hz, 1H), 2.18 (ddd, \( J = 14.5, 9.7, 6.3 \) Hz, 1H), 1.67 (ddd, \( J = 14.5, 7.7, 2.8 \) Hz, 1H), 1.01 (d, \( J = 7.0 \) Hz, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 172.3, 137.9, 115.9, 87.1, 76.0, 55.8, 51.7, 48.9, 44.9, 43.6, 41.8, 38.0, 16.2; IR (Neat Film NaCl) 2953, 5873, 1731, 1436, 1295, 1207, 1041, 917 cm\textsuperscript{-1}; HRMS (EI+) \( m/z \) calc’d for C\textsubscript{13}H\textsubscript{18}O\textsubscript{3} [M]: 222.1256, found 222.1216; \([\alpha]_D^{15.1} = -0.49^\circ \) (c 0.72, CH\textsubscript{2}Cl\textsubscript{2}, 98% ee).

Acetal 214. \( R_f = 0.29 \) (2:1 hexanes/EtOAc); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 5.39 (s, 1H), 4.80 (ddd, \( J = 6.5, 6.5, 4.5 \) Hz, 1H), 4.00 (d, \( J = 10.6 \) Hz, 1H), 3.98 (d, \( J = 10.7 \) Hz, 1H), 3.48 (s, 3H), 3.13 (app t, \( J = 6.7 \) Hz, 1H), 2.89 (d, \( J = 3.3 \) Hz, 1H), 2.61 (ddd, \( J = 6.9, 6.9, 3.3 \) Hz, 1H), 2.39–2.30 (m, 1H), 2.06 (ddd, \( J = 14.4, 8.4, 6.3 \) Hz, 1H), 1.60 (ddd, \( J = 13.3, 8.5, 4.5 \) Hz, 1H), 1.11 (d, \( J = 7.0 \) Hz, 3H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) 179.0, 107.4, 86.7, 70.9, 56.8, 52.4, 51.5, 44.7, 40.8, 38.6, 37.2, 16.9; IR (Neat Film NaCl)
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2961, 2877, 1772, 1353, 1150, 1128, 1100, 1062, 936, 710 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{12}$H$_{16}$O$_4$ [M]$^{+}$: 224.1049, found 224.1052; [$\alpha$]$_D^{18.3}$ $+73.0^\circ$ (c 1.13, CH$_2$Cl$_2$, 98% ee). Relative stereochemistry determined by NOE interactions shown below.

![NOE interactions](image1)

**Acetal 215.** $R_f = 0.19$ (2:1 hexanes/EtOAc); mp = 151.5–153 °C (Et$_2$O); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.30 (s, 1H), 4.89 (dd, $J = 12.9$, 7.2 Hz, 1H), 4.19 (d, $J = 9.6$ Hz, 1H), 4.11 (d, $J = 9.6$ Hz, 1H), 3.49 (s, 3H), 3.33 (dd, $J = 7.0$, 6.3 Hz, 1H), 2.58 (d, $J = 4.0$ Hz, 1H), 2.40 (ddd, $J = 10.0$, 6.0, 4.1 Hz, 1H), 2.30–2.22 (m, 1H), 2.16 (ddd, $J = 14.5$, 7.4, 7.4 Hz, 1H), 1.55 (ddd, $J = 14.0$, 11.1, 5.7 Hz, 1H), 1.03 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 177.2, 108.4, 86.6, 73.2, 56.5, 55.5, 50.1, 42.8, 41.2, 38.7, 38.2, 15.3; IR (Neat Film NaCl) 2934, 1766, 1460, 1359, 1199, 1171, 1143, 1130, 1115, 1063, 1045, 916, 904, 691 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{12}$H$_{16}$O$_4$ [M]$^{+}$: 224.1049, found 224.1044; [$\alpha$]$_D^{17.9}$ $-56.7^\circ$ (c 0.62, CH$_2$Cl$_2$, 98% ee). Crystals suitable for X-ray analysis were obtained by slow evaporation from Et$_2$O. See Appendix 3 for the crystallography report.

![Reactions](image2)
Acid 218. To a solution of olefin 216 (41.0 mg, 0.184 mmol, 1.0 equiv) in THF (3.7 mL, 0.05 M) cooled to 0 °C was added KOTMS (236 mg, 1.84 mmol, 10 equiv) in one portion. After 5 min the reaction was warmed to room temperature and monitored by TLC. At 12 h the reaction was cooled to 0 °C and slowly quenched with 10% HCl (4 mL) and diluted with brine (4 mL) and EtOAc (10 mL). The layers were separated and the aq layer was extracted with EtOAc (3 x 10 mL), the combined organics were dried over Na₂SO₄, filtered, and concentrated to a pale yellow oil. The crude was purified by flash chromatography on SiO₂ (6:1 → 3:1 hexanes/EtOAc, CH₂Cl₂ load) to afford acid 218 (35.2 mg, 0.169 mmol, 92% yield) as a white solid. \( R_f = 0.21 \) (2:1 hexanes/EtOAc); \( ^{1}H \) NMR (600 MHz, CDCl₃) \( \delta \) 6.04 (dd, \( J = 17.5, 10.8 \) Hz, 1H), 5.20 (dd, \( J = 10.8, 1.2 \) Hz, 1H), 5.17 (dd, \( J = 17.5, 1.2 \) Hz, 1H), 4.61 (ddd, \( J = 6.4, 6.4, 1.6 \) Hz, 1H), 4.02 (d, \( J = 9.1 \) Hz, 1H), 3.54 (d, \( J = 9.1 \) Hz, 1H), 3.22 (d, \( J = 7.3 \) Hz, 1H), 3.05 (app t, \( J = 7.1 \) Hz, 1H), 2.91 (app q, \( J = 7.6 \) Hz, 1H), 2.40 (d septuplets, \( J = 10.4, 7.0 \) Hz, 1H), 2.20 (ddd, \( J = 14.7, 10.4, 5.8 \) Hz, 1H), 1.73 (ddd, \( J = 14.7, 6.3, 1.7 \) Hz, 1H), 1.05 (d, \( J = 7.1 \) Hz, 3H); \( ^{13}C \) NMR (126 MHz, CDCl₃) \( \delta \) 178.6, 134.5, 116.2, 87.2, 78.8, 52.8, 51.2, 44.7, 42.5, 39.0, 37.2, 17.2; IR (Neat Film NaCl) 3085 (br), 2958, 2930, 1731, 1704, 1418, 1283, 1241, 1086, 1041, 996, 921 cm⁻¹; HRMS (EI+) \( m/z \) calc’d for \( C_{12}H_{16}O_3 \) [M]⁺: 208.1100, found 208.1094; \( [\alpha]_D^{15.3} +28.3^\circ \) (c 0.97, CH₂Cl₂, 98% ee).
**Diazoketone 220.** To a solution of acid 218 (62.5 mg, 0.300 mmol, 1.0 equiv) in CH₂Cl₂ (6.0 mL, 0.05 M) at 0 °C was added a solution of oxalyl chloride (353 µL of a 1.7 M solution in CH₂Cl₂, 0.600 mmol, 2.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 45 min at 0 °C, at which point the stir bar was removed, PhMe was added (6 mL), and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in CH₂Cl₂ (2 mL) and THF (4 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (199, ca. 30 mL) containing IRA-67 (161 mg, ca. 0.9 mmol, 3.0 equiv) at 0 °C. The flask was further washed with CH₂Cl₂ (4 mL) and THF (2 mL) and quantitatively transferred. After 3.5 h the cooling bath was removed and the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small SiO₂ plug (Et₂O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO₂ (6:1 → 2:1 hexanes/Et₂O) to afford α-diazoketone 220 (63.2 mg, 0.272 mmol, 91% yield) as a bright yellow oil that solidifies in a ~20 °C freezer. $R_f = 0.24$ (3:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl₃) δ 6.01 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.15 (d, $J = 10.9$ Hz, 1H), 5.10 (br s, 1H), 5.05 (d, $J = 17.5$ Hz, 1H), 4.59 (app t, $J = 6.1$ Hz, 1H), 3.92 (d, $J = 9.0$ Hz, 1H), 3.63 (d, $J = 9.0$ Hz, 1H), 3.11 (br d, $J = 14.8$, 2H), 2.96 (app t, $J = 6.9$ Hz, 1H), 2.44–2.35 (m, 1H), 2.20 (ddd, $J = 15.4$, 10.5, 5.8 Hz, 1H), 1.70 (dd, $J = 14.7$, 6.3 Hz, 1H), 0.99 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl₃) δ 193.7, 134.9, 115.7, 87.2, 78.3, 54.8, 53.3, 51.9, 50.4, 42.6, 38.3, 37.3, 17.2; IR (Neat Film NaCl) 3081, 2956, 2100, 1635, 1373,
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1047, 919 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc'd for \(\text{C}_{13}\text{H}_{17}\text{N}_{2}\text{O}_{2}\) [M + H]: 233.1290, found 233.1296; \([\alpha]_{D}^{20.2}\) –66.3\(^{\circ}\) (c 0.99, CH\(_2\)Cl\(_2\), 98% ee).

**Diazoketone 221.** \(\alpha\)-Diazoketone was prepared by the same procedure as described for diazoketone 220 using acid 218 (17.3 mg, 83.1 \(\mu\)mol, 1.0 equiv), but with freshly prepared and KOH-dried diazoethane (219, ca. 20 mL). After 4 h at 0 \(^{\circ}\)C the excess diazoethane was removed via water aspirator. The pale orange solution was filtered through a small SiO\(_2\) plug (Et\(_2\)O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO\(_2\) (6:1 \(\rightarrow\) 4:1 hexanes/Et\(_2\)O, CH\(_2\)Cl\(_2\) load) to afford \(\alpha\)-diazoketone 221 (13.0 mg, 52.8 \(\mu\)mol, 64% yield) as a bright yellow oil. \(R_f = 0.38\) (2:1 hexanes/Et\(_2\)O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.95 (dd, \(J = 17.5, 10.9\) Hz, 1H), 5.10 (d, \(J = 10.8\) Hz, 1H), 5.05 (d, \(J = 17.6\) Hz, 1H), 4.57 (app t, \(J = 5.7\) Hz, 1H), 3.86 (d, \(J = 9.3\) Hz, 1H), 3.66 (d, \(J = 9.3\) Hz, 1H), 3.34 (d, \(J = 6.8\) Hz, 1H), 3.28 (dd, \(J = 14.9, 7.5\) Hz, 1H), 2.93 (app t, \(J = 6.9\) Hz, 1H), 2.45–2.36 (m, 1H), 2.16 (ddd, \(J = 15.1, 10.6, 5.7\) Hz, 1H), 1.94 (s, 3H), 1.70 (dd, \(J = 14.5, 5.9\) Hz, 1H), 0.98 (d, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 14.3, 134.8, 115.5, 87.0, 77.3, 53.0, 52.5, 47.7, 42.3, 36.7, 36.3, 17.3, 8.3; IR (Neat Film NaCl) 2957, 2926, 2064, 1631, 1286, 1050 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for \(\text{C}_{14}\text{H}_{19}\text{O}_{2}\text{N}_{2}\) [M + H]: 247.1447, found 247.1457; \([\alpha]_{D}^{19.9}\) +71.6\(^{\circ}\) (c 0.57, CH\(_2\)Cl\(_2\), 98% ee).
Cyclooctadienone 222. A solution of α-diazoketone 220 (69.2 mg, 0.271 mmol) in PhMe (54 mL, 5 mM) was partitioned equally into three nondried 20 mL microwave reaction vessels containing a stir bar under ambient atmosphere. Each vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 160 °C, and the temperature was maintained for 15 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by crude $^1$H NMR analysis (CDCl$_3$). The crude material was purified by flash chromatography on SiO$_2$ (9:1 $\rightarrow$ 6:1 $\rightarrow$ 3:1 hexanes/EtOAc) to give 222 (43.9 mg, 0.215 mmol, 79% yield) as a colorless oil that solidifies in a –20 °C freezer. $R_f = 0.35$ (3:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.08 (dd, $J = 12.4$, 6.5 Hz, 1H), 5.93 (app dt, $J = 12.4$, 1.9 Hz, 1H), 5.54 (dtdd, $J = 4.8$, 3.2, 2.6, 1.7 Hz, 1H), 4.59 (dd, $J = 14.1$, 6.9 Hz, 1H), 4.38 (d, $J = 12.1$ Hz, 1H), 4.32 (d, $J = 12.2$ Hz, 1H), 3.44 (ddd, $J = 9.4$, 2.2, 1.0 Hz, 1H), 3.28 (dd, $J = 14.3$, 9.8 Hz, 1H), 3.18–3.13 (m, 1H), 2.99 (ddd, $J = 14.3$, 6.2, 1.2 Hz, 1H), 2.41–2.32 (m, 1H), 2.18 (dddd, $J = 13.1$, 7.1, 6.1, 1.2 Hz, 1H), 1.44 (dd, $J = 13.2$, 13.2, 5.9 Hz, 1H), 1.11 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 204.4, 146.1, 139.2, 131.6, 114.2, 85.1, 74.6, 52.9, 47.8, 40.1, 38.9, 15.0; IR (Neat Film NaCl) 2958, 2874, 1691, 1666, 1116, 1064, 1032, 974, 867 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_{13}$H$_{17}$O$_2$ [M + H]$^+$: 205.1229, found 205.1223; [α]$_D^{20.4}$ −642° (c 1.38, CH$_2$Cl$_2$, 98% ee).
Wolff/Cope rearrangement for cyclooctadienone 223 and cyclopropane 224. A solution of α-diazoketone 221 (17.7 mg, 71.9 µmol) in heptane (14.4 mL, 5 mM) was prepared in a nondried 20 mL microwave reaction vessel under ambient atmosphere and sealed. The contents were irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 150 °C, and the temperature was maintained for 10 min. The reaction was cooled to room temperature and TLC analysis showed consumption of 221. The solution was concentrated in vacuo and purified by preparative TLC on SiO₂ (3:1 hexanes/EtOAc, develop twice) to afford α-methyl cyclooctadienone 223 (6.6 mg, 30.2 µmol, 42% yield) as a colorless oil and cyclopropane 224 as a single diastereomer.

Cyclooctadienone 223. $R_f = 0.41$ (3:1 hexanes/EtOAc); $^1$H NMR (600 MHz, CDCl₃) δ 5.80 (app dq, $J = 7.2, 1.3$ Hz, 1H), 5.52–5.48 (m, 1H), 4.58 (ddd, $J = 7.3, 7.3, 6.2$ Hz, 1H), 4.38 (d, $J = 12.1$ Hz, 1H), 4.31 (ddd, $J =$ 10.7, 3.0, 1.6 Hz, 1H), 3.36 (ddddd, $J =$ 9.3, 8.1, 2.4, 1.1 Hz, 1H), 3.24 (dd, $J = 15.6, 9.5$ Hz, 1H), 3.02–2.98 (comp m, 2H), 2.36–2.14 (m, 1H), 2.16 (ddd, $J = 13.2, 7.1, 1.0$ Hz, 1H), 1.84 (app t, $J = 1.5$ Hz, 3H), 1.47 (ddd, $J = 13.3, 13.3, 5.9$ Hz, 1H), 1.08 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl₃) δ 207.6, 146.6, 137.2, 132.5, 113.7, 85.1, 74.5, 53.3, 47.0, 46.8, 40.3, 38.9, 20.8, 15.0; IR (Neat Film NaCl) 2956, 2923, 2874, 1693, 1667, 1452, 1375, 1076, 1045, 1020, 973, 873, 838 cm⁻¹; HRMS (MM: ESI/APCI) $m/z$ calc’d for C₁₄H₁₉O₂ [M + H]⁺: 219.1380, found 219.1379; [α]$_D^{25}$ 573° (c 0.35, CHCl₃, 98% ee)
**Cyclopropane 224.** \( R_f = 0.36 \) (3:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\))

\[ \delta = 4.80 \text{ (ddd, } J = 7.2, 7.2, 6.0 \text{ Hz, } 1\text{H}), 3.94 \text{ (d, } J = 9.3 \text{ Hz, } 1\text{H}), 3.84 \text{ (d, } J = 9.3 \text{ Hz, } 1\text{H}), 2.86 \text{ (d, } J = 1.8 \text{ Hz, } 1\text{H}), 2.84 \text{ (dd, } J = 7.4, 5.8 \text{ Hz, } 1\text{H}), 2.25 \text{ (d, } J = 2.9 \text{ Hz, } 1\text{H}), 2.16 \text{ (dddd, } J = 10.5, 10.5, 8.6, 4.1 \text{ Hz, } 1\text{H}), 2.12 \text{–} 2.07 \text{ (m, } 1\text{H}), 2.04 \text{ (ddd, } J = 9.0, 4.6, 1.8 \text{ Hz, } 1\text{H}), 1.56 \text{–} 1.54 \text{ (comp m, } 2\text{H}), 1.49 \text{ (ddd, } J = 13.6, 10.9, 5.8 \text{ Hz, } 1\text{H}), 1.22 \text{ (s, } 3\text{H}), 0.96 \text{ (d, } J = 6.7 \text{ Hz, } 3\text{H}); \]^13C NMR (126 MHz, CDCl\(_3\)) \( \delta = 198.7, 86.3, 74.3, 67.1, 57.9, 51.0, 49.7, 46.7, 43.1, 38.8, 37.4, 32.7, 15.2, 9.4; IR (Neat Film NaCl) 2953, 2923, 2868, 1776, 1449, 1073, 1015, 937 cm\(^{-1}\); HRMS (MM: ESI/APCI) \( m/z \) calc’d for C\(_{14}\)H\(_{19}\)O\(_2\) [M + H]: 219.1380, found 219.1382; \([\alpha]_D^{25} +46.1^\circ\) (c 0.38, CHCl\(_3\), 98% ee)

### 3.7.2.4 D-RING FRAGMENTS

**Cycloheptane-1,3-dione (227).**\(^{45}\) NaI (156.74 g, 1.046 mol, 1.25 equiv) was placed in a 3 L 3-neck flask and dried under high vacuum at 90 °C for 12 h and then cooled to ambient temperature under N\(_2\). CH\(_3\)CN (1.3 L, 0.65 M) was added to dissolve the NaI and to the resulting solution was added cyclopentanone (254, 70.7 g, 74.3 mL, 0.840 mol, 1.0 equiv) followed by Et\(_3\)N (106.25 g, 146.3 mL, 1.050 mol, 1.25 equiv). The flask was fitted with an oven-dried addition funnel and was charged with TMSCl (104.03 g, 122 mL, 0.958 mol, 1.15 equiv), which was added dropwise over 30 min. The resulting suspension was stirred for an additional 1 h at ambient temperature. Pentane (1.0 L) was
added and the biphasic system was stirred vigorously for 10 min. The layers were separated and the CH$_3$CN layer was extracted with pentane (3 x 400 mL). The combined pentane extracts were washed with H$_2$O (2 x 500 mL), brine (500 mL), dried over Na$_2$SO$_4$, filtered, and carefully concentrated under reduced pressure (down to 100 torr) to afford the desired silyl enol ether (131.4 g, 0.840 mol, quantitative yield) as a colorless oil. This material was used directly in the following reaction without further purification. 

$R_f = 0.83$ (4:1 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.78 (dt, $J = 3.9, 2.0$ Hz, 1H), 2.45–2.33 (comp m, 4H), 1.89–1.79 (comp m, 2H), 0.27 (s, 9H). All other spectral data are consistent with reported values.

The obtained silyl enol ether (89.7 g, 0.574 mol, 1.0 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a stopper, an addition funnel, and an overhead stirrer. Hexanes (900 mL) were added followed by Et$_3$N (80.7 g, 111.2 mL, 0.798 mol, 1.4 equiv). Dichloroacetyl chloride (101.70 g, 66.4 mL, 0.690 mol, 1.2 equiv) was dissolved in hexanes (400 mL), transferred to the closed addition funnel, and added dropwise to the reaction over 9.5 h with vigorous stirring. After 18 h of stirring at 23 °C, the brown suspension was vacuum filtered through a coarse sintered-glass funnel. The filter cake was thoroughly rinsed with EtOAc (3 x 500 mL) while agitating the precipitate with a stirring rod. The clear brown solution was concentrated under reduced pressure and then filtered through a pad of Al$_2$O$_3$ (neutral, 7 x 18 cm) eluting with EtOAc. The resulting solution was concentrated under reduced pressure to afford dichlorocyclobutanone 255 (124.7 g, 0.467 mol, 82% yield) as a dark brown oil that crystallized in a −20 °C freezer. This material was used directly in the next reaction without further purification. $R_f = 0.58$ (6:1 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$)
δ 3.66 9d, J = 8.4 Hz, 1H), 2.55 (dd, J = 13.3, 6.8 Hz, 1H), 2.12–1.84 (comp m, 4H), 1.64–1.51 (m, 1H), 0.25 (s, 9H). All other spectral data are consistent with reported values.

The above dichlorocyclobutanone 255 (53.4 g, 0.200 mol, 1.0 equiv) was placed in a 3 L 3-neck round-bottom flask fitted with a thermometer, an addition funnel and an overhead stirrer. This material was dissolved in i-PrOH and purified water (170 mL each). The suspension was cooled to −10 °C (internally) in a MeOH/ice bath. To this cooled solution was added Zn dust (58.8 g, 0.899 mol, 4.5 equiv) in four portions (5 min between each). The addition funnel was charged with a solution of AcOH (66.1 g, 63 mL, 1.10 mol, 5.5 equiv) dissolved in purified water (130 mL) and this solution was added to the reaction in a dropwise manner at such a rate to keep the internal temperature below 0 °C (typically added over 1.5 h). Upon complete addition, the suspension was stirred for an additional 30 min at −10 °C (internal) and then the cooling bath was removed and the reaction was allowed to warm to ambient temperature. After 8.5 h, the reaction mixture was filtered through a coarse sintered-glass funnel and rinsed with i-PrOH (100 mL). The filtrate was cooled to 0 °C and slowly neutralized by portionwise addition of K2CO3 (74.6 g, 0.54 mol, 2.7 equiv) with vigorous stirring (overhead stirrer). The viscous suspension was filtered and rinsed with H2O (100 mL) and EtOAc (300 mL). The biphasic system was concentrated under reduced pressure to ~200 mL to remove a large portion of the i-PrOH and extracted with CH2Cl2 (100 mL portions until TLC clear). The combined organics were dried over MgSO4, filtered, and concentrated under reduced pressure to afford cycloheptane-1,3-dione (227) (24.2 g, 0.192 mol, 96% yield) as a pale orange oil. Rf = 0.16 (4:1 hexanes/EtOAc); 1H NMR (300 MHz, CDCl3) δ 3.59 (s, 2H),
2.60–2.56 (comp m, 4H), 2.02–1.94 (comp m, 4H). All other spectral data are consistent with reported values.

Vinylogous ester 228. To a solution of 227 (35.8 g, 0.284 mol, 1.0 equiv) in toluene (280 mL, 1 M) in a flask fitted with a Dean–Stark trap and reflux condenser was added i-BuOH (168.3 g, 208 mL, 2.27 mol, 8.0 equiv) and PPTS (1.07 g, 4.26 mmol, 0.0015 equiv). The solution was immersed into an oil bath at 130 °C and monitored by TLC. Upon consumption of the starting material (typically within 4–6 h), the reaction was allowed to cool to room temperature and the resulting dark orange solution was washed with sat. aq NaHCO₃ (200 mL). The aqueous phase was extracted with EtOAc (3 x 150 mL), the combined organics were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford a thick dark orange oil. The crude oil was flushed through a plug of silica gel (7 x 9 cm SiO₂, 1:4 → 3:7 → 1:1 hexanes/Et₂O) to afford the vinylogous ester 228 (43.5 g, 0.239 mol, 84% yield) as a pale orange oil. Rf = 0.22 (2:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.37 (s, 1H), 3.49 (d, J = 6.6 Hz, 2H), 2.60–2.56 (comp m, 4H), 2.00 (septuplet, J = 6.6 Hz, 1H), 1.88–1.77 (comp m, 4H), 0.96 (d, J = 6.8 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 202.5, 176.6, 106.0, 75.0, 41.9, 33.1, 27.9, 23.7, 21.5, 19.3; IR (Neat Film NaCl) 2958, 2872, 1646, 1607, 1469, 1237, 1190, 1174 cm⁻¹; HRMS (EI+) m/z calc'd for C₁₁H₁₈O₂ [M]+: 182.1307; found 182.1310.
Vinylogous β-ketoester (±)-181. To a solution of i-Pr₂NH (3.06 mL, 21.9 mmol, 2.05 equiv) in PhMe (75 mL) cooled to −78 °C was added a solution of n-BuLi (8.36 mL, 21.3 mmol, 2.0 equiv; 2.55 M in hexane) via syringe. The flask was placed in a 0 °C ice bath for 10 min, and then cooled back to −78 °C at which point a solution of 228 (1.9434 g, 10.7 mmol, 1.0 equiv) in PhMe (7 mL) was added dropwise via cannula. The flask was washed with extra PhMe (5 mL) to ensure complete transfer. After 30 min, allyl chloroformate (1.25 mL, 11.7 mmol, 1.1 equiv) was added dropwise and the cooling bath was removed. After 1 h at room temperature the reaction was quenched with 1 N KHSO₄ (25 mL) and the layers were separated. The aq layer was extracted with Et₂O (2 x 40 mL) and the combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated to a viscous yellow oil.

The crude oil was dissolved in MeCN (43 mL, 0.25 M) and to this was added Cs₂CO₃ (4.34 g, 13.3 mmol, 1.25 equiv) and MeI (2.0 mL, 32.0 mmol, 3.0 equiv). The flask was fitted with a reflux condenser and placed in an 80 °C oil bath with vigorous stirring. After 6–8 h the reaction was warmed to room temperature, diluted with EtOAc (50 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO₂ (9:1 → 6:1 → 3:1 hexanes/EtOAc, PhMe load) to give vinylogous β-ketoester (±)-181 (2.4416 g, 8.71 mmol, 81% yield over two steps) as a pale yellow oil. $R_f = 0.43$ (4:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl₃) δ 5.86
(ddddd, $J = 17.1, 10.7, 5.6, 5.6$ Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, $J = 17.1, 2.9, 1.5$ Hz, 1H), 5.20 (app d, $J = 10.5$ Hz, 1H), 4.59 (ddddd, $J = 19.0, 13.2, 5.6, 1.2$ Hz, 2H), 3.50 (dd, $J = 9.3, 6.8$ Hz, 1H), 3.47 (dd, $J = 9.3, 6.6$ Hz, 1H), 2.59 (dd, $J = 17.8, 9.8, 3.9$ Hz, 1H), 2.45–2.38 (comp m, 2H), 2.02–1.94 (m, 1H), 1.84–1.75 (m, 1H), 1.70 (ddd, $J = 14.4, 7.3, 4.4$ Hz, 1H), 1.43 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm$^{-1}$; HRMS (El+) $m/z$ calc’d for C$_{16}$H$_{24}$O$_4$ [M]$^+$: 280.1675; found 280.1686.

Alternative procedure using allyl cyanoformate. To a solution of $i$-Pr$_2$NH (4.66 g, 6.46 mL, 46.1 mmol, 1.2 equiv) in THF (180 mL) cooled to 0 °C in a 500 mL round-bottom flask was added n-BuLi (17.2 mL, 44.2 mmol, 2.57 M in hexanes, 1.15 equiv) dropwise over 15 min by use of syringe pump. After 15 min stirring at 0 °C, the mixture was cooled to −78 °C and a solution of vinylogous ester 228 (7.01 g, 38.4 mmol, 1.0 equiv) dissolved in THF (20 mL) and added in a dropwise manner over 20 min by use of a syringe pump. After an additional 1 h of stirring at −78 °C, allyl cyanoformate (4.69 g, 4.60 mL, 42.2 mmol, 1.1 equiv) was added in a dropwise manner over 10 min. The mixture was stirred at −78 °C for 2.5 h and quenched with 50% sat. aq NH$_4$Cl (60 mL) and allowed to warm to ambient temperature. The reaction mixture was diluted with Et$_2$O (100 mL) and the phases were separated. The aq phase was extracted with Et$_2$O (2 x 100 mL) and the combined organic phases were dried over MgSO$_4$, filtered and concentrated under reduced pressure to afford a pale orange oil (10.5 g, >100%, some allyl cyanoformate left).
The crude oil was converted to vinylogous $\beta$-ketoester 181 as above using CH$_3$CN (130 mL, 0.3 M), MeI (16.35 g, 7.2 mL, 115 mmol, 3.0 equiv), and Cs$_2$CO$_3$ (16.76 g, 49.9 mmol, 1.3 equiv). Purification by flash chromatography on SiO$_2$ (19:1 $\rightarrow$ 9:1, hexanes/EtOAc, dry-loaded using Celite) afforded vinylogous $\beta$-ketoester (±)-181 (8.51 g, 30.4 mmol, 79% yield over two steps) as a pale yellow oil.

**Screen for ketone (→)-229.** To a dry flask was added Pd$_2$(pmdba)$_3$ (2.5 mol %) and ligand (6.25 mol %) and the contents were evacuated/purged 3x with N$_2$. To this was added solvent (0.1 M, most of it) and the contents were stirred for 30 min in a 30 °C oil bath, at which point a solution of (±)-181 (1.0 equiv) in remaining solvent was transferred via cannula. When judged complete by TLC analysis, the reaction was filtered through a small plug of SiO$_2$ eluting with Et$_2$O and concentrated in vacuo. Purification by flash chromatography (15:1 $\rightarrow$ 9:1 hexanes/EtOAc) or preparative TLC (4:1 hexanes/EtOAc) provided ketone 229 for analytical analysis. $R_f$ = 0.31 (3:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.72 (dddd, $J$ = 16.6, 10.5, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.05–5.00 (m, 2H), 3.50 (dd, $J$ = 9.3, 6.6 Hz, 1H), 3.47 (dd, $J$ = 9.3, 6.6 Hz, 1H), 2.53–2.42 (m, 2H), 2.38 (dd, $J$ = 13.7, 7.1 Hz, 1H), 2.20 (dd, $J$ = 13.7, 7.8 Hz, 1H), 1.98 (app septuplet, $J$ = 6.6 Hz, 1H), 1.86–1.70 (comp m, 3H), 1.62–1.56 (m, 1H), 1.14 (s, 3H), 0.95 (app d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; IR (Neat Film NaCl) 2960, 2933, 2873,
1614, 1470, 1387, 1192, 1171, 998, 912 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc'd for \(\text{C}_{15}\text{H}_{24}\text{O}_{2}\) [M]\(^+\): 236.1776; found 236.1767. HPLC conditions: 1% i-PrOH in hexanes, OD-H column, \(t_R\) (min): major = 6.3, minor = 7.3.

**Scale-up of ketone \((-\rightharpoonup)-229\).** \(\text{Pd}_2(\text{pmdba})_3\) (496 mg, 0.453 mmol, 0.0125 equiv) and ligand \((S)-55\) (439 mg, 1.13 mmol, 0.0312 equiv) were placed in a 500 mL round-bottom flask and the flask was evacuated and backfilled with \(\text{N}_2\) (3 cycles with 10 min evacuation per cycle). Toluene (150 mL, sparged with \(\text{N}_2\) for 1 h immediately prior to use) was added and the dark purple suspension was immersed into a 30 °C oil bath. After 30 min stirring the solution had changed to a dark orange color and vinylogous \(\beta\)-ketoester \((\pm)-181\) (10.16 g, 36.24 mmol, 1.0 equiv) dissolved in toluene (31 mL sparged with \(\text{N}_2\) immediately before use) was added via positive pressure cannulation. Upon addition of \((\pm)-181\), the dark orange catalyst solution immediately turned olive green. The reaction mixture was stirred at 30 °C for 21 h (consumption by TLC), allowed to cool to ambient temperature, filtered through a small plug of \(\text{SiO}_2\) (5.5 x 2 cm, \(\text{Et}_2\text{O}\) eluent) and concentrated under reduced pressure. Purification by flash chromatography on \(\text{SiO}_2\) (5 x 15 cm, 19:1 hexanes/EtOAc, dry-loaded on \(\text{SiO}_2\)) afforded ketone \((-\rightharpoonup)-229\) (8.38 g, 35.46 mmol, 98% yield) as a pale yellow oil. \([\alpha]_D^{25.6} -69.04^\circ\) (\(c\ 1.08, \text{CHCl}_3, 88\%\ ee\)).
Reduction of ketone (−)-229. To a flask charged with Et₂O (15 mL) cooled to 0 °C was added LiAlH₄ (71.2 mg, 1.88 mmol, 0.55 equiv) in one portion. After 10 min, a solution of ketone 229 (806.1 mg, 3.41 mmol, 1.0 equiv) in Et₂O (2 mL) was added via cannula, washing the transfer flask with excess Et₂O to ensure quantitative transfer. After consumption of 229 by TLC analysis (1 h), the reaction was quenched by slow addition of 10% HCl (10 mL). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8–15 h. The layers were separated and the aq phase was extracted with Et₂O (3 x 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 5 mL) and purified by flash chromatography on SiO₂ (9:1 → 3:1 hexanes/EtOAc) to afford β-hydroxyketone 231 (558.8 mg, 3.07 mmol, 90% yield) as a colorless oil that forms a semisolid in a −20 °C freezer and cycloheptenone 180 (40.8 mg, 0.248 mmol, 7% yield) as a colorless oil.

β-Hydroxyketone 231. \( R_f = 0.23 \) (7:3 hexanes/EtOAc); \(^1\text{H} \) NMR (500 MHz, CDCl₃) \( \delta \) major diastereomer: 5.88 (dddd, \( J = 15.1, 9.0, 7.6, 7.6 \) Hz, 1H), 5.12–5.08 (m, 2H), 3.70 (dd, \( J = 4.9, 3.9 \) Hz, 1H), 2.86 (dd, \( J = 15.6, 1.7 \) Hz, 1H), 2.65 (dd, \( J = 15.6, 7.3 \) Hz, 1H), 2.54–2.43 (m, 2H), 2.24 (dd, \( J = 13.7, 7.8 \) Hz, 1H), 2.07 (dd, \( J = 13.4, 7.3 \) Hz, 1H), 1.99 (dd, \( J = 15.9, 4.4 \) Hz, 1H), 1.82–1.69 (comp m, 2H), 1.45–1.41 (m, 1H), 0.96 (s, 3H); minor diastereomer: 5.83 (dddd, \( J = 14.9, 10.3, 7.6, 7.6 \) Hz, 1H), 5.12–5.06 (m, 2H), 3.68 (dd, \( J = 4.1, 2.4 \) Hz, 1H) 2.80 (dd, \( J = 15.4, 2.4 \) Hz, 1H), 2.74 (dd, \( J =
15.4, 8.1 Hz (1H), 2.46–2.38 (m, 2H), 2.18 (dd, \( J = 13.9, 7.3 \) Hz, 1H), 2.09 (dd, \( J = 12.9, 7.8 \) Hz, 1H), 1.82–1.65 (comp m, 3H) 1.50–1.47 (m, 1H), 1.02 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) major diastereomer: 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; minor diastereomer: 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7 one peak overlapping; IR (Neat Film NaCl) 3436 (br), 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1246, 1168, 1106, 1069, 999, 913, 840 \( \text{cm}^{-1} \); HRMS (EI+) \( m/z \) calc'd for C\(_{11}\)H\(_{18}\)O\(_2\) [M]\(^+\): 182.1307; found 182.1313; \([\alpha]_D^{22.8} -57.1^\circ \) (c 2.56, CHCl\(_3\), 1.5:1 dr and 88% ee).

**Cycloheptenone 180.** \( R_f = 0.54 \) (7:3 hexanes/EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.04 (dd, \( J = 12.9, 0.7 \) Hz, 1H), 5.82 (d, \( J = 12.9 \) Hz, 1H), 5.75 (dddd, \( J = 17.1, 10.3, 7.8, 7.1 \) Hz, 1H), 5.10 (ddddd, \( J = 10.3, 1.2, 1.2, 1.2 \) Hz, 1H), 5.08–5.03 (m, 1H), 2.65–2.52 (m, 2H), 2.19 (app dd, \( J = 13.7, 6.8 \) Hz, 1H), 2.11 (app dd, \( J = 13.7, 8.1 \) Hz, 1H), 1.84–1.76 (m, 3H), 1.68–1.63 (m, 1H), 1.10 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 204.7, 152.5, 133.8, 128.6. 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772 \( \text{cm}^{-1} \); HRMS (EI+) \( m/z \) calc'd for C\(_{11}\)H\(_{16}\)O [M]\(^+\): 164.1201; found 164.1209; \([\alpha]_D^{21.0} -9.55^\circ \) (c 1.07, CHCl\(_3\), 88% ee).

**Ring contraction screen to produce acyclocypentene 225.** A benzene solution of \( \beta \)-hydroxyketone 231 was transferred to a dry 1-dram vial and concentrated in vacuo to
obtain a starting mass. To this vial was added a stir bar, 1,4-diisopropylbenzene (by mass, as internal standard), and the contents were solvated in either t-BuOH or THF (0.1 M). After complete solvation, an appropriate additive (t-BuOH, TFE, or HFIP; 1.5 equiv) followed by a base (1.5 equiv) were added, the head space of the vial was purged with nitrogen, and the vial was capped with a teflon-lined cap and placed on the appropriate heating block (40 or 60 °C). Reaction progress was initially followed by TLC analysis, and when necessary aliquots were removed and flushed through a small SiO$_2$ plug with EtOAc for GC analysis. GC conditions: 90 °C isothermal for 5 min, then ramp 10 °C/min to 250 °C, DB-WAX column, $t_R$ (min): 1,4-diisopropylbenzene = 5.3, acylcyclopentene 225 = 9.3, $\beta$-hydroxyketone 231 = 17.1 and 17.2 (two diastereomers).

![Chemical reaction](image)

**Scale-up of acylcyclopentene 225.** To a solution of $\beta$-hydroxyketone 231 (6.09 g, 33.4 mmol, 1.0 equiv) dissolved in THF (334 mL, 0.1 M) in a 500 mL flask was added 2,2,2-trifluoroethanol (5.04 g, 3.67 mL, 50.1 mmol, 1.5 equiv) and LiOH (1.20 g, 50.1 mmol, 1.5 equiv). The flask was fitted with a reflux condenser, purged with a stream of N$_2$, and placed in a 60 °C oil bath. After 18 h the suspension was allowed to cool to ambient temperature, diluted with Et$_2$O (150 mL), dried over Na$_2$SO$_4$ (30 min stirring), filtered, and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The crude product was purified by flash chromatography on SiO$_2$ (5 x 15 cm, 15:1 hexanes/Et$_2$O) and concentrated carefully to afford
acylcyclopentene 225 (5.29 g, 32.2 mmol, 96% yield) as a colorless fragrant oil. $R_f = 0.67$ (4:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.45 (app t, $J = 1.7$ Hz, 1H), 5.76 (dddd, $J = 16.4, 10.7, 7.3, 7.3$ Hz, 1H), 5.07–5.03 (comp m, 2H), 2.59–2.48 (comp m, 2H), 2.21–2.14 (comp m, 2H), 2.30 (s, 3H), 1.85 (ddd, $J = 12.9, 8.3, 6.3$ Hz, 1H), 1.64 (ddd, $J = 6.1, 8.5, 12.9$ Hz), 1.11 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993, 914, 862 cm$^{-1}$; HRMS (EI+) $m/z$ calc'd for C$_{11}$H$_{16}$O [M]$: 164.1201$; found 164.1216; $[\alpha]_D^{21.4}$ $+$17.3° ($c$ 0.955, CHCl$_3$, 88% ee). GC conditions: 80 °C isothermal, GTA column, $t_R$ (min): major = 54.7, minor = 60.2.

**Semicarbazone 232.** A 15 mL round-bottom flask was charged with sodium acetate (150 mg, 1.83 mmol, 1.2 equiv), and semicarbazide hydrochloride (204 mg, 1.83 mmol, 1.2 equiv). The solids were dissolved in purified water (1.7 mL). Acylcyclopentene 225 (250 mg, 1.52 mmol, 1.0 equiv) was added neat and the mixture was heated to 60 °C for 4 h. The slurry was allowed to cool to ambient temperature while stirring and vacuum filtered (water aspirator). The white solid was dried under reduced pressure to afford semicarbazone 232 (311 mg, 1.41 mmol, 92% yield). The ee of 232 at this point was found to be 91% (measured by hydrolysis to acylcyclopentene 225). Semicarbazone 232
(300 mg, 1.36 mmol) was transferred to a round-bottom flask, the solids were suspended in toluene/hexanes (1:1), and the mixture was heated to 90 °C with stirring. After a few minutes stirring, the solids had dissolved completely to afford a clear, colorless solution. Heating was discontinued and the stirring mixture was allowed to cool to 23 °C while still immersed in the oil bath. After 10 h had elapsed, the slurry was vacuum filtered to afford 232 (246 mg, 1.11 mmol, 82% yield). The ee at this point was found to be 94.5% (measured by hydrolysis to 225 and chiral GC analysis). A second recrystallization following the above procedure (241 mg, 1.09 mmol) afforded 232 (201 mg, 0.908 mmol, 83% yield). The ee at this point was found to be 97.9% (measured by hydrolysis to 225). $R_f = 0.30$ (9:1 CHCl₃/MeOH); mp = 145–146 °C (1:1 toluene/hexanes); $^1$H NMR (300 MHz, CDCl₃) δ 8.52 (br s, 1H), 6.06 (br s, 1H), 5.85 (app t, $J = 1.6$ Hz, 1H), 5.76 (dddd, $J = 16.7, 9.3, 7.4, 7.4$ Hz, 1H), 5.47 (br s, 1H), 5.06–4.98 (comp m, 2H), 2.67–2.49 (m, 2H), 2.15–2.12 (m, 2H), 1.98 (s, 3H), 1.82 (ddd, $J = 12.8, 8.2, 6.9$ Hz, 1H), 1.62 (ddd, $J = 12.8, 8.5, 6.4$ Hz, 1H), 1.07 (s, 3H); $^{13}$C NMR (75 MHz, CDCl₃) δ 158.1, 145.0, 141.7, 141.2, 135.6, 117.2, 49.2, 45.9, 36.2, 30.8, 26.3, 12.8; IR (Neat Film NaCl) 3473, 3266, 3189, 2946, 2858, 1698, 1579, 1478, 1437, 1377, 1349, 1321, 1130, 1109, 993, 910, 845, 768 cm⁻¹; HRMS (TOF MS ES+) $m/z$ calc'd for $C_{12}H_{20}N_3O [M + H]^+$: 222.1606; found: 222.1610; $[\alpha]_D^{21.5} +39.8^\circ$ (c 0.84, CHCl₃, 97.9% ee).
Hydrolysis to acyclclopentene 225. Semicarbazone 232 (191.8 mg, 0.867 mmol) was dissolved in THF (1.92 mL) and aq HCl (3.84 mL, 6 M) was added. The resulting biphasic mixture was stirred vigorously at 23 °C for 30 h. The reaction mixture was diluted with Et₂O (10 mL), the phases were separated, and the aqueous phase was extracted with Et₂O (2 x 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated carefully under vacuum allowing for a film of ice to form on the outside of the flask. The residue was filtered through a short pad of SiO₂ (4:1 hexanes/Et₂O) to afford 225 (132.6 mg, 0.81 mmol, 93% yield); [α]D²¹⁺19.6° (c 1.035, CHCl₃, 97.9% ee).

Iodoarene 233. To a solution of semicarbazone 232 (50 mg, 0.23 mmol, 91% ee, 1.0 equiv) in m-xylene (2.2 mL) was added 4-iodobenzylamine (63 mg, 0.27 mmol, 1.2 equiv). The resulting pale yellow solution was immersed in a 150 °C oil bath. After 9 h, the mixture was allowed to cool to ambient temperature and concentrated under reduced pressure to afford a pale yellow solid. The crude solid was purified by flash chromatography on SiO₂ (9:1 → 7:3 hexanes/EtOAc) to afford iodoarene 233 (88 mg, 0.20 mmol, 89% yield) as a white solid. X-ray-quality crystals were obtained by slow vapor diffusion of pentane into a chloroform solution of 233. Rf = 0.52 (9:1 CHCl₃/MeOH); mp = 123–124°C (CHCl₃/n-pentane); ¹H NMR (500 MHz, CDCl₃) δ 7.88
(s, 1H), 7.66–7.64 (m, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.50 (t, J = 6.1 Hz, 1H), 5.86 (app t, J = 1.5 Hz, 1H), (dddd, J = 16.9, 9.0, 7.6, 7.6 Hz, 1H), 5.04–5.01 (comp m, 2H), 4.46 (d, J = 6.3 Hz, 2H), 2.60–2.49 (comp m, 2H), 2.18–2.10 (comp m, 2H); 1.95 (s, 3H), 1.82 (ddd, J = 12.9, 8.5, 6.3 Hz, 1H), 1.62 (ddd, J = 12.9, 8.5, 6.1 Hz, 1H), 1.07 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 156.3, 144.5, 141.5, 141.4, 139.2, 137.8, 135.6, 129.4, 117.2, 92.6, 49.3, 45.9, 43.2, 36.2, 30.9, 26.3, 12.5; IR (Neat Film NaCl) 3411, 3194, 3075, 2946, 2920, 2863, 1677, 1528, 1486, 1401, 1323, 1259, 1142, 1114, 1057, 1000, 913, 845 cm\(^{-1}\); HRMS (FAB+) m/z calc'd for C\(_{19}\)H\(_{25}\)N\(_3\)O\(_I\) [M + H]\(^{+}\): 438.1043; found 438.1036; \([\alpha]\)\(_D\)\(^{22.2}\) +31.4° (c 0.385, CHCl\(_3\), 91% ee).

Acetal 235. To a solution of acyclocyclopentene 225 (5.29 g, 32.2 mmol, 1.0 equiv) in toluene (322 mL) in a 1 L round-bottom flask was added neopentyl glycol (234) (20.1 g, 193.2 mmol, 6.0 equiv) and PPTS (809 mg, 3.22 mmol, 0.1 equiv). The flask was fitted with a Dean–Stark trap and a condenser and the mixture was placed in a 135 °C oil bath and heated to reflux. After 25 h the mixture was allowed to cool to ambient temperature, diluted with Et\(_2\)O (250 mL), and poured into sat. aq NaHCO\(_3\) (100 mL). The aq phase was extracted with Et\(_2\)O (2 x 100 mL) and the combined organic phases were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to afford a white semisolid. The crude product was purified by flash chromatography on SiO\(_2\) (1:0 \(\rightarrow\) 99:1 \(\rightarrow\) 98:2 hexanes/EtOAc) to afford acetal 235 (6.59 g, 26.3 mmol, 82% yield) as a pale yellow oil.
$R_f = 0.62$ (7:3 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.80 (dddd, $J = 16.7$, 9.3, 7.4, 7.4 Hz, 1H), 5.52 (app t, $J = 1.8$ Hz, 1H), 5.06–4.99 (comp m, 2H), 3.59 (dd, $J = 11.2$, 0.8 Hz, 1H), 3.51 (dd, $J = 11.2$, 0.8 Hz, 1H), 3.31 (d, $J = 11.2$ Hz, 2H), 2.37–2.19 (m, 2H), 2.13 (app dt, $J = 7.4$, 1.1 Hz, 2H), 1.853 (ddd, $J = 12.8$, 8.8, 6.1 Hz, 1H), 1.41 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.69 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.1, 138.2, 136.1, 116.9, 98.8, 71.8, 71.7, 49.0, 46.2, 36.4, 31.4, 29.8, 27.8, 26.9, 22.8, 22.2; IR (Neat Film NaCl) 3075, 2952, 2906, 2868, 1640, 1472, 1455, 1182, 1118, 1041, 996, 950, 911, 862 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{16}$H$_{27}$O$_2$ [M + H]$^+$: 251.2011; found 251.2011; $[\alpha]_D^{20.9}$ +11.5° (c 1.01, CHCl$_3$, 88% ee).

**Dioxolane 256.** To a solution of 225 (388.1 mg, 2.36 mmol, 1.0 equiv) in benzene (11.8 mL) in a 25 mL round-bottom flask was added ethylene glycol (255) (880 mg, 791 µL, 14.2 mmol, 6.0 equiv) and PPTS (59.4 mg, 0.24 mmol, 0.1 equiv). The flask was fitted with a condenser and a Dean–Stark trap and immersed into a 115 ºC oil bath and heated to reflux. After 18 h at reflux, the mixture was allowed to cool to ambient temperature, diluted with Et$_2$O (50 mL), and washed with brine (10 mL). The aq phase was extracted with Et$_2$O (2 x 10 mL) and the combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a colorless oil. The crude product was purified by flash chromatography on SiO$_2$ (15:1 $\rightarrow$ 9:1 hexanes/EtOAc) to afford dioxolane 256 (381.4 mg, 1.83 mmol, 78% yield) as a colorless
oil.  \( R_f = 0.49 \) (7:3 hexanes/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 5.76 (dddd, \( J = 17.1, 9.3, 7.6, 7.6 \) Hz, 1H), 5.50, (br s, 1H), 5.02–4.99 (comp m, 4H), 3.98–3.84 (comp m, 2H), 2.36 (ddddd, \( J = 10.3, 8.1, 5.9, 1.7 \) Hz, 1H), 2.30 (ddddd, \( J = 10.3, 8.1, 6.1, 1.7 \) Hz, 1H), 2.09 (d, \( J = 7.3 \) Hz, 2H), 1.82 (ddd, \( J = 12.9, 8.5, 6.1 \) Hz, 1H), 1.62 (ddd, \( J = 12.7, 8.8, 5.9 \) Hz, 1H), 1.48–1.47 (m, 3H), 1.03 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 142.9, 136.0, 135.7, 116.8, 107.4, 64.7, 64.7 (two lines), 48.4, 46.1, 36.8, 30.6, 26.5, 24.0; IR (Neat Film NaCl) 2951, 2888, 1454, 1372, 1192, 1108, 1043, 996, 946, 912, 858 \text{ cm}^{-1}; HRMS (El+) \( m/z \) calc'd for C\(_{12}\)H\(_{17}\)O\(_2\) [M – CH\(_3\)]\(^+\): 193.1229; found 193.1232.

**Alcohol 236.** To a solution of acetal 235 (1.51 g, 6.03 mmol, 1.0 equiv) in 1,4-dioxane (45 mL) and purified H\(_2\)O (15 mL) was added 2,6-lutidine (1.29 g, 1.40 mL, 12.0 mmol, 2.0 equiv). The mixture was cooled to 0 °C and NaIO\(_4\) (5.13 g, 24.0 mmol, 4.0 equiv) was added followed by OsO\(_4\) (30.5 mg, 0.120 mmol, 0.02 equiv). The resulting suspension was stirred for 4.5 h at 0 °C and then vacuum filtered, rinsing with EtOAc (100 mL). The aq phase was separated and extracted with EtOAc (2 x 25 mL), the combined organic phases were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to afford the desired product 1.82 g (>100%, contains some 2,6-lutididine) as a clear brown oil. This material was used in the subsequent step without purification.
The crude product was dissolved in EtOH (7.5 mL) and cooled to –21 °C by use of a MeOH/ice bath. A solution of NaBH₄ (227.0 mg, 6.00 mmol, 1.0 equiv) dissolved in EtOH (7.5 mL) and precooled to 0 °C was added dropwise over 25 min to the reaction mixture via positive pressure cannulation. After an additional 1 h stirring at –21 °C, the reaction was quenched by slow addition of H₂O (4.5 mL). The reaction mixture was allowed to warm to 0 °C, concentrated under reduced pressure to ca. 10 mL and extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford a pale brown oil. The crude material was purified by flash chromatography on SiO₂ (19:1 → 9:1 → 4:1 hexanes/EtOAc) to afford alcohol 236 (1.18 g, 4.64 mmol, 77% yield over two steps) as a pale yellow oil. R₉ = 0.38 (7:3 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.57 (app t, J = 1.7 Hz, 1H), 3.71 (ddd, J = 7.3, 7.3, 5.4 Hz, 2H), 3.52 (app t, J = 11.0 Hz, 2H), 3.34 (11.0 Hz, 2H), 2.38–2.26 (comp m, 2H), 1.88 (ddd, J = 12.9, 8.5, 6.1 Hz, 1H), 1.71 (t, J = 7.3 Hz, 2H), 1.69 (ddd, J = 12.9, 8.5, 5.9 Hz, 1H), 1.42 (s, 3H), 1.21 (t, J = 5.1 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 0.71 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 141.1, 138.1, 98.6, 71.7, 60.2, 47.5, 44.1, 36.9, 31.1, 29.7, 27.4, 27.1, 22.7, 22.2; IR (Neat Film NaCl) 3428 (br), 3041, 2951, 2868, 1472, 1456, 1396, 1370, 1353, 1321, 1259, 1242, 1181, 1117, 1082, 1040, 1015, 950, 911, 862, 809, 793 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₅H₂₇O₃ [M + H]⁺: 255.1960; found 255.1951; [α]D¹⁹.⁹ –3.25° (c 0.99, CHCl₃, 88% ee).
**Iodide 237.** A 25 mL flask was charged with PPh$_3$ (881.3 mg, 3.36 mmol, 1.5 equiv) and imidazole (457.5 mg, 6.72 mmol, 3.0 equiv) and the flask was evacuated and backfilled with Ar (3x). The solids were dissolved in CH$_2$Cl$_2$ (8.0 mL, typically solvated within 10 min). The flask was wrapped in aluminum foil and I$_2$ (869.6 mg, 3.36 mmol, 1.5 equiv) was added. After 10 min, the mixture was cooled to 0 °C and a solution of alcohol 236 (571.2 mg, 2.24 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (3.0 mL) was added via syringe. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to 23 °C. After an additional 3 h stirring, hexanes (11 mL) was added and the resulting slurry was filtered through a plug of Celite (5 x 1 cm) eluting with hexanes/Et$_2$O (1:1, 100 mL). The filtrate was concentrated under reduced pressure, resuspended in hexanes (50 mL), filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on SiO$_2$ (1:0 → 99:1 → 98:2 → 90:10 hexanes/Et$_2$O, dry-loaded on Celite) to afford iodide 237 (753 mg, 2.07 mmol, 92% yield) as a colorless oil. $R_f = 0.71$ (7:3 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.51 (s, 1H), 3.50 (app t, 11.5 Hz, 2H), 3.34 (d, $J = 11.2$ Hz, 2H), 3.19–3.06 (comp m, 2H), 2.38–2.25 (comp m, 2H), 2.12–2.02 (comp m, 2H), 1.84 (ddd, $J = 13.2$, 8.8, 5.9 Hz, 1H), 1.67 (ddd, $J = 13.2$, 8.8, 5.6 Hz, 1H), 1.41 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.71 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 142.5, 136.6, 98.6, 71.9, 71.9 (two lines), 51.2, 46.8, 36.1, 31.4, 29.8, 27.5, 26.4, 22.8, 22.3, 1.1; IR (Neat Film NaCl) 3039, 2956, 2863, 1470, 1450, 1390, 1365, 1315, 1254,
1173, 1119, 1083, 1039, 1011, 944, 915, 866, 814 cm\(^{-1}\); HRMS (FAB+) \(m/z\) calc’d for \(\text{C}_{15}\text{H}_{26}\text{O}_{2} [M + H]^+\): 365.0978; found 365.0980; \([\alpha]_{D}^{20.3} +31.2^\circ\) (c 1.03, CHCl\(_3\), 88% ee).

### 3.7.2.5 MODEL FRAGMENT COUPLING AND C-RING ANNULATION

**2-Methyl cyclooctenone (238).** A 500 mL round-bottom flask was charged with NaI (18.74 g, 125 mmol, 1.25 equiv), MeCN (140 mL) was added, and the system was evacuated and backfilled with Ar. Cycloheptanone (257) (11.2 g, 11.8 mL, 100 mmol, 1.0 equiv) was added followed by Et\(_3\)N (16.7 g, 17.4 mL, 125 mmol, 1.25 equiv) and dropwise addition of TMSCl (12.4 g, 14.6 mL, 114 mmol, 1.14 equiv). The resulting suspension was stirred at 23 °C for 30 min and then petroleum ether (100 mL) was added. The biphasic system was stirred vigorously for 10 min, the petroleum ether layer was decanted, and the MeCN layer was extracted with petroleum ether (3 x 50 mL). The combined petroleum ether layers were washed with H\(_2\)O (2 x 50 mL), brine (50 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude oil was purified by short path distillation (8.7 torr, bp = 75–81°C) to afford the desired silyl enol ether (18.4 g, 99.8 mmol, 99.8% yield) as a colorless oil.

A solution of the above silyl enol ether (8.20 g, 44.5 mmol) in Et\(_2\)O (22.8 mL) and 1,1-dichloroethane (17.8 g, 15.1 mL, 180 mmol, 4.0 equiv) in a 250 mL round-bottom flask was cooled to –40 °C by use of a MeCN/CO\(_2\)\((s)\) bath. To this was added \(n\)-BuLi
(58.7 mL, 135 mmol, 2.3 M in hexanes, 3.0 equiv) in a dropwise manner over 3 h by use of a syringe pump. The resulting mixture was stirred for an additional 1 h at -40 °C, at which time the reaction was warmed to 0 °C for 2 h, quenched with H₂O (20 mL) and allowed to warm to ambient temperature. The phases were separated and the organic phase was washed with H₂O (4 x 20 mL) until the aqueous phase showed neutral pH. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the desired cyclopropane (11.1 g, 45.0 mmol, quantitative) as a clear, pale yellow oil. This material was used in the following reaction without further purification.

To a solution of the above cyclopropane (11.1 g, 45.0 mmol, 1.0 equiv) in MeOH (136 mL) was added Et₃N (41.0 g, 56 mL, 405 mmol, 9.0 equiv). The flask was fitted with a condenser and the mixture was immersed into a 85 °C oil bath and heated to reflux. After 65 h, the mixture was allowed to cool to ambient temperature and concentrated carefully under reduced pressure (the compound is somewhat volatile). The residue was suspended in pentane (50 mL), filtered, and concentrated under reduced pressure. The final traces of Et₃N were removed by dissolving the residue in Et₂O (100 mL) and washing with KHSO₄ (20 mL, 1.0 M). The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on SiO₂ (1:0 → 19:1 hexanes/Et₂O) to 2-methyl cyclooctenone (239) (4.21 g, 30.5 mmol, 68% yield over three steps) as a colorless oil. 

\[ R_f = 0.43 \text{ (4:1 hexanes/Et}_2\text{O)}; \] 

\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{)} \delta 6.09 \text{ (app tq, } J = 6.9, 1.5 \text{ Hz, 1H), 2.65–2.61 (comp m, 2H), 2.42–2.35 (comp m, 2H), 1.86–1.77 (comp m, 3H), 1.84 (q, } J = 1.4 \text{ Hz, 2H), 1.64–1.49 (comp m, 4H); } ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 208.9, \]
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137.5, 135.0, 42.9, 28.6, 25.9, 23.3, 22.8, 21.1; IR (Neat Film NaCl) 2928, 1685, 1654, 1452, 1377, 1099, 850 cm⁻¹; HRMS (MM: ESI/APCI) m/z calc’d for C₉H₁₅O [M + H]⁺: 139.1117, found 139.1114.

**Ketone 239.** Ammonia (ca. 5 mL) was condensed into a 2-neck round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar at −78 °C, and to this was added lithium wire (9.3 mg, 1.3 mmol, 3.0 equiv). The solution turned dark blue. The mixture was stirred for 20 min, at which point a solution of 2-methyl cyclooctenone (238, 60.2 mg, 0.436 mmol, 1.0 equiv) in a 0.21 M H₂O solution in Et₂O (2 mL, prepared by dissolving H₂O (94 µL) in Et₂O (25 mL) in a flame-dried round-bottom flask under argon) was added via cannula transfer. The vial was further washed and transferred with a portion of anhydrous Et₂O (1 mL). The bright blue color remained after addition and the solution was stirred for 10 min, at which point a solution of iodide (±)-237 (324 mg, 0.980 mmol, 2.0 equiv) in Et₂O (2 mL) was added dropwise via cannula. During the addition of iodide (±)-237, the color of the solution changed from blue to colorless and stirring was continued in the acetone/CO₂(s) bath. After 2 h, the cooling bath was replaced with a MeCN/CO₂(s) cooling bath held between −45 and −35 °C. The mixture was stirred for an additional 2 h, at which point solid NH₄Cl (523 mg) was added, the cooling bath was removed, and the reaction was allowed to reach room temperature. After most of the ammonia had evaporated, the reaction was diluted with H₂O (10 mL)
and Et₂O (25 mL). The aqueous layer was extracted with Et₂O (5 x 15 mL) and the combined organics were washed with brine (10 mL), dried with MgSO₄, filtered, and concentrated. The crude residue was purified by flash chromatography on SiO₂ (95:5 hexanes/EtOAc) to afford desired ketone 239 (122.9 mg, 0.326 mmol, 75% yield) as a 1:1.2 mixture of diastereomers. \( R_f = 0.70 \) (3:7 hexanes/Et₂O); \(^1\)H NMR (500 MHz, C₆D₆) δ major diastereomer: 5.58 (app t, \( J = 1.7 \) Hz, 1H), 3.55 (d, \( J = 11.0 \) Hz, 1H), 3.48 (d, \( J = 11.0 \) Hz, 1H), 3.31 (d, \( J = 11.0 \) Hz, 2H), 2.40–2.36 (comp m, 3H), 2.03 (ddd, \( J = 10.7, 7.1, 3.4 \) Hz, 1H), 1.81–1.69 (comp m, 3H), 1.62 (s, 3H), 1.60–1.50 (comp m, 3H), 1.42–1.22 (comp m, 8H), 1.19 (s, 3H), 1.18–1.10 (comp m, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.53 (s, 3H); minor diastereomer: 5.56 (app t, \( J = 1.7 \) Hz, 1H), 3.52 (d, \( J = 11.0 \) Hz, 1H), 3.48 (d, \( J = 10.7 \) Hz, 1H), 3.30 (d, \( J = 11.0 \) Hz, 2H), 2.40–2.36 (comp m, 3H), 2.02 (ddd, \( J = 10.7, 7.1, 3.4 \) Hz, 1H), 1.81–1.69 (comp m, 3H), 1.62 (s, 3H), 1.62 (s, 3H), 1.60–1.50 (comp m, 3H), 1.42–1.22 (comp m, 8H), 1.19 (s, 3H), 1.18–1.10 (comp m, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.52 (s, 3H); \(^{13}\)C NMR (126 MHz, C₆D₆) δ mixture of two diastereomers: 218.1 (two lines), 142.4 (two lines), 137.9, 137.8, 98.9 (two lines), 71.9, 71.8 (three lines), 49.8 (two lines), 48.7 (two lines), 36.9, 36.8, 36.5 (two lines), 35.9, 35.8, 34.6, 34.5, 34.2, 34.1, 31.9 (two lines), 30.4 (two lines), 29.7, 28.1, 28.0, 27.2, 27.1, 26.2, (two lines), 25.3 (two lines), 24.5, 22.9, 22.2, 22.1, 19.2, 19.1; IR (Neat Film NaCl) 2932, 2858, 1698, 1469, 1448, 1396, 1368, 1254, 1239, 1180, 1117, 1083, 1040, 950, 911, 863, 810, 793 cm⁻¹; HRMS (FAB+) \( m/z \) calc’d for C₂₃H₄₁O₃ [M + H]^+: 377.3056; found 377.3043.
Silyl enol ether 240. Enone 238 (100 mg, 0.724 mmol, 1.0 equiv) was placed in a 1-dram vial, evacuated and backfilled with N₂ (3x), and solvated in THF (350 µL). A separate flask containing RhH(PPh₃)₄ (20.9 mg, 0.0181 mmol, 0.025 equiv) was evacuated and backfilled with N₂ (3 cycles with 5 min evacuation per cycle) and then THF (1.1 mL) was added. A separate vial containing an excess of PhMe₂SiH was degassed by evacuation/backfilling with N₂ (3x). The required amount of PhMe₂SiH (631 mg, 720 µL, 4.63 mmol, 6.4 equiv) was added to the catalyst suspension via syringe and the resulting clear orange solution was immersed in a 30 °C oil bath. After 10 min, the THF solution of enone 238 was added via positive pressure cannulation. After 25 h the reaction was allowed to cool to ambient temperature, filtered through a plug of SiO₂ (2 x 1 cm, Et₂O) and concentrated under reduced pressure to afford a pale orange oil. The crude material was purified by flash chromatography on SiO₂ (99:1 → 98:2 hexanes/PhH) to afford silyl enol ether 240 (150.2 mg, 0.547 mmol, 76% yield) as a colorless oil. \( R_f = 0.52 \) (hexanes); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta 7.65-7.61 \) (comp m, 2H), 7.42–7.34 (comp m, 3H), 2.18–2.14 (comp m, 2H), 2.06–2.02 (comp m, 2H), 1.59 (s, 3H), 1.55–1.38 (comp m, 8H), 0.44 (s, 6H); \(^1^3\)C NMR (75 MHz, CDCl₃) \( \delta 145.1, 138.7, 133.5, 129.6, 127.9, 113.9, 31.9, 31.6, 29.0, 28.7, 26.8, 26.5, 16.1, –0.4; \) IR (Neat Film NaCl) 3075, 2951, 2863, 1638, 1450, 1393, 1370, 1254, 1241, 1179, 1117, 1080, 1037, 1011, 995, 949, 910, 861, 809 cm⁻¹; HRMS (FAB+) \( m/z \) calc’d for C₁₇H₂₆OSi \([M]^+\): 274.1753; found 274.1752.
Ketone 239. Silyl enol ether 240 (39.7 mg, 0.145 mmol, 1.0 equiv) was placed in a 10 mL round-bottom flask, the flask was evacuated and backfilled with N₂ (3x), solvated in THF (1.45 mL, 0.1 M) and cooled to 0 °C. To this solution was added MeLi (57 µL, 0.152 mmol, 2.66 M in dimethoxymethane, 1.05 equiv) was added dropwise over 5 min. After an additional 1 h stirring at 0 °C, HMPA (260 mg, 252 µL, 1.45 mmol) was added in a dropwise manner over 5 min, at which point the reaction was cooled in a dry ice/acetone bath to −78 °C. The resulting clear solution mixture was stirred for 10 min followed by dropwise addition of Me₂Zn (145 µL, 0.145 mmol, 1.0 M in heptane, 1.0 equiv). After an additional 10 min, a solution of iodide (±)-237 (63.4 mg, 0.0174 mmol) in THF (200 µL) was added dropwise over 2 min. After 1 h at −78 °C, the reaction was allowed to gradually warm to ambient temperature. After a further 21 h at 23 °C, the reaction mixture was diluted with Et₂O and washed with H₂O (10 mL). The aqueous phase was extracted with Et₂O (2 x 10 mL) and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography on SiO₂ (99:1 → 98:2 → 95:5 → 90:10 hexanes/Et₂O) to afford ketone 239 (43.9 mg, 0.117 mmol, 80% yield) as a 1:1.25 mixture of diastereomers.
Ketoalcohol 241. To THF (12.5 mL) cooled to 0 °C was added LiAlH₄ (56.9 mg, 1.50 mmol, 1.2 equiv) followed by dropwise addition of a solution of ketone 239 (472 mg, 1.25 mmol, 1.0 equiv) in THF (4.7 mL). The suspension was stirred at 0 °C for 1.5 h and quenched by slow dropwise addition of 10% HCl (10 mL). The biphasic mixture was stirred at 0 °C for 2 h, allowed to warm to 23 °C and stirred for an additional 30 min. The reaction was diluted with Et₂O (25 mL), the phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on SiO₂ (7:3 hexanes/EtOAc) to afford a mixture of diastereomers of ketoalcohol 241 (296 mg, 1.01 mmol, 81% yield) as a colorless viscous oil. R_f = 0.22 (7:3 Hexanes-Et₂O); ¹H NMR (500 MHz, CDCl₃) δ

**major set of diastereomers:** 6.48 (q, J = 1.7, 2H), 3.69 (app d, J = 7.1 Hz, 1H), 3.68 (app d, J = 7.1 Hz, 1H), 2.56–2.52 (comp m, 4H), 2.30 (s, 6H), 1.95–1.20 (comp m, 36 H), 1.10 (s, 6H), 1.09 (s, 6H); **minor set of diastereomers:** 6.47 (q, J = 2.2 Hz, 2H), 3.76 (app d, J = 8.8 Hz, 2H), 2.56–2.52 (comp m, 4H), 2.30 (s, 6H), 1.95–1.20 (comp m, 36 H), 0.96 (s, 3H), 0.95 (s, 3H), 0.78 (two lines, s, 3H each); ¹³C NMR (126 MHz, CDCl₃) δ

**mixture of four diastereomers:** 197.7 (two lines), 152.9 (two lines), 152.8, 143.4 (two lines), 78.2 (two lines), 77.5, 50.1 (two lines), 50.0 (two lines), 40.3 (two lines), 39.6 (two lines), 36.3, 36.2, 35.3, 35.2, 34.7 (three lines), 34.5 (two lines), 33.6 (two lines), 32.3, 32.3 (three lines), 32.1, 29.7, 29.6, 29.1 (two lines), 28.1 (two lines), 27.9 (two
Imidazoyl thiocarbonate 242. To a solution of ketoalcohol 241 (66.0 mg, 0.226 mmol, 1.0 equiv) in CH₂Cl₂ (4.7 mL) was added DMAP (8.28 mg, 0.068 mmol, 0.3 equiv) and 1,1‘-thiocarbonyldiimidazole (TCDI) (201.4 mg, 1.13 mmol, 5.0 equiv). The resulting yellow solution was stirred at 23 °C. After 29 h, the reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography on SiO₂ (9:1 → 4:1 hexanes/EtOAc) to afford imidazoyl thiocarbonate 242 (89.2 mg, 0.222 mmol, 98% yield) as a viscous colorless oil. Rₜ = 0.19 (7:3 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ major set of diastereomers: 8.32 (s, 1H), 8.30 (s, 1H), 7.60 (s, 2H), 7.03 (s, 2H), 6.37 (s, 1H), 6.34 (s, 1H), 5.65 (app d, J = 8.5 Hz, 2H), 2.63–2.53 (comp m, 2H), 2.53–2.42 (comp m, 2H), 2.23 (s, 3H), 2.21 (s, 3H), 2.09–2.03 (comp m, 2H), 1.84–1.22 (comp m, 34 H), 1.03 (s, 6H), 1.02 (two lines, s, 3H each); minor set of diastereomers: 8.30 (s, 1H), 8.29 (s, 1 H), 7.59 (s, 1H), 7.55 (s, 1H), 7.03 (s, 2H), 6.45 (s, 1H), 6.44 (s, 1H), 5.77 (app d, J = 9.3 Hz, 2H), 2.63–2.53 (comp m, 2H), 2.53–2.42 (comp m, 2H), 2.31 (two lines, s, 3H each), 2.09–2.03 (comp m, 2H), 1.84–1.22 (comp m, 34 H), 1.13 (two lines, s, 3H each), 0.95 (s, 3H), 0.94 (s,
3H), \(^{13}\text{C} \text{NMR} \ (126 \text{ MHz, CDCl}_3) \delta \text{ mixture of four diastereomers:} \ 197.5, 197.4 \\
(\text{two lines}), 184.1, 152.0, 151.9 \ (\text{two lines}), 151.8, 143.8, 143.7, 143.6 \ (\text{two lines}), 136.8, \\
136.7, 130.9 \ (\text{two lines}), 118.0, 117.9, 117.8, 91.7, 91.6, 91.3, 91.2 \ 50.0, 49.9, 49.7 \ (\text{two \\
lines}), 40.2 \ (\text{two lines}), 39.9 \ (\text{two lines}), 36.3, 36.1 \ (\text{two lines}), 36.0, 35.2, 34.8, 34.7, \\
34.6, 34.5, 34.4, 32.5, 32.4, 32.3, 31.3, 30.5 \ (\text{two lines}), 29.9, 29.8, 29.7, 29.6, 28.7, 28.6, \\
27.6, 27.4 \ (\text{two lines}), 26.8 \ (\text{two lines}), 26.7, 26.4, 26.2, 25.7, 25.6, 25.3 \ (\text{two lines}), 25.1 \\
(\text{two lines}), 23.3 \ (\text{two lines}), 22.6 \ (\text{two lines}), 22.1 \ (\text{two lines}), 21.5, 21.4; \ IR \ (\text{Neat Film} \\
\text{NaCl}) \ 3158, 3121, 2930, 2853, 1664, 1618, 1530, 1460, 1383, 1328, 1282, 1228, 1099, \\
1037, 1013, 967, 889, 871, 830, 734 \text{ cm}^{-1}; \ HRMS \ (\text{EI+}) \ m/\zeta \ \text{calc'd for } \text{C}_{23}\text{H}_{34}\text{N}_{2}\text{O}_{2}\text{S } [\text{M}]^+: \\
402.2341; \text{found } 402.2354.

**Ketone 243.** Imidazoyl thiocarbonate 242 (41.2 mg, 0.102 mmol, 1.0 equiv) was placed in a 50 mL round-bottom 2-neck flask fitted with a condenser, solvated in PhH (18.4 mL), and the solution was sparged with N\(_2\) for 1 h. The reaction mixture was immersed into an 85 °C oil bath and heated to reflux. A separate flask was charged with AIBN (4.19 mg, 0.026 mmol, 0.25 equiv), evacuated and backfilled with N\(_2\) (3x), and PhH (2.0 mL, sparged with N\(_2\) for 1 h prior to use) was added followed by \(n\)-Bu\(_3\)SnH (59.4 mg, 54 \(\mu\)L, 0.204 mmol, 2.0 equiv). The solution of AIBN/\(n\)-Bu\(_3\)SnH was added dropwise to substrate 242 over 5 h via syringe pump. The reaction was stirred for an additional 12 h at reflux, allowed to cool to ambient temperature, and concentrated under
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reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography on SiO$_2$ impregnated with AgNO$_3$ (hexanes eluent) to afford a mixture of diastereomers of the desired ketone $243$ (23.4 mg, 0.0846 mmol, 83% yield) as a colorless oil. Samples of sufficient purity for characterization were obtained by flash chromatography (1:0 $\rightarrow$ 99:1 $\rightarrow$ 98:1 hexanes/Et$_2$O) and subsequent preparative TLC on SiO$_2$ (20 x 20 cm, PhMe, developed thrice) of the fractions containing mainly the desired set of diastereomers.

**Major diastereomer.** $R_f = 0.52$ (4:1 hexanes/Et$_2$O); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.27 (ddd, $J = 10.8, 7.3, 7.3$ Hz, 1H), 2.38 (app dt, $J = 7.0, 1.2$ Hz, 1H), 2.27–2.22 (m, 1H), 2.20 (s, 3H), 1.78–1.74 (m, 2H), 1.67–1.10 (comp m, 12H), 0.98 (s, 3H), 0.96 (s, 3H), 0.89–0.81 (comp m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.3, 56.9, 49.5, 42.7, 42.0, 37.9, 36.4, 34.6, 31.7, 31.6, 31.5, 30.9, 30.4, 26.8, 26.0, 25.6, 23.3, 23.0, 22.4; IR (Neat Film NaCl) 2920, 2853, 1708, 1460, 1377, 1199, 1179 cm$^{-1}$; HRMS (EI+) $m/z$ calc'd for C$_{19}$H$_{32}$O [M]$^+$: 276.2453; found 276.2450.

**Minor set of diastereomers.** $R_f = 0.58$ (4:1 hexanes/Et$_2$O); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.90 (ddd, $J = 10.0, 8.3, 5.6$ Hz, 1H), 2.71–2.64 (m, 1H), 2.35 (app t, $J = 7.3$ Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.07–1.85 (comp m, 4H), 1.76–1.06 (comp m, 33H), 1.04 (s, 3H), 1.03 (s, 3H), 1.00–0.82 (comp m, 6H), 0.77 (s, 3H), 0.76 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 211.5, 211.2, 58.8, 55.9, 44.6, 44.5, 41.3, 40.9 (two lines), 39.6, 36.4, 35.2, 34.6, 34.0, 33.1, 32.1, 32.0, 30.7, 29.9 (two lines), 29.5, 29.4, 29.2, 29.0, 28.8, 28.7, 27.9, 27.2, 26.4, 26.2, 25.8, 25.4, 24.6, 24.5, 24.3, 22.8, 22.1, 19.8; IR (Neat Film NaCl) 2919, 2848, 1737, 1711, 1460, 1383, 1352, 1261, 1173 cm$^{-1}$; HRMS (EI+) $m/z$ calc'd for C$_{19}$H$_{32}$O [M]$^+$: 276.2453; found 276.2441.
Attempted reductive alkylation of the asymmetric AB and D-ring systems. Reductive alkylations of cyclooctadienones 223 and 222 were attempted using the Li/NH₃ conditions with a large excess of iodide 237 described above to afford the enolate protonation product ketones 244 and 245, respectively, as the only products.

**α-Methyl cyclooctanone 244.** ¹H NMR (500 MHz, C₆D₆) δ 4.84–4.80 (m, 1H), 4.42–4.39 (m, 1H), 4.25 (dm, J = 12.5 Hz, 1H), 4.08 (dm, J = 12.5 Hz, 1H), 3.07 (dm, J = 16.5 Hz, 1H), 2.98 (br m, 1H), 2.61–2.54 (m, 1H), 2.39–2.32 (m, 1H), 1.79–1.76 (m, 3H), 1.66–1.58 (m, 1H), 1.44–1.38 (m, 1H), 1.15 (dm, J = 14.0 Hz, 1H), 0.88 (d, J = 7.5 Hz, 3H), 0.86 (d, J = 3H).

**Cyclooctanone 245.** ⁷R = 0.28 (3:1 hexanes/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.39–5.35 (m, 1H), 4.64 (ddd, J = 6.5, 3.1, 3.1 Hz, 1H), 4.43 (d pentets, J = 12.6, 1.9 Hz, 1H), 4.27–4.22 (m, 1H), 3.47–3.41 (m, 1H), 3.16–3.14 (m, 1H), 2.98–2.92 (m, 1H), 2.72 (ddd, J = 13.6, 5.3, 2.7 Hz, 1H), 2.38–2.32 (m, 1H), 2.20–2.04 (comp m, 3H), 1.83–1.78 (m, 1H), 1.77–1.75 (comp m, 2H), 0.91 (d, J = 7.3 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃)
δ 213.8, 143.3, 112.6, 88.5, 73.3, 48.9, 47.4, 46.0, 44.6, 40.4, 38.1, 24.1, 16.5; IR
(Neat Film NaCl) 2952, 2918, 1707, 1432, 1246, 1145, 1074 cm⁻¹; HRMS (MM:
ESI/APCI) m/z calc’d for C₁₃H₁₇O₂ [M – H]⁺: 205.1234, found 205.1225; [α]D²⁵ -4.35°
(c 0.953, CHCl₃, 98% ee).

α-Methyl cyclooctanone 244. Ammonia (ca. 5 mL) was condensed into a 2-neck
round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar cooled
to −78 °C, and to this was added lithium wire (3.3 mg, 0.5 mmol, 11 equiv). The solution
turned dark blue. The cooling bath was replaced with a MeCN/CO₂(s) bath held between
−45 and −35 °C. The mixture was stirred for 20 minutes, at which point
cyclooctadienone 22 (9.3 mg, 0.045 mmol, 1.0 equiv) in THF (1 mL) was added
dropwise via cannula transfer. The vial was further washed and transferred with a
portion of anhydrous THF (1 mL). The bright blue color remained after addition. As
quickly as possible, MeI (100 µL, 1.61 mmol, 35 equiv) was added to the stirred solution
by syringe, and the reaction color changed from blue to clear. After 1 h, solid NH₄Cl
(100 mg) was added to the reaction, the cooling bath was removed, and the reaction was
allowed to reach room temperature. After most of the ammonia had evaporated, the
reaction was diluted with H₂O (10 mL) and Et₂O (25 mL). The aqueous layer was
extracted with Et₂O (5 x 15 mL) and the combined organics were washed with brine (2 x
10 mL), dried with MgSO₄, filtered and concentrated. The crude residue was purified by
flash chromatography on SiO$_2$ (2 x 10 cm, 25:1 → 10:1 hexanes/EtOAc) to afford α-methyl cyclooctanone 244 (8.0 mg, 36 μmol, 80% yield) as a single major diastereomer with a minor amount of cyclooctanone 245.

**α-Allyl cyclooctenone 248.** Ammonia (ca. 7 mL) was condensed into a 2-neck round-bottom flask fitted with a septum, an argon inlet, and a glass-coated stir bar cooled to −78 °C, and to this was added lithium wire (5.6 mg, 0.81 mmol, 45 equiv). The solution turned dark blue. The cooling bath was replaced with a MeCN/CO$_2$(s) bath held between −40 and −35 °C. The mixture was stirred for 20 minutes, at which point cyclooctadienone 222 (3.7 mg, 0.018 mmol, 1.0 equiv) dissolved in a 0.009 M t-BuOH solution in THF (2 mL, prepared by dissolving t-BuOH (21.5 μL) in THF (25 mL) in a flamed dried round-bottom flask under argon) was transferred dropwise via cannula. The bright blue color remained after addition and the solution was stirred for 30 s, after which allyl bromide (200 μL, 2.31 mmol, 128 equiv) was added by syringe. Stirring was continued for 30 min after which the cold bath was removed, NH$_4$Cl (420 mg) was added in a single portion and the reaction was allowed to reach room temperature. The reaction was diluted with H$_2$O (5 mL) and extracted with Et$_2$O (5 x 20 mL). The combined organics were washed with H$_2$O (5 mL) then brine (5 mL), dried with MgSO$_4$, and concentrated in vacuo. The crude residue was purified by flash chromatography on SiO$_2$ (15:1 → 4:1 hexanes/EtOAc) to afford α-allyl cyclooctanone 248 (3.2 mg, 13 μmol, 72%
yield) as a single major diastereomer with a minor amount of cyclooctanone 245. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.66–5.58 (m, 1H), 5.31–5.29 (m, 1H), 5.01–4.96 (m, 2H), 4.58–4.56 (m, 1H), 4.36 (d, \(J = 11\) Hz, 1H), 4.17 (m, \(J = 11\) Hz, 1H), 3.44 (d, \(J = 15.5\) Hz, 1H), 3.07 (br m, 1H), 2.76–2.70 (m, 1H), 2.52–2.38 (m, 1H), 2.28–2.23 (m, 2H), 2.08–1.97 (m, 2H) 1.87–1.79 (m, 2H), 1.70–1.64 (m, 2H), 0.82 (d, \(J = 7.5\) Hz, 3H).

\[
\begin{align*}
244 (R = Me) \\
248 (R = allyl)
\end{align*}
\]

Representative procedure for the soft enolization to silyl enol ethers 249 and 250.

To a solution of sodium iodide (1.2 mg, 0.008 mmol, 2 equiv) and \(\alpha\)-allyl cyclooctanone 248 (1.0 mg, 0.004 mmol, 1 equiv) in MeCN (0.5 mL) was added Et\(_3\)N (162 \(\mu\)L of a 0.05 M solution in MeCN, 0.008 mmol, 2 equiv) followed by TMSCl (121 \(\mu\)L of a 0.05 M solution in MeCN, 0.006 mmol, 1.5 equiv). After 1.5 h the solution was diluted with pentane (1 mL) and stirred for several minutes. The pentane was removed by pipette and the acetonitrile was further extracted with pentane (4 x 1 mL). The combined pentane extracts were dried with Na\(_2\)SO\(_4\), filtered and concentrated to afford crude silyl enol ether 250 (2.0 mg) as a single isomer by \(^1\)H NMR analysis. This compound was used directly in subsequent reactions. \(R_f = unstable\ to\ SiO_2\).
3.8 NOTES AND REFERENCES


(3) Variecolin number convention (ref 1a).

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(12) The preparation of tricarbonyliron-cyclobutadiene ether complexes of allylic alcohols is typically accomplished with bromide 258 (see ref. 11e). In our hands, this procedure was variable and furnished only modest yields of ether 188.

\[
\text{HO} \quad \underset{\text{Br}}{\text{Fe(CO)}_3} \quad \text{KH, THF \quad 0 \rightarrow 23 \degree C} \quad \underset{\text{Fe(CO)}_3}{\text{Fe(CO)}_3}
\]


(18) We also investigated the group-selective differentiation of diol 253 without success.


(20) The Lewis acids La(OTf)$_3$ or Sm(OTf)$_3$ effect the conversion of acetal 191 to dimethyl acetal 254 as the sole product.

(21) Our equilibration results suggest that the formation of acetal 191 is the kinetic product of the unsymmetrical ozonolysis, and is apparently due to the proximity of substituents attached to the cyclobutane ring.

(22) The recycling of acetals 191 and 197 via this equilibration/olefination sequence provides olefin 193 and recovered acetal 191 in excellent yield over two steps.


(25) (a) Schneider, M. Angew. Chem. 1975, 87, 717–718. (b) Brown, J. M.; Golding, 

(26) (a) Sudrik, S. G.; Chavan, S. P.; Chandrakumar, K. R. S.; Sourav, P.; Date, S. K.; 

344, 1008–1016. (b) Tietze, L. F.; Stadler, C.; Böhnke, N.; Brasche, G.; Grube, 
A. Synlett 2007, 485–487. (c) For a related example, see: Deardorff, D. R.; 
Windham, C. Q.; Craney, C. L. Organic Syntheses; Wiley & Sons, New York, 

(28) Alcohol isomer 210 is not reactive under these Mitsunobu conditions.

(29) TLC analysis of the reaction progress indicated cycloadduct 213 as the major 
product, however, we are thus far unable to obtain isolated yields due to the 
volatility of this compound and its challenging isolation from a large volume of 
acetone.
The reactivity differences observed for this substrate (212) and the model system (188) underline the difference in the C(3) stereochemistry and its impact on the cycloaddition.

The reaction yield for the two steps post cycloaddition/ozonolysis is excellent (94%), indicating the low overall yield for the four steps is the result of either problematic cycloaddition or ozonolysis procedures. The difficulties we have encountered with the volatility and purification of cycloadduct 213 are suggestive of the major limitation of this reaction sequence.

The absolute stereochemistry of acetal 215 could not be determined from the X-ray diffraction data. See Appendix 3 for details.

For selected examples of α-diazoketone formation using diazoethane (219), see:


(35) Application of photochemical/thermal reaction conditions to $\alpha$-diazoketone 221 produced similar results.


(38) Variation of reaction temperature did not impact the ratio of products for the rearrangement of 221.


The catalyst derived from Pd(0) and fluorinated ligand 230 is highly effective for reactive substrates such as allyl enol carbonates (ref 46). However, alkylation reactions of vinylogous β-ketoester (±)-181 using this catalyst proceed at a slow rate, even with 10 mol % of the palladium complex, presumably due to a slower rate of decarboxylation. The related increase in reaction times often result in catalyst decomposition prior to complete conversion of substrate.

The remarkable stability of β-hydroxyketone 231 is likely the result of transannular interactions or some other form of ring strain. This is comparable to the observation that cycloheptane-1,3-dione (227) exists exclusively in the diketo-
form in solution, and contrasts with propensity for six-membered analogue cyclohexane-1,3-dione to be completely enolized in solution. See ref 45b.

(49) Preliminary investigations employing sodium methoxide/methanol conditions produced minor quantities of conjugate addition adducts of cycloheptenone 180.

(50) A number of intermediates are possible for the proposed retro-aldol/aldol sequence, such as ketoaldehyde 226 and several diastereomeric aldol addition adducts. ¹H NMR analysis of crude reaction filtrates exhibit a characteristic aldehyde peak, along with numerous other compounds. Addition of TFE to reactions containing these compounds facilitated the conversion to the desired acylcyclopentene 225, further supporting their role as intermediates in the transformation.


(52) We presume that the fluorinated lithium alkoxide is generated in situ due to the large difference in pKa values (H₂O = 15.7, TFE = 12.5, HFIP = 9.3 [water]; H₂O = 31.2, TFE = 23.5, HFIP = 18.2 [DMSO]).


(54) Preliminary studies aimed at the conversion of pure cycloheptenone 180 to acylcyclopentene 225 using our optimal basic aldol conditions have not been successful.

See Appendix 3 for details.

Our initial studies employing derivative 256 revealed the propensity of the dioxolane protecting group toward cleavage under mild conditions.


We are currently unable to determine the stereochemistry of the newly formed C(11) stereocenter.

(66) We surveyed numerous conditions varying catalysts, solvents, silanes, and temperatures without further improvement.


APPENDIX 1

Synthetic Summary toward the Asymmetric Total Synthesis of Variecolin

Scheme A1.1. Retrosynthetic analysis of variecolin
Scheme A1.2. Intramolecular cycloaddition and unsymmetrical ozonolysis toward the AB ring

Scheme A1.3. α-Diazoketone synthesis and Wolff/Cope rearrangement to AB ring fragments
Scheme A1.4. Asymmetric alkylation and ring contraction to the D-ring fragment

Scheme A1.5. Enrichment of acycliclopentene 225 for the D-ring fragment
Scheme A1.6. AB ring reductive alkylation and soft enolization poised for fragment coupling

Scheme A1.7. Proposed completion of variecolin
APPENDIX 2

Spectra Relevant to Chapter 3:

Progress toward the Asymmetric Total Synthesis of Variecolin
Figure A2.1. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 178.
Figure A2.2. Infrared spectrum (neat film/NaCl) of 178.

Figure A2.3. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 178.
Figure A2.4. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 180.
Figure A2.5. Infrared spectrum (neat film/NaCl) of 180.

Figure A2.6. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 180.
Figure A2.7. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 181.
Figure A2.8. Infrared spectrum (neat film/NaCl) of 181.

Figure A2.9. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 181.
Figure A2.10. $^1$H NMR spectrum (300 MHz, C$_6$D$_6$) of 183.
Figure A2.11. $^1H$ NMR spectrum (300 MHz, CD$_3$OD) of 1b4.

$^1H$ NMR spectrum (300 MHz, CD$_3$OD) of 1b4.
Figure A2.12. Infrared spectrum (neat film/NaCl) of 184.

Figure A2.13. $^{13}$C NMR spectrum (126 MHz, $C_6D_6$) of 184.
Figure A2.14. $^1H$ NMR spectrum (500 MHz, C$_6$D$_6$) of 185.

**$^1H$ NMR spectrum (500 MHz, C$_6$D$_6$)**

Fe(CO)$_3$ 185 O

NH

C

Cl

3
Figure A2.15. Infrared spectrum (neat film/NaCl) of 185.

Figure A2.16. $^{13}$C NMR spectrum (126 MHz, $C_6D_6$) of 185.
Figure A2.17. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 186.
Figure A2.18. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 187.
Figure A2.19. $^1$H NMR spectrum (300 MHz, C$_6$D$_6$) of 188.
Figure A2.20. Infrared spectrum (neat film/NaCl) of 188.

Figure A2.21. $^{13}$C NMR spectrum (126 MHz, $C_6D_6$) of 188.
Figure A2.22. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 189.
Figure A2.23. Infrared spectrum (neat film/NaCl) of 189.

Figure A2.24. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 189.
Figure A.2.5. $^1H$ NMR spectrum (500 MHz, CDCl$_3$) of 190.
Figure A2.26. Infrared spectrum (neat film/NaCl) of 190.

Figure A2.27. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 190.
Figure A.28. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 191.
Figure A2.29. Infrared spectrum (neat film/NaCl) of 191.

Figure A2.30. $^{13}$C NMR spectrum (126 MHz, CDCl₃) of 191.
Figure A2.31. $^1H$ NMR spectrum (300 MHz, CDCl$_3$) of 192.
Figure A.2.32. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 193.
Figure A2.33. Infrared spectrum (neat film/NaCl) of 193.

Figure A2.34. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 193.
Figure A2.35. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 197.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.36. Infrared spectrum (neat film/NaCl) of 197.

Figure A2.37. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 197.
Figure A2.38: $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 198.
Figure A2.39. Infrared spectrum (neat film/NaCl) of 198.

Figure A2.40. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 198.
Figure A2.41. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 200.
Figure A2.42. Infrared spectrum (neat film/NaCl) of 200.

Figure A2.43. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 200.
Figure A2.44. $^1$H NMR spectrum (500 MHz, $C_6D_6$) of 201.
Figure A2.45. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 201.
**Figure A2.46.** Infrared spectrum (neat film/NaCl) of 201.

**Figure A2.47.** $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 201.
Figure A2.48. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 203.
Figure A2.49. Infrared spectrum (neat film/NaCl) of 203.

Figure A2.50. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 203.
Figure A2.51. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 208.
Figure A2.52. $^1H$ NMR spectrum (500 MHz, CDCl$_3$) of 209.
Figure A2.53. Infrared spectrum (neat film/NaCl) of \textbf{209}.

Figure A2.54. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of \textbf{209}.
Figure A2.55. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 211.
Figure A2.56. Infrared spectrum (neat film/NaCl) of 211.

Figure A2.57. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 211.
Figure A2.58. $^1$H NMR spectrum (300 MHz, CD$_3$OD) of 212.
Figure A2.59. Infrared spectrum (neat film/NaCl) of 212.

Figure A2.60. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 212.
Figure A2.61. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 213.
Figure A2.62. Infrared spectrum (neat film/NaCl) of 213.

Figure A2.63. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 213.
Figure A2.64. $^1H$ NMR spectrum (500 MHz, CDCl$_3$) of 214.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.65. Infrared spectrum (neat film/NaCl) of 214.

Figure A2.66. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 214.
Figure A2.67. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of 215.
Figure A2.68. Infrared spectrum (neat film/NaCl) of 215.

Figure A2.69. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 215.
Figure A2.70. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 216.
Figure A2.71. Infrared spectrum (neat film/NaCl) of 216.

Figure A2.72. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 216.
Figure A2.7.3. \(^1\)H NMR spectrum (500 MHz, CDCl\(_3\)) of 217.
Figure A2.74. Infrared spectrum (neat film/NaCl) of 217.

Figure A2.75. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 217.
Figure A2.76. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of 218.

$^1$H NMR spectrum (600 MHz, CDCl$_3$) of 218.
Figure A2.77. Infrared spectrum (neat film/NaCl) of 218.

Figure A2.78. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 218.
Figure A2.79. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 220.
Figure A2.80. Infrared spectrum (neat film/NaCl) of 220.

Figure A2.81. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 220.
Figure A2.82. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 221.
Figure A2.83. Infrared spectrum (neat film/NaCl) of 221.

Figure A2.84. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 221.
Figure A2.85. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 222.
Figure A.86. Infrared spectrum (neat film/NaCl) of 222.

Figure A.87. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 222.
Figure A2.88. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of 223.
Figure A2.89. Infrared spectrum (neat film/NaCl) of 223.

Figure A2.90. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 223.
Figure A.291. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 224.
Figure A2.92. Infrared spectrum (neat film/NaCl) of 224.

Figure A2.93. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 224.
Figure A2.94. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 225.
Figure A2.95. Infrared spectrum (neat film/NaCl) of 225.

Figure A2.96. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 225.
Figure A2.97. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 227.
Figure A2.98. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 228.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.99. Infrared spectrum (neat film/NaCl) of 228.

Figure A2.100. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 228.
Figure A2.101. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 229.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.102. Infrared spectrum (neat film/NaCl) of 229.

Figure A2.103. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 229.
Figure A2.104. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 231.
Figure A2.105. Infrared spectrum (neat film/NaCl) of 231.

Figure A2.106. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 231.
Figure A2.107. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 232.
Figure A2.108. Infrared spectrum (neat film/NaCl) of 232.

Figure A2.109. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 232.
Figure A2.110. $^1H$ NMR spectrum (500 MHz, CDCl$_3$) of 233.
Figure A2.111. Infrared spectrum (neat film/NaCl) of 233.

Figure A2.112. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 233.
Figure A2.113. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 235.
Figure A2.114. Infrared spectrum (neat film/NaCl) of 235.

Figure A2.115. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 235.
Figure A2.116. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 236.
Figure A2.117. Infrared spectrum (neat film/NaCl) of 236.

Figure A2.118. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 236.
Figure A2.119. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 237.
Figure A2.120. Infrared spectrum (neat film/NaCl) of 237.

Figure A2.121. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 237.
Figure A2.122. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 238.
Figure A2.123. Infrared spectrum (neat film/NaCl) of 238.

Figure A2.124. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 238.
Figure A2.125. $^1$H NMR spectrum (500 MHz, C$_6$D$_6$) of 239.
Figure A2.126. Infrared spectrum (neat film/NaCl) of 239.

Figure A2.127. $^{13}$C NMR spectrum (126 MHz, $C_6D_6$) of 239.
Figure A2.128. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 240.
Figure A2.129. Infrared spectrum (neat film/NaCl) of 240.

Figure A2.130. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 240.
Figure A2.131. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 241.
Figure A2.132. Infrared spectrum (neat film/NaCl) of \(241\).

Figure A2.133. \(^{13}\)C NMR spectrum (126 MHz, \(CDCl_3\)) of \(241\).
Figure A2.134. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 242.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.135. Infrared spectrum (neat film/NaCl) of 242.

Figure A2.136. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 242.
Figure A2.137. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the major diastereomer of 243.
Figure A2.138. Infrared spectrum (neat film/NaCl) of the major diastereomer of 243.

Figure A2.139. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of the major diastereomer of 243.
Figure A2.140. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the minor diastereomer of 243.
Figure A2.141. Infrared spectrum (neat film/NaCl) of the minor diastereomer of 243.

Figure A2.142. $^{13}$C NMR spectrum (neat film/NaCl) of the minor diastereomer of 243.
Figure A2.143. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 245.
Figure A2.144. Infrared spectrum (neat film/NaCl) of 245.

Figure A2.145. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 245.
Figure A2.146. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 253.
Appendix 2—Spectra Relevant to Chapter 3

Figure A2.147. Infrared spectrum (neat film/NaCl) of 253.

Figure A2.148. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 253.
Figure A2.149. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of Z54.
Figure A2.150. Infrared spectrum (neat film/NaCl) of 254.

Figure A2.151. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 254.
Figure A2.152. $^1H$ NMR spectrum (300 MHz, CDCl$_3$) of 255.
Figure A2.153. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 256.
Figure A2.154. Infrared spectrum (neat film/NaCl) of 256.

Figure A2.155. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 256.
APPENDIX 3

X-Ray Crystallography Reports Relevant to Chapter 3:
Progress toward the Asymmetric Total Synthesis of Variecolin

A3.1  CRYSTAL STRUCTURE ANALYSIS OF 215

Figure A3.1.1. Acetal 215 is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 718289.
Appendix 3—X-Ray Crystallography Reports Relevant to Chapter 3

Table A3.1.1. Crystal data and structure refinement for **215** (CCDC 718289)

<table>
<thead>
<tr>
<th>Crystal data and structure refinement</th>
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<tbody>
<tr>
<td>Empirical formula</td>
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<tr>
<td>Formula weight</td>
</tr>
<tr>
<td>Crystallization solvent</td>
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<tr>
<td>Crystal habit</td>
</tr>
<tr>
<td>Crystal size</td>
</tr>
<tr>
<td>Crystal color</td>
</tr>
</tbody>
</table>

**Data Collection**

| Type of diffractometer                        | Bruker KAPPA APEX II                           |
| Wavelength                                    | 0.71073 Å MoKα                                 |
| Data collection temperature                   | 100(2) K                                       |
| θ range for 9805 reflections used in lattice determination | 3.31 to 34.80°                                 |
| Unit cell dimensions                          | a = 6.3017(3) Å, b = 11.7387(5) Å, c = 14.4000(6) Å |
| Volume                                        | 1065.22(8) Å³                                 |
| Z                                             | 4                                             |
| Crystal system                                | Orthorhombic                                  |
| Space group                                   | P2₁2₁2₁                                      |
| Density (calculated)                          | 1.398 Mg/m³                                    |
| F(000)                                        | 480                                           |
| Data collection program                       | Bruker APEX2 v2.1-0                            |
| θ range for data collection                   | 2.24 to 35.05°                                 |
| Completeness to θ = 35.05°                    | 97.3%                                         |
| Index ranges                                  | −10 ≤ h ≤ 10, −17 ≤ k ≤ 18, −23 ≤ l ≤ 22       |
| Data collection scan type                     | ω scans; 13 settings                           |
| Data reduction program                        | Bruker SAINT-Plus v7.34A                       |
| Reflections collected                         | 37096                                         |
| Independent reflections                       | 4514 [Rₑₘ = 0.1080]                            |
| Absorption coefficient                        | 0.104 mm⁻¹                                    |
| Absorption correction                         | None                                          |
| Max. and min. transmission                    | 0.9794 and 0.9694                              |
Table A3.1.1 (cont.)

**Structure solution and Refinement**

<p>| | |</p>
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<tbody>
<tr>
<td>Structure solution program</td>
<td>SHELXS-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Primary solution method</td>
<td>Direct methods</td>
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<tr>
<td>Secondary solution method</td>
<td>Difference Fourier map</td>
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<tr>
<td>Hydrogen placement</td>
<td>Difference Fourier map</td>
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<td>Structure refinement program</td>
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<tr>
<td>Refinement method</td>
<td>Full matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>4514 / 0 / 209</td>
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<tr>
<td>Treatment of hydrogen atoms</td>
<td>Unrestrained</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.899</td>
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<tr>
<td>Final R indices [I&gt;2σ(I), 4349 reflections]</td>
<td>R1 = 0.0286, wR2 = 0.0740</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0301, wR2 = 0.0744</td>
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<tr>
<td>Type of weighting scheme used</td>
<td>Sigma</td>
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<td>Weighting scheme used</td>
<td>w=1/σ²(Fo²)</td>
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<tr>
<td>Average shift/error</td>
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</tr>
<tr>
<td>Absolute structure determination</td>
<td>Not able to determine reliably</td>
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<tr>
<td>Absolute structure parameter</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.339 and -0.290 e.Å⁻³</td>
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</table>

**Special Refinement Details**

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100 K.

Refinement of F² against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F², conventional R-factors (R) are based on F, with F set to zero for negative F². The threshold expression of F² > 2σ(F²) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F² are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances,
angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Figure A3.1.2. Acetal 215.
Table A3.1.2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for acetal 215 (CCDC 718289). $U_{eq}$ is defined as the trace of the orthogonalized $U_{ij}$ tensor

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$U_{eq}$</th>
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</thead>
<tbody>
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<td>O(1)</td>
<td>3796(1)</td>
<td>867(1)</td>
<td>1413(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>O(2)</td>
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<td>-917(1)</td>
<td>2033(1)</td>
<td>18(1)</td>
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<tr>
<td>O(3)</td>
<td>-426(1)</td>
<td>-1149(1)</td>
<td>3528(1)</td>
<td>14(1)</td>
</tr>
<tr>
<td>O(4)</td>
<td>2465(1)</td>
<td>-2244(1)</td>
<td>3980(1)</td>
<td>14(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>2711(1)</td>
<td>953(1)</td>
<td>3797(1)</td>
<td>12(1)</td>
</tr>
<tr>
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<td>-331(1)</td>
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<td>11(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>2043(1)</td>
<td>-173(1)</td>
<td>2600(1)</td>
<td>11(1)</td>
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<td>1818(1)</td>
<td>1127(1)</td>
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<td>12(1)</td>
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<td>-785(1)</td>
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<td>4468(1)</td>
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Table A3.1.3. Bond lengths [Å] and angles [°] for acetal 215 (CCDC 718289)

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<th>Bond Lengths</th>
<th>Bond Angles</th>
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<td>O(1)-C(9)</td>
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<tr>
<td>O(4)-C(10)</td>
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<td>O(4)-C(12)</td>
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<tr>
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<tr>
<td>C(1)-H(1)</td>
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<tr>
<td>C(1)-H(9)</td>
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<tr>
<td>C(2)-C(11)</td>
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<tr>
<td>C(2)-H(2)</td>
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<tr>
<td>C(3)-C(11)</td>
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<td>C(3)-C(10)</td>
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<tr>
<td>C(3)-C(4)</td>
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<td>C(4)-C(5)</td>
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<td>C(6)-H(6B)</td>
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<tr>
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<tr>
<td>C(7)-H(7)</td>
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<tr>
<td>C(8)-H(8A)</td>
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<td>C(8)-H(8C)</td>
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<td>C(9)-H(9A)</td>
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<td>C(9)-H(9B)</td>
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<tr>
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<td>C(4)-C(1)-H(1)</td>
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<tr>
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<tr>
<td>C(10)-C(2)-C(3)</td>
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Table A3.1.3 (cont.)

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<th>Distance (Å)</th>
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<td>O(3)-C(11)-C(3)</td>
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<td>O(4)-C(12)-H(12A)</td>
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</tr>
<tr>
<td>O(4)-C(12)-H(12B)</td>
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</tr>
<tr>
<td>H(12A)-C(12)-H(12B)</td>
<td>114.0(11)</td>
</tr>
<tr>
<td>O(4)-C(12)-H(12C)</td>
<td>103.4(11)</td>
</tr>
<tr>
<td>H(12A)-C(12)-H(12C)</td>
<td>106.4(12)</td>
</tr>
</tbody>
</table>

Table A3.1.4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^4$) for acetal 215 (CCDC 718289). The anisotropic displacement factor exponent takes the form: $-2\pi^2 |h^2 a^* a^* U^{11} + ... + 2 \ h \ k \ a^* b^* U^{12}|$

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<tr>
<th></th>
<th>$U^{11}$</th>
<th>$U^{22}$</th>
<th>$U^{33}$</th>
<th>$U^{23}$</th>
<th>$U^{13}$</th>
<th>$U^{12}$</th>
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<td>O(3)</td>
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<td>-20(2)</td>
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<tr>
<td>O(4)</td>
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<td>24(2)</td>
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Table A3.1.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for acetal 215 (CCDC 718289)

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<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U_{iso}</th>
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<tr>
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<td>H(5)</td>
<td>3332(18)</td>
<td>2403(11)</td>
<td>1957(8)</td>
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<tr>
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<td>854(10)</td>
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<td>H(6B)</td>
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<td>2206(10)</td>
<td>2698(7)</td>
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<td>H(8B)</td>
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<td>4526(9)</td>
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<td>-3258(13)</td>
<td>4249(8)</td>
<td>28(3)</td>
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### A3.2 CRYSTAL STRUCTURE ANALYSIS OF 233

Figure A3.2.1. Semicarbazone 233 is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 686849.

![Crystal Structure](image)

**Table A3.2.1** Crystal data and structure refinement for 233 (CCDC 686849)

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<tbody>
<tr>
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</tr>
<tr>
<td>Formula weight</td>
<td>437.31</td>
</tr>
<tr>
<td>Crystallization solvent</td>
<td>Dichloromethane/pentane</td>
</tr>
<tr>
<td>Crystal habit</td>
<td>Needle</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.28 x 0.11 x 0.07 mm$^3$</td>
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<tr>
<td>Crystal color</td>
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**Data Collection**

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<td>Wavelength</td>
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<td>Data collection temperature</td>
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### Table A3.2.1 (cont.)

<table>
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<td>Unit cell dimensions</td>
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<tr>
<td>a = 17.160(4) Å</td>
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</tr>
<tr>
<td>b = 5.5921(14) Å</td>
<td>β = 90.689(6)°</td>
</tr>
<tr>
<td>c = 19.984(5) Å</td>
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</tr>
<tr>
<td>Volume</td>
<td>1917.6(8) Å</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
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<td>880</td>
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<td>Data collection program</td>
<td>Bruker APEX2 v2.1-0</td>
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<td>θ range for data collection</td>
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<tr>
<td>Completeness to θ = 29.84°</td>
<td>88.9 %</td>
</tr>
<tr>
<td>Index ranges</td>
<td>–23 ≤ h ≤ 23, –7 ≤ k ≤ 7, –26 ≤ l ≤ 25</td>
</tr>
<tr>
<td>Data collection scan type</td>
<td>ω scans; 16 settings</td>
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<td>Data reduction program</td>
<td>Bruker SAINT-Plus v7.34A</td>
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<td>Semi-empirical from equivalents (TWNABS)</td>
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<td>Max. and min. transmission</td>
<td>0.7460 and 0.5010</td>
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**Structure solution and Refinement**

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<th>Value</th>
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<td>Structure solution program</td>
<td>SHELXS-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Primary solution method</td>
<td>Direct methods</td>
</tr>
<tr>
<td>Secondary solution method</td>
<td>Difference Fourier map</td>
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<tr>
<td>Hydrogen placement</td>
<td>Geometric positions</td>
</tr>
<tr>
<td>Structure refinement program</td>
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</tr>
<tr>
<td>Refinement method</td>
<td>Full matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>8962 / 1 / 437</td>
</tr>
<tr>
<td>Treatment of hydrogen atoms</td>
<td>Riding</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.609</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ(I), 7203 reflections]</td>
<td>R1 = 0.0409, wR2 = 0.0481</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0619, wR2 = 0.0493</td>
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Table A3.2.1 (cont.)

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<tr>
<th>Type of weighting scheme used</th>
<th>Weighting scheme used</th>
<th>Max shift/error</th>
<th>Average shift/error</th>
<th>Absolute structure determination</th>
<th>Absolute structure parameter</th>
<th>Largest diff. peak and hole</th>
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</thead>
<tbody>
<tr>
<td>Sigma</td>
<td>$w=1/\sigma^2(Fo^2)$</td>
<td>0.002</td>
<td>0.000</td>
<td>Anomalous differences</td>
<td>0.003(11)</td>
<td>0.807 and $-0.967 \text{ e.Å}^{-3}$</td>
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</tbody>
</table>

**Special Refinement Details**

The structure was refined as a single component, although the crystals were twins, using an HKLF4 format reflection file prepared with TWINABS (see below). The two orientations were separated using CELL_NOW as follows.

Rotated from first domain by 178.9 degrees about reciprocal axis $-0.032 \ 1.000 \ 0.104$ and real axis $-0.001 \ 1.000 \ 0.007$. Twin law to convert hkl from first to this domain (SHELXL TWIN matrix):

$$
\begin{bmatrix}
-1.000 & -0.065 & 0.016 \\
-0.003 & 0.998 & 0.014 \\
-0.022 & 0.207 & -0.999 \\
\end{bmatrix}
$$

From Saint integration; Twin Law, Sample 1 of 1 transforms h1.1(1)→h1.2(2)

$$
\begin{bmatrix}
-0.99897 & -0.07583 & 0.01646 \\
-0.00750 & 0.99693 & 0.01538 \\
-0.02464 & 0.19596 & -0.99910 \\
\end{bmatrix}
$$

Twinabs;

PART 1 - Refinement of parameters to model systematic errors

18757 data (4443 unique) involve domain 1 only, mean I/\sigma I 13.7
18551 data (4364 unique) involve domain 2 only, mean I/\sigma I 7.1
Appendix 3—X-Ray Crystallography Reports Relevant to Chapter 3

10342 data (4106 unique) involve 2 domains, mean I/σ 19.2

HKLF 4 dataset constructed from all observations involving domains 1..2
8970 Corrected reflections written to file twin4.hkl
Reflections merged according to point-group 2
Minimum and maximum apparent transmission: 0.501007 0.745969
Additional spherical absorption correction applied with μr = 0.2000

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100 K.

Refinement of $F^2$ against ALL reflections. The weighted R-factor ($wR$) and goodness of fit (S) are based on $F^2$, conventional R-factors (R) are based on F, with F set to zero for negative $F^2$. The threshold expression of $F^2 > 2σ(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on $F^2$ are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.
Figure A3.2.2. Semicarbazone 233.

Table A3.2.2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for semicarbazone 233 (CCDC 686849). $U_{eq}$ is defined as the trace of the orthogonalized $U_{ij}$ tensor.

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<th>z</th>
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### Appendix 3 — X-Ray Crystallography Reports Relevant to Chapter 3

#### Table A3.2.3. Bond lengths [Å] and angles [°] for semicarbazone 233 (CCDC 686849)

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Bond lengths and angles for semicarbazone 233 (CCDC 686849) are reported in this table.
Table A3.2.3 (cont.)

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### Table A3.2.4. Anisotropic displacement parameters (Å² x 10⁴) for semicarbazone 233 (CCDC 686849).

The anisotropic displacement factor exponent takes the form: -2π² | h²a²U₁₁ + ... + 2hk U₁₂ |

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</tr>
<tr>
<td>C(7A)</td>
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<td>280(18)</td>
<td>330(20)</td>
<td>-40(17)</td>
<td>-16(16)</td>
<td>-38(18)</td>
</tr>
<tr>
<td>C(8A)</td>
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<td>257(18)</td>
<td>260(20)</td>
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<td>-61(17)</td>
<td>19(16)</td>
</tr>
<tr>
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<td>-9(18)</td>
<td>-26(15)</td>
</tr>
<tr>
<td>C(10A)</td>
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<td>410(20)</td>
<td>430(20)</td>
<td>-69(17)</td>
<td>3(18)</td>
<td>-44(17)</td>
</tr>
<tr>
<td>C(11A)</td>
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<td>240(20)</td>
<td>330(20)</td>
<td>21(16)</td>
<td>-31(15)</td>
<td>-26(17)</td>
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<td>283(18)</td>
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<td>-23(16)</td>
<td>-60(16)</td>
<td>-30(16)</td>
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<tr>
<td>C(13A)</td>
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<td>440(20)</td>
<td>-99(15)</td>
<td>-50(18)</td>
<td>42(16)</td>
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<tr>
<td>C(14A)</td>
<td>190(20)</td>
<td>305(19)</td>
<td>490(30)</td>
<td>-7(15)</td>
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<td>19(15)</td>
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<td>-26(19)</td>
<td>-18(15)</td>
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<td>540(30)</td>
<td>114(18)</td>
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<td>9(18)</td>
<td>40(20)</td>
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<tr>
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<td>270(20)</td>
<td>480(20)</td>
<td>420(30)</td>
<td>-75(18)</td>
<td>-70(20)</td>
<td>77(18)</td>
</tr>
<tr>
<td>C(19A)</td>
<td>410(30)</td>
<td>600(20)</td>
<td>510(20)</td>
<td>40(20)</td>
<td>-88(19)</td>
<td>120(30)</td>
</tr>
</tbody>
</table>

### Notes
- Uₐₙ = Uₐₛ/10²
- Uₐₙ = Uₐₙ/10⁴

---

Appendix 3 — X-Ray Crystallography Reports Relevant to Chapter 3
### Table A3.2.4 (cont.)

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
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</thead>
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<td>C(15B)</td>
<td>340(20)</td>
<td>290(18)</td>
<td>266(19)</td>
<td>-75(16)</td>
<td>-25(16)</td>
<td>33(18)</td>
</tr>
<tr>
<td>C(16B)</td>
<td>720(40)</td>
<td>680(30)</td>
<td>610(30)</td>
<td>-170(20)</td>
<td>-50(30)</td>
<td>380(30)</td>
</tr>
<tr>
<td>C(17B)</td>
<td>840(30)</td>
<td>400(20)</td>
<td>510(30)</td>
<td>-150(20)</td>
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<td>-90(20)</td>
</tr>
<tr>
<td>C(18B)</td>
<td>500(30)</td>
<td>540(30)</td>
<td>520(30)</td>
<td>-104(19)</td>
<td>110(30)</td>
<td>-49(19)</td>
</tr>
<tr>
<td>C(19B)</td>
<td>1060(50)</td>
<td>830(40)</td>
<td>420(30)</td>
<td>40(20)</td>
<td>60(30)</td>
<td>500(30)</td>
</tr>
</tbody>
</table>

### Table A3.2.5. Hydrogen bonds for semicarbazone 233 (CCDC 686849) [Å and °]

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2A)-H(2A)...O(1B)#1</td>
<td>0.88</td>
<td>2.13</td>
<td>2.972(3)</td>
<td>159.7</td>
</tr>
<tr>
<td>N(2B)-H(2B)...O(1A)#2</td>
<td>0.88</td>
<td>2.04</td>
<td>2.895(3)</td>
<td>163.1</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
#1 x,y-1,z
#2 x,y+1,z
CHAPTER 4

Enantioselective Allylic Alkylations of Vinylogous \( \beta \)-Ketoester Derivatives: Total Synthesis of (+)-Carissone†

4.1 INTRODUCTION

Cyclic, unsaturated ketones possessing \( \gamma \)-substitution (e.g., 261) are highly useful intermediates for applications in complex molecule synthesis (Figure 4.1.1). Such \( \gamma \)-substituted enone moieties are typically accessed via transformations of masked, cyclic 1,3-dicarbonyl compounds made popular by Stork and Danheiser. These so-called vinylogous esters (e.g., 259) enable the regioselective functionalization of the ring, and are amenable to the preparation of numerous compounds possessing an array of substitution. A principle challenge to accessing members of this substrate class is the stereoselective construction of a quaternary stereocenter at the \( \gamma \)-position of the enone. Although methods for the asymmetric introduction of this moiety exist, we envisioned

† Studies toward the synthesis of (+)-carissone were performed primarily by Samantha R. Levine as a Marcella R. Bonsall Summer Undergraduate Research Fellow and partially sponsored by the Dalton Fund. Portions of this work were also conducted in collaboration with Krastina V. Petrova and Justin T. Mohr. These works have been published. See: (a) Levine, S. R.; Krout, M. R.; Stoltz, B. M. Org. Lett. 2009, 11, 289–292. (b) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. Org. Lett. 2009, 11, 293–295.
Chapter 4—Enantioselective Alkylations of Vinylogous $\beta$-Ketoesters: Synthesis of (+)-Carissone

an enantioselective approach that harnesses the palladium-catalyzed alkylation methodology that has recently been developed in our laboratory.\textsuperscript{5} Herein, we detail our investigations of this important class of substrates and uncover a complex interplay between reaction selectivity and substrate structure and electronics.

Figure 4.1. Representative transformations of vinylogous esters.

\[ \text{alkylation} \]

\[ \text{alkylation} \]

\[ \text{alkylation} \]

4.2 ENANTIOSELECTIVE DECARBOXYLATIVE ALKYLATIONS OF VINYLOGOUS $\beta$-KETOESTER DERIVATIVES

Our explorations of the asymmetric alkylation of vinylogous esters focused on the application of racemic $\beta$-ketoester derivatives. These substrates offer a practical advantage over enol carbonate and silyl enol ether substrates due to their ease of preparation and purification, as well as increased stability as enolate precursors.\textsuperscript{6} The design of methods directed toward the preparation and functionalization of seven-membered rings en route to the synthesis of natural products is an ongoing area of research in our laboratory,\textsuperscript{7} and thus our asymmetric alkylation studies initiated with the seven-membered ring vinylogous ester substrate class.
4.2.1 EFFECT OF SOLVENT

The optimization of the decarboxylative alkylation of vinylogous ester derivatives centered on vinylogous β-ketoester (+)-181 (Table 4.2.1). Exposure of this substrate to our typical reaction conditions employing a palladium(0) catalyst and (S)-t-Bu-PHOX ((S)-55) in THF at 30 °C smoothly generated α-quaternary ketone 229 in 94% yield and 84% ee (entry 1). While this substrate class exhibited good reactivity, the selectivity provided by ligand 55 was lower than anticipated. Previous studies in our laboratory have established a minor role of solvent for selectivity of the asymmetric alkylation reactions,5a although in certain circumstances solvent can have a notable effect on selectivity.5c Accordingly, a survey of common reaction solvents revealed similar yields of ketone 229 with a distinct enhancement in selectivity. The use of ethereal solvents provided a modest increase in enantioselectivity, with conditions in Et₂O producing 229 in 86% ee (entries 2–5). Substitution with aromatic solvents benzene and toluene enabled a more substantial improvement in selectivity, with up to 88% ee in toluene (entries 6 and 7). Our results indicate that alkylations of substrates such as 181 are readily influenced by solvent, and thus it is a necessary variable for future vinylogous β-ketoester studies.
4.2.2  EFFECT OF SUBSTRATE SUBSTITUTION

In addition to the optimization of solvent for the alkylation selectivity, we also examined the identity of the vinylogous moiety. The vinylogous ester substrate class contrasts most other substrates that we have examined in that they allow structural variations while maintaining similar functional reactivity for subsequent transformations. For example, the vinylogous ester 259 depicted in Figure 4.1.1 could possess OR where R = Me, Et, and i-Bu, and all three substrates would be unique, yet could function in a similar manner for each subsequent transformation, ultimately providing the same product at the end of the reaction sequence (i.e., 261). This significant feature greatly expands the substrate potential for the transformation and allows the examination of the role of electronics toward reactivity and selectivity.

Table 4.2.1. Solvent screen for the Pd-catalyzed alkylation of vinylogous β-ketoester (±)-181

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>94</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1,4-dioxane</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>2-methyl THF</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>TBME</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>Et2O</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>benzene</td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>toluene</td>
<td>91</td>
<td>88</td>
</tr>
</tbody>
</table>

\( ^a \text{pmdba} = \text{bis(4-methoxybenzylidene)acetone.} \)

\( ^b \text{Isolated yield.} \)

\( ^c \text{Enantiomeric excess determined by chiral HPLC.} \)
In our studies of vinylogous β-ketoester derivatives, we observed that substitution of the R group with ether derivative 263 furnished quaternary ketone 264 in similar selectivity (cf. entries 1–3, Table 4.2.2). Modification of the ether group to an acyl functionality facilitated the construction of ketones 266 and 268 with enhanced selectivity (88 and 90% ee, respectively), with benzoate 268 providing the best results (entries 4–6). The use of a thiophenyl-derived vinylogous ester 269 produced a similar result, affording vinylogous thioester 270 in 89% ee (entry 7). This limited data set demonstrates that reducing the electron density of the vinylogous moiety results in a marked improvement in selectivity and facilitates an increase in the reaction rate.\(^8\) We can rationalize the electronic role of substitution and reaction rate as a decrease in the energy required for the cleavage of a C–C bond in the decarboxylation event.\(^9\) However, the influence on selectivity is complex. As we descend down each entry in Table 4.2.2, the resulting enolate pK\(_a\) is distinctly reduced, suggesting that the electronics of the palladium–enolate complex impact the reaction such that an electron-deficient complex enhances selectivity,\(^10\) although the exact correlation is difficult to discern.\(^11\) Nonetheless, the versatile nature of this substrate class holds the potential for interesting applications.
4.2.3 EXTENSIONS TO SIX-MEMBERED RINGS

The established viability of seven-membered vinylogous β-ketoester substrates for our asymmetric alkylation method encouraged the extension to six-membered derivatives. Application of the six-membered analog 271 with our standard conditions required an increase in reaction temperature to 50 °C to achieve complete conversion to ketone 272, although with a noticeable decrease in selectivity to 83% ee (entry 1, Table 4.2.3). Solvent identity displays a key role for six-membered substrates, as the use of toluene for the production of 272 increased the selectivity to 86% ee (entry 2). Moreover, substitution at the α-position of the β-ketoester to an ethyl group afforded ketone 274 in 86% ee (entry 3). Examination of substrates that possess substitution α to the vinylogous moiety afforded strikingly different results. Substrate reactivity for the production of vinylogous ester 275 was exceedingly slow at 50 °C, and an increase to 80 °C facilitated complete conversion to 276 with a modest 75% ee (entries 4 and 5).
However, the utilization of a vinylogous thioester 277 enabled complete conversion at 50 °C to α-quaternary vinylogous thioester 278 in a remarkable 92% ee, with an absence of solvent influence (entries 6 and 7).

Table 4.2.3. Six-membered vinylogous β-ketoester substrates

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>R³</th>
<th>substrate</th>
<th>product</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Me</td>
<td>271</td>
<td>272</td>
<td>THF</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Me</td>
<td>271</td>
<td>272</td>
<td>toluene</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>3²</td>
<td></td>
<td>Et</td>
<td>273</td>
<td>274</td>
<td>THF</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>4²</td>
<td></td>
<td></td>
<td>275</td>
<td>276</td>
<td>toluene</td>
<td>19</td>
<td>79</td>
</tr>
<tr>
<td>5²</td>
<td></td>
<td></td>
<td>275</td>
<td>276</td>
<td>toluene</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>277</td>
<td>278</td>
<td>toluene</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>277</td>
<td>278</td>
<td>THF</td>
<td>88</td>
<td>92</td>
</tr>
</tbody>
</table>

² Reaction performed using 5 mol % Pd(dmldab)₂. ³ β-ketoester starting material was isolated in 69% yield. ⁴ At 80 °C.

In general, substrates that possess a six-membered ring require additional energy to break the C–C bond in the decarboxylation event of the β-ketoester compared to seven-membered rings, resulting in increased reaction temperatures and times (see the subsection 4.3.3.1). A comparison of substrates 271 and 275 underscores the difference in reactivity and selectivity resulting from the addition of a methyl group to the α-position (cf. entries 2 and 4). Moreover, adjusting the electronics of the vinylogous moiety exhibits a large impact on selectivity (cf. entries 4 and 6). Taken together, these
seemingly trivial substrate changes have a significant impact on reactivity and selectivity, making it difficult to delineate reaction trends.

4.2.4 FUTURE STUDIES OF VINYLOGOUS $\beta$-KETOESTER SUBSTRATES

Our preliminary asymmetric alkylation studies of vinylogous $\beta$-ketoester substrates have displayed a range of selectivities and reactivities, indicating a complex role of substrate structure and electronics of the vinylogous moiety. Future efforts for this class of substrates will expand on substrate substitution for both seven and six-membered rings to examine the generality of the transformation. In addition to the increase in number of substrates, a thorough investigation encompassing solvent variation and substrate electronics could enable the development of predictive tools for general use. Furthermore, the utility of enol carbonate vinylogous ester derivatives and ligands possessing variable electronic properties are viable options for challenging substrates.\textsuperscript{10} The elaboration of the various vinylogous products obtained from the asymmetric alkylation reaction into useful intermediates is of importance for the utility of this class of molecules. Importantly, the reactivities and selectivities observed for the vinylogous ester derivatives provide access to a variety of enantioenriched $\alpha$-quaternary enones using Stork–Danheiser chemistry and provide a firm precedent for future studies.
4.3 CATALYTIC ENANTIOSELECTIVE APPROACH TO THE EUDESMAINE SESQUITERPENOIDS

The production of highly enantioenriched materials from the enantioselective alkylation of vinylogous β-ketoester derivatives enables their use for various applications. Specifically, we sought to harness this transformation as the key enantioselective reaction in a multistep synthesis. Here we detail our efforts to utilize the asymmetric alkylation of vinylogous β-ketoester derivatives toward a general approach to the eudesmane sesquiterpenoids.

4.3.1 BACKGROUND OF THE EUDESMAINE SESQUITERPENOIDS

The flowering plants of the family Asteraceae (Compositae) have many historical uses, including rubber, medicines, edible oils and vegetables, and pesticides. Among these floras are a large number of species abundant in structurally diverse sesquiterpenoids, particularly ones that contain the eudesmane skeleton (Figure 4.3.1). Over 1000 eudesmanes have been identified from these sources with their structures diverging based on oxygenation and oxidation patterns within the carbon framework.
This ever-growing\textsuperscript{15} class of important secondary metabolites possesses a wide range of biological properties including plant growth inhibition, insect antifeedant, antibacterial, antifungal, and antitumor activities. Representative eudesmanes comprise antibacterial agents (+)-carissone \textsuperscript{(279)}\textsuperscript{16} and (+)-3-oxocostusic acid \textsuperscript{(280)}\textsuperscript{17}, as well as P/Q-type calcium channel blocker (–)-α-eudesmol \textsuperscript{(281)}\textsuperscript{18} (Figure 4.3.1). These examples typify common structural motifs within this class of sesquiterpenoids, primarily the C(10) all-carbon quaternary stereocenter and stereogenic C(7) substituent. The structural similarities and interesting biology associated with this class of molecules has stimulated several synthetic efforts, most of which employ semisynthetic or chiral pool strategies.\textsuperscript{19,20,21} To date, no catalytic asymmetric approach toward these eudesmanes has been developed. Herein, we report an approach\textsuperscript{22} that incorporates our recent method for the catalytic asymmetric formation of enantioenriched all-carbon quaternary stereocenters into a general synthetic strategy for this class of sesquiterpenoids.
4.3.2 RETROSYNTHETIC ANALYSIS OF THE EUDESMANE CARBOCYCLIC CORE

In devising a strategy to access the eudesmanes, we simplified our target structure to enone 283, which has been utilized in the preparation of structures such as 282 and embodies many features present in various family members (cf. 283 and 279, 280) (Scheme 4.3.1). We envisioned that the stereochemistry of the C(7) substituent could arise by means of the diastereoselective hydrogenation of a substituted cyclohexene (i.e., 284), the stereochemical outcome of which would be controlled by the C(10) quaternary stereocenter. This cyclohexene could be obtained from a ring-closing metathesis of triolefin 285, which would be derived from an appropriately substituted α-quaternary ketone (i.e., 286). Thus, we sought to develop an efficient and selective preparation of the C(10) quaternary stereocenter as the key control element in our synthetic approach toward the eudesmanes.

Scheme 4.3.1. Retrosynthetic analysis of the eudesmanes
4.3.3 TOTAL SYNTHESIS OF (+)-CARISSONE

4.3.3.1 Pd-CATALYZED ENANTIOSELECTIVE ALKYLATION OF VINYLOGOUS ESTER DERIVATIVES

The enantioselective alkylation of ketone enolates is an area of intense investigation in our laboratory.\(^5\) This method has resulted in the preparation of a wide range of carbonyl compounds with adjacent quaternary stereocenters with high levels of selectivity and excellent yields, some of which have proved valuable in synthetic endeavors.\(^7e,10b,23\) The application of α-quaternary ketones such as 286 for the devised strategy would require a carbonyl transposition (i.e., 286 → 285), and we therefore chose to exploit the unique properties of vinylogous esters (i.e., 286 where R\(^2\) = OR) pioneered by Stork and Danheiser\(^2\) for this purpose.

Our initial studies for the asymmetric generation of quaternary stereocenters utilizing vinylogous ester derivatives focused on enol carbonates due to preliminary investigations\(^4a,10b\) that have demonstrated successes for similar substrates. Exposure of allyl enol carbonate 287 to typical reaction conditions consisting of a palladium(0) catalyst and ligand (S)-55\(^24\) in toluene generated vinylogous ester (+)-276, albeit in variable yield and selectivity (Table 4.3.1, entry 1). Unfortunately, the instability of 287 impeded further studies, as these results were highly dependent on the composition of this enol carbonate.\(^25\) Given the range of substrate possibilities for this transformation,\(^5d\) we next focused on racemic β-ketoester (±)-275. Surprisingly, this substrate proved only modestly reactive at 50 °C, producing ketone 276 in 19% yield and 79% ee (entry 2).\(^26\) Increasing the reaction temperature to 80 °C enabled complete conversion to ketone 276, although with slightly reduced selectivity (entry 3). As the lack of reactivity seemed to
be a major complication with this substrate, we considered vinylogous thioesters (i.e., (±)-277) for their reported activation properties. Indeed, racemic β-ketoester (±)-277 did prove more reactive and produced ketone (+)-278 at 50 °C in good yield and 92% ee (entry 4). A screen of solvents revealed that benzene (entry 5) and ethereal solvents (entries 6 and 7) provided similar selectivities to toluene.

Table 4.3.1. Asymmetric allylation of vinylogous ester derivatives

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solvent</th>
<th>T (°C)</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>287</td>
<td>toluene</td>
<td>25</td>
<td>276</td>
<td>22-61</td>
<td>84-88</td>
</tr>
<tr>
<td>2</td>
<td>275</td>
<td>toluene</td>
<td>50</td>
<td>276</td>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>275</td>
<td>toluene</td>
<td>80</td>
<td>276</td>
<td>86</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>277</td>
<td>toluene</td>
<td>50</td>
<td>278</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>277</td>
<td>benzene</td>
<td>50</td>
<td>278</td>
<td>61&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>277</td>
<td>THF</td>
<td>50</td>
<td>278</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>277</td>
<td>1,4-dioxane</td>
<td>50</td>
<td>278</td>
<td>90</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields. <sup>b</sup> Enantiomeric excess determined by chiral HPLC or SFC. <sup>c</sup> β-Ketoester (±)-275 was recovered in 69% yield. <sup>d</sup> β-Ketoester (±)-277 was recovered in 26% yield.

### 4.3.3.2 PREPARATION OF THE BICYCLIC CORE

With optimal conditions for the preparation of 278, we sought to demonstrate the feasibility of using this ketone for the total synthesis of (+)-carissone (279). Accordingly, racemic β-ketoester (±)-277 was transformed to (−)-278 in 85% yield<sup>27</sup> and 92% ee using ligand (R)-55 to correlate with the natural antipode of 279 (Scheme 4.3.2). Subsequent
conversion of vinylogous thioester 278 into vinylogous ester 288 was achieved with sodium methoxide in refluxing methanol. Exposure of the resulting vinylogous ester to the substituted allylmagnesium bromide generated from 289 provided enone 290 in 94% yield. We were encouraged by the success of allylmagnesium bromide additions to vinylogous ester 288 and investigated similar reactions of various organometallic reagents with vinylogous thioester 278; however, several conditions afforded intractable mixtures with no desired products. Nonetheless, ring-closing metathesis of enone 290 using Grubbs’ catalyst 291 efficiently prepared the desired substrate (i.e., 292) for the diastereoselective hydrogenation. Gratifyingly, the heterogeneous hydrogenation of 292 utilizing Rh/Al₂O₃ catalyst in methanol and subsequent TBS cleavage provided alcohol 293 in good overall yield with excellent diastereoselectivity. This notable transformation generates alcohol 293 with the C(10) and C(7) stereocenters in the desired syn configuration required for 279. Conversion of alcohol 293 to ester 294 was achieved by a two-step process involving Dess–Martin oxidation, followed by chlorite oxidation with diazomethane workup.
4.3.3.3 COMPLETION OF (+)-CARISSONE AND A FORMAL SYNTHESIS OF (-)-α-EUDESMOL

The availability of ester 294 in the desired configuration enabled preparation of (+)-carissone (279) in short order. Diastereoselective reduction of the enone carbonyl under Luche conditions,\(^{35}\) followed by treatment of the resulting alcohol with methylmagnesium bromide\(^{21}\) provided diol 295\(^{19a}\) in 73% yield (Scheme 4.3.3). The preparation of this diol intersects Aoyama’s synthesis (–)-α-eudesmol (281)\(^{19c}\) and represents a formal total synthesis. Furthermore, facile allylic oxidation with manganese dioxide gave (+)-carissone (279) having spectroscopic data (\(^1\)H NMR, \(^{13}\)C NMR, IR, HRMS, optical rotation) identical to those reported for natural 279.
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Scheme 4.3.3. End game for (+)-carissone (279) and the formal synthesis of (−)-α-eudesmol (281)

4.4 CONCLUSION

In summary, we have described the palladium-catalyzed asymmetric alkylation of various vinylogous $\beta$-ketoester substrates to provide access to enantioenriched $\alpha$-quaternary ketones in high yields. Our studies revealed a significant influence of solvent, substrate structure, and electronics on the reactivity and selectivity of the transformation. Importantly, the incorporation of electron-withdrawing groups on the vinylogous moiety increases reaction rates and enhances selectivities over traditional vinylogous esters. We have demonstrated the utility of the resulting $\alpha$-quaternary products in a general synthetic approach for the total synthesis of the eudesmane sesquiterpenoids. Fundamental to this strategy is the use of the resulting C(10) quaternary stereocenter to control the C(7) stereochemistry via a diastereoselective hydrogenation, providing a highly selective and efficient route to the antibacterial agent (+)-carissone (279). Studies to understand the interplay between substrate reactivity and selectivity for the asymmetric alkylation of vinylogous ester derivatives, as well as the
use of the resulting enantioenriched products in the synthesis of other bioactive natural substances, are currently underway.
4.5 EXPERIMENTAL SECTION

4.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. All the starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Brine solutions refer to saturated aqueous sodium chloride solutions. TMEDA was distilled from sodium under nitrogen prior to use. Benzenethiol was distilled under nitrogen prior to use. For data regarding the conversion of (±)-181 to (−)-229, see Chapter 3 of this thesis. Previously reported methods were used to prepare (S)-t-BuPHOX ((S)-55) and (R)-t-BuPHOX ((R)-55), as well as Pd₂(pmdba)₃. Grubbs’ catalyst 291 was a generous gift from Materia, Inc. Rhodium was purchased from Strem as a 1 wt % loading on alumina powder in reduced form. Diazomethane (199) was freshly prepared from Diazald as a solution in Et₂O. Manganese dioxide was purchased from Aldrich in activated form, ~85%, <5 µm, and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or KMnO₄ staining. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 µm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD and OD-H columns.
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(4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min flow rate and visualization at 254 nm. Analytical chiral supercritical fluid chromatography was performed with a Berger Analytix SFC (Thar Technologies) utilizing a Chiralpak AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 2 mL/min flow rate at 30 °C and visualization at 244 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm in spectrophotometric grade solvents. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to Me$_4$Si (δ 0.0 ppm). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm$^{-1}$). Melting points are uncorrected. High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility.
4.5.2 PREPARATIVE PROCEDURES

4.5.2.1 ASYMMETRIC ALKYLATION OF VINYLOGOUS β-KETOESTER DERIVATIVES

**Vinylogous ester 296.** To a solution of dione 227 (574.6 mg, 4.55 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (22.8 ml, 0.2 M) was added MOM-Cl (381 µL, 5.01 mmol, 1.1 equiv) followed by i-Pr$_2$NEt (873 µL, 5.01 mmol, 1.1 equiv). After 12 h the reaction was diluted with CH$_2$Cl$_2$ (25 mL), washed with 1 N HCl, sat aq NaHCO$_3$, brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO$_2$ (4:1 $\rightarrow$ 2:1 hexanes/EtOAc) to give 296 (441.9 mg, 2.596 mmol, 57% yield) as a pale yellow oil. $R_f = 0.16$ (2:1 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.50 (s, 1H), 4.97 (s, 2H), 3.43 (s, 3H), 2.59–2.55 (comp m, 4H), 1.90–1.74 (comp m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.4, 173.8, 108.0, 94.2, 57.0, 42.0, 32.9, 23.8, 21.4; IR (Neat Film NaCl) 2942, 1645, 1611, 1454, 1376, 1215, 1153, 1071, 972, 924 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_9$H$_{15}$O$_3$ [M + H]$^+$: 171.1021, found 171.1055.

![Chemical structure of 296](image-url)

1. LDA, PhMe, -78 °C; allyl chloroformate -78 $\rightarrow$ 23 °C
2. NaNH, Mel, THF 0 $\rightarrow$ 23 °C

(66% yield, two steps)

![Chemical structure of 263](image-url)
Vinylogous β-ketoester 263. To a solution of \( i-\text{Pr}_2\text{NH} \) (764 µL, 5.45 mmol, 2.1 equiv) in PhMe (18 mL) cooled to \(-78 \, ^\circ\text{C}\) was added a solution of \( n-\text{BuLi} \) (2.09 mL of a 2.55 M solution in hexane, 5.32 mmol, 2.05 equiv). The flask was placed in a 0 \( ^\circ\text{C}\) cooling bath for 10 min, cooled back down to \(-78 \, ^\circ\text{C}\), and to this was added a solution of vinylogous ester 296 (441.9 mg, 2.60 mmol, 1.0 equiv) in PhMe (2 mL, wash with extra 2 mL). After 30 min, allyl chloroformate (290 µL, 2.73 mmol, 1.05 equiv) was added dropwise and the bath was removed. The reaction was quenched with 1 N KHSO\(_4\) (15 mL) after stirring at room temperature for 30 min, the layers were separated, and the aq was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The combined organics were washed with brine, dried over MgSO\(_4\), filtered, and concentrated in vacuo.

The resulting crude oil was dissolved in THF (5.2 mL, 0.5 M) and cooled to 0 \( ^\circ\text{C}\) in an ice bath. To this was added NaH (124.6 mg, 3.12 mmol, 1.2 equiv) in one portion, and after 30 min, MeI (485 µL, 7.79 mmol, 3.0 equiv) was added and the cooling bath was removed. After 4 h, the reaction was quenched with 50% sat. aq NH\(_4\)Cl (15 mL) and diluted with Et\(_2\)O (15 mL), the layers were separated, and the aq was extracted with Et\(_2\)O (3 x 15 mL). The combined organics were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The crude was purified by flash chromatography on SiO\(_2\) (6:1 \( \rightarrow \) 3:1 \( \rightarrow \) 2:1 hexanes/EtOAc) to afford vinylogous β-ketoester 263 (459.6 mg, 1.71 mmol, 66% yield over two steps) as a colorless oil. \( R_f = 0.22 \) (4:1 hexanes/EtOAc);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 5.87 (dd, \( J = 17.2, 10.4, 5.6, 5.6 \, Hz, 1H\)), 5.57 (d, \( J = 1.1 \, Hz, 1H\)), 5.29 (app dq, \( J = 17.2, 1.6 \, Hz, 1H\)), 5.21 (app dq, \( J = 10.4, 1.3 \, Hz, 1H\)), 4.99 (d, \( J = 6.1 \, Hz, 1H\)), 4.96 (d, \( J = 6.1 \, Hz, 1H\)), 4.66–4.52 (comp m, 2H), 3.43 (s, 3H), 2.61 (dd, \( J = 18.1, 9.8, 4.1, 1.2 \, Hz, 1H\)), 2.48–2.38 (comp m, 2H), 2.06–1.92 (m, 1H), 1.87–
Vinylogous ester 264. A typical asymmetric alkylation reaction was run on 28.6 mg (0.100 mmol) of 263 at 30 °C in THF (0.1 M) for 9 h using (S)-55 and Pd₂(pmdba)₃. The crude material was purified by flash chromatography on SiO₂ (6:1 hexanes/EtOAc, PhMe load) to provide 264 (17.8 mg, 0.0794 mmol, 79% yield) as a pale yellow oil. \( R_f = 0.31 \) (1:1 hexanes/EtOAc); IR (Neat Film NaCl) 2934, 1620, 1454, 1389, 1216, 1148, 1067, 992, 957, 924, 879 cm⁻¹. HPLC conditions: 0.5% EtOH in hexanes, OD-H column, \( t_R \) (min): major = 12.69, minor = 13.59.

Vinylogous pivalate 297. To a solution of diketone 227 (229.7 mg, 1.82 mmol, 1.0 equiv) dissolved in CHCl₃ (9.1 mL, 0.2 M) was added pyridine (147 µL, 1.82 mmol, 1.0 equiv), PivCl (247 µL, 2.00 mmol, 1.1 equiv), and DMAP (44.5 mg, 0.364 mmol, 0.2 equiv), and the resulting solution was placed in a 40 °C oil bath. After 24 h, the reaction was diluted with CH₂Cl₂ (10 mL), washed with 1 N HCl (10 mL), then sat. aq NaHCO₃ (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude oil was
purified by flash chromatography on SiO₂ (9:1 → 6:1 hexanes/EtOAc, PhMe load) to give 297 (213.2 mg, 1.01 mmol, 56% yield) as a colorless oil. \( R_f = 0.23 \) (6:1 hexanes/EtOAc); \(^1^H\) NMR (300 MHz, CDCl₃) \( \delta \) 5.80–5.79 (m, 1H), 2.64 (dd, \( J = 7.0, 5.4 \) Hz, 2H), 2.58 (dd, \( J = 6.7, 5.5 \) Hz, 2H), 1.97–1.81 (comp m, 4H), 1.24 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 201.7, 176.3, 167.5, 122.1, 43.2, 39.1, 33.4, 27.0, 24.4, 21.7; IR (Neat Film NaCl) 2974, 2938, 2873, 1749, 1667, 1650, 1481, 1458, 1369, 1275, 1114 cm\(^{-1}\); HRMS (EI+) \( m/z \) calc’d for C\(_{12}\)H\(_{18}\)O\(_3\) [M]+: 210.1256, found 210.1253.

Vinylogous \( \beta \)-ketoester 265. To a solution of \( i \)-Pr\(_2\)NH (333 \( \mu \)L, 2.38 mmol, 1.2 equiv) in THF (8 mL) at 0 °C was added a solution of \( n \)-BuLi (890 \( \mu \)L of a 2.45 M solution in hexane, 2.18 mmol, 1.1 equiv). After 30 min, the solution was cooled to –78 °C and a solution of vinylogous pivalate 297 (416.5 mg, 1.98 mmol, 1.0 equiv) in THF (2 mL) was added dropwise via cannula transfer. After 1 h at –78 °C, allyl cyanofomate (237 \( \mu \)L, 2.18 mmol, 1.1 equiv) was added. After 30 min the reaction was quenched with 50% sat. aq NH₄Cl (10 mL) and warmed to room temperature. The layers were separated and the aq layer was extracted with Et₂O (3 x 15 mL), the combined organics were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO₂ (9:1 → 3:1 hexanes/Et₂O) to provide the desired acylated intermediate (274.0 mg, 0.93 mmol, 47% yield).
The resulting intermediate was dissolved in THF (4.7 mL, 0.2 M) and cooled to 0 °C, at which point NaH (44.7 mg, 1.12 mmol, 1.2 equiv) was added in one portion. After 20 min, MeI (173 µL, 2.79 mmol, 3.0 equiv) was added and the cooling bath was removed. The reaction was quenched with 50% sat. aq NH₄Cl after 10 h, diluted with Et₂O (10 mL), the layers were separated and the aq layer was extracted with Et₂O (3 x 10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated to a crude oil. Purification by flash chromatography on SiO₂ (9:1 → 6:1 hexanes/Et₂O) provided vinylogous β-ketoester 265 (253.2, 0.821 mmol, 41% yield over two steps) as a colorless oil. Rf = 0.34 (3:1 hexanes/Et₂O); ¹H NMR (300 MHz, CDCl₃) δ 5.87 (dddd, J = 17.2, 10.4, 5.7, 5.7 Hz, 1H), 5.83 (d, J = 1.0 Hz, 1H), 5.29 (app dq, J = 17.2, 1.5 Hz, 1H), 5.21 (app dq, J = 10.4, 1.3 Hz, 1H), 4.62 (app dt, J = 5.6, 1.4 Hz, 2H), 2.61 (dddd, J = 18.6, 8.7, 4.3, 1.4 Hz, 1H), 2.50–2.39 (comp m, 2H), 2.07–1.94 (m, 1H), 1.91–1.81 (m, 1H), 1.76 (ddd, J = 11.0, 7.6, 2.9 Hz, 1H), 1.43 (s, 3H), 1.24 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 176.1, 173.2, 164.6, 131.8, 121.0, 118.5, 66.1, 66.0, 60.0, 39.2, 34.0, 33.7, 27.0, 23.5, 21.6, 15.4; IR (Neat Film NaCl) 2977, 2934, 1746, 1685, 1650, 1454, 1379, 1274, 1233, 1180, 1103, 1027, 980, 909 cm⁻¹; HRMS (FAB⁺) m/z calc’d for C₁₇H₂₅O₅ [M + H]⁺: 309.1702, found 309.1619.

**Vinylogous pivalate 266.** A typical asymmetric alkylation reaction was run on 42.0 mg (0.136 mmol) of 265 at 30 °C in Et₂O (0.1 M) for 2 h using (S)-55 and Pd₂(pmdba)₃. The crude material was purified by preparative TLC on SiO₂ (3:1
hexanes/Et₂O) to provide 266 (30.2 mg, 0.114 mmol, 84% yield) as a pale yellow oil. 
\[ R_f = 0.34 \] (1:1 hexanes/EtOAc); \[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \[ \delta = 5.72–5.71 \text{ (m, 1H), 5.70 (dd, } J = 16.6, 10.5, 7.4, 7.4 \text{ Hz, 1H), 5.08–5.06 (m, 1H), 5.05–5.06 (m, 1H), 5.05–5.00 (m, 1H), 2.49 (dd, } J = 6.3, 5.3 \text{ Hz, 2H), 2.30 (app qd, } J = 13.7, 7.4 \text{ Hz, 2H), 1.92–1.61 (comp m, 4H), 1.25 (s, 9H), 1.15 (s, 3H); } ^13C \text{NMR (75 MHz, CDCl}_3 \] \[ \delta = 206.2, 176.4, 162.7, 133.8, 120.6, 118.4, 52.5, 44.6, 39.2, 34.9, 27.1, 24.3, 20.0; IR (Neat Film NaCl) 2976, 2936, 2873, 1749, 1656, 1480, 1461, 1379, 1276, 1105, 914 \text{ cm}^{-1}. \] HPLC conditions: 0.25% \( i \)-PrOH in hexanes, OD-H column, \( t_R \) (min): major = 10.24, minor = 11.73.

Vinylogous benzoate 298. Prepared in the exact manner as vinylogous pivalate 297 using 220.5 mg (1.75 mmol) of diketone 227. The crude material was purified by flash chromatography on SiO₂ (6:1 \( \rightarrow \) 4:1 hexanes/EtOAc, PhMe load) to provide 298 (291.8 mg, 1.27 mmol, 72% yield) as a pale yellow oil. 
\[ R_f = 0.26 \] (4:1 hexanes/EtOAc); \[ ^1H \text{NMR (300 MHz, CDCl}_3 \] \[ \delta = 8.08–8.05 \text{ (comp m, 2H), 7.66–7.60 (m, 1H), 7.51–7.46 (comp m, 2H), 5.99 (s, 1H), 2.77–2.69 (comp m, 4H), 2.05–1.87 (comp m, 4H); } ^13C \text{NMR (75 MHz, CDCl}_3 \] \[ \delta = 201.7, 167.4, 164.3, 134.0, 130.2, 129.8, 128.8, 122.6, 43.3, 33.5, 24.5, 21.8; IR (Neat Film NaCl) 3064, 2941, 2870, 1733, 1663, 1652, 1601, 1452, 1315, 1262, 1202, 1176, 1112, 1090, 1052, 1024, 878, 855, 708, 524 \text{ cm}^{-1}; \] HRMS (EI+) \( m/z \) calc’d for C₁₄H₁₄O₃ [M]⁺: 230.0943, found 230.0940.
Vinylogous \(\beta\)-ketoester 267. Prepared in the exact manner as vinylogous \(\beta\)-ketoester 265. Purified by flash chromatography on SiO\(_2\) (9:1 \(\rightarrow\) 6:1 hexanes/EtOAc) to afford 267 (229.6 mg, 0.699 mmol, 33\% yield over two steps) as a pale yellow oil. 

\[ R_f = 0.37 \text{ (4:1 hexanes/EtOAc); } ^1H\text{NMR (300 MHz, CDCl}_3) \delta 8.06-8.03 \text{ (comp m, 2H), 7.64–7.58 (m, 1H), 7.49–7.44 (comp m, 4H), 6.01 (d, } J = 6.0 \text{ Hz, 1H), 5.90 (ddd, } J = 17.0, 10.6, 5.7, 5.7 \text{ Hz, 1H), 5.31 (app dq, } J = 17.2, 1.4 \text{ Hz, 1H), 5.22 (ddd, } J = 10.4, 2.3, 1.2 \text{ Hz, 1H), 4.65 (app dt, } J = 5.7, 1.3 \text{ Hz, 2H), 2.77 (ddddd, } J = 18.6, 8.9, 4.1, 1.4 \text{ Hz, 1H), 2.65–2.47 (comp m, 2H), 2.13–2.01 \text{ (m, 1H), 1.97–1.76 (m, 1H), 1.81 (ddd, } J = 14.3, 7.6, 3.5 \text{ Hz, 1H), 1.47 (s, 3H); } ^13C\text{NMR (75 MHz, CDCl}_3) \delta 198.8, 173.2, 164.3, 164.1, 133.9, 131.8, 130.2, 129.0, 128.7, 121.4, 118.6, 66.1, 60.0, 34.1, 33.9, 23.4, 21.8; \text{HRMS (FAB+) } m/z \text{ calc’d for C}_{19}H_{21}O_5 \text{ [M + H]}^+: 329.1389, \text{ found 329.1378.}

Vinylogous benzoate 268. A typical asymmetric alkylation reaction was run on 39.5 mg (0.120 mmol) of 267 at 30 °C in THF (0.1 M) for 8 h (overnight) using (S)-55 and Pd\(_3\)(pmdba)\(_3\). The crude material was purified by preparative TLC on SiO\(_2\) (4:1 hexanes/EtOAc) to provide 268 (2.1 mg, 0.102 mmol, 85\% yield) as a colorless oil. 

\[ R_f = 0.47 \text{ (4:1 hexanes/EtOAc); } ^1H\text{NMR (300 MHz, CDCl}_3) \delta 8.08–8.04 \text{ (comp m, 2H), 7.64–7.58 (m, 1H), 7.51–7.45 (comp m, 2H), 5.90 (app t, } J = 1.1 \text{ Hz, 1H), 5.74 (ddd, } J =
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16.3, 10.8, 7.4, 7.4, 1H), 5.10–5.09 (m, 1H), 5.07–5.03 (m, 1H), 2.68–2.63 (comp m, 2H), 2.34 (app qt, J = 13.8, 1.1 Hz, 2H), 1.99–1.67 (comp m, 4H), 1.19 (s, 3H). HPLC conditions: 2% i-PrOH in hexanes, OD-H column, \( t_R \) (min): major = 10.86, minor = 12.39.

**Vinylogous thioester 299.** To a solution of dione 227 (1.3727 g, 10.88 mmol, 1.0 equiv) in MeCN (12.1 mL, 0.9 M) cooled to 0 °C was added Et\(_3\)N (1.70 mL, 12.2 mmol, 1.12 equiv) and MsCl (884 µL, 11.4 mmol, 1.05 equiv). The reaction was slowly warmed to 23 °C over 1 h, then cooled to 0 °C and Et\(_3\)N (1.70 mL, 12.2 mmol, 1.12 equiv) followed by freshly distilled PhSH (1.15 mL, 11.21 mmol, 1.03 equiv) were added. The reaction was slowly warmed to 23 °C overnight. When starting material was consumed, the reaction was quenched with sat. aq Na\(_2\)CO\(_3\) (30 mL), extracted with Et\(_2\)O (3 x 50 mL), the organics were dried over MgSO\(_4\), filtered, and concentrated under reduced pressure to a yellow oil. The crude oil was purified by flash chromatography on SiO\(_2\) (3:1 → 1:1 hexanes/Et\(_2\)O) to afford 299 as a pale yellow solid (1.5617 g, 7.154 mmol, 66% yield). \( R_f = 0.31 \) (1:1 hexanes/Et\(_2\)O); mp = 73–75 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.48–7.46 (comp m, 2H), 7.43–7.40 (comp m, 3H), 5.48 (s, 1H), 2.65 (dd, \( J = 6.1, 6.1 \) Hz, 2H), 2.55 (dd, \( J = 6.3, 6.3 \) Hz, 2H), 1.93–1.88 (comp m, 2H), 1.84–1.79 (comp m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 200.6, 163.5, 163.4, 135.6, 130.2, 130.0, 129.7, 124.3, 41.4, 33.0, 24.9, 21.0; IR (Neat Film NaCl) 3058, 2939, 2866, 1648. 1586,
1475, 1440, 1267, 1190, 1016, 750, 691 cm\(^{-1}\); HRMS (EI+) \textit{m/z} calc'd for \text{C}_{13}\text{H}_{14}\text{OS} [\text{M}]^+\): 218.0765, found 218.0758.

**Vinylogous β-ketoester 269.** To a solution of \(i\)-Pr\(_2\)NH (590 µL, 4.21 mmol, 1.3 equiv) in THF (14 mL) at 0 °C was added a solution of \(n\)-BuLi (1.56 mL of a 2.5 M solution in hexane, 3.89 mmol, 1.2 equiv). After 30 min, the solution was cooled to −78 °C and a solution of vinylogous thioester 299 (707.5 mg, 3.24 mmol, 1.0 equiv) in THF (2.2 mL) was added dropwise via cannula transfer. After 1 h at −78 °C, allyl cyanofomate (389 µL, 3.56 mmol, 1.1 equiv) was added. After 2 h the reaction was quenched with 50% sat. aq NH\(_4\)Cl (5 mL) and warmed to room temperature. The layers were separated and the aq layer was extracted with Et\(_2\)O (3 x 10 mL), the combined organics were washed with brine (10 mL), dried over MgSO\(_4\), filtered, and concentrated in vacuo.

The resulting crude oil was dissolved in THF (4.7 mL) and cooled to 0 °C, at which point NaH (149 mg, 3.73 mmol, 1.15 equiv) was added in two portions. After 20 min, MeI (605 µL, 9.72 mmol, 3 equiv) was added and the cooling bath was removed. The reaction was quenched with 50% sat. aq NH\(_4\)Cl after 11 h, diluted with Et\(_2\)O (10 mL), the layers were separated and the aq layer was extracted with Et\(_2\)O (3 x 10 mL). The combined organics were washed with brine, dried over MgSO\(_4\), filtered, and concentrated to a crude yellow oil. Purification by flash chromatography on SiO\(_2\) (6:1 → 3:1 hexanes/Et\(_2\)O) provided vinylogous β-ketoester 269 (0.3426 g, 1.08 mmol, 34% yield.
over two steps) as a pale yellow oil. \( R_f = 0.25 \) (3:1 hexanes/Et\(_2\)O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.46–7.38 (comp m, 5H), 5.86 (dddd, \( J = 10.5, 5.6, 5.6, 0.7 \) Hz, 1H), 5.56 (d, \( J = 1.5 \) Hz, 1H), 5.29 (dddd, \( J = 17.1, 1.5, 1.5, 1.5 \) Hz, 1H), 5.23 (dddd, \( J = 10.5, 1.2, 1.2, 1.2 \) Hz, 1H), 4.60 (dddd, \( J = 19.5, 5.9, 1.5, 1.5 \) Hz, 2H), 2.67 (dddd, \( J = 17.6, 10.3, 3.7, 1.7 \) Hz, 1H), 2.50–2.43 (comp m, 2H), 2.08–1.98 (m, 1H), 1.86–1.77 (m, 1H), 1.68 (ddd, \( J = 14.2, 6.4, 5.4 \) Hz, 1H), 1.38 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 197.6, 173.6, 159.5, 135.6, 131.8, 130.1, 129.9, 123.8, 118.7, 66.0, 58.8, 34.2, 33.7, 23.9, 23.8; IR (Neat Film NaCl) 3060, 2982, 2935, 1735, 1650, 1597, 1474, 1440, 1197, 916, 749, 691 cm\(^{-1}\); HRMS (EI+) \textit{m/z} calc'd for C\(_{18}\)H\(_{20}\)O\(_3\)S [M]+: 316.1133, found 316.1119.

Vinylogous thioester 270. A typical asymmetric alkylation reaction was run on 78.2 mg (0.287 mmol) of 269 at 25 °C in Et\(_2\)O (0.1 M) for 5 h using (S)-55 and Pd(dmdba)\(_2\). The crude material was purified by flash chromatography on SiO\(_2\) (15:1 → 9:1 hexanes/Et\(_2\)O, PhMe load) to provide 270 (67.1 mg, 0.246 mmol, 86% yield) as a pale yellow oil. \( R_f = 0.46 \) (3:1 hexanes/Et\(_2\)O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.49–7.46 (comp m, 2H), 7.42–7.38 (comp m, 3H), 5.66 (dddd, \( J = 16.8, 10.1, 7.3, 7.3 \) Hz, 1H), 5.54 (s, 1H), 5.04–4.98 (comp m, 2H), 2.59–2.48 (m, 2H), 2.29 (dd, \( J = 13.7 7.3 \) Hz, 1H), 2.20 (dd, \( J = 13.7, 7.6 \) Hz, 1H), 1.93–1.77 (comp m, 2H), 1.64–1.58 (m, 1H), 1.09 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 206.0, 155.7, 135.5, 134.2, 130.4, 129.8, 129.8, 124.0, 118.1, 51.3, 44.6, 36.3, 35.2, 24.3, 22.5; IR (Neat Film NaCl) 3074, 2931, 2865, 1650, 1597, 1474, 1440, 1197, 916, 749, 691 cm\(^{-1}\); HRMS (EI+) \textit{m/z} calc'd for C\(_{17}\)H\(_{20}\)SO
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[\text{M}^+]: 272.1235, found 272.1243; [\alpha]_D^{24.8} -86.35^\circ \ (c \ 0.905, \text{CH}_2\text{Cl}_2, \ 89\% \ ee). \ HPLC \ conditions: \ see \ derivative \ 300.

\textbf{Acrylate 300.} \ To a solution of vinylogous thioester 270 (19.4 mg, 0.0712 mmol, 1.0 equiv) was added methyl acrylate (128 \ \mu L, 0.142 mmol, 20 equiv), followed by Grubbs’ catalyst 291 (3.1 mg, 0.0036 mmol, 0.05 equiv) and CH$_2$Cl$_2$ (100 \ \mu L). The vial was flushed with argon, capped, and immersed in a 40 °C oil bath overnight. After 10 h, the reaction was concentrated under reduced pressure and purified by preparative TLC on SiO$_2$ (3:1 hexanes/Et$_2$O) to give acrylate 300 (21.9 mg, 0.0663 mmol, 93% yield) as a pale yellow oil. $R_f = 0.19 \ (3:1 \ \text{hexanes/Et}_2\text{O}); \ ^1\text{H NMR} \ (500 \ MHz, \text{CDCl}_3) \ \delta \ 7.50-7.40 \ (\text{comp m, 5H}), \ 6.84 \ (\text{ddd, } J = 15.7, \ 8.0, \ 8.0 \ Hz, \ 1H), \ 5.81 \ (\text{ddd, } J = 15.4, \ 1.3, \ 1.3 \ Hz, \ 1H), \ 5.51 \ (s, \ 1H), \ 3.72 \ (s, \ 3H), \ 2.56 \ (\text{dd, } J = 7.0, \ 5.0 \ Hz, \ 2H), \ 2.46 \ (\text{ddd, } J = 13.8, \ 7.4, \ 1.3 \ Hz, \ 1H), \ 2.33 \ (\text{ddd, } J = 13.8, \ 7.4, \ 1.3 \ Hz, \ 1H), \ 1.90-1.75 \ (\text{comp m, 3H}), \ 1.69-1.61 \ (m, \ 1H), \ 1.14 \ (s, \ 3H); \ ^{13}\text{C NMR} \ (125 \ MHz, \text{CDCl}_3) \ \delta \ 204.7, \ 166.7, \ 157.0, \ 145.3, \ 135.6, \ 130.1, \ 130.0, \ 129.9, \ 124.0, \ 123.3, \ 51.6, \ 51.3, \ 42.8, \ 36.3, \ 35.3, \ 24.8, \ 22.5; \ IR \ (\text{Neat Film NaCl}) \ 3057, \ 2934, \ 1723, \ 1654, \ 1597, \ 1439, \ 1272, \ 1197, \ 1113, \ 986, \ 751, \ 692 \ \text{cm}^{-1}; \ HRMS \ (\text{EI}^+) \ m/z \ \text{calc'd for } \text{C}_{19}\text{H}_{22}\text{O}_{3}\text{S} \ [\text{M}^+]^+: \ 330.1290, \ \text{found} \ 330.1293; \ [\alpha]_D^{25.1} -58.79^\circ \ (c \ 0.355, \ \text{CH}_2\text{Cl}_2, \ 89\% \ ee). \ HPLC \ conditions: \ 3\% \ \text{EtOH} \ \text{in hexanes, AD column, } t_R \ (\text{min}): \ \text{major} = 22.3, \ \text{minor} = 18.7.
Vinylogous β-ketoester 271. To a solution of i-Pr₂NH (854 μL, 6.09 mmol, 2.05 equiv) in PhMe (20 mL) cooled to −78 °C was added a solution of n-BuLi (2.32 mL of a 2.56 M solution in hexane, 5.94 mmol, 2.0 equiv). The flask was placed in a 0 °C cooling bath for 10 min, cooled back down to −78 °C, and to this was added a solution of vinylogous ester 301 (500 mg, 2.97 mmol, 1.0 equiv) in PhMe (3 mL, wash with extra 1 mL). After 30 min, allyl chloroformate (332 μL, 3.12 mmol, 1.05 equiv) was added dropwise and the bath was removed. The reaction was quenched with 1 N KHSO₄ (15 mL) after stirring at room temperature for 30 min, the layers were separated, and the aq was extracted with Et₂O (2 x 10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo.

The resulting crude oil was dissolved in MeCN (12 mL, 0.25 M), and to this was added Cs₂CO₃ (1.160 g, 3.56 mmol, 1.2 equiv) and MeI (555 μL, 8.90 mmol, 3.0 equiv). The reaction was placed in an 80 °C oil bath and stirred vigorously, and after 17 h the contents were warmed to room temperature. The reaction was diluted with EtOAc (25 mL), dried over MgSO₄, filtered, and concentrated to a crude oil. Purification by flash chromatography on SiO₂ (6:1 → 2:1 → 1:2 hexanes/Et₂O) to afford vinylogous β-ketoester 271 (679.8 mg, 2.55 mmol, 86% yield over two steps) as a colorless oil. \( R_f = 0.53 \) (2:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 5.94–5.81 (m, 1H), 5.36 (s, 3H), 5.29 (app dq, \( J = 17.2, 1.6, 1H \)), 5.20 (app dq, \( J = 10.5, 1.3 \) Hz, 1H), 4.61 (ddd, \( J = 5.5, 2.9, 1.5 \) Hz, 2H), 3.60 (d, \( J = 6.5 \) Hz, 2H), 2.65–2.35 (comp m, 4H), 2.01 (septuplet,
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$J = 6.8$ Hz, 1H), 1.88 (ddd, $J = 13.0, 8.0, 4.8$ Hz, 1H), 1.42 (s, 3H), 0.97 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 196.7, 176.9, 172.7, 131.9, 118.2, 101.8, 75.0, 65.7, 52.5, 31.8, 27.8, 26.5, 20.7, 19.2; HRMS (FAB+) $m/z$ calc’d for C$_{15}$H$_{23}$O$_4$ [M + H]$^+$: 267.1596, found 267.1594.

Vinylogous ester 272. A typical asymmetric alkylation reaction was run on 26.6 mg (0.100 mmol) of 271 at 50 °C in PhMe (0.1 M) for 33 h using (S)-55 and Pd(dmdba)$_2$. The crude material was purified by flash chromatography on SiO$_2$ (9:1 → 6:1 hexanes/EtOAc) to provide 272 (17.5 mg, 078.7 µmol, 79% yield) as a colorless oil. $R_f = 0.37$ (6:1 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 5.81–5.68 (m, 1H), 5.25 (s, 1H), 5.08 (s, 1H), 5.05–5.02 (m, 1H), 3.58 (d, $J = 3.5$ Hz, 2H), 2.42 (t, $J = 6.4$ Hz, 2H), 2.36 (dd, $J = 13.6, 7.7$ Hz, 1H), 2.18 (dd, $J = 13.6, 7.7$ Hz, 1H), 2.02 (septuplet, $J = 6.7$ Hz, 1H), 1.92 (app dt, $J = 13.4, 6.2$ Hz, 1H), 1.70 (app dt, $J = 13.5, 6.2$ Hz, 1H), 1.08 (s, 3H), 0.97 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.7, 176.2, 134.5, 118.0, 101.4, 74.8, 43.3, 41.7, 31.9, 27.9, 26.1, 22.3, 19.2; IR (Neat Film NaCl) 2962, 2932, 2875, 1654, 1611, 1384, 1368, 1239, 1194, 1178, 996, 912, 840 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{14}$H$_{22}$O$_2$ [M + H]$^+$: 223.1698, found 223.1706. HPLC conditions: 5% $i$-PrOH, OD-H column, $t_R$ (min): major = 5.75, minor = 6.40.
**4.5.2.2 ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-CARISSONE**

Vinyllogous ester 302. Diketone 301 (3.000 g, 23.78 mmol, 1.0 equiv) was partially dissolved in PhH (42.5 mL, 0.56 M), and i-BuOH (12.75 mL, 137.9 mmol, 5.8 equiv) and p-TsOH•H₂O (226 mg, 1.19 mmol, 0.05 equiv) were added with vigorous stirring. A Dean–Stark adapter and a water-cooled condenser were attached to the flask and the contents were warmed to reflux in a 104 °C oil bath. Upon consumption of 301 by TLC analysis (ca. 3.5 h), the reaction was cooled to ambient temperature, diluted with Et₂O (50 mL), and poured into saturated aq NaHCO₃ (20 mL). The layers were separated and the aq layer was extracted with Et₂O (3 x 15 mL). The organics were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to afford a pale brown oil. To this oil was added PhMe (ca. 10 mL) followed by further concentration in vacuo. Purification by bulb-to-bulb distillation yielded vinyllogous ester 302 (3.988 g, 21.88 mmol, 92% yield) as a clear, colorless oil. \( R_f = 0.48 \) (2:1 EtOAc/hexanes); bp = 135–140 °C at 0.8 torr; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta 3.76 \) (d, \( J = 6.5 \) Hz, 2H), 2.54 (ddd, \( J = 6.1, 1.5, 1.5 \) Hz, 2H), 2.34 (t, \( J = 7.1 \) Hz, 2H), 2.08–1.90 (comp m, 3H), 1.72 (app t, \( J = 1.5 \) Hz, 3H), 0.99 (d, \( J = 6.7 \) Hz, 6H). All other spectral data are consistent with reported values.
Methyl vinylogous ester 303.\(^{40}\) To a solution of \(\text{i-Pr}_2\text{NH}\) (1.12 mL, 7.99 mmol, 1.9 equiv) in THF (26 mL, 0.15 M) at 0 °C was added dropwise a solution of \(n\)-BuLi (2.55 M in hexanes, 3.06 mL, 7.80 mmol, 1.85 equiv). After 15 min, a solution of vinylogous ester 302 (765.2 mg, 4.198 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise via cannula transfer. The resulting solution was cooled to −78 °C and stirred for 45 min, to which a solution of MeI (485 µL, 7.80 mmol, 1.85 equiv) in THF (5.0 mL) was added over 30 min via positive-pressure cannula transfer. The cooling bath was allowed to expire over ca. 4 h and the reaction was quenched with brine (15 mL), the phases were separated, and the aq layer was extracted with hexanes (3 x 25 mL). The combined organics were washed with brine, dried over MgSO\(_4\), filtered, and concentrated in vacuo to a yellow oil. Purification by flash chromatography (4:1 \(\rightarrow\) 2:1 hexanes/Et\(_2\)O) afforded methyl vinylogous ester 303 (659 mg, 3.36 mmol, 80% yield) as a pale yellow oil. \(R_f = 0.48\) (2:1 hexanes/EtOAc); \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 3.73 (ddd, \(J = 15.6, 9.2, 6.5\) Hz, 2H), 2.61 (ddd, \(J = 17.3, 5.3, 1.2\) Hz, 1H), 2.55–2.44 (m, 1H), 2.35–2.19 (m, 1H), 2.06 (app dq, \(J = 8.3, 4.8\) Hz, 1H), 1.98 (app septet, \(J = 6.6\) Hz, 1H), 1.71 (dd, \(J = 1.6, 1.6\) Hz, 3H), 1.73–1.60 (m, 1H), 1.14 (d, \(J = 6.9\) Hz, 3H), 0.99 (d, \(J = 6.7\) Hz, 6H). All other spectral data are consistent with reported values.
**Enol carbonate 287.** To a solution of $i$-Pr$_2$NH (1.56 mL, 11.15 mmol, 1.2 equiv) in THF (85 mL, 0.11 M) at 0 ºC was added a solution of $n$-BuLi (2.55 M in hexanes, 4.0 mL, 10.22 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to stir for 30 min and then cooled to −78 ºC. A solution of ketone 303 (1.824 g, 9.29 mmol, 1.0 equiv) in THF (10 mL) was added dropwise via cannula and stirred for 1 h. TMEDA (1.67 mL, 11.15 mmol, 1.2 equiv) was then added via syringe and the resulting solution stirred for 75 min. To this solution was added allyl chloroformate (1.08 mL, 10.13 mmol, 1.09 equiv) via syringe and the reaction mixture was stirred at −78 ºC for an additional hour. The reaction was quenched with saturated aq NaHCO$_3$ (40 mL) and H$_2$O (40 mL), and the flask was transferred to a 23 ºC water bath and allowed to equilibrate. The phases were separated and the aqueous was extracted with Et$_2$O (2 x 200 mL). The combined organics were washed with brine, dried over MgSO$_4$, and concentrated in vacuo to afford enol carbonate 287 as a yellow oil (2.472 g); $^1$H NMR analysis shows 287 is the major product with other impurities present. $R_f$ = unstable to SiO$_2$; $^1$H NMR (500 MHz, CDCl$_3$) δ 5.97 (dddd, $J$ = 16.4, 10.8, 5.8, 5.8 Hz, 1H), 5.42 (app d, $J$ = 17.2 Hz, 1H), 5.33 (app d, $J$ = 10.4 Hz, 1H), 4.72 (dd, $J$ = 5.7, 0.8 Hz, 2H), 3.86 (d, $J$ = 6.7 Hz, 2H), 2.85 (app t, $J$ = 7.9 Hz, 2H), 2.52 (app t, $J$ = 7.9 Hz, 2H), 2.19 (s, 3H), 1.92 (app septuplet, $J$ = 6.7 Hz, 1H), 1.82 (s, 3H), 0.93 (d, $J$ = 6.7 Hz, 6H); IR (Neat Film NaCl) 2963, 1760, 1736, 1699, 1361, 1248, 1170, 990 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{13}$H$_{19}$O$_4$ [M − C$_3$H$_7$]: 239.1283, found 239.1273.

This material was unstable to various purification attempts (distillation or flash chromatography using silica gel or Florisil) and storage. Aromatic carbonate 304 was identified as a colorless oil from this complex mixture. $R_f$ = 0.51 (4:1 hexanes/EtOAc);
$^1$H NMR (500 MHz, CDCl₃) δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 6.00 (dddd, $J = 17.1$, 10.5, 5.7, 5.7 Hz, 1H), 5.43 (dddd, $J = 17.2$, 1.4, 1.4, 1.4 Hz, 1H), 5.33 (dddd, $J = 10.5$, 1.2, 1.2, 1.2 Hz, 1H), 4.75 (app dt, $J = 5.8$, 1.3 Hz, 2H), 3.70 (d, $J = 6.4$ Hz, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.09 (app septuplet, $J = 6.6$ Hz, 1H), 1.03 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl₃) δ 156.3, 153.0, 148.7, 131.4, 127.7, 121.8, 119.5, 119.4, 109.1, 74.9, 69.2, 28.6, 19.5, 15.7, 9.2; IR (Neat Film NaCl) 2960, 2874, 1762, 1494, 1470, 1365, 1244, 1202, 1172, 1115, 1048, 799 cm⁻¹; HRMS (FAB+) $m/z$ calc’d for C₁₆H₂₂O₄ [M]: 278.1518, found 278.1517.

**β-Ketoester (+)-275.** To a –78 °C solution of i-Pr₂NH (425 µL, 3.03 mmol, 1.9 equiv) in PhMe (10 mL) was added dropwise n-BuLi (2.55 M in hexanes, 1.16 mL, 2.96 mmol, 1.85 equiv). The reaction vessel was placed in an ice/water bath and allowed to stir for 10 min, and then cooled to –78 °C. A solution of vinylogous ester 302 (291 mg, 1.60 mmol, 1.0 equiv) in PhMe (1.4 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (173 µL, 1.63 mmol, 1.02 equiv) was added dropwise, and the reaction vessel was allowed to warm to 23 °C over 1 h. After stirring for 4 h, the reaction was slowly quenched with aq KHSO₄ (1 N, 4 mL) and the resulting biphasic mixture was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et₂O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL),
dried over MgSO$_4$, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

The resulting crude yellow oil was dissolved in MeCN (5.9 mL, 0.27 M), and Cs$_2$CO$_3$ (603 mg, 1.85 mmol, 1.16 equiv), and MeI (276 µL, 4.44 mmol, 2.8 equiv) were added. A water-cooled condenser was attached to the flask and the resulting suspension was warmed to reflux in an 80 °C oil bath with vigorous stirring. After 10 h, the reaction was cooled to room temperature and diluted with EtOAc (25 mL). The organics were dried with MgSO$_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (15:1 → 9:1 → 4:1 hexanes/EtOAc) afforded β-ketoester (±)-275 as pale yellow oil (246 mg, 55% yield over two steps). $R_f = 0.27$ (2:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.82 (dddd, $J = 17.2$, 10.7, 5.4, 5.4 Hz, 1H), 5.22 (dddd, $J = 17.2$, 1.6, 1.6, 1.6 Hz, 1H), 5.15 (dddd, $J = 10.5$, 1.2, 1.2, 1.2 Hz, 1H), 4.56 (dddd, $J = 13.5$, 5.4, 1.5, 1.5 Hz, 2H), 3.72 (ddd, $J = 9.2$, 6.6, 3.2 Hz, 2H), 2.69–2.62 (m, 1H), 2.53–2.44 (comp m, 2H), 1.95 (app septuplet, $J = 6.6$ Hz, 1H), 1.85–1.80 (m, 1H), 1.70 (dd, $J = 1.5$, 1.5 Hz, 3H), 1.36 (s, 3H), 0.95 (dd, $J = 6.7$, 0.8 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 195.8, 172.6, 170.3, 131.9, 117.8, 113.8, 73.9, 65.5, 51.6, 31.2, 28.8, 23.0, 20.8, 19.1, 19.0, 8.0; IR (Neat Film NaCl) 2961, 2935, 2875, 1733, 1649, 1618, 1460, 1382, 1354, 1237, 1176, 1103, 983 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_{16}$H$_{25}$O$_4$ [M + H]$^+$: 281.1753, found 281.1740.

Vinylogous Thioester 305.\textsuperscript{4a} To a solution of diketone 301 (2.500 g, 19.82 mmol,
1.0 equiv) in MeCN (22.0 mL, 0.9 M) was added Et$_3$N (3.1 mL, 22.2 mmol, 1.12 equiv) and the solution was allowed to stir for 5 min, then cooled to 0 °C. Methanesulfonyl chloride (1.63 mL, 21.0 mmol, 1.06 equiv) was added, and the reaction was warmed to 23 °C over 2 h. Stirring was continued for 5 h, at which point the reaction was cooled to 0 °C. Triethylamine (3.1 mL, 22.2 mmol, 1.12 equiv) was added, followed by benzenethiol (2.1 mL, 20.4 mmol, 1.03 equiv). The reaction was allowed to warm to 23 °C over 2 h and stirring was continued for 9 h. Saturated aq Na$_2$CO$_3$ (35 mL) was added, the phases were separated, and the aq phase was extracted with Et$_2$O (3 x 60 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (4:1 → 2:1 hexanes/Et$_2$O) afforded vinylogous thioester 305 as a white crystalline solid (3.565 g, 16.33 mmol, 82% yield). $R_f = 0.34$ (1:1 hexanes/Et$_2$O); mp = 85 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.51–7.49 (m, 2H), 7.44–7.37 (comp m, 3H), 2.38 (t, $J = 6.5$ Hz, 2H), 2.18 (tq, $J = 6.5, 2.0$ Hz, 2H), 1.97 (t, $J = 2.0$ Hz, 3H), 1.87 (app pentuplet, $J = 6.0$ Hz, 2H). All other spectral data are consistent with reported values.

**β-Ketoester (±)-277.** To a –78 °C solution of i-Pr$_2$NH (2.63 mL, 18.78 mmol, 2.00 equiv) in PhMe (70 mL) was added dropwise n-BuLi (2.53 M in hexanes, 7.24 mL, 2.00 equiv). The reaction vessel was warmed to 0 °C, allowed to stir for 10 min, and cooled to –78 °C. A solution of vinylogous thioester 305 (2.00 g, 9.16 mmol, 1.00 equiv) in PhMe
(15 mL) was added dropwise via cannula to the reaction vessel, and the resulting solution was allowed to stir for 30 min. Allyl chloroformate (1.02 mL, 9.62 mmol, 1.05 equiv) was added dropwise and the reaction vessel was allowed to warm to 23 °C over 1 h. Stirring was continued for 4 h, at which point aq KHSO₄ (1 N, 70 ml) was slowly added and the resulting solution was allowed to stir for 10 min. The phases were separated, and the aq phase was extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The isolated crude yellow oil was used in the next step without further purification.

To a solution of the crude yellow oil (3.32 g) in CH₃CN (40 mL) in a flask with an attached reflux condenser was added cesium carbonate (4.48 g, 13.74 mmol, 1.50 equiv) and MeI (1.71 mL, 27.48 mmol, 3.00 equiv). The resulting suspension was refluxed at 80 °C for 5 h, at which point additional MeI (1.00 mL, 16.06 mmol, 1.75 equiv) was added. The reaction was refluxed at 80 °C for 2 h, cooled to room temperature, filtered through Celite (EtOAc eluent), dried over Na₂SO₄, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (18% EtOAc in hexanes) afforded β-ketoester (±)-277 as a colorless oil that solidifies to a white solid over time or in a –20 °C freezer (2.26 g, 7.14 mmol, 78% yield over two steps). Rf = 0.35 (30% EtOAc in hexanes); mp 34 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.51–7.35 (comp m, 5H), 5.87 (app ddt, J = 10.5, 17.1, 5.4 Hz, 1H), 5.27 (app ddt, J = 17.1, 1.7, 1.8 Hz, 1H), 5.22 (app ddt, J = 9.9, 1.7, 1.2 Hz, 1H), 4.65 (ddddd, J = 1.5, 1.8, 13.5 Hz, 1H), 4.55 (ddddd, J = 1.5, 1.8, 5.7, 13.5 Hz, 1H), 2.41–2.32 (m, 1H), 2.30–2.21 (m, 1H), 2.16–2.06 (1H), 2.00 (t, J = 1.8 Hz, 3H), 1.78 (ddd, J = 4.5, 8.1, 13.2 Hz, 1H), 1.38 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 193.0, 172.6, 156.7, 135.6, 131.9, 129.7, 129.5, 128.9, 118.1, 65.7,
Ketone (+)-276 from enol carbonate 287. A 1 dram vial containing a stir bar was charged with Pd$_2$(pmdba)$_3$ (4.9 mg, 0.0045 mmol, 0.025 equiv) and (S)-55 (4.4 mg, 0.0112 mmol, 0.0625 equiv), sealed with a septum, and the atmosphere was purged by three evacuate/purge cycles. To this was added PhMe (0.9 mL) and the ligation reaction was stirred for 30 min in a 25 °C oil bath, upon which time a solution of enol carbonate 287 (50.2 mg, 0.179 mmol, 1.0 equiv) in PhMe (0.9 mL, 0.1 M total) was added via cannula. After 21.5 h the reaction was diluted with Et$_2$O (2 mL), filtered through a SiO$_2$ plug, and concentrated in vacuo. The filtrate was purified by flash chromatography on SiO$_2$ (15:1 → 4:1 hexanes/EtOAc) to afford ketone 276 as a pale yellow oil (22–61% yield, 84–88% ee). $R_f = 0.49$ (4:1 hexanes/EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.73 (dddd, $J = 16.6, 10.6, 7.4, 7.4$ Hz, 1H), 5.06–5.04 (m, 1H), 5.04–5.01 (m, 1H), 3.74 (dd, $J = 9.7, 6.7$ Hz, 2H), 2.59–2.47 (comp m, 2H), 2.33 (dd, $J = 13.7, 7.2$ Hz, 1H), 2.16 (dddd, $J = 13.7, 7.6, 1.0, 1.0$ Hz, 1H), 1.98 (app septuplet, $J = 6.6$ Hz, 1H), 1.90 (dd, $J = 13.3, 7.2, 5.7$ Hz, 1H), 1.72–1.67 (m, 1H), 1.70 (dd, $J = 1.6, 1.6$ Hz, 3H), 1.06 (s, 3H), 0.99 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.7, 169.5, 134.8, 117.8, 113.3, 73.8, 42.5, 41.9, 31.5, 29.0, 22.5, 22.4, 19.2, 8.0; IR (Neat Film NaCl) 3076, 2962, 2931, 1622,
1463, 1381, 1355, 1229, 1113, 1002, 915 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₅H₂₄O₂ [M]+: 236.1776, found 236.1771; [α]D²¹.₂ +13.2° (c 0.20, CH₂Cl₂, 88% ee). SFC conditions: 5% i-PrOH, AD column, tᵣ (min): major = 5.18, minor = 6.02.

**Ketone (+)-276 from β-ketoester (±)-275.** A 2-dram vial containing a stir bar was charged with Pd₂(pmdba)₃ (10.6 mg, 0.00968 mmol, 0.025 equiv) and (S)-55 (9.4 mg, 0.0242 mmol, 0.0625 equiv). This was connected to a 1-dram vial containing a stir bar and β-ketoester (±)-275 (108.6 mg, 0.387 mmol, 1.0 equiv) via a cannula, and PhMe (3.9 mL, 0.1 M) was added to the vial containing the Pd/L and immediately immersed in liquid N₂. The vials were rigorously degassed by three freeze-pump-thaw cycles and warmed to 23 °C. After ligation for 30 min (purple → orange color change), the catalyst solution was transferred to the substrate via cannula and immersed in an 80 °C oil bath, at which point the reaction immediately turned yellow in color. After 23 h the reaction was cooled to ambient temperature, diluted with Et₂O (4 mL), and filtered through a small SiO₂ plug. The filtrate was concentrated and purified by flash chromatography as above to afford ketone 276 as a colorless oil (78.5 mg, 0.332 mmol, 86% yield, 75% ee).
Ketone (+)-278 from β-ketoester (±)-277. The reaction was performed exactly as described for enol carbonate 287 using β-ketoester (±)-277 (41.8 mg, 0.132 mmol, 1.0 equiv). After complexation of the metal for 30 min at 25 °C, a solution of the substrate was added and the reaction was warmed to 50 °C in an oil bath. After 23 h, the reaction was cooled to room temperature, diluted with Et₂O, and filtered through a SiO₂ plug. The filtrate was concentrated and purified by flash chromatography (15:1 → 9:1 hexanes/EtOAc) to afford ketone 278 as a colorless oil (31.0 mg, 0.114 mmol, 86% yield, 92% ee). R_f = 0.35 (9:1 hexanes/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.52–7.48 (m, 2H), 7.43–7.35 (comp m, 3H), 5.68 (dddd, J = 16.6, 10.4, 7.6, 7.6 Hz, 1H), 5.03 (dddd, J = 9.9, 2.4, 0.9, 0.6 Hz, 1H), 5.01 (dddd, J = 17.4, 2.4, 1.5, 1.2 Hz, 1H), 2.32 (app ddt, J = 13.8, 7.2, 1.2 Hz), 2.19–2.10 (comp m, 3H), 1.96 (app t, J = 1.8 Hz, 3H), 1.81 (dd, 13.5, 6.4, 6.4 Hz, 1H), 1.66–1.56 (m, 1H), 1.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 199.5, 155.6, 135.6, 134.4 130.3, 129.6, 129.5, 128.8, 118.2, 43.1, 41.7, 33.1, 26.9, 22.3, 12.9; IR (Neat Film NaCl) 3074, 2964, 2929, 1652, 1582, 1440, 1339, 1287, 1228 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₇H₂₀OS [M + H]⁺: 273.1313, found 273.1317; [α]D²⁹ +56.7° (c 1.36, CH₂Cl₂, 92% ee). HPLC conditions: 4% EtOH in hexanes, AD column, t_R (min): major = 7.24, minor = 9.48.

Scale up of ketone (−)-278 from β-ketoester (±)-277. In a glove box, a flask containing a stir bar was charged with Pd₂(pmdba)₃ (493.1 mg, 045 mmol, 0.025 equiv)
and ligand \((R)-55\) (435.9 mg, 1.125 mmol, 0.0625 equiv). The solids were dissolved in PhMe (150 mL) and stirred for 45 min (purple \(\rightarrow\) orange color change). To this was added a solution of \(\beta\)-ketoester \((\pm)-277\) (5.6956 g, 18.00 mmol, 1.0 equiv) in PhMe (30 mL, 0.1 M total). The flask was transferred out of the glove box, placed under an argon atmosphere and warmed in a 50 °C oil bath (orange \(\rightarrow\) yellow color change). After 66 h, the reaction was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography (as above, dry load onto SiO\(_2\)) afforded ketone \((-)-278\) as a pale yellow oil (4.184 g, 15.36 mmol, 85% yield, 92% ee) and recovered \(\beta\)-ketoester \((\pm)-277\) (500.5 mg, 1.582 mmol, 9% yield). \([\alpha]_D^{25.4} = -57.4^\circ\) (c 1.00, \(\text{CH}_2\text{Cl}_2\), 92% ee).

\[ \text{Methoxy vinylogous ester } (-)-288. \]

To a 3-neck flask equipped with water-cooled reflux condenser charged with dry MeOH (33.7 mL, 0.26 M) at 0 °C was added hexanes-washed Na\(^0\) (1.047 g, 45.5 mmol, 5.2 equiv), after which the bath was removed. The contents were stirred at 23 °C until all Na\(^0\) was dissolved. A solution of ketone 278 (2.3991 g, 8.81 mmol, 1.0 equiv) in MeOH (10 mL) was added dropwise via cannula to the generated NaOMe and the resulting solution was heated in an oil bath at 70 °C. Upon consumption of 278 by TLC analysis (4:1 hexanes/EtOAc), the reaction mixture was cooled to ambient temperature and transferred to a separate flask with Et\(_2\)O and concentrated in vacuo to a thick yellow slurry. This was dissolved in saturated aq NaHCO\(_3\) (150 mL), stirred for ca. 20 min, and extracted with Et\(_2\)O (3 x 100 mL). The
organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to a yellow oil. Purification by flash chromatography (15:1 → 6:1 hexanes/EtOAc) afforded ketone (−)-288 as a colorless oil that solidifies in a −20 °C freezer to an off-white semisolid (1.5241 g, 7.845 mmol, 89% yield). $R_f = 0.40$ (4:1 hexanes-EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.74 (dddd, $J = 16.8$, 10.5, 7.5, 7.5 Hz, 1H), 5.07–5.05 (m, 1H), 5.05–5.02 (m, 1H), 3.80 (s, 3H), 2.62–2.49 (comp m, 2H), 2.33 (dd, $J = 13.7$, 7.2 Hz, 1H), 2.17 (dddd, $J = 13.8$, 7.6, 1.0, 1.0 Hz, 1H), 1.92 (ddd, $J = 13.4$, 7.2, 5.8 Hz, 1H), 1.72 (ddd, $J = 13.4$, 6.7, 5.6 Hz, 1H), 1.68 (dd, $J = 1.6$, 1.6 Hz, 3H), 1.06 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 202.6, 169.6, 134.8, 117.9, 113.2, 55.0, 42.5, 41.9, 31.4, 22.4, 21.8, 7.9; IR (Neat Film NaCl) 2929, 1620, 1461, 1375, 1356, 1234, 1154, 1116, 999, 916 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{12}$H$_{18}$O$_2$ [M$^+$]: 194.1307, found 194.1310; $[\alpha]_D^{22.9} = -10.6^\circ$ (c 1.26, CH$_2$Cl$_2$, 92% ee).

**TBS-acrylate 307.**$^{41}$ To a solution of α-hydroxymethylacrylate 306$^{42}$ (4.7012 g, 36.19 mmol, 1.0 equiv) and TBSCI (6.00 g, 39.8 mmol, 1.1 equiv) in CH$_2$Cl$_2$ (72 mL, 0.5 M) at 0 °C was added Et$_3$N (15.1 mL, 108.6 mmol, 3.0 equiv) and DMAP (442 mg, 3.62 mmol, 0.1 equiv). The reaction was allowed to stir for 30 min, at which point the cooling bath was removed and the contents warmed to 23 °C and stirred overnight. The reaction mixture was filtered into a separatory funnel and washed with 1N HCl (70 mL),
saturated aq NaHCO₃ (100 mL), and brine (100 mL). The organics were dried over MgSO₄, filtered, and concentrated in vacuo to afford TBS-acrylate 307 as a colorless oil (8.806 g). The material was used in the next step without purification. \( R_f = 0.63 \) (6:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 6.25 (dd, \( J = 2.0, 2.0 \) Hz, 1H), 5.90 (dd, \( J = 2.0, 2.0 \) Hz, 1H), 4.37 (dd, \( J = 2.1, 2.1 \) Hz, 2H), 4.21 (q, \( J = 7.1 \) Hz, 2H), 1.30 (t, \( J = 7.1 \) Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

**Allylic alcohol 308.** To a solution of crude TBS-acrylate 307 (8.806 g, 36.03 mmol, 1.0 equiv) in THF (144 mL, 0.25 M) cooled to \(-78^\circ \)C was added dropwise \( i \)-Bu₂AlH (neat, 14.1 mL, 79.3 mmol, 2.2 equiv) over 15 min. The resulting solution was stirred at \(-78^\circ \)C until complete consumption by TLC analysis (4:1 hexanes/EtOAc), at which point the excess \( i \)-Bu₂AlH was quenched with dry EtOAc (4 mL). The resulting solution was stirred for 10 min at \(-78^\circ \)C, then warmed to 0 °C and aged for 30 min. A solution of Rochelle’s salt (75 mL, 1 M) was then added slowly with vigorous stirring. The cooling bath was removed and the contents were vigorously stirred until two homogeneous layers appeared (several hours). The phases were separated and the aq layer was extracted with Et₂O (3 x 75 mL), the combined organics were washed with brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated in vacuo to afford 308 as a cloudy colorless oil (7.29 g). The crude material was used in the next reaction without purification. \( R_f = 0.19 \) (4:1 hexanes/EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 5.10 (s, 1H), 5.08 (s, 1H), 4.24 (s, 2H), 4.17 (d, \( J = 5.5 \) Hz, 2H), 1.95 (t, \( J = 6.0 \) Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

**Allylic bromide 289.** To a solution of crude allylic alcohol 308 (7.29 g, 36.04 mmol, 1.0 equiv) in CH₂Cl₂ (120 mL, 0.3 M) cooled to 0 °C was added CBr₄ (17.942,
54.1 mmol, 1.5 equiv) and PPh\(_3\) (11.331 g, 43.2 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C until consumption by TLC analysis (4:1 hexanes/EtOAc; required ca. 30 min). The reaction was then quenched slowly with saturated aq NaHCO\(_3\) (40 mL) and warmed to ambient temperature while stirring. The phases were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over MgSO\(_4\), filtered, and concentrated in vacuo to afford a yellow oil containing a Ph\(_3\)PO precipitate. This material was dry loaded on SiO\(_2\) and purified by flash chromatography (24:1 → 15:1 → 3:1 hexanes/Et\(_2\)O). Fractions containing the desired product were repurified by flash chromatography on SiO\(_2\) (49:1 → 24:1 hexanes/acetone) to afford allylic bromide 289 as a pale yellow oil (5.4251 g, 20.45 mmol, 57% yield over 3 steps). \(R_f = 0.48\) (24:1 hexanes/Et\(_2\)O); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 5.26–5.25\) (m, 1H), 5.23 (ddd, \(J = 1.4, 1.4, 1.4\) Hz, 1H), 4.27 (dd, \(J = 1.4, 1.4\) Hz, 2H), 4.01 (s, 2H), 0.92 (s, 9H), 0.10 (s, 6H). All other spectral data are consistent with reported values.

**Triolefin (−)-290.** To a flask containing Mg\(^0\) turnings (125.4 mg, 5.16 mmol, 3.0 equiv) was added Et\(_2\)O (30 mL) and a chip of I\(_2\). The contents were stirred for 25 min at 23 °C and then cooled to 0 °C. A solution of allylic bromide 289 (1.141 g, 4.30 mmol, 2.5 equiv) in Et\(_2\)O (5 mL) was transferred via cannula to the Mg/Et\(_2\)O and stirred for 30 min at 0 °C, then warmed to 23 °C over 30 min. A solution of ketone 288 (333.5 mg,
1.72 mmol, 1.0 equiv) in THF (5 mL) was transferred dropwise to the allylmagnesium bromide via cannula, followed by washings to total 35 mL of THF. Upon consumption of ketone 288 by TLC analysis (4:1 hexanes/EtOAc), the reaction was quenched slowly with aq ammonium chloride (50 mL) and stirred until complete dissolution of Mg\(^0\). The phases were separated and the aq phase was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over MgSO\(_4\), filtered, and concentrated to a pale yellow oil. Purification by flash chromatography (9:1 → 4:1 hexanes/Et\(_2\)O, dry load onto SiO\(_2\)) afforded the desired triolefin 290 as a colorless oil (563.4 mg, 1.616 mmol, 94% yield). \(R_f = 0.62\) (4:1 hexanes/EtOAc); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.54 (dddd, \(J = 17.6, 10.3, 7.3, 7.3\) Hz, 1H), 5.06 (dd, \(J = 3.2, 1.7\) Hz, 1H), 4.97 (ddd, \(J = 10.3, 2.2, 1.2\) Hz, 1H), 4.92 (ddd, \(J = 16.9, 2.4, 1.2, 1.2\) Hz, 1H), 4.56 (d, \(J = 1.2\) Hz, 2H), 3.95 (s, 2H), 2.75 (dd, \(J = 17.1, 17.1\) Hz, 2H), 2.36 (ddddd, \(J = 17.1, 17.1, 10.3, 5.1\) Hz, 1H), 2.33 (ddddd, \(J = 17.1, 17.1, 7.1, 5.4\) Hz, 1H), 2.01 (ddddd, \(J = 13.9, 13.9, 13.9, 7.6\) Hz, 2H), 1.89 (s, 3H), 1.60 (ddd, 13.4, 6.8, 5.1 Hz, 1H), 1.41 (ddd, 13.4, 10.0, 5.1 Hz, 1H), 0.98 (s, 9H), 0.87 (s, 3H), 0.06 (s, 6H); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 196.6, 158.9, 144.4, 134.5, 134.3, 118.0, 110.3, 67.1, 43.2, 39.2, 34.2, 33.9, 33.2, 26.1, 23.9, 18.5, 12.5, –5.2; IR (Neat Film NaCl) 3078, 2930, 2857, 1668, 1610, 1463, 1337, 1081, 1005, 912, 836, 776 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc’d for C\(_{21}\)H\(_{36}\)O\(_2\)Si \([M]^+\): 348.2485, found 348.2499; [\(\alpha\)]\(_D\)\(^{21.0}\) –37.3° (c 1.11, CH\(_2\)Cl\(_2\), 92% ee).
Cyclohexene \((-\text{292})\). Triolefin \textbf{290} (280.1 mg, 0.804 mmol, 1.0 equiv) was dissolved in PhH (16 mL, 0.05 M) and sparged with N\(_2\) for 15 min. Grubbs’ catalyst \textbf{291} (20.5 mg, 0.0241 mmol, 0.03 equiv) was added to the solution and the flask was placed in a 40 °C oil bath. Upon consumption by TLC analysis (3:1 hexanes/Et\(_2\)O), the reaction was cooled to ambient temperature and ethyl vinyl ether (8 mL) was added to the solution. After stirring for ca. 30 min the solution was concentrated in vacuo. Purification via flash chromatography (9:1 → 4:1 hexanes/Et\(_2\)O) afforded cyclohexane \textbf{292} as a colorless oil (256.3 mg, 0.800 mmol, 99% yield). \(R_f = 0.30\) (3:1 hexanes/Et\(_2\)O); \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.58 (dddd, \(J = 5.4, 1.5, 1.5, 1.5\) Hz, 1H), 3.93 (d, \(J = 1.2\) Hz, 1H), 2.86 (d, \(J = 22.0\) Hz, 1H), 2.60 (d, \(J = 21.7\) Hz, 1H), 2.32–2.29 (comp m, 2H), 1.87 (d, \(J = 1.2\) Hz, 3H), 1.83 (dd, \(J = 16.9, 2.0\) Hz, 1H), 1.61 (dd, \(J = 16.9, 6.1\) Hz, 1H), 1.45–1.35 (comp m, 2H), 0.99 (s, 9H), 0.85 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\) 196.4, 157.4, 135.1, 129.5, 119.5, 66.7, 39.6, 36.4, 35.1, 34.3, 29.7, 26.1, 24.0, 18.6, 11.2, –5.1, –5.2; IR (Neat Film NaCl) 2929, 2857, 1668, 1615, 1463, 1305, 1257, 1158, 1086, 1048, 837, 776 cm\(^{-1}\); HRMS (EI+) \(m/z\) calcd for C\(_{19}\)H\(_{31}\)O\(_2\)Si [M + H – H\(_2\)]\(^+\): 319.2093, found 319.2096; \([\alpha]_D^{21.2}\) –9.4° (c 0.60, CH\(_2\)Cl\(_2\), 92% ee).
Enone (+)-309. Cyclohexene 292 (25.0 mg, 78.0 µmol, 1.0 equiv) was dissolved in MeOH (3.1 mL, 25 mM) and Rh/Al₂O₃ catalyst (40.1 mg, 3.90 µmol, 0.05 equiv) was added with vigorous stirring. The vial was placed under an atmosphere of hydrogen via a balloon and stirred at 26 °C. Upon consumption by TLC (3:1 hexanes/Et₂O, developed thrice), the solids were filtered over Celite washing with EtOAc and concentrated in vacuo. Purification via flash chromatography (9:1 hexanes/Et₂O) afforded the desired enone 309 as a colorless oil (14.8 mg, 45.9 µmol, 59% yield, 10:1 dr). \( R_f = 0.36 \) (3:1 hexanes/Et₂O, developed twice); \(^1\)H NMR (500 MHz, \( C_6D_6 \), major diastereomer) \( \delta \) 3.33 (ddd, \( J = 14.0, 9.8, 5.1 \) Hz, 2H), 2.63 (ddd, \( J = 14.7, 1.7, 1.7 \) Hz, 1H), 2.38–2.26 (comp m, 2H), 1.96 (s, 3H), 1.68 (dd, \( J = 13.7, 13.7 \) Hz, 1H), 1.44 (ddd, \( J = 13.4, 13.4, 3.7 \) Hz, 1H), 1.42–1.39 (m, 1H), 1.31–1.23 (comp m, 2H), 1.08 (ddd, \( J = 14.2, 14.2, 3.6 \) Hz, 1H), 0.99 (s, 9H), 0.84 (s, 3H), 0.06 (s, 6H); \(^{13}\)C NMR (126 MHz, \( C_6D_6 \)) \( \delta \) 197.0, 160.0, 129.2, 68.1, 41.6, 41.5, 37.7, 36.0, 34.1, 30.9, 26.1, 24.7, 22.2, 18.5, 11.2, −5.2 (2C); IR (Neat Film NaCl) 2928, 2857, 1668, 1612, 1472, 1256, 1098, 838, 776 cm\(^{-1}\); HRMS (FAB+) \( m/z \) calc’d for \( C_{19}H_{35}O_2Si [M + H]^+ \): 323.2406, found 323.2402; \([\alpha]_D^{21.4} +73.0^\circ \) (c 0.53, CH₂Cl₂, 92% ee).
Alcohol (+)-293. Enone 309 (40.3 mg, 0.125 mmol, 1.0 equiv) was dissolved in THF (2.5 mL, 50 mM) and aq 1 N HCl (1.0 mL) was added with vigorous stirring. Upon consumption by TLC (2:1 hexanes/EtOAc), brine was added, the layers were separated, and the aq layer was extracted with Et₂O (3 x 4 mL). The combined organics were washed with saturated aq NaHCO₃, this aq was back extracted with Et₂O (2 x 5 mL), the organics were dried over MgSO₄, filtered, and concentrated in vacuo. Purification via flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded alcohol 293 as a colorless oil (24.5 mg, 0.118 mmol, 94% yield, 10:1 dr). \( R_f = 0.37 \) (1:1 hexanes/EtOAc); \( ^1H \) NMR (500 MHz, C₆D₆, major diastereomer) \( \delta 3.12 \) (d, \( J = 5.5 \) Hz, 2H), 2.52 (ddd, \( J = 14.6, 1.9, 1.9 \) Hz, 1H), 2.37–2.24 (comp m, 2H), 1.92 (dd, \( J = 1.3, 1.3 \) Hz, 3H), 1.52 (ddd, \( J = 13.1, 13.1, 3.1 \) Hz, 1H), 1.43 (ddd, \( J = 13.4, 13.4, 5.3 \) Hz, 1H), 1.36–1.33 (m, 1H), 1.29–1.21 (comp m, 3H), 1.17–1.09 (m, 1H), 1.03 (ddd, \( J = 12.9, 12.9, 3.3 \) Hz, 1H), 0.79 (s, 3H), 0.74 (br s, 1H); \( ^{13}C \) NMR (126 MHz, C₆D₆) \( \delta 197.2, 160.1, 129.1, 67.7, 41.5, 41.4, 37.7, 35.9, 34.1, 30.8, 24.6, 22.2, 11.3; IR (Neat Film NaCl) 3418 (br), 2924, 1660, 1652, 1608, 1453, 1352, 1150, 1083, 1013 cm⁻¹; HRMS (EI+) \( m/z \) calc’d for \( C_{13}H_{20}O_2 \) [M]+: 208.1463, found 208.1463; \([\alpha]_D^{23} +120.9^\circ \) (c 0.35, CH₂Cl₂, 92% ee).

Ester (+)-294. To a solution of alcohol 293 (24.5 mg, 0.118 mmol, 1.0 equiv) in CH₂Cl₂ (2.4 mL, 50 mM) at 0 °C was added Dess–Martin periodinane (69.8 mg, 0.165 mmol, 1.4 equiv), and after 5 min the bath was removed and the reaction was
stirred at room temperature. Upon completion by TLC analysis (2:1 hexanes/EtOAc), the reaction was diluted with 1:1 hexanes/Et₂O (4 mL) and filtered through a small silica gel plug. Heptanes (5 mL) were added and the filtrate was concentrated in vacuo to a white solid. Purification by filtration through a silica gel plug (3:1 → 1:1 hexanes/Et₂O) afforded a colorless oil (22.3 mg) that was used in the next step.

The resulting material was dissolved in t-BuOH (1.7 mL), to which 2-methyl-2-butene (85 µL, 0.80 mmol, 7.4 equiv) was added with stirring. To this was added a solution of NaH₂PO₄•H₂O (103 mg, 0.746 mmol, 6.9 equiv) and NaClO₂ (89.9 mg, 0.995 mmol, 9.2 equiv) in water (850 µL) over ca. 5 min. Upon consumption by TLC analysis (1:1 hexanes/EtOAc), the t-BuOH was removed on a rotovap, water (2 mL) was added to this slurry, and 1 N HCl was added dropwise until pH < 3. The resulting aq layer was extracted with Et₂O (4 x 4 mL), a stir bar was added and the extract was cooled in an ice/water bath. A fresh solution of CH₂N₂ in Et₂O (5 mL) was added and the bath was allowed to expire. After the solution was colorless it was dried over MgSO₄, filtered, and concentrated in vacuo. Purification via flash chromatography (3:1 → 2:1 hexanes/Et₂O) afforded ester 294 as a colorless oil that solidifies to a white solid over time or in a −20 °C freezer (24.4 mg, 0.103 mmol, 87% yield over two steps). The diastereomers are separable by flash chromatography with 3:1 hexanes/Et₂O. \( R_f = 0.59 \) (1:1 hexanes/EtOAc); mp = 46–48 °C; \(^1\)H NMR (500 MHz, C₆D₆, major diastereomer) \( \delta \)

3.38 (s, 3H), 2.83–2.76 (m, 1H), 2.30–2.09 (comp m, 4H), 1.82 (m, 3H), 1.66–1.62 (comp m, 2H), 1.32 (ddd, \( J = 13.6, 13.6, 4.9 \) Hz, 1H), 1.17 (ddd, \( J = 13.2, 3.9, 3.9 \) Hz, 1H), 1.12 (ddd, \( J = 13.5, 2.8, 2.8 \) Hz, 1H), 0.91–0.85 (m, 1H), 0.72 (s, 3H); \(^13\)C NMR (126 MHz, C₆D₆) \( \delta \)

196.8, 174.7, 157.7, 129.9, 51.3, 43.5, 40.9, 37.4, 35.4, 34.0, 29.9,
Diol (+)-295. To a solution of ester 294 (10.1 mg, 42.7 µmol, 1.0 equiv) in MeOH (1.7 mL, 25 mM) was added CeCl₃•7H₂O (47.8 mg, 128 µmol, 3.0 equiv), followed by cooling to ca. −45 °C in a MeCN/CO₂(s) bath. Solid NaBH₄ (3.2 mg, 85.5 µmol, 2.0 equiv) was added, and upon consumption by TLC analysis (1:1 hexanes/EtOAc), acetone (5 drops) was added, followed by brine (1 mL) and EtOAc (1 mL). The suspension was warmed to room temperature, the aq layer was extracted with EtOAc (2 x 4 mL), dried over MgSO₄, filtered, and concentrated in vacuo to a colorless film (9.1 mg). This material was used directly in the following reaction.

To a solution of the crude material in THF (1.5 mL, 25 mM) at 0 °C was added a solution of MeMgBr (71 µL, 2.7 M in THF, 191 µmol, 5 equiv) and the bath was removed after 5 min. Upon consumption by TLC analysis (1:1 hexanes/EtOAc), the reaction was cooled in an ice/water bath, and MeOH (200 µL), brine (1 mL), saturated aq NH₄Cl (1mL), and EtOAc (2 mL) were added. The aq layer was extracted with EtOAc (2 x 4 mL), dried over MgSO₄, filtered, and concentrated in vacuo. Purification via flash chromatography (2:1 hexanes/EtOAc) afforded diol 295 as a colorless film that solidifies over time to an off-white solid (7.4 mg, 31.0 µmol, 73% yield over two steps, >20:1 dr).
Chapter 4—Enantioselective Alkylations of Vinylogous β-Ketoesters: Synthesis of (+)-Carissone

$R_f = 0.30 \ (1:1 \ \text{hexanes/EtOAc}); \ \text{mp} = 123–126 \ ^\circ \text{C}; \ ^1\text{H} \ \text{NMR} \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 4.03 \ (\text{app t, } J = 6.6 \ \text{Hz, 1H}), 2.60 \ (\text{app dt, } J = 13.5, 2.8 \ \text{Hz, 1H}), 1.94–1.88 \ (m, 1H), 1.73 \ (s, 3H), 1.71–1.23 \ (\text{comp m, 11H}), 1.21 \ (s, 6H), 1.08 \ (s, 3H); \ ^{13}\text{C} \ \text{NMR} \ (126 \ \text{MHz, CDCl}_3) \ \delta \ 139.7, 126.9, 72.9, 71.7, 50.7, 41.7, 36.2, 35.3, 29.0, 27.4, 27.0, 26.9, 24.8, 23.2, 15.2; \ \text{IR} \ (\text{Neat Film NaCl}) \ 3366 \ (\text{br}), 2934, 2863, 1455, 1374, 1277, 1138, 1076, 1014, 922, 734 \ \text{cm}^{-1}; \ \text{HRMS} \ (\text{FAB+}) \ m/z \ \text{calc’d for C}_{15}\text{H}_{26}\text{O}_2 [\text{M}]^+: 238.1933, \ \text{found} \ 238.1921; \ [\alpha]_D^{21.6} +21.6^\circ \ (c \ 0.34, \ \text{MeOH}, \ 92\% \ \text{ee}).

![Chemical Reaction]

(+)-Carissone (279). To a solution of diol 295 (3.1 mg, 13.0 µmol, 1.0 equiv) in CH$_2$Cl$_2$ (520 µL, 25 mM) was added oven-dried 4 Å MS (15 mg), followed by MnO$_2$ (13.3 mg, 130 µmol, 10 equiv). Upon consumption by TLC (1:1 hexanes/EtOAc), the reaction was diluted with Et$_2$O (2 mL) and filtered through a small plug of silica gel, washing with Et$_2$O. This was concentrated in vacuo to afford (+)-carrisone (279) as a colorless film (3.1 mg, 131 µmol, 100% yield). $R_f = 0.34 \ (1:1 \ \text{hexanes/EtOAc}); \ ^1\text{H} \ \text{NMR} \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 2.86 \ (\text{app dt, } J = 14.4, 2.6 \ \text{Hz, 1H}), 2.51 \ (\text{ddd, } J = 16.9, 13.3, 6.4 \ \text{Hz, 1H}), 2.39 \ (\text{app dt, } J = 16.8, 3.8 \ \text{Hz, 1H}), 1.90 \ (\text{app t, } J = 13.9 \ \text{Hz, 1H}), 1.82–1.69 \ (\text{comp m, 4H}), 1.78 \ (s, 3H), 1.55–1.36 \ (\text{comp m, 3H}), 1.26 \ (s, 3H), 1.25 \ (s, 3H), 1.20 \ (s, 3H); \ ^{13}\text{C} \ \text{NMR} \ (126 \ \text{MHz, CDCl}_3) \ \delta \ 199.1, 162.6, 128.8, 72.4, 49.6, 41.9, 37.3, 35.8, 33.7, 28.7, 27.5, 26.7, 22.5, 22.4, 10.9; \ \text{IR} \ (\text{Neat Film NaCl}) \ 3448 \ (\text{br}), 2970, 2935, 1652, 1608, 1452, 1353, 1300, 1212, 1189, 1149, 1014, 918, 817 \ \text{cm}^{-1}; \ \text{HRMS} \ (\text{FAB+}) \ m/z...
calc’d for C_{15}H_{25}O_2 [M + H]^+: 237.1855, found 237.1844; [α]_D^{23.1} +119.6° (c 0.31, CHCl₃, 92% ee); lit. [α]_D^{22} +138.7° (c 0.163, CHCl₃).
4.6 NOTES AND REFERENCES


(6) Difficulties for the selective preparation of enol carbonate vinylogous ester derivatives have been noted. See Ref 4a.


(8) Qualitatively, the reaction rates for the electron deficient acyl substrates are faster than the traditional vinylogous esters. For example, substrates 181 and 263 require 10–16 h to reach complete conversion, whereas substrates 265, 267, and 269 reach full conversion in 2–4 h.

(9) We have recently obtained spectroscopic and crystallographic evidence indicating that a Pd–β-keto carboxylate complex is the resting state of the catalytic cycle for


(11) Asymmetric alkylation reactions that feature stabilized enolates typically proceed with excellent conversion and low enantioselectivity, further complicating the interpretation of the influence of enolate pKa for this transformation.


(25) Enol carbonate 287 was unstable to air, forming complex reaction mixtures that substantially affected yields and selectivities for the alkylation. Aromatic carbonate 304 was identified from this mixture. See supporting information for more details.

(26) The reactivity of vinylogous β-ketoester (±)-275 contrasts significantly with that of related derivative (±)-271. See the subsection 4.2.3.

(27) β-ketoester (±)-275 was recovered in 9% yield.


(29) Studies employing allylmagnesium bromide generated from 289, MeLi, or MeMgBr nucleophiles were unsuccessful. Difficulties with these types of additions into vinylogous thioesters have been noted. See ref 4a.


(31) A variety of homogeneous and heterogeneous catalysts were screened for the hydrogenation of 292. Of those that were reactive, most promoted undesired reactivity, including enone reduction and further decomposition. Rh/Al₂O₃ proved to be a mild catalyst at 1 atm H₂ in MeOH for this substrate.

(32) The stereochemistry of 293 was initially verified using NOE correlations. See the subsection 4.5.2.2 for details.


APPENDIX 4

Spectra Relevant to Chapter 4:

*Enantioselective Allylic Alkylation of Vinylogous β-Ketoester Derivatives: Total Synthesis of (+)-Carissone*
Figure A4.1. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 275.
Figure A4.2. Infrared spectrum (neat film/NaCl) of 275.

Figure A4.3. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 275.
Figure A4.4. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 276.
Figure A4.5. Infrared spectrum (neat film/NaCl) of 276.

Figure A4.6. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 276.
Figure A4.7. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 277.
Figure A4.8. Infrared spectrum (neat film/NaCl) of 277.

Figure A4.9. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 277.
Figure A4.10. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 278.
Figure A4.11. Infrared spectrum (neat film/NaCl) of 278.

Figure A4.12. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 278.
Figure A.13. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of (+)-cariscone (279).
Figure A4.14. Infrared spectrum (neat film/NaCl) of (+)-carissone (279).

Figure A4.15. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of (+)-carissone (279).
Figure A4.16. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 287.
Figure A4.17. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 288.
Figure A4.18. Infrared spectrum (neat film/NaCl) of 288.

Figure A4.19. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 288.
Figure A4.20. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 289.

1H NMR spectrum (300 MHz, CDCl$_3$) of 289.
Figure A4.21. $^1$H NMR spectrum (500 MHz, $C_6D_6$) of 290.
Figure A4.22. Infrared spectrum (neat film/NaCl) of 290.

Figure A4.23. $^{13}$C NMR spectrum (126 MHz, C$_6$D$_6$) of 290.
Figure A4.24. $^1$H NMR spectrum (500 MHz, $CD_6$) of 292.
Figure A4.25. Infrared spectrum (neat film/NaCl) of 292.

Figure A4.26. $^{13}$C NMR spectrum (126 MHz, $C_6D_6$) of 292.
Figure A4.27. $^1$H NMR spectrum (500 MHz, CD$_6$) of 293.
Figure A4.28. Infrared spectrum (neat film/NaCl) of 293.

Figure A4.29. $^{13}$C NMR spectrum (126 MHz, C$_6$D$_6$) of 293.
Figure A4.30. \( ^1H \) NMR spectrum (500 MHz, \( CD_3J \)) of 294.
Appendix 4—Spectra Relevant to Chapter 4

Figure A4.31. Infrared spectrum (neat film/NaCl) of 294.

Figure A4.32. $^{13}$C NMR spectrum (126 MHz, C$_6$D$_6$) of 294.
Figure A4.33. \(^1\)H NMR spectrum (500 MHz, CDCl\(_3\)) of 295.

\[ \text{HO} \quad (+)-295 \]
Figure A4.34. Infrared spectrum (neat film/NaCl) of 295.

Figure A4.35. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 295.
Figure A4.36. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 304.
Figure A4.37. Infrared spectrum (neat film/NaCl) of 304.

Figure A4.38. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 304.
Figure A.4.39: $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 307.

[Diagram of the NMR spectrum with chemical structure]
Figure A4.40. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 308.
Figure A4.1. $^1$H NMR spectrum (500 MHz, CD$_3$OD) of the major diastereomer of 309.
Figure A4.42. Infrared spectrum (neat film/NaCl) of the major diastereomer of 309.

Figure A4.43. $^{13}$C NMR spectrum (126 MHz, C$_6$D$_6$) of the major diastereomer of 309.
CHAPTER 5

Synthesis, Structural Analysis, and Gas-Phase Studies of 2-Quinuclidonium Tetrafluoroborate†

5.1 INTRODUCTION AND BACKGROUND

5.1.1 THE AMIDE LINKAGE

The amide bond is one of the most fundamental motifs in biology and chemistry as it plays the essential role of linking functionality between amino acids in peptides. Extensive studies over the past century have delineated the unique properties of this indispensable functional group.1 Typical amides exhibit remarkable stability, with half-lives in aqueous solution exceeding hundreds of years.2 This stability is in part due to resonance stabilization between the π-orbitals of the O–C–N linkage (Figure 5.1.1).1,3 The significant contribution of this resonance structure also gives rise to a planar

† This work was performed in collaboration with Tony Ly, a graduate student in laboratory of Prof. Ryan Julian at the University of California, Riverside, Don K. Pham, a summer NSF REU fellow in the Julian group, Dr. Kousuke Tani, a postdoctoral scholar in the Stoltz group, and Dr. Ryan R. Julian, assistant Prof. of Chemistry at the University of California, Riverside. These works have been published. See: (a) Ly, T.; Krout, M.; Pham, D. K.; Tani, K.; Stoltz, B. M.; Julian, R. R. J. Am. Chem. Soc. 2007, 129, 1864–1865. (b) Tani, K.; Stoltz, B. M. Nature 2006, 441, 731–734.
geometry about the peptide bond, as demonstrated by a high C–N rotational barrier (~20 kcal/mol) and the propensity for protonation at oxygen over nitrogen.\textsuperscript{1,4}

Disruption of the preferred planar geometry dramatically changes the stability and reactivity of the amide functionality. Nonplanar distortions typically lead to increased nitrogen basicity, pyramidalization of nitrogen, increased hydrolytic lability, and selective reactivity of electrophiles with nitrogen.\textsuperscript{1,5,6} Though more rare than standard amides, twisted amides are critical design elements in peptide hydrolysis,\textsuperscript{7} antibiotic efficacy of β-lactams,\textsuperscript{1} and protein folding, with importance in autoimmunosuppression.\textsuperscript{8}

\section*{5.1.2 2-QUINUCLIDONE}

The intriguing qualities of these twisted amides were first recognized in 1938 when one of the simplest families was introduced—molecules containing the 1-azabicyclo[2.2.2]octan-2-one system, the quintessential member being 2-quinuclidone (311).\textsuperscript{9} In this original report, Lukeš surmised that the most effective way to obtain an amide in twisted conformation is to constrain the nitrogen at the bridgehead of a bicyclic system. Following the report of these “anti-Bredt” lactams,\textsuperscript{10} Woodward became interested in the properties of 2-quinuclidone as it related to studies toward quinine (~1941) and later in the context of the structural elucidation of penicillin.\textsuperscript{11} The
Woodward laboratory’s inability to synthesize 311 from amino acid 310 was attributed to the unstable nature of this amide bond (Figure 5.1.2a), and was supported by the ease of the construction of constitutional isomer 313 from 312 (Figure 5.1.2b). These observations were of significance to the penicillins, as they indicated that their characteristic reactivity arises not only from ring strain of the β-lactam, but also as a result of nonplanar amide distortions in the fused bicycle.

Figure 5.1.2. a) Woodward’s failed synthesis of 311 from amino acid 310. b) Facile amide bond formation to afford constitutional isomer 313.

Subsequent studies toward 2-quinuclidone included a report by Yakhontov\textsuperscript{12} that claimed to have synthesized 311 using the Woodward approach for amide bond formation. The formation of the strained bicyclic lactam proceeded surprisingly with an aqueous workup, with the reported product (311) characterized only by elemental analysis for nitrogen. A later study by Pracejus\textsuperscript{13} failed to isolate 311 by the method of Yakhontov, calling the original synthesis into question. However, the preparation of a variety of methyl-substituted 2-quinuclidone derivatives (315–318) using the amino acid
cyclization approach supported the notion that the original Yakhontov synthesis was flawed, at least in the isolation of 311 (Scheme 5.1.1).  

Scheme 5.1.1. Synthesis of methyl-substituted 2-quinuclidone derivatives

![Scheme 5.1.1](image)

Although the definitive characterization and isolation of 311 has remained elusive despite its apparent simplicity, this quintessential twisted amide has been the subject of computational investigations. Studies of this model amide are of particular interest to explore the significance of this distortion phenomenon to provide insights into a number of research areas. Owing to the colorful history and challenges associated with the preparation, isolation, characterization of 311, we pursued a synthesis using an alternative approach to the classic route for amide bond formation.

### 5.2 THE SYNTHESIS AND CHARACTERIZATION OF 2-QUINUCLIDONIUM TETRAFLUOROBORATE

In this section we describe our synthetic approach that has enabled the unambiguous preparation and characterization of the quintessential twisted amide 2-quinuclidone (311) as its HBF₄ salt. The studies presented in section 5.2 are a partial account of work performed by Dr. Kousuke Tani.
5.2.1 SYNTHESIS OF 2-QUINUCLIDONIUM VIA AN INTRAMOLECULAR SCHMIDT–AUBÉ CYCLIZATION

At the outset of these studies, a strategy was considered that refrained from the use of typical peptide coupling reagents to aid in purification of the likely reactive molecule. It was envisioned that reactions that harnessed the release of dinitrogen could impart significant driving force to assemble the strained bicyclic system. One such approach\(^\text{19}\) that met these criteria was the intramolecular Schmidt–Aubé cyclization of ketoazide \textbf{320}, which has seen wide use for the synthesis of N-substituted lactams since its initial discovery (Scheme 5.2.1).\(^\text{20}\) Moreover, this method recently has been used for the preparation of other types of twisted lactams.\(^\text{21}\)

Scheme 5.2.1. Retrosynthetic analysis of 2-quinuclidone using the Schmidt–Aubé reaction

The preparation of ketoazide \textbf{320} was accomplished as shown in Scheme 5.2.2. Bayer–Villiger oxidation of norcamphor (\textbf{321}) provided bicyclic lactone \textbf{322} that was reduced with LiAlH\(_4\) to generate syn-diol \textbf{323} in good yield. Selective tosylation of \textbf{323} and S\(_\text{N}\)2 displacement with sodium azide produced azide \textbf{325}. Alcohol oxidation using Dess–Martin periodinane afforded the requisite ketoazide \textbf{320}. 
Initial studies toward the intramolecular Schmidt–Aubé reaction of ketoazide 320 demonstrated that a selection of strong acids (e.g., TFA, TfOH, HBF₄, and Tf₂NH) produced a noticeable gas evolution with consumption of 320. A survey of various acids and solvents established HBF₄ in Et₂O as the optimal conditions for the transformation of 320 into isomeric bicyclic lactams 311•HBF₄ and 326•HBF₄ (76:24, respectively). The observation of the two structural isomers 311:326 in ~3:1 ratio of indicated a moderately selective C–N migration of bond a from intermediate 319 to generate 2-quinuclidonium tetrafluoroborate (311•HBF₄) as a major reaction component, whereas minor product 326•HBF₄ is derived from migration of bond b from 319. The crystallinity of the crude lactams facilitated purification by selective recrystallization with MeCN/Et₂O to afford pure 2-quinuclidonium tetrafluoroborate (311•HBF₄) as colorless crystals.
5.2.2 CHARACTERIZATION, PROPERTIES, AND REACTIVITY

The structure of 311•HBF₄ was unambiguously determined by spectroscopic evaluation. The carbonyl infrared absorption band for 311•HBF₄ was observed at 1822 cm⁻¹ (KBr). This value compares well with the HCl salts of known [2.2.2]bicyclic lactams 316 and 318 (1818 and 1811 cm⁻¹, respectively) and is more consistent with that of an acid chloride (1820–1750 cm⁻¹) or anhydride (1870–1770 cm⁻¹) than an amide (1690–1650 cm⁻¹). Additionally, the ¹³C chemical shift of the carbonyl group was observed at δ 175.9 ppm (CD₃CN). Crystals suitable for X-ray analysis enabled the identification of all hydrogens from the electron density map. The structure depicted in Figure 5.2.1 shows that 311•HBF₄ exists in the N-protonated form, which has been supported by calculations (see subsection 5.3.1) and highlights the twisted nature of the amide.

Figure 5.2.1. ORTEP drawing of 311•HBF₄ (shown with 50% probability ellipsoids; BF₄ omitted for clarity).
Table 5.2.1 summarizes selected bond lengths and distortion parameters obtained from the X-ray structure of 311•HBF₄ and previously calculated structures. Two crystallographically independent molecules corresponding to 311•HBF₄ were observed in the unit cell. The observed bond lengths for the N–C(O) were 1.526 and 1.484 Å while the C=O bond lengths were 1.192 and 1.168 Å. These distances are in good agreement to calculated values for N-protonated 311•H⁺ and show a minimal decrease in the length of C=O bond while the N–C(O) bond is significantly longer than a typical amide (cf. formamide).⁴b,¹⁵c Winkler and Dunitz have described distortion parameters for the quantitative evaluation of the twisting of an amide bond, and include the pyramidalization about the nitrogen (χₙ) and carbon (χₑ) atoms and the torsion about the C–N bond (τ).²⁴ For a representative planar amide (e.g., formamide), these parameters are all 0°.²⁵ The structures of 311•HBF₄ possessed a χₙ of 58.9 and 59.5°, while the τ was found to be 90.8 and 90.9°. These values compare well with nonplanar formamide and quantitatively establish the highly twisted nature of 311•HBF₄.

<table>
<thead>
<tr>
<th>compound</th>
<th>bond length (Å)</th>
<th>distortion parameters (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N–C(O)</td>
<td>C=O</td>
</tr>
<tr>
<td>311•HBF₄ (X-ray)</td>
<td>1.526(5)</td>
<td>1.192(4)</td>
</tr>
<tr>
<td></td>
<td>1.484(6)</td>
<td>1.168(6)</td>
</tr>
<tr>
<td>311 (N-protonated, calc'd)</td>
<td>1.504</td>
<td>1.167</td>
</tr>
<tr>
<td>311 (calc'd)</td>
<td>1.433</td>
<td>1.183</td>
</tr>
<tr>
<td>formamide (planar, calc'd)</td>
<td>1.349</td>
<td>1.193</td>
</tr>
<tr>
<td>formamide (perpendicular, calc'd)</td>
<td>1.423</td>
<td>1.179</td>
</tr>
</tbody>
</table>

ᵃ Ref 24. ᵇ Ref 4. ᶜ Ref 25.
The reactivity of 2-quinuclidonium tetrafluoroborate was investigated. \( \text{311}\cdot\text{HBF}_4 \) is hypersensitive to hydrolysis, with a \( t_{1/2} = <15 \text{ s} \) in neat \( \text{D}_2\text{O} \), as well as unstable to manipulations in common nucleophilic solvents (e.g., DMSO, MeOH, pyridine). Furthermore, attempts to neutralize the salt of \( \text{311} \) with various bases lead to the formation of polymeric material, highlighting that the fortuitous protonation of \( \text{311} \) upon Schmidt–Aubé cyclization to \( \text{311}\cdot\text{HBF}_4 \) was critical to avoid decomposition. These observations provide further support for the increased reactivity that results from nonplanar distortions of the amide bond.

5.3 GAS-PHASE STUDIES

To gain further insight into twisted amides we explored the gas-phase chemistry of \( \text{311} \). In this section we present the first experimental results characterizing the basicity of \( \text{311} \), which is found to be more basic than typical amides. In addition, we report an intriguing gas-phase dissociation as well as a second synthetic route to \( \text{311}\cdot\text{H}^+ \), which only occurs in the gas phase.

5.3.1 PROTON AFFINITY VIA THE EXTENDED KINETIC METHOD

The kinetic method, which relies on competitive fragmentation of proton-bound dimers, was employed to determine the proton affinity (PA) of \( \text{311} \) relative to a series of reference bases (shown in Figure 5.3.1) according to previously established methods.\(^\text{26}\) Briefly, dimers were introduced into an LTQ linear ion trap mass spectrometer by electrospraying solutions of the tetrafluoroborate salt of \( \text{311} \) in dry acetonitrile and a
Chapter 5—Synthesis, Structural Analysis, and Gas-Phase Studies of 2-Quinuclidonium

reference base. The noncovalently bound dimers were then subjected to collision-induced dissociation (CID) to determine the most basic site (which retains the proton more often). The results are shown in Figure 5.3.1. Analysis of the data yields a PA of 230.6 kcal/mol for 311 using the simple kinetic method. Application of the more rigorous extended kinetic method\textsuperscript{27} yields a value of 230.4 kcal/mol, suggesting that entropic effects have a minimal impact on the measured PA. Calculations at the B3LYP 6-311++G** level of theory yield a PA of 225.7 kcal/mol. Previous calculations predicted a PA of 228.9 kcal/mol.\textsuperscript{4} Thus 311 is found to be very basic by theory and experiment. By comparison, typical amides have PAs in the range of 210–215 kcal/mol (Figure 5.3.2).\textsuperscript{28} In terms of basicity, 311 behaves more like a secondary or tertiary amine owing to the lack of resonance within the amide. In addition, the site of protonation differs for twisted amides with protonation at the nitrogen being favored by \(~21.5\) kcal/mol according to our calculations.\textsuperscript{29} In the process of collecting data to establish the PA of 311, reference bases were found to separate into two groups. The less bulky bases give the data shown in Figure 5.3.1, which corresponds to dimers that are capable of hydrogen bonding to the nitrogen of 311. The remaining reference bases are too bulky to access the nitrogen and presumably interact with the carbonyl oxygen of 311.\textsuperscript{30}
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Figure 5.3.1. Data from kinetic method experiments showing the relative PA versus natural log of the ratio of ion intensities minus protonation entropies. Three representative collision energies are shown for each reference base. The collinearity of all three lines indicates few entropic effects. The PA of 311 is determined to be 230.4 kcal/mol by the extended kinetic method.

Figure 5.3.2. Representative amide and amine experimentally determined PAs (kcal/mol).

5.3.2 COLLISION-INDUCED DISSOCIATION PATHWAY

The gas-phase properties of 2-quinuclidone (311) were explored further by collision-induced dissociation (CID) experiments. The CID spectrum for 311•H⁺ is shown in Figure 5.3.3i. Surprisingly, a single loss of 44 Da is the only major product that is observed, indicating that a single fragmentation pathway is energetically favored. Because of the bicyclic nature of 311•H⁺, two covalent bonds must be broken en route to the observed fragmentation. A loss of 44 Da further requires at least one hydrogen
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We propose the mechanism shown in Scheme 5.3.1a to account for the observed loss. Homolytic cleavage of the amide to bond to 327 leads to abstraction of one out of two equivalent hydrogens facing the radical (327 → 328). Two possible McLafferty-type rearrangements (one is shown in Scheme 5.3.1a) then lead to the second hydrogen transfer and the production of isomeric dihydropyridiniums 329 and 330 with the loss of ethenol (331). In order to verify this mechanism, a series of four compounds labeled with stable isotopes were prepared (332–335) (Scheme 5.3.1b).

Figure 5.3.3. i) CID spectrum of 311•H+ (m/z = 126) with a single fragment being detected. ii) CID spectrum of 310•H+ (m/z = 144). The loss of water generates 311•H+, which simultaneously fragments. iii) MS3 CID spectrum of the reisolated peak at m/z 126 from spectrum ii confirming that 311•H+ is generated by the loss of water.
The synthesis of variously labeled derivatives of $311\cdot\text{HBF}_4$ is shown in Scheme 5.3.2. Using a route identical to our original synthesis of $311$, substitution of monotosylate $324$ with $1\cdot^{15}$N-sodium azide and oxidation with Dess–Martin periodinane provided ketoazide $336$, which was subjected to the optimized Schmidt–Aubé conditions, and upon recrystallization, afforded $^{15}$N-labeled $332\cdot\text{HBF}_4$ (Scheme 5.3.2a). The incorporation of $^{13}$C into $311$ required a new approach starting from $^{13}$C$_2$-acetic acid ($337$). Accordingly, Mitsunobu substitution of alcohol $338$ generated crystalline ester $339$ (Scheme 5.3.2b). Enol silane generation and modified Mukaiyama–Michael addition to cyclopentenone employing buffered TBSOTf constructed ketoester $340$ in 79% yield over two steps. Reduction of both carbonyls using LiAlH$_4$, chemoselective oxidation$^{33}$ of the secondary alcohol, and mesylation of the resulting primary alcohol yielded ketomesylate $341$. Typical azide substitution and cyclization then gave $^{13}$C$_2$-labeled $333\cdot\text{HBF}_4$. A similar procedure using the conjugate addition with acceptor 3-$d$-cyclopentenone ($342$)$^{34}$ provided monodeuterated ketoester $344$ that was transformed to D-labeled $334\cdot\text{HBF}_4$. 

Scheme 5.3.1. a) Proposed CID fragmentation mechanism of $311\cdot\text{H}^+$. b) Isotopically labeled mechanistic probes
over five steps (Scheme 5.3.2c). Reduction of lactone 322 with LiAlD₄ and two-step conversion to mesylate 345 enabled the preparation of D₂-labeled 335•HBF₄ (Scheme 5.3.2d).

Scheme 5.3.2: Synthetic route for the preparation of isotopically labeled mechanistic probes.

a) $^{15}$N-labeled 332•HBF₄; b) $^{13}$C₂-labeled 333•HBF₄; c) D-labeled 334•HBF₄; d) D₂-labeled 335•HBF₄
The preparation of various labeled derivatives enabled the verification of our proposed fragmentation mechanism. CID of \(332\cdot H^+\) yields a single product that retains the \(^{15}\text{N}\) label as expected.\(^{35}\) Similarly, \(333\cdot H^+\) and \(334\cdot H^+\) both fragment by yielding a single observable product with both \(^{13}\text{C}\) or deuterium labels retained, respectively, in agreement with our mechanism.\(^{35}\) Additionally, fragmentation of \(335\cdot H^+\) confirms that hydrogen transfer occurs.\(^{35}\) In this case, two products are observed, with the difference between them being the loss of one or retention of two deuteriums. The loss of hydrogen is favored by a factor of 1.7, suggesting that isotope effects\(^{36}\) may play a role in this reaction. Nevertheless, in each experiment the labeled atoms were lost or retained in agreement with the mechanism shown in Scheme 5.3.1a. As predicted, the amide bond is weakened by the lack of resonance stabilization and is the first bond to break upon collisional excitation.

### 5.3.3 Gas-Phase Synthesis of 2-Quinuclidonium by Eliminating Water

Further insight into the chemistry of twisted amides can be obtained by synthesizing them in the absence of solvent. \(311\cdot HBF_4\) is observed to rapidly hydrolyze in the presence of water (see subsection 5.2.2), and attempts to drive the reverse reaction in solution have been unsuccessful.\(^{11a}\) Similarly, attempts to synthesize \(311\) with the acid chloride of \(310\) have met with frustration.\(^{13}\) Nevertheless, collisional excitation of the hydrolyzed derivative \(310\cdot H^+\) in the gas phase yields quantitatively a product with the same mass as \(311\cdot H^+\) as shown in Figure 5.3.3ii. Following reisolation and collisional cooling of this peak, the MS\(^3\) CID spectrum is identical to that obtained by fragmenting
311•H⁺ (compare Figure 5.3.3i and iii). Similarly, all isotopically labeled compounds react exclusively by eliminating water, followed by the same elimination that would be expected if 311•H⁺ were generated as the product. Thus it is possible to selectively synthesize 311•H⁺ by eliminating water from 310, as shown in Scheme 5.3.3, if the water can be rigorously removed from the reaction system. This is not a difficulty in the gas phase; however, the data in Figure 5.3.3ii also suggest that there is a high barrier to this process. Elimination of water to yield 311•H⁺ also results spontaneously in further fragmentation. As mentioned above, this requires the cleavage of two covalent bonds. Therefore, this reaction appears to be difficult in solution for two reasons: a high barrier to activation and back reactions with water.

Scheme 5.3.3. Gas-phase elimination of water to construct 311•H⁺ and 318•H⁺

5.3.4 COMPARISON TO 6,6,7,7-TETRAMETHYL-2-QUINUCLIDONE

These results are further confirmed by examination of 318, which has four additional methyl groups and can be generated from the acid chloride in solution. CID of the hydrolyzed product 346•H⁺ yields exclusively 318•H⁺ without the accompanying loss of additional fragments. The synthesis is again confirmed by comparing fragmentation with the authentic molecule; comparison of Figure 5.3.4i with Figure 5.3.4iii reveals that even
very low abundance peaks are reproduced. In addition, the voltage amplitude required to
carry out the dehydration of $346\cdot H^+$ (Scheme 5.3.3) is 20% lower in magnitude when
compared to the voltage required for $310\cdot H^+$. Thus, the energy required to generate
$318\cdot H^+$ by eliminating water is much lower, in agreement with the observed synthetic
routes in solution. The gas-phase syntheses suggest that $318$ is more nucleophilic than
$311$ and should therefore be more basic as well. Attempts to determine the PA of $318$
experimentally by the kinetic method met with frustration. The steric hindrance of the
additional methyl groups prevents access to the bridgehead nitrogen. However, theory
can be used to estimate the proton affinity. The calculated PA for $318$ at the B3LYP/6-
$311++G^{**}$ level is 234.7 kcal/mol, which is significantly higher than that for $311$
(230.4 kcal/mol) and supports the idea of enhanced nucleophilicity for $318$. The
predicted increase in PA with increasing alkyl substitution is evident with the various
piperidine derivatives depicted in Figure 5.3.2. However, $318$ is also much more stable
toward hydrolysis, indicating that stability does not share a simple relationship with
basicity for twisted amides.$^{14d}$
Figure 5.3.4. i) CID spectrum of $318\cdot H^+$ (m/z = 182). ii) CID spectrum of $346\cdot H^+$ (m/z = 200). In this case, the synthesis proceeds cleanly without spontaneous fragmentation. iii) MS$^3$ CID spectrum showing that all fragment peaks are reproduced when the gas-phase product is compared to the bona-fide sample in spectrum i.

5.4 FUTURE STUDIES

The availability of 2-quinuclidone as its tetrafluoroborate salt ($311\cdot \text{HBF}_4$) has enabled the analysis of physical and chemical properties that were previously available only by theoretical calculations.$^4$ However, experimentation can provide intriguing details and insights beyond what theory can explore as evidenced by subsections 5.3.2–5.3.4. Now that we have a powerful method for the construction of these unique twisted lactams, we can further assess their properties and combine experiment with theory to further the understanding of twisted amides. One particular area of interest is the relationship between the ring size of the bicyclic system and the resulting amide distortion.$^4$
We envisioned 1-azabicyclo[2.2.1]heptan-2-one (349) in efforts to pursue a more strained derivative of the bridgehead bicyclic lactams (cf. 311). By analogy, a comparison of ring strains in the parent bicyclic alkane systems reveals that the removal of a carbon from bicyclo[2.2.2]octane (347) to bicyclo[2.2.1]heptane (348) increases the ring strain from 7.4 to 14.1 kcal/mol, respectively (Figure 5.4.1a). We have calculated the proton affinity of 349 to be 231.7 kcal/mol, which makes it slightly more basic than 2-quinuclidone (311) and less basic than tetramethyl derivative 318 (Figure 5.4.1b). This indicates that a predicted increase ring strain affects the nitrogen basicity, although ring strain does not necessarily correlate to an increase in basicity. A detailed theoretical or experimental study of 349 could provide insights into this strained amide.

Figure 5.4.1. a) Comparison of strain energies of related bicyclic systems (kcal/mol). b) Comparison of proton affinity values for select bicyclic twisted amides (kcal/mol).

A proposed synthetic route to 349 utilizing the Schmidt–Aubé cyclization is shown in Scheme 5.4.1. Intermolecular [2 + 2] cycloaddition of dichloroketene generated from
and Zn(Cu) couple with alkyne should provide dichlorocyclobutenone. Reductive dechlorination and olefin hydrogenation with benzyl cleavage could generate ketoalcohol. Conversion to azide over two steps and subsequent HBF-promoted intramolecular cyclization should construct. The devised synthetic route could enable rapid access to for thorough experimental evaluation.

Scheme 5.4.1. Proposed synthesis of employing the Schmidt–Aubé cyclization

\[
\begin{align*}
350 & \quad \text{Cl}C\text{C} & \quad \text{O} \\
351 & \quad \text{O}Bn \\
352 & \quad \text{O}Bn \\
353 & \quad \text{O}N \text{H} \\
354 & \quad \text{N} \text{H}O \\
349\text{H}^+ & \\
\end{align*}
\]

Another interesting example with regard to ring size is the theoretical molecule 1-azabicyclo[3.3.3]undecan-2-one (355). The parent amine (manxine, 356) is extraordinary in that it exhibits a near coplanar geometry about the nitrogen in both neutral and protonated forms. Greenberg has calculated the PA of amide 355 and found that the bicyclo[3.3.3] system favors O-protonation over N-protonation by 3.5 kcal/mol, suggesting that increase in ring size reduces strain and induces planarity of the nitrogen. As 355 approaches the geometric requirements for an unstrained amide linkage, it has the potential to form a hyperstable amide. The concept of hyperstability, as described by
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Schleyer and co-workers for bridgehead olefins,\(^\text{43}\) specifies that the strain energy in the enolized lactam is less than that of the parent lactam and could result in interesting reactivity of this larger bicyclic amide.

Figure 5.4.2. Bicyclo[3.3.3] bridgehead amide 355 and amine 356.

A proposed synthesis of 355 is presented in Scheme 5.4.2. Enolization of vinylogous ester 228 and alkylation with iodide 357,\(^\text{44}\) followed by reductive carbonyl transposition could afford \(\gamma\)-substituted cycloheptenone 358. Olefin hydrogenation with benzyl cleavage and two-step azide conversion would produce cyclization substrate 359. Exposure to acidic conditions should facilitate carbonyl addition to intermediate 360 that can undergo a C–N migration in two possible ways to form desired 355 and isomer 361. The planned route to 355 could provide material to support the evaluation of this intriguing amide.
5.5 CONCLUSION

In summary, we have achieved the first unambiguous synthesis, isolation, and X-ray characterization of the quintessential twisted amide 2-quinuclidone (311) as its HBF$_4$ salt. Our synthesis highlights the power of the Schmidt–Aubé reaction for the construction of highly strained amides. We have performed a thorough structural and chemical analysis of 311 and quantitatively established its highly twisted nature. Gas-phase investigations have assessed the basicity of 311 for the first time, revealing an intriguing dissociation mechanism and a second synthesis by eliminating water in the gas phase. Our results indicate that the gas-phase chemistry of these molecules closely reflects the properties observed in solution. Moreover, the studies herein demonstrate the importance of combining theory and experiment to further our understanding of this extraordinary class of compounds. Future studies on the role of ring size and the resulting effect on amide distortion and properties are proposed.
5.6 EXPERIMENTAL SECTION

5.6.1 MATERIALS AND METHODS

5.6.1.1 CHEMICAL SYNTHESIS

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents passed through activated alumina columns under argon. All commercially obtained reagents were used as received. Hexamethylphosphoramide was distilled from CaH$_2$ and stored in a Schlenk tube under argon. 3-$d$-cyclopentenone (342) and 6,6,7,7-tetramethyl-2-quinuclidone (318) were prepared by known methods. Labeled sodium azide (1-$^{15}$N, 98 atom% $^{15}$N) and acetic acid (337, 1,2-$^{13}$C$_2$, 99 atom% $^{13}$C) were purchased from Cambridge Isotope Laboratories. Lithium aluminum deuteride (98 atom% $d$) was purchased from Aldrich. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at 23 °C. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV quenching and charring with p-anisaldehyde, ceric ammonium molybdate, or potassium permanganate stains. ICN silica gel (particle size 0.032–0.063 mm) was used for flash column chromatography. $^1$H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me$_4$Si ($\delta$ 0.0).$^{45}$ Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 126 MHz) and are reported relative to Me$_4$Si ($\delta$ 0.0).$^{45}$ Data for $^{13}$C NMR spectra are
reported in terms of chemical shift, multiplicity, and coupling constant. $^2$H NMR spectra were recorded on a Varian Inova 500 (at 76 MHz) and are reported relative to Me$_4$Si ($\delta$ 0.0). Data for $^2$H NMR spectra are reported in terms of chemical shift and multiplicity. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of frequency of absorption (cm$^{-1}$). Melting points are uncorrected. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

5.6.1.2  EXTENDED KINETIC METHOD, GAS-PHASE SYNTHESIS, AND CALCULATIONS

All mass spectra were obtained using an LTQ linear ion trap mass spectrometer (Thermo Electron, Waltham, MA) equipped with a standard electrospray ionization source. Voltages were optimized to maximize the [311 + H$^+$ + B$_{ref}$] dimer peak intensities for kinetic method experiments. All reference bases were purchased from Sigma-Aldrich and were used without further purification.

To minimize hydrolysis of 311•HBF$_4$, samples containing 300 $\mu$M of 311 and reference base were prepared with dry acetonitrile unless otherwise noted and immediately infused into the electrospray source. The noncovalently bound dimers were then isolated and subjected to CID at normalized collision energies ranging from 18% to 85%. These percentages correspond to excitation voltage amplitudes of 0.00641 to 0.0303 V for a 100 m/z ion. To obtain tandem MS data, 30 $\mu$M solutions were prepared and analyzed as above under standard instrument tune conditions. Amino acid derivatives were prepared by either allowing a sample sufficient time to hydrolyze (ca.
Proton affinities were calculated using hybrid density functional theory as implemented in Gaussian 03 Version 6.1 Revision D.01. Candidate structures were built using GaussView 3.0 and then submitted for optimization and vibrational frequency calculation at the B3LYP/6-31G* level. Total energies were calculated at the B3LYP/6-311++G** level. Total energies, zero point energies (ZPE), and thermal corrections were obtained from the optimization/frequency output. Zero point corrections were scaled by an empirical factor of 0.9877 as recommended by Andersson and Uvdal.\textsuperscript{46} The basis set superposition error (BSSE) was calculated using the counterpoise (CP) method of Boys and Bernardi.\textsuperscript{47}
5.6.2 PREPARATIVE PROCEDURES

2-Quinuclidonium tetrafluoroborate (311·HBF$_4$). To a solution of 320 (356.5 mg, 2.33 mmol, 1.0 equiv) in Et$_2$O (4.7 mL, 0.5 M) at 0 °C was added an ethereal solution of HBF$_4$ (642 µL of a 54 wt % solution, 4.66 mmol, 2.0 equiv) at which time immediate gas evolution was observed. The cooling bath was removed and stirred at room temperature until gas evolution ceased (ca. 8 h) and TLC analysis confirmed consumption of 320. The supernatant of the resulting suspension was removed by syringe and the remaining white solid was washed with Et$_2$O (3 x 3 mL) and dried in vacuo. This crude white solid was transferred into a glove box and purified by double recrystallization using slow diffusion of Et$_2$O into a MeCN solution of the crude. Specifically, the crude was dissolved in a minimal quantity of MeCN, filtered through a pipette with a small filter paper plug, and washed further with minimal MeCN. The resulting vial containing the MeCN solution of the crude was placed in a larger chamber, filled ~1/3 full with Et$_2$O, and the larger chamber was capped and placed in a −20 °C freezer. After 36–48 h, the chamber was equilibrated to ambient, the supernatant was decanted, and the resulting white solid was washed with excess Et$_2$O, and recrystallized using the same procedure. Isolation and drying of the resulting solid under vacuum afforded 311·HBF$_4$ (292.1 mg, 1.37 mmol, 59% yield) as white needles. Mp = 185–200 °C dec; $^1$H NMR (300 MHz, CD$_3$CN) δ 8.02 (br, 1H), 3.85–3.60 (m, 4H), 2.99 (d, $J$ = 3.0 Hz, 2H), 2.51 (septuplet, $J$ =
3.0 Hz, 1H), 2.10–1.90 (m, 4H); $^{13}$C NMR (75 MHz, CD$_3$CN) δ 175.9, 48.1, 40.1, 25.7, 22.7; IR (KBr) 3168, 2981, 1468, 1398, 1336, 1312, 948, 823, 799, 766, 716 cm$^{-1}$; HRMS (FAB+) $m/z$ calc’d for C$_7$H$_{12}$NO [M + H]$^+$: 126.0919, found 126.0920.

**Naphthalen-2-ylmethyl acetate (363).** Ph$_3$P (0.787 g, 3.0 mmol, 1.5 equiv) and alcohol 362 (0.475 g, 3.0 mmol, 1.5 equiv) were dissolved in THF (13.4 mL, 0.15 M). Acetic acid (114 µL, 2.0 mmol, 1.0 equiv) was added and the solution was cooled to 0 °C in an ice/water bath. DIAD (591 µL, 3.0 mmol, 1.5 equiv) dissolved in THF (1 mL) was added dropwise over 5 min via positive pressure cannulation. After 1 h, the reaction was quenched with 5 mL saturated NaHCO$_3$, extracted with hexanes (3 x 20 mL), the organics were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to an off-white solid. The resulting crude material was purified by flash chromatography on SiO$_2$ (15:1 → 9:1 hexanes/Et$_2$O, PhMe loaded) to afford 363 (0.3830 g, 1.91 mmol, 96% yield) as a white solid. $R_f = 0.28$ (9:1 hexanes/Et$_2$O); mp = 53–55 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.89–7.85 (comp m, 4H), 7.53–7.47 (comp m, 3H), 5.30 (s, 2H), 2.16 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.1, 133.5, 133.4, 133.3, 128.5, 128.1 (2C), 127.9, 127.5 (2C), 126.5, 126.4, 126.1, 66.6, 21.2; IR (Neat Film NaCl) 3055, 2953, 1736, 1378, 1364, 1248, 1030, 951, 896, 863, 822, 744, 480 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{13}$H$_{12}$O$_2$ [M]$^+$: 200.0837, found 200.0844.
Ketoester 364. To a cooled solution of \( i\text{-Pr}_2\text{NH} \) (341 µL, 2.44 mmol, 1.15 equiv) in THF (2.12 mL, 1 M) at 0 °C was added \( n\text{-BuLi} \) (2.5 M in hexane) dropwise. After stirring for 15 min at 0 °C, the solution was cooled to \(-78\) °C and a solution of acetate 363 (424.0 mg, 2.12 mmol, 1.0 equiv) in THF (1 mL) was added dropwise via positive pressure cannulation. After 15 min, HMPA (332 µL, 1.91 mmol, 0.9 equiv), then TBSCl (351.0 mg, 2.33 mmol, 1.1 equiv) in THF (0.80 mL) were added and the cooling bath was removed. The reaction was warmed to ambient temperature and concentrated under reduced pressure. The resulting thick oil was dissolved in 9:1 hexanes/Et\(_2\)O (50 mL) and washed with distilled water (3 x 20 mL, pH \(\approx 7\)) and sat. brine. The organic layer was dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The resulting yellow oil solidified after several hours under high vacuum to afford TBS-silylenol ether 343 (650.9 mg), which was used without further purification in the subsequent reaction. \( R_f = \text{unstable to SiO}_2. \)

To a solution of 343 (1.2 equiv), cyclopentenone (145 µL, 1.72 mmol, 1.0 equiv), and 2,6-di-\textit{tert}-butylpyridine (465 µL, 2.07 mmol, 1.2 equiv) in CH\(_2\)Cl\(_2\) (20.7 mL, 0.1 M) cooled to \(-78\) °C was added a solution of TBSOTf (475 µL, 2.07 mmol, 1.2 equiv) in CH\(_2\)Cl\(_2\) (2.1 mL) dropwise over 15 min. Following consumption of cyclopentenone by TLC analysis (ca. 15 min), the cooling bath was removed and the reaction was quenched.
with 15 mL of 3% aq HCl. After stirring for 30 min the layers were separated and the aq layer was extracted with CH₂Cl₂ (3 x 25 mL), the organics dried over MgSO₄, filtered, and concentrated under reduced pressure to a yellow solid. The crude product was purified by flash chromatography on SiO₂ (9:1 → 4:1 → 3:1 hexanes/EtOAc, dry load) to afford ketoester 364 (385.4 mg, 1.37 mmol) as a light yellow oil. \( R_f = 0.23 \) (1:1 hexanes/Et₂O); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.87–7.82 (comp m, 4H), 7.53–7.49 (comp m, 2H), 7.45 (dd, \( J = 8.5, 1.9 \) Hz, 1H), 5.30 (s, 2H), 2.70–2.57 (m, 1H), 2.55 (d, \( J = 1.1 \) Hz, 1H), 2.53 (d, \( J = 2.9 \) Hz, 1H), 2.51–2.45 (m, 1H), 2.38–2.11 (comp m, 3H), 1.90 (ddd, \( J = 18.1, 9.8, 1.1 \) Hz, 1H), 1.66–1.51 (m, 1H); \(^13\)C NMR (75 MHz, CDCl₃) \( \delta \) 218.4, 172.0, 133.3 (2C), 133.2, 128.6, 128.1, 127.9, 127.7, 126.5 (2C), 126.0, 66.7, 44.7, 39.9, 38.4, 33.6, 29.4; IR (Neat Film NaCl) 3049, 2956, 1737, 1271, 116, 817 cm⁻¹; HRMS (EI⁺) \( m/z \) calc’d for C₁₈H₁₈O₃ [M⁺]: 282.1256, found 282.1257.

Diol 365. To a slurry of LiAlH₄ (74.3 mg, 1.96 mmol, 4.0 equiv) in THF (4.9 mL, 0.1M) at 0 °C was added ketoester 364 (138.1 mg, 0.498 mmol, 1.0 equiv) in 1.0 mL THF. The cooling bath was removed and the reaction was stirred for 2.5 h at ambient temperature. The reaction was then cooled to 0 °C and carefully quenched by slow addition of Na₂SO₄•10H₂O. When gas evolution had ceased, the flask was diluted up to 25 mL with EtOAc and stirred vigorously at ambient temperature for 2 h. The fine precipitate was then filtered through Celite, washing with excess EtOAc, and the
resulting filtrate was concentrated under reduced pressure to an off-white solid. This residue was purified by flash chromatography on SiO\textsubscript{2} (2:1 → 1:0 EtOAc/hexanes) to afford ~1:1 mixture of diastereomers of diol \textit{365} (42.6 mg, 0.320 mmol, 65% yield) as a colorless oil. \( R_f = 0.15 \) (3:1 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CD\textsubscript{3}OD) \( \delta \) 4.26 (anti diastereomer, app dq, \( J = 8.4, 2.9 \) Hz, 0.47H), 4.21 (syn diastereomer, app pentet, \( J = 5.9 \) Hz, 0.53H), 3.56 (app t, \( J = 6.8 \) Hz, 2H), 2.20 (ddd, \( J = 16.4, 7.8, 7.8 \) Hz, 0.53H), 2.14 (ddd, \( J = 14.2, 7.6, 7.6 \) Hz, 0.53H), 1.98–1.90 (comp m, 1.5H), 1.81–1.72 (comp m, 1.5H), 1.65–1.60 (comp m, 1.5H), 1.59–1.51 (comp m, 1.5H), 1.44–1.31 (m, 1H), 1.19–1.12 (m, 1H); \(^{13}\)C NMR (125 MHz, CD\textsubscript{3}OD) \( \delta \) 74.1 (syn), 62.2, 62.1 (syn), 43.1, 42.9 (syn), 40.6 (syn), 40.1, 36.1 (syn), 35.8 (syn), 35.6, 35.2, 31.5, 31.2 (syn); IR (Neat Film NaCl) 3323 (br), 2931, 2864, 1434, 1344, 1052, 1013 cm\(^{-1}\); HRMS (EI+) \( m/z \) calc’d for C\(_7\)H\(_{14}\)O\(_2\) [M]^+ : 130.0994, found 130.0994.

**Ketomesylate 366.**\(^{33}\) To a solution of diol \textit{365} (87.6 mg, 0.673 mmol, 1.0 equiv) in CH\(_3\)CN (2.8 mL, 0.167 M) in a vial was added CAN (36.9 mg, 0.673 mmol, 0.1 equiv), NaBrO\(_3\) (101.5 mg, 0.673 mmol, 1.0 equiv), and distilled H\(_2\)O (1.2 mL) and vigorously stirred. Following consumption of diol \textit{365} by TLC (ca. 6 h), the reaction was concentrated under reduced pressure. The resulting slurry was taken up in 10 mL H\(_2\)O, extracted with EtOAc (3 x 25 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure to afford a crude yellow oil (85.5 mg).
The resulting crude material was dissolved in CH₂Cl₂ (1.35 mL, 0.5 M), cooled to 0 °C, and MsCl (77.4 µL, 1.0 mmol, 1.5 equiv) and Et₃N (167 µL, 1.2 mmol, 1.8 equiv) were added sequentially. After 5 min, the reaction was quenched with saturated aq NaHCO₃ (1 mL) and diluted up to 10 mL with CH₂Cl₂. The biphasic solution was further diluted with sat. aq NaHCO₃ (2 mL) and sat. brine (2 mL), the layers were separated, and the aq layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated to a light yellow solid under reduced pressure. This residue was purified by flash chromatography on SiO₂ (2:1 → 1:2 hexanes/EtOAc, dry load) to afford ketomesylate 366 (115.4 mg, 0.560 mmol, 83% yield over two steps) as a colorless oil. R₂ = 0.31 (3:1 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 4.29 (app dt, J = 6.4, 2.4, 2.4 Hz, 2H), 3.02 (s, 3H), 2.51–2.42 (m, 1H), 2.40–2.12 (comp m, 4H), 1.95–1.89 (comp m, 2H), 1.84 (ddd, J = 17.6, 7.7, 1.3 Hz, 1H), 1.64–1.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 218.3, 68.2, 44.8, 38.5, 37.6, 35.0, 33.8, 29.4; IR (Neat Film NaCl) 3023, 2935, 1737, 1350, 1173, 954 cm⁻¹; HRMS (EI+) m/z calc’d for C₈H₁₄O₄S [M]⁺: 206.0613; found 206.0622.

**Ketoazide 320.** To a solution of mesylate 366 (50.2 mg, 0.243 mmol, 1.0 equiv) in DMF (0.50 mL, 0.5 M) was added NaN₃ (17.4 mg, 0.268 mmol, 1.1 equiv), and the mixture was warmed to 70 °C until consumption of 366 by TLC. The reaction was cooled to 0 °C and stirred for 15 min, followed by dilution with Et₂O. The suspension was filtered through a plug of Celite with Et₂O, concentrated under reduced pressure, and purified by
flash chromatography SiO$_2$ (6:1 → 3:1 hexanes/Et$_2$O, PhMe load) to afford ketoazide 320 (32.8 mg, 0.214 mmol, 88% yield) as a colorless oil. $R_f = 0.25$ (3:1 hexanes/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 3.36 (t, $J = 7.1$ Hz, 2H), 2.50–2.10 (m, 5H), 1.90–1.70 (m, 3H), 1.54 (m, 1H). All other spectral data are consistent with reported values.

$^{15}$N-labeled azidoalcohol 367. Prepared by a known method using (1-$^{15}$N)-NaN$_3$. The reaction was purified by flash chromatography on SiO$_2$ (3:1 → 1:1 hexanes/Et$_2$O, PhMe load) to afford $^{15}$N-labeled azidoalcohol 367 (186.1 mg, 1.19 mmol, 99% yield) as colorless oil. $R_f = 0.14$ (1:1 hexanes/Et$_2$O); IR (Neat Film NaCl) 3344, 2946, 2868, 2074, 1339, 1243 cm$^{-1}$; HRMS (FAB+) m/z calc’d for C$_7$H$_{14}$N$_2$O$^{15}$N [M + H]$^+$: 157.1107, found 157.1141. All other spectral data are consistent with reported values.

$^{15}$N-labeled ketoazide 336. Prepared by a known method. The reaction was purified by flash chromatography on SiO$_2$ (6:1 → 3:1 hexanes/Et$_2$O) to afford ketoazide 336 (155.5 mg, 1.00 mmol, 87% yield) as colorless oil. $R_f = 0.26$ (1:1 hexanes/Et$_2$O); IR (Neat Film NaCl) 2931, 2873, 2076, 1740, 1242, 1160 cm$^{-1}$. All other spectral data are consistent with reported values.
1-^{15}\text{N}-2\text{-quinuclidonium tetrafluoroborate (332•HBF}_4\text{). Prepared by a known method. The crude reaction precipitate was transferred to a glove box and recrystallized twice by slow diffusion of Et}_2\text{O into CH}_3\text{CN at } -20 \text{ °C to afford 332•HBF}_4 \text{ (127.7 mg, 0.598 mmol, 65% yield) as white needles. HRMS (FAB+) } m/z \text{ calc’d for C}_7\text{H}_{12}\text{O}^{^{15}}\text{N}[\text{M + H}]^+: 127.0889, \text{ observed 127.0855; } m/z \text{ calc’d for C}_7\text{H}_{12}\text{NO}[\text{M + H}]^+: 126.0919, \text{ observed 126.0915; relative peak ratio = 1:1. }

^{13}\text{C}_2\text{-labeled acetate 339. Prepared as above to afford 339 (0.8326 g, 4.12 mmol, 97% yield) as an off-white solid. } \text{Mp = 54–56 °C; } ^1\text{H NMR (300 MHz, CDCl}_3\text{) } \delta 7.87–7.83 \text{ (comp m, 4H), 7.53–7.45 (comp m, 3H), 5.27 (d, } J_{^1\text{H}–^{13}\text{C}} = 3.2 \text{ Hz, 2H), 2.13 (dd, } J_{^1\text{H}–^{13}\text{C}} = 129.7, 6.9 \text{ Hz); } ^{13}\text{C NMR (75 MHz, CDCl}_3\text{) } \delta 170.9 \text{ (d, } J_{^{13}\text{C}–^{13}\text{C}} = 59.4 \text{ Hz), 21.1 (d, } J_{^{13}\text{C}–^{13}\text{C}} = 59.2 \text{ Hz); IR (Neat Film NaCl) } 3054, 2955, 1693, 1360, 1276, 1218, 1024, 970, 951, 897, 864, 823, 744 \text{ cm}^{-1}; \text{ HRMS (EI+) } m/z \text{ calc’d for } \text{C}_{11}\text{H}_{12}\text{O}_2^{^{13}}\text{C}_2 \text{[M]}^+: 202.0904, \text{ found 202.0913.}
**13C₂-labeled ketoester 340.** Prepared as above to afford 340 (0.4204 g, 1.42 mmol, 79% yield) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.87–7.82 (comp m, 4H), 7.53–7.49 (comp m, 2H), 7.45 (dd, J = 8.5, 1.6 Hz, 1H), 5.30 (d, J = 3.2 Hz, 2H), 2.54 (dddd, J_H-13C = 129.2, 6.9 Hz, J = 10.9, 2.0 Hz, 2H), 2.71–2.58 (m, 1H), 2.49 (ddd, J = 16.8, 7.4 Hz, J_H-13C = 1.3 Hz, 1H), 2.28–2.11 (comp m, 3H), 1.96 (dddd, J = 18.1, 10.4, 5.3 Hz, J_H-13C = 1.3 Hz, 1H), 1.67–1.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 172.0 (d, J_{13C-13C} = 57.2 Hz), 39.9 (d, J_{13C-13C} = 57.5 Hz); IR (Neat Film NaCl) 3054, 2958, 1740, 1690, 1403, 1150, 1124, 818, 754 cm⁻¹; HRMS (EI⁺) m/z calc’d for C₁₆H₁₈O₃¹³C₂ [M]⁺: 284.1323, found 284.1322. All other spectral data are consistent with reported values.

**13C₂-labeled diol 368.** Prepared as above to afford ~1:1 mixture of diastereomers of 368 (54.9 mg, 0.415 mmol, 74% yield) as a colorless oil. ¹H NMR (300 MHz, CD₃OD) δ 4.26 (dddd, J = 5.6, 5.6, 2.9, 2.9 Hz, 0.44H), 4.21 (dddd, J = 4.8, 4.8, 4.8, 4.8, 0.56 H), 3.56 (dddd, J_H-13C = 140.2, 6.9 Hz, J = 6.9, 2.4 Hz, 2H), 2.18–2.09 (m, 1H), 2.0–1.7 (comp m, 3H), 1.65–1.49 (m, 1H), 1.46–1.28 (comp m, 2H), 1.23–1.09 (m, 1H); ¹³C NMR (75 MHz, CD₃OD) δ 62.2 (d, J_{13C-13C} = 37.3 Hz, 0.44C), 62.1 (d, J_{13C-13C} = 37.3 Hz,
0.56C), 40.6 (d, $J_{13C-13C} = 37.3$ Hz, 0.56C), 40.1 (d, $J_{13C-13C} = 37.3$ Hz, 0.44C). All other spectral data are consistent with reported values.

![Diagram](image)

**13C$_2$-labeled ketomesylate 341.** Prepared as above to afford 341 (71.7 mg, 0.344 mmol, 83% yield over two steps) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.30 (dddd, $J_{H-13C} = 149.4$, 6.4 Hz, $J = 6.4$, 2.7 Hz, 2H), 3.03 (s, 3H), 2.47 (ddd, $J = 17.8$, 7.5 Hz, $J_{H-13C} = 1.0$ Hz, 1H), 2.41–2.08 (comp m, 5H), 1.85 (ddddd, $J = 17.8$, 10.1, 5.1 Hz, $J_{H-13C} = 1$ Hz, 1H), 1.74–1.66 (m, 1H), 1.63–1.52 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 68.1 (d, $J_{13C-13C} = 37.9$ Hz), 35.0 (d, $J_{13C-13C} = 38.2$ Hz); HRMS (EI+) $m/z$ calc’d for C$_6$H$_{14}$SO$_4^{13}$C$_2$ [M]$^+$: 208.0680, found 208.0688. All other spectral data are consistent with reported values.

![Diagram](image)

**13C$_2$-labeled ketoazide 369.** Prepared as above to afford 369 (28.5 mg, 0.184 mmol, 96% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.36 (app ddt, $J_{H-13C} = 141.4$, 6.9 Hz, $J = 3.2$ Hz, 2H), 2.44 (dd, $J = 17.8$, 8.0 Hz, 1H), 2.37–2.11 (comp m, 4H), 2.00–1.91 (m, 1H), 1.83 (dd, $J = 17.6$, 9.8, 4.8 Hz, 1H), 1.62–1.49 (comp m, 2H); $^{13}$C NMR
(75 MHz, CDCl₃) δ 50.0 (d, \( J_{13C-13C} = 36.8 \) Hz), 34.6 (d, \( J_{13C-13C} = 36.8 \) Hz). All other spectral data are consistent with reported values.

5,6-\(^{13}\)C₂-2-quinuclidonium tetrafluoroborate (333•HBF₄). Prepared as above to afford 333•HBF₄ (36.5 mg, 0.170 mmol, 60% yield) as white needles. \(^1\)H NMR (300 MHz, CD₃CN) δ 7.99 (br s, 1H), 3.69 (m, 2H), 3.69 (m, \( J_{H-13C} = 150.4 \) Hz, 2H), 2.97 (app d, \( J = 5.4, 3.3 \) Hz, 3H), 2.55–2.47 (m, 1H), 1.98 (m, 2H), 1.98 (m, \( J_{H-13C} = 135.4 \) Hz, 2H); \(^{13}\)C NMR (75 MHz, CD₃CN) δ 47.9 (d, \( J_{13C-13C} = 32.6 \) Hz), 22.6 (d, \( J_{13C-13C} = 32.6 \) Hz); HRMS (FAB+) \( m/z \) calc’d for C₅H₁₂NO\(^{13}\)C₂ [M + H]⁺: 128.0986, observed 128.0960.

D-labeled ketoester 344. Prepared as above to afford 344 (0.3283 g, 1.15 mmol, 68% yield) as a pale yellow oil. \(^1\)H NMR (300 MHz, CDCl₃) δ 7.87–7.82 (comp m, 4H), 7.53–7.49 (comp m, 2H), 7.45 (dd, \( J = 8.5, 1.6 \) Hz, 1H), 5.30 (s, 2H), 2.53 (dd, \( J = 16.6, 16.6 \) Hz, 2H), 2.48 (d, \( J = 18.6 \) Hz, 1H), 2.37–2.11 (comp m, 3H), 1.89 (d, \( J = 18.6 \) Hz, 1H), 1.64–1.51 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 218.4, 172.0, 133.3 (2C), 128.6, 128.1, 127.9, 127.6, 126.5 (2C), 126.0, 66.7, 44.6, 39.7, 38.4, 33.2 (t, \( J_{CD} = 20.2 \) Hz),
29.2; $^2$H NMR (76 MHz, CHCl$_3$) δ 2.66 (s); HRMS (EI+) $m/z$ calc’d for C$_{18}$H$_{17}$O$_3$H [M]: 283.1319, found 283.1323. All other spectral data are consistent with reported values.

D-labeled diol 370. Prepared as above to afford ~1:1 mixture of diastereomers of 370 (46.0 mg, 0.351 mmol, 71% yield) as a colorless oil. $^1$H NMR (300 MHz, CD$_2$OD) δ 4.26 (ddd, $J$ = 8.2, 3.5, 2.4 Hz, 0.45H), 4.21 (ddd, $J$ = 11.3, 6.4, 6.4 Hz, 0.55H), 3.56 (app t, $J$ = 6.9 Hz, 2H), 2.13 (dd, $J$ = 13.3, 6.4 Hz, 0.45H), 1.99–1.88 (m, 0.55H), 1.82–1.70 (comp m, 2H), 1.59 (dt, $J$ = 22.3, 6.9, 3H), 1.44–1.30 (m, 1H), 1.14 (dd, $J$ = 12.0, 4.5 Hz, 1H); $^{13}$C NMR (75 MHz, CD$_2$OD) δ 74.1, 62.2, 62.1, 43.0, 42.7, 40.5, 40.0, 35.8, 35.6, 35.6 (t, $J_{CD}$ = 19.5 Hz), 34.8 (t, $J_{CD}$ = 19.5 Hz), 31.4, 31.1; $^2$H NMR (76 MHz, CH$_3$OH) δ 2.14 (s), 1.87 (s). All other spectral data are consistent with reported values.

D-labeled ketomesylate 371. Prepared as above to afford 371 (60.3 mg, 0.291 mmol, 83% yield over two steps) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 4.30 (app dt, $J$ = 6.1, 2.7 Hz, 2H), 3.03 (s, 3H), 2.46 (d, $J$ = 18.1 Hz, 1H), 2.40–2.12 (comp m, 3H), 1.91 (app t, $J$ = 6.4 Hz, 2H), 1.85 (d, $J$ = 18.6 Hz, 1H), 1.61–1.50 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 218.3, 68.1, 44.7, 38.5, 37.7, 34.9, 33.4 (t, $J_{CD}$ = 19.8 Hz),
29.3; $^2$H NMR (76 MHz, CHCl$_3$) $\delta$ 2.35 (s); HRMS (EI+) $m/z$ calc’d for C$_8$H$_{13}$O$_4$S$_2$H$^+$: 207.0676, found 207.0673. All other spectral data are consistent with reported values.

D-labeled ketoazide 372. Prepared as above to afford 372 (39.3 mg, 0.255 mmol, 88% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.36 (ddd, $J$ = 6.8, 6.8, 2.9 Hz, 2H), 2.43 (d, $J$ = 18.3 Hz, 1H), 2.36–2.30 (m, 1H), 2.23–2.14 (comp m, 2H), 1.83 (d, $J$ = 18.1 Hz, 1H), 1.74 (ddd, $J$ = 6.8, 6.8, 3.7 Hz, 2H), 1.58–1.51 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 218.6, 50.0, 44.8, 38.5, 34.6, 34.3 (t, $J_{CD}$ = 19.8 Hz), 29.4; $^2$H NMR (76 MHz, CHCl$_3$) $\delta$ 2.29 (s). All other spectral data are consistent with reported values.

4-$d$-2-quinuclidonium tetrafluoroborate (334·HBF$_4$). Prepared as above to afford 334·HBF$_4$ (33.0 mg, 0.154 mmol, 67% yield) as white needles. $^1$H NMR (300 MHz, CD$_3$CN) $\delta$ 7.95 (br s, 1H), 3.78–3.58 (m, 4H), 2.96 (s, 2H), 2.00–1.95 (m, 4H); $^2$H NMR (76 MHz, CH$_3$CN) $\delta$ 2.49 (s); HRMS (FAB+) $m/z$ calc’d for C$_7$H$_{11}$NO$^2$H [M + H]$^+$: 127.0982, observed 127.0943.
**D₂-labeled syn-diol 373.** Prepared by a known method using LiAlD₄. *syn*-Diol 373 isolated as a colorless oil (0.6317 g, 4.78 mmol, 97% yield) with >98% d-incorporation. ¹H NMR (300 MHz, CD₃OD) δ 4.21 (ddddd, J = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 2.14 (ddd, J = 13.6, 7.2, 7.2 Hz, 1H), 2.01–1.85 (m, 1H), 1.83–1.70 (comp m, 2H), 1.64–1.55 (comp m, 3H), 1.48–1.31 (m, 1H), 1.15 (ddddd, J = 14.4, 9.6, 5.6, 0.5 Hz, 1H); ¹³C NMR (75 MHz, CD₃OD): δ 74.1, 61.4, 42.9, 40.4, 36.0, 35.8, 31.2; ²H NMR (76 MHz, CH₃OH) δ 3.51 (s); HRMS (EI+) m/z calc’d for C₇H₁₂O₂D₂H₂ [M]+: 132.1119, found 132.1113. All other spectral data are consistent with reported values.

**D₂-labeled ketomesylate 345.** Prepared as above to afford 345 (0.3775 g, 1.81 mmol, 65% yield over two steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 3.01 (s, 3H), 2.49–2.40 (m, 1H), 2.39–2.10 (comp m, 4H), 1.89 (d, J = 6.9 Hz, 2H), 1.83 (ddddd, J = 17.5, 7.4, 1.3 Hz, 1H), 1.63–1.47 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 218.3, 67.6 (pentet, J_CD = 22.7 Hz), 44.8, 38.4, 37.6, 34.7, 33.7, 29.4; ²H NMR (76 MHz, CHCl₃) δ 4.29 (s); HRMS (EI+) m/z calc’d for C₈H₁₂SO₂D₂H₂ [M]+: 208.0738, found 208.0741. All other spectral data are consistent with reported values.
**D$_2$-labeled ketoazide 374.** Prepared as above to afford 374 (143.6 mg, 0.925 mmol, 97% yield) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.48–2.39 (m, 1H), 2.37–2.11 (comp m, 4H), 1.83 (ddd, $J$ = 17.6, 9.8, 1.3 Hz, 1H), 1.74 (d, $J$ = 6.7 Hz, 2H), 1.61–1.50 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 218.6, 49.3 (pentet, $J_{CD} = 21.7$ Hz), 44.8, 38.5, 34.6, 34.4, 29.4; $^2$H NMR (76 MHz, CHCl$_3$) $\delta$ 3.32 (s). All other spectral data are consistent with reported values.

**6,6-$d_2$-2-quinuclidonium tetrafluoroborate (335•HBF$_4$).** Prepared as above to afford 335•HBF$_4$ (15.3 mg, 0.0712 mmol, 27% yield) as white needles. $^1$H NMR (300 MHz, CD$_3$CN) $\delta$ 7.96 (br s, 1H), 3.77–3.58 (m, 2H), 2.97 (d, $J$ = 3.2 Hz, 2H), 2.51 (app pentet, $J$ = 3.2 Hz, 1H), 2.15 (m, 2H), 2.02–1.94 (m, 2H); $^2$H NMR (76 MHz, CH$_3$CN) $\delta$ 3.68 (s), 3.59 (s); HRMS (FAB+) $m/z$ calc’d for C$_7$H$_{10}$NO$^2$H$_2$ [M + H]$^+$: 128.1044, observed 128.1042.
6,6,7,7-tetramethyl-2-quinuclidonium tetrafluoroborate (318•HBF₄). 6,6,7,7-tetramethyl-2-quinuclidone (318, 24.9 mg, 0.137 mmol, 1.0 equiv) was dissolved in Et₂O (1.0 mL, 0.14 M) and HBF₄ in Et₂O (54 wt % solution, 38 µL, 0.274 mmol, 2.0 equiv) was added in one portion. The reaction was stirred for 30 min and the precipitate was collected by filtration and dried under vacuum to afford 318•HBF₄ (31.6 mg, 0.117 mmol, 86% yield) as a tan solid. HRMS (FAB+) m/z calc’d for C₁₁H₂₀NO [M + H]⁺: 182.1545, observed 182.1552.

5.6.3 COMPUTATIONALLY OPTIMIZED STRUCTURES

Bond lengths below are given in angstroms (Å). Structures were optimized at the B3LYP/6-31G* level. Total energies were then calculated at the B3LYP/6-311++G** level.

Figure 5.6.1. Optimized structure of 2-quinuclidone (311).

O=C–N–C dihedral angles: +121°, −121°

Total energy: −403.4361217 hartrees
Figure 5.6.2. Optimized structure of N-protonated 2-quinuclidone (311•H⁺).

O=C–N–C dihedral angles: +119°, −119°
Total energy: −403.8028617 hartrees

Figure 5.6.3. Optimized structure of 6,6,7,7-tetramethyl-2-quinuclidone (318).

O=C–N–C dihedral angles: +118°, −118°
Total energy: −560.726844 hartrees
Figure 5.6.4. Optimized structure of N-protonated 6,6,7,7-tetramethyl-2-quinuclidone (318•H+).

O=C–N–C dihedral angles: +116°, −116°

Total energy: −561.03524 hartrees
5.6.4 **EXTENDED KINETIC METHOD PLOTS**

Figure 5.6.5. *Plot of the extended kinetic method of 311 with direct entropy correction.*

\[
y = -0.236x + 0.5653
\]

The y-intercepts from the entropy corrected kinetic method were plotted against the slopes at 18%, 25%, 35%, 50%, and 85% normalized collision energies. The slope of the line shown below is equal to \([\text{PA}_{\text{quin}} - \text{PA}_{\text{avg}}]\).
The second trend observed is associated with the proton affinity of the carbonyl oxygen of 2-quinuclidone (311). Bulky bases: (a) 3-aminopyridine; (b) 3,5-lutidine; (c) diisobutylamine; (d) 2,4-lutidine; (e) 1,4-diazabicyclo[2.2.2]-octane.

5.6.5 MS² SPECTRA OF ISOTOPICALLY LABELED DERIVATIVES AND THEIR HYDROLYSIS PRODUCTS

Fragmentation patterns of all isotopically labeled compounds (332–335) are in agreement with mechanism proposed in Scheme 5.3.1a.
Figure 5.6.7. MS² spectrum of 332 ($^{15}$N).

Figure 5.6.8. MS² spectrum of 333 ($^{13}$C₂).
Figure 5.6.9. MS² spectrum of 334 (D).

Figure 5.6.10. MS² spectrum of 335 (D₂).
5.7 NOTES AND REFERENCES


(19) A separate C–H activation approach was pursued incorporating the loss of dinitrogen. However, neither 311 nor any products consistent with its decomposition were observed.


(22) The ratio of 311:326 was determined by exposure to MeOH and analysis of the ring-opened products.


(29) Previous calculations have determined a 22.8 kcal/mol difference in energy for the site of protonation of 311. See ref 4b.

(30) See subsection 5.6.4 for details.


(35) See subsection 5.6.5 for details.


The parent bicyclic amines 375 and 376 possess a similar pKₐ values (10.90 and 10.53, respectively), however their nucleophilic reactivities are significantly different with 375 as the stronger nucleophile. See: Hine, J.; Chen, Y.-J. J. Org. Chem. 1987, 52, 2091–2094.


This cyclization has been used for substituted cyclobutanone systems. See ref 20.


APPENDIX 5

Spectra Relevant to Chapter 5:

Synthesis, Structural Analysis, and Gas-Phase Studies

of 2-Quinuclidonium Tetrafluoroborate
Figure A5.1. $^1$H NMR spectrum (300 MHz, CD$_3$CN) of 333•HBF$_4$. 
Figure A5.2. $^{13}$C NMR spectrum (75 MHz, CD$_3$CN) of 333•HBF$_4$. 

Appendix 5—Spectra Relevant to Chapter 5

464
Figure A5.3. $^1H$ NMR spectrum (300 MHz, CD$_3$CN) of 334·HBF$_4$. 
Figure A5.4. $^{2}H$ NMR spectrum (76 MHz, CH$_3$CN) of $334\cdot$HBF$_4$. 
Figure A5.5. $^1$H NMR spectrum (300 MHz, CD$_3$CN) of 335•HBF$_4$. 

$\text{H}_3$335•HBF$_4$.
Figure A5.6. $^2$H NMR spectrum (75 MHz, CH$_3$CN) of 335-HBF$_4$. 
Figure A5.7. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 339.
Figure A5.8. $^{13}$C NMR spectrum (75 MHz, CDCl₃) of 339.
Figure A5.9. $^1H$ NMR spectrum (300 MHz, CDCl$_3$) of 340.
Figure A5.10. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 340.
Appendix 5—Spectra Relevant to Chapter 5

Figure A5.11. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 341.
Figure A5.12. \(^{13}\)C NMR spectrum (75 MHz, CDCl\(_3\)) of 341.
Figure A5.13. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 344.
Figure A5.14. $^1$H NMR spectrum (76 MHz, CHCl$_3$) of 344.

Figure A5.15. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 344.
Appendix 5 — Spectra Relevant to Chapter 5

Figure A5.16. $^1$H NMR spectrum (300 MHz, CDCl₃) of 345.

$^1$H NMR spectrum (300 MHz, CDCl₃) of 345.
Figure A5.17. $^1$H NMR spectrum (76 MHz, CHCl$_3$) of 345.

Figure A5.18. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 345.
Figure A5.19. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 363.
Appendix 5—Spectra Relevant to Chapter 5

Figure A5.20. Infrared spectrum (neat film/NaCl) of 363.

Figure A5.21. $^{13}$C NMR spectrum (125 MHz, CDCl$_3$) of 363.
Figure A5.22. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 364.
Figure A5.23. Infrared spectrum (neat film/NaCl) of 364.

Figure A5.24. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 364.
Figure A5.25. $^1$H NMR spectrum (500 MHz, CD$_3$OD) of 365.
Figure A5.26. Infrared spectrum (neat film/NaCl) of 365.

Figure A5.27. $^{13}$C NMR spectrum (125 MHz, CD$_3$OD) of 365.
Figure A5.28: $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 366.
Figure A5.29. Infrared spectrum (neat film/NaCl) of 366.

Figure A5.30. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 366.
Figure A5.31: $^1$H NMR spectrum (300 MHz, CD$_3$OD) of 368.
Figure A5.32. $^{13}$C NMR spectrum (75 MHz, CD$_3$OD) of 368.
Figure A5.33. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 369.
Figure A5.34. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 369.
Figure A5.35. $^1$H NMR spectrum (300 MHz, CD$_3$OD) of 370.
Appendix 5—Spectra Relevant to Chapter 5

Figure A5.36. $^2$H NMR spectrum (76 MHz, $\text{CH}_3\text{OH}$) of 370.

Figure A5.37. $^{13}$C NMR spectrum (75 MHz, $\text{CD}_2\text{OD}$) of 370.
Figure A.38. $^1H$ NMR spectrum (300 MHz, CDCl$_3$) of 371.
Figure A5.39. $^2$H NMR spectrum (76 MHz, CHCl$_3$) of 371.

Figure A5.40. $^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 371.
Figure A5.41. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 372.
Figure A5.42. $^1$H NMR spectrum (76 MHz, CHCl$_3$) of 372.

Figure A5.43. $^{13}$C NMR spectrum (125 MHz, CDCl$_3$) of 372.
Figure A5.44. $^1$H NMR spectrum (300 MHz, CD$_3$OD) of 372.
Figure A5.45. $^2$H NMR spectrum (76 MHz, CH$_3$OH) of 373.

Figure A5.46. $^{13}$C NMR spectrum (75 MHz, CD$_3$OD) of 373.
Figure A5.47. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 374.
Figure A5.48. $^1H$ NMR spectrum (76 MHz, CHCl$_3$) of 374.

Figure A5.49. $^{13}C$ NMR spectrum (75 MHz, CDCl$_3$) of 374.
APPENDIX 6

An Improved and Highly Efficient Copper(I)-
Catalyzed Preparation of (S)-t-Bu-PHOX

A6.1 INTRODUCTION AND BACKGROUND

Phosphinoxazoline (PHOX) ligands\textsuperscript{1} have emerged as versatile chiral scaffolds for an array of transition-metal-catalyzed processes. As an important member of this class of P/N-chelates, (S)-t-Bu-PHOX (55)\textsuperscript{2} has been critical to the development of palladium(0)-catalyzed decarboxylative alkylation\textsuperscript{3} and protonation\textsuperscript{4} technologies in our laboratory. Investigations of these methods prompted the synthesis of numerous PHOX derivatives.\textsuperscript{5} Ultimately, the efficacy of a copper(I) iodide-catalyzed diarylphosphine–aryl bromide coupling reported by Buchwald and co-workers\textsuperscript{6} enabled a mild and modular strategy toward the preparation of these useful ligands.\textsuperscript{3a,7} In this appendix, we detail our improvements to this coupling reaction that increase yields, reduce reagent quantities, and simplify purification.
The Ullman-type coupling strategy has proven general for the preparation of a number of structurally and electronically diverse PHOX derivatives.\(^7\) However, recent scale-up efforts of our optimal ligand, (S)-t-Bu-PHOX (((S)-55)), to support applications in natural product total synthesis\(^8\) revealed a significant limitation to our standard Cu(I)-catalyzed coupling conditions. In particular, various coupling reactions failed to reach complete conversion (i.e., \(377 \rightarrow 55\)), thus requiring tedious chromatographic purification. Upon consideration of our standard conditions, we identified several likely problematic factors for scale-up, including relatively high catalyst and ligand loadings, as well as excessive quantities of Cs\(_2\)CO\(_3\) and diphénylphosphine. Due to the growing utility of this ligand in asymmetric catalysis,\(^5\) and consequently, the synthesis of biologically relevant substances, we sought to improve these conditions to facilitate the large-scale preparation of 55.

A6.2 REACTION OPTIMIZATION

Our efforts to maximize the reaction efficiency for the production of 55 first required a reliable coupling (Table A6.2.1, entry 1). We quickly recognized that it was essential to maintain vigorous stirring throughout the reaction,\(^9\) a straightforward task on smaller
scales but more difficult as quantities of heterogeneous solids increased. A successful coupling was observed as the CuI was reduced to 5 mol % (entries 2–4) to still provide complete conversions. Decreasing the equivalents of Ph₂PH and Cs₂CO₃ further improved conversion of 377 (entry 5). An increase in substrate concentration resulted in similar reactivity, enabling excellent results with 0.5 mol % CuI and a small excess of Ph₂PH in PhMe at 0.5 M (entries 6 and 7). Copper loadings can be further reduced to 0.1 mol %, although prolonged resulted in incomplete conversion (entry 8).

Table A6.2.1. Optimization of the coupling conditions

<table>
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<th>378 (mol%)</th>
<th>Ph₂PH (equiv)</th>
<th>Cs₂CO₃ (equiv)</th>
<th>[PhMe] (M)</th>
<th>conversion (%)</th>
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<td>3.75</td>
<td>0.12</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>7</td>
<td>1.88</td>
<td>3.75</td>
<td>0.12</td>
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<tr>
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<td>3.75</td>
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<tr>
<td>5</td>
<td>1</td>
<td>5</td>
<td>1.5</td>
<td>1.88</td>
<td>0.12</td>
<td>98</td>
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<tr>
<td>6</td>
<td>1</td>
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<td>1.25</td>
<td>1.5</td>
<td>0.25</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
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<td>0.50</td>
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<td>1.25</td>
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<td>98</td>
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</table>

*Conversion measured by ¹H NMR analysis of crude reaction filtrates after 6–16 h.*

With our optimized conditions in hand, we examined several common inorganic bases to determine their utility for this coupling. Standard use of Cs₂CO₃ produced excellent conversions and high yields of 55 on a variety of reaction scales (Table A6.2.2, entries 1 and 2). Surprisingly, other carbonates such as Li₂CO₃ and Na₂CO₃ were
ineffective (entries 3 and 4). Good reactivities were observed for both K$_2$CO$_3$ (entries 5 and 6) and K$_3$PO$_4$ (entry 7), however lower conversions were achieved.

Table A6.2.2. Inorganic base screen

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<th>yield (%)$^b$</th>
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<td>94</td>
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<tr>
<td>2$^c$</td>
<td>Cs$_2$CO$_3$</td>
<td>21</td>
<td>&gt;99</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Li$_2$CO$_3$</td>
<td>24</td>
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<td>—</td>
</tr>
<tr>
<td>4</td>
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<td>K$_2$CO$_3$</td>
<td>24</td>
<td>94</td>
<td>68</td>
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<tr>
<td>6$^d$</td>
<td>K$_3$CO$_3$</td>
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<td>97</td>
<td>72</td>
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<td>7</td>
<td>K$_3$PO$_4$</td>
<td>24</td>
<td>71</td>
<td>55</td>
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</table>

$^a$ Reactions performed at 2.5 mmol of 378 using 1.25 equiv of Ph$_3$PH and 1.5 equiv of base in PhMe (0.5 M). $^b$ Isolated yield. $^c$ Performed on 20 mmol. $^d$ With 3 equiv of base.

A6.3 CRYSTALLIZATION AND IMPROVED PURIFICATION

During the course of our investigations, we have obtained numerous reaction filtrates composed of varying mixtures of 55 and 377 (e.g., entries 5–7, Table A6.2.2). The previous combination of these two chromatographically similar compounds necessitated difficult column purification. In our search for an alternative purification method, we fortuitously discovered that acetonitrile promotes the rapid and selective crystallization of 55 as large blocks. Application of this procedure to impure samples enabled facile recovery of 55 (yields obtained for entries 5–7, Table A6.2.2) and produced high quality crystals for X-ray analysis (Figure A6.3.1). In addition to the new purification
procedure, our newly optimized conditions employing 0.5 mol % catalyst facilitate complete conversion of 377 (entries 1 and 2, Table A6.2.2), thus simplifying the isolation of 55. A straightforward silica gel plug to remove copper salts and excess diphenylphosphine, followed by concentration of the remaining filtrate, layering with acetonitrile, and final removal of volatiles under vacuum provided ligand 55 as a white crystalline solid in excellent yield and >99% purity as determined by various analytical methods.

Figure A6.3.1. X-ray crystal analysis of (S)-t-Bu-PHOX ((S)-55). The molecular structure is drawn with 50% probability ellipsoids.

A6.4 CONCLUSION

In summary, we have described a significant improvement to our original copper(I) iodide catalyzed diarylphosphine–aryl bromide coupling reaction that enables reliable and efficient access to (S)-t-Bu-PHOX (55). Our optimized conditions employ 0.5 mol % of the copper(I) iodide catalyst and feature reduced quantities of Cs₂CO₃ and diphenylphosphine with increased substrate concentrations convenient for large-scale
preparation. Coupling reactions typically proceed to complete conversion, facilitating a simplified purification procedure consisting of a silica gel plug, and our discovery of a selective acetonitrile crystallization provides 55 as a stable, crystalline solid in high yields and >99% purity. We believe our findings can be extended to a general synthesis of PHOX ligands and provide opportunities for future discoveries in asymmetric catalysis.
A6.5 EXPERIMENTAL SECTION

A6.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. CuI (98%) was purchased from Strem and used as received. Ph$_2$PH (99%) was purchased from Strem and cannula transferred to a dry Schlenk storage tube under nitrogen to prolong reagent life. Cs$_2$CO$_3$ (ReagentPlus, 99%) and diamine 378 were purchased from Sigma Aldrich and used as received. Bromooxazoline 377 was prepared according to ref 7b. The reaction stirring rate was set at ca. 700 setting on an IKAmag RET basic stir/hot plate (a range between 500–800 rpm is sufficient). Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash chromatography. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to Me$_4$Si (δ 0.0 ppm).$^{12}$ Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). $^{31}$P NMR spectra were recorded on a Varian Mercury 300 (at 121 MHz) and are reported relative to an H$_3$PO$_4$ external standard (δ 0.0 ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm$^{-1}$). Melting points were acquired using a
Buchi Melting Point B-545 instrument and the values are uncorrected. High-resolution mass spectra were acquired from the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.
(S)-t-Bu-PHOX ((S)-55). To a 250 mL Schlenk flask equipped with a Teflon valve, a 14/20 glass joint, and a large stir bar was added copper(I) iodide (19.0 mg, 0.10 mmol, 0.005 equiv), diphenylphosphine (4.35 mL, 25.0 mmol, 1.25 equiv), diamine 378 (53.3 µL, 0.50 mmol, 0.025 equiv) and toluene (20 mL). The colorless contents were stirred at ambient temperature for 20 min, and the flask was charged with bromooxazoline 377 (5.642 g, 20.0 mmol, 1.0 equiv), Cs₂CO₃ (9.775 g, 30.0 mmol, 1.5 equiv), and toluene (20 mL, 0.50 M total) to wash the neck and walls of the flask. The Teflon valve was closed and the yellow heterogeneous reaction was placed in a 110 °C oil bath and vigorously stirred. Following consumption of starting material by TLC analysis, the reaction was allowed to cool to ambient temperature, filtered through a pad of Celite, and the filter cake washed with CH₂Cl₂ (2 x 40 mL). The filtrate was concentrated under reduced pressure to a pale yellow semi-solid, dissolved in a minimal amount of dichloromethane (ca. 40 mL) and ethyl ether (ca. 50 mL), and dry-loaded onto 10 g of silica gel. This material was flushed through a silica gel plug eluting with 24:1 hexanes/Et₂O until excess Ph₂PH elutes, then with a 9:1 CH₂Cl₂/Et₂O mixture until the desire product elutes. The combined fractions are concentrated to a viscous pale yellow oil and layered with ca. 5 mL acetonitrile to facilitate crystallization. The flask was swirled while crystals form within seconds, and after ca. 15 minutes, the flask is placed under high vacuum to remove volatiles to afford (S)-55 (7.033 g, 18.15 mmol, 90.8% yield) as white blocks. \( R_f = 0.64 \) (4:1 hexanes/Et₂O, developed twice); mp = 114–115 °C (MeCN); \(^{31}\text{P NMR} \) (121 MHz, CDCl₃) δ –5.33 (s); \(^{1}\text{H NMR} \) (300 MHz, CDCl₃) δ 7.94
(ddd, \( J = 7.4, 3.5, 1.3 \) Hz, 1H), 7.36 (app dt, \( J = 7.4, 1.3 \) Hz, 1H), 7.33–7.21 (comp m, 11H), 6.86 (ddd, \( J = 7.4, 4.0, 1.3 \) Hz, 1H), 4.08 (dd, \( J = 10.1, 8.2 \) Hz, 1H), 4.01 (dd, \( J = 8.0, 8.0 \) Hz, 1H), 3.88 (dd, \( J = 10.1, 8.0 \) Hz, 1H), 0.73 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 162.8 (d, \( J_{\text{CP}} = 2.8 \) Hz), 138.9 (d, \( J_{\text{CP}} = 25.3 \) Hz), 138.7 (d, \( J_{\text{CP}} = 12.4 \) Hz), 138.4 (d, \( J_{\text{CP}} = 9.7 \) Hz), 134.5 (d, \( J_{\text{CP}} = 21.2 \) Hz), 134.2, 133.7 (d, \( J_{\text{CP}} = 20.3 \) Hz), 132.1 (d, \( J_{\text{CP}} = 19.8 \) Hz), 130.5, 130.0 (d, \( J_{\text{CP}} = 3.2 \) Hz), 128.6 (d, \( J_{\text{CP}} = 20.2 \) Hz), 128.5, 128.4 (2 lines), 128.2, 76.8, 68.4, 33.7, 25.9; IR (Neat Film NaCl) 3053, 2954, 2902, 2867, 1652, 1477, 1434, 1353, 1336, 1091, 1025, 966, 743, 696, 503 cm\(^{-1}\); HRMS (FAB+) m/z calc’d for \( \text{C}_{25}\text{H}_{27}\text{NOP} [\text{M} + \text{H}]^+ \): 388.1830, found 388.1831; \([\alpha]_D^{23} = -61.5^\circ \) (c 0.925, CHCl\(_3\), >99% ee); Anal. calc’d. for \( \text{C}_{25}\text{H}_{27}\text{NOP} \): C, 77.50; H, 6.76; N, 3.62. Found: C, 77.10; H, 6.62; N, 3.71.
A6.6 NOTES AND REFERENCES


Appendix 6—An Improved Cu(I)-Catalyzed Preparation of (S)-t-Bu-PHOX


(9) See subsection A6.5.2 for details.

(11) For a detailed X-ray crystallography report of (S)-55, see Appendix 8.

APPENDIX 7

Spectra Relevant to Appendix 6:

An Improved and Highly Efficient Copper(I)-
Catalyzed Preparation of (S)-t-Bu-PHOX
Figure A7.1. $^1$H NMR spectrum (300 MHz, CDCl$_3$) of 55.
Figure A7.2. $^{31}$P NMR spectrum (121 MHz, CDCl$_3$) of 55.

Figure A7.3. $^{13}$C NMR spectrum (126 MHz, CDCl$_3$) of 55.
APPENDIX 8

X-Ray Crystallography Reports Relevant to Appendix 6:

An Improved and Highly Efficient Copper(I)-
Catalyzed Preparation of (S)-t-Bu-PHOX

A8.1 CRYSTAL STRUCTURE ANALYSIS OF (S)-55

Figure A8.1.1. (S)-t-Bu-PHOX ((S)-55) is shown with 50% probability ellipsoids. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 646767.
Table A8.1.1. Crystal data and structure refinement for (S)-55 (CCDC 664767)

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**Data Collection**

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Special Refinement Details

Refinement of F^2 against ALL reflections. The weighted R-factor (wR) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of F^2 > 2σ(F^2) is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined.
by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.s is used for estimating e.s.d.s involving l.s. planes.

Figure A8.1.2. (S)-t-Bu-PHOX ((S)-55).
Table A8.1.2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for (S)-55 (CCDC 664767). $U_{\text{eq}}$ is defined as the trace of the orthogonalized $U_{ij}$ tensor.

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Table A8.1.4. Anisotropic displacement parameters ($\AA^2 \times 10^4$) for (S)-55 (CCDC 664767). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [ h^2 a^* U^{11} + ... + 2hk a^* b^* U^{12} ]$

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The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hardcopy and electronic characterization folders have been created that contain copies of the original $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR, $^2$H NMR, and IR spectra. All notebooks and spectral data are stored in the Stoltz archives.
### Table A9.1. Notebook cross-reference for compounds of Chapter 3 and Appendix 2

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Table A9.2. Notebook cross-reference for compounds of Chapter 4 and Appendix 4

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345–350.


University of British Columbia, Vancouver, Canada, 2002.


Yoganathan, K.; Rossant, C.; Glover, R. P.; Cao, S.; Vittal, J. J.; Ng, S.; Huang, Y.;


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ABOUT THE AUTHOR

Michael R. Krout was born on November 2, 1979 in Lewisburg, PA to Raymond and Debra Krout. He spent his childhood with his older brother, Jan, and twin brother, Eric, in the small rural town of Mifflinburg, PA. His enthusiasm for science was stimulated by a challenging course instructed by Mr. Daryl Dreese, who emphasized the fundamental skills of observation and creativity in science. Michael attended Mifflinburg Area High where he competed in varsity football and pursued advanced math and science studies.

In 1998, he began undergraduate studies at Indiana University of Pennsylvania in Indiana, PA. Although he majored in biochemistry, an audited summer course (for “fun”) in organic chemistry, lectured by John T. Wood, triggered a new challenge and inspired his pursuit of advanced organic coursework and two summer internships that solidified his zeal for organic chemistry. In 2002, Michael graduated summa cum laude with a B.S. in biochemistry, along with minors in biology, chemistry, and mathematics.

In 2003, Michael ameliorated his chemistry skills for eight months in the Department of Medicinal Chemistry at Merck in West Point, PA, and then moved to sunny Pasadena, CA to pursue doctoral studies with Professor Brian M. Stoltz (an IUP alum!) at the California Institute of Technology. In 2009, he earned his Ph.D. in chemistry for investigations involving progress toward the asymmetric total synthesis of variecolin and gas-phase studies of the twisted amide 2-quinuclidione. Three weeks prior to his defense in August of 2009, he married his fiancée, Kristy Dax. In October of 2009, Michael began his NIH-sponsored postdoctoral studies under the direction of Professor David Y. Gin at the Memorial Sloan–Kettering Cancer Center in New York, NY.