Development of New Asymmetric Organocatalytic Methods and Progress Towards the Total Synthesis of Guanacastepene A

Thesis by

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For Mom, Dad
and Melinda
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Abstract

The development of a new iminium-activation approach towards asymmetric organic catalysis is described. This strategy has been successfully applied to a 1,3-dipolar cycloaddition reaction to produce the first enantioselective catalytic [3+2] cycloaddition between nitrones and â,â-unsaturated aldehydes. This methodology highlights the ability of this new organocatalytic strategy to access chemical transformations not attainable though traditional Lewis acid catalysis.

We have also applied this iminium-activation strategy towards the successful development of an enantioselective organocatalytic intramolecular Diels-Alder (IMDA) reaction. This variant of the IMDA reaction is capable of accessing a range of stereochemically complex [4.3.0] and [4.4.0] ring systems in good yields and with excellent selectivities. Furthermore, we have successfully developed the first asymmetric Type II intramolecular Diels-Alder cyclization. Finally, the utility of this methodology was demonstrated in the efficient total synthesis of (−)-solanapyrone D where an asymmetric organocatalytic IMDA reaction comprised the pivotal bond construction.

Progress has been made towards the total synthesis of guanacastepene A. Significant efforts were directed towards a pursuing a 3-component coupling/ intramolecular Diels-Alder approach towards the natural product. IMDA precursors were synthesized in an efficient and convergent manner. It was found, however, that these substrates were unable to undergo the desired cyclization. By modifying our synthetic approach towards guanacastepene A, we found that the stereochemically complex cyclohexene portion of the natural product could be synthesized via an intermolecular Diels-Alder. Therefore recent efforts have been directed towards the pursuing a more convergent intermolecular Diels-Alder/ conjugate addition/ Dieckman condensation strategy towards guanacastepene A.
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Chapter 1

New Strategies for Organic Catalysis

I. Background

Over the last 50 years, great strides have been made in the area of metal-based enantioselective catalysis, which in turn has provided the synthetic chemist with a wealth of new asymmetric oxidation, reduction, \( \pi \)-bond activation and Lewis acid catalyzed methodology.\(^1\) However, there are relatively few examples in the literature where purely organic molecules are used as asymmetric reaction catalysts. This is true despite the potential economic and practical benefits that organic catalysts offer. In contrast to their metal-based counterparts, organic chemicals are generally insensitive to oxygen and moisture and thus do not require the use of special, expensive air- and moisture-free experimental techniques. Furthermore, nature provides an abundance of organic compounds in an enantiopure form (e.g., \( \alpha \)-amino acids, \( \alpha \)-hydroxy acids, carbohydrates), making chiral organic catalysts easily accessible from the natural chiral pool. As a consequence, using simple organic catalysts should be generally inexpensive, operationally easy, and time, and energy, efficient.

Although there is a scarcity of chemical literature on the topic of asymmetric organic catalysis (organocatalysis), relative to its metal-based counterpart, the benefits of organocatalysis have not been lost on the chemical community. Over the last 40 years, a number of important contributions have been published, demonstrating the value of non-metal based catalysis.

Interestingly, two of the earliest reported asymmetric catalytic reactions involved the use of organic catalyst systems. In 1960, Pracejus published seminal work on the development of an asymmetric catalytic ketene methanolysis reaction.\(^2\) In the presence of 1 mol\% of catalyst 3, the methanolysis of phenyl-\( \alpha \)-o-trimethyleneketene (1) produced methyl ester 2 in 76\% ee (eq. 1). About 10 years later, two research groups independently showed that \( L \)-proline 4 catalyzed the asymmetric Robinson
annulation of the symmetrical triketone 5 to afford the corresponding ketol (6) with good levels of enantiocontrol (eq. 2). This reaction, known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, remained relatively under-explored for the next 25 years until List and coworkers were able to demonstrate the first intermolecular variant of this aldol reaction in 2000.

![Ketene methanalysis (Pracejus)](image1)

\[ \text{Ketene methanalysis (Pracejus)} \]

\[ \begin{align*}
\text{H} & \rightarrow 1 \text{ mol\% catalyst 3} \rightarrow \text{MeOH} \\
& \rightarrow \text{40\% ee}
\end{align*} \]

\[ (1) \]

![Aldol reaction (Hajos-Parrish-Eder-Sauer-Wiechert)](image2)

\[ \text{Aldol reaction (Hajos-Parrish-Eder-Sauer-Wiechert)} \]

\[ \begin{align*}
\text{H} & \rightarrow 3 \text{ mol\% catalyst 4} \rightarrow \text{DMF} \\
& \rightarrow \text{93\% ee}
\end{align*} \]

\[ (2) \]

Some of the most notable examples of asymmetric organocatalytic transformations in recent years include seminal contributions by O’Donnell and Corey in the area of phase transfer catalysis. Corey and coworkers have found that optimized quinuclidine catalyst 7 can effect the alkylation of ketone 8 to produce the protected (-)-amino ester 9 with excellent selectivity (eq. 3). In an extension of this work, he later reported the use of catalyst 7 in the epoxidation of 1,2-unsaturated aryl ketones, producing epoxides with ee’s greater than 90%.

One of the most general and successful approaches to enantioselective acyl transfer is the alcohol desymmetrization of Fu and coworkers (eq. 4). Although these structures do contain a ferrocenyl backbone, the chemistry occurs entirely on the nitrogen of the DMAP ring, and thus the catalytically active portion of the molecule is purely organic in nature. Miller and coworkers have also pursued the use of minimal peptides as enzyme mimics for asymmetric acyl transfer processes.
Other notable examples include development of organic catalyst systems by Jacobsen and Corey that are capable of facilitating the asymmetric hydrocyanation of imines. Whereas Jacobsen uses a high-throughput combinatorial method to identify useful peptide-like catalysts (eq. 5a), such as 13a, Corey uses a C₂ symmetric guanidine catalyst (13b) (eq. 5b). Notably, both catalyst methods generate hydrocyanation products with good to excellent ee’s.
One of the most widely recognized enantioselective organic catalyst systems is that developed by Shi, Yang, and Denmark for the epoxidation of olefins. These systems use chiral ketone catalysts, such as 18, to mediate the asymmetric transfer of oxygen from oxone to unfunctionalized olefins with excellent levels of selectivity (eq. 6).

The research outlined above represents some of the most important contributions put forth over the last several decades to advance the field of asymmetric synthesis. However, these examples also highlight an important limitation that organocatalysis has suffered from since its inception. In general, the activation mechanism by which most organic catalysts operate was applicable to only a single transformation, and hence a new catalyst had to be developed for each new reaction type investigated. Furthermore, there were few general activation mechanisms known to be amenable to organic catalysis, thus making it difficult to devise catalysts systems that could be applied to a range of chemical transformations. This was in sharp contrast to the area of metal-mediated asymmetric catalysis, which has shown that metal complexes derived from BINOL, BINAP, Salen, and bisoxazoline ligand systems can catalyze a broad range of transformations with varying activation pathways. Therefore, we became interested in developing a new general strategy for organic catalysis that would allow chiral organic compounds to serve as reaction catalysts for a variety of chemical transformations.

II. Iminium-Activation Approach to Enantioselective Organocatalysis

This new approach was founded on principles and concepts borrowed from asymmetric Lewis acid catalysis, a field that has been proven to be generally applicable to a range of chemical reactions. In considering a general Lewis acid catalyzed process, such as the Diels-Alder reaction shown in Scheme 1, it is apparent that there were two key features to the mechanism of this reaction that make it so successful. First, Lewis acid coordination of the substrate activates it through LUMO-lowering electronics towards reaction with another reactant partner. The resultant rate acceleration ensures the participation of the chiral Lewis acid in the bond-forming transition state, therefore promoting the formation of enantioenriched products. Secondly, the kinetic lability of
the product-Lewis acid bond permits the catalyst to turn over upon completion of the reaction, therefore allowing it to go on and catalyze another Diels-Alder reaction. This feature is key to creating a catalyst system that employs substoichiometric amounts of the chiral catalyst.

Scheme 1. A generic Lewis acid catalyzed process: The Diels-Alder reaction

We speculated that the equilibrium dynamics and π-orbital electronics of the Lewis acid system (eq. 7) could be emulated in a carbogenic system though the reversible formation of iminium ions from α,β-unsaturated aldehydes and chiral secondary amines (eq. 8). Although, to our knowledge, this iminium-catalysis strategy had not been previously documented prior to our studies, this hypothesis was supported by established methodological studies of other research groups. Work published by Jung and coworkers in 1989 on the Diels-Alder reaction revealed that α,β-unsaturated iminium ions are significantly more reactive as dienophiles than α,β-unsaturated aldehydes, acid chlorides, ketones, nitriles, or esters.\textsuperscript{13} This suggested that formation of the chiral iminium would provide enough LUMO-lowering activation to achieve the needed rate acceleration for the enantioselective bond-forming step. Furthermore, Grieco and coworkers had demonstrated that transiently generated iminium ions will undergo Aza-Diels-Alder reactions under aqueous conditions.\textsuperscript{14} This provided good precedent for the ability of electron-rich substrates to undergo a selective reaction with \textit{transiently} generated iminiums in the presence of other aldehydes.
This new iminium activation strategy was attractive from the standpoint that simple chiral amines might be able to function as asymmetric catalysts (Scheme 2). Furthermore, since this approach was based on general principles borrowed from Lewis acid catalysis, this methodology could potentially be applied to a wide range of chemical transformations that traditionally utilize metal catalysts.

The proposed iminium-activation catalytic cycle for a general reaction (shown here for the specific case of the Diels-Alder) would begin with the condensation of the secondary amine catalyst (19) with an $\alpha,\beta$-unsaturated aldehyde (20) to produce the iminium species 21. This LUMO-lowered intermediate is then activated to undergo a cyclization reaction with cyclopentadiene to generate the iminium-bound product 22. Hydrolysis of 22 liberates the product 23 while regenerating the catalyst (19) so that it can participate in another reaction cycle.

**Scheme 2.** Iminium-activation catalytic cycle

The following two chapters detail our efforts towards demonstrating the utility of this new methodology. Chapter Two discusses the successful development of an asymmetric organocatalytic variant of a 1,3-dipolar cycloaddition that had been traditionally inaccessible using metal catalysts. Chapter Three details our elaboration of a general organocatalytic intramolecular Diels-Alder reaction, and the application of this methodology toward the total synthesis of the natural product solanapyrone D. These organocatalytic transformations illustrate the ability of this methodology to access stereochemically complex products in high enantiopurity.
References


Chapter 2

Enantioselective Organic Catalysis of the 1,3-Dipolar Cycloaddition of Nitrones and \( \alpha, \beta \)-Unsaturated Aldehydes

I. Introduction

Chapter 1 of this thesis detailed a new approach towards organic catalysis, which we felt could be applicable to a diverse spectrum of chemical transformations. This new iminium-activation strategy was first tested on the bimolecular Diels-Alder reaction by Kateri Ahrendt; preliminary studies produced promising results that indicated that this was indeed a viable approach (vide infra). Therefore we immediately became interested in extending this methodology to other chemical processes, especially those inaccessible via traditional Lewis acid catalysis. In this context, the cycloaddition reaction between nitrones and \( \alpha, \beta \)-unsaturated aldehydes was chosen for study and this chapter details our efforts towards the successful development of the first asymmetric, organocatalytic 1,3-dipolar cycloaddition reaction (eq. 1).

\[
\begin{align*}
\text{R}^1\text{N}^+\text{R}^2 & \xrightarrow{\text{R}_3\text{N}^-\text{R}_4} \text{R}^2\text{N}^-\text{R}_4 + \text{HX} \\
\text{R} \equiv \text{CHO} & \text{eq. 1} 
\end{align*}
\]

A. Background

A wealth of literature attests to the synthetic utility of the 1,3-dipolar cycloaddition reaction, and amongst the various dipoles studied in this process, nitrones are arguably one of the most useful.\(^1\) The 1,3-dipolar cycloaddition reaction of alkenes 1 with nitrones 2 is one of the most efficient methods for generating isoxazolidine ring systems 3. In one step, this reaction can provide access to up to three contiguous stereocenters in a heterocyclic framework, all from relatively simple starting materials.\(^2\) Furthermore, the highly ordered transition state of this reaction often allows the regio- and stereochemical preference of a given nitrone to be predicted. The isoxazolidines 3
formed in these reactions have proven to be versatile synthetic building blocks, due largely to the ease with which they can be opened to form chiral 1,3-amino alcohols (eq. 2). This cycloaddition/reductive cleavage route has been extensively used to access a range of biologically important compounds, such as nucleosides, []-amino acids, alkaloids, amino sugars, and []-lactams.

![Diagram of cycloaddition](image)

Because three chiral centers are formed simultaneously in the nitrone reaction, there is a potential to form up to 8 different isoxazolidine isomers. Coercing the reaction to produce only one of the 8 possible isomers requires the control of three different selectivity elements: regioselectivity, diastereoselectivity, and enantioselectivity.

The reaction of a nitrone and a mono-substituted alkene produces two possible regioisomers: a 4-substituted isoxazolidine and a 5-substituted isoxazolidine (Figure 1). Regioselectivity is controlled by both steric and electronic factors, with strong electronics often taking precedence over steric control elements. The cycloaddition of electron-rich or electron-neutral alkenes with nitrones produces mainly 5-substituted isoxazolidine products for both steric and electronic reasons. These so-called “inverse-electron demand” cycloadditions are governed primarily by \( \text{LUMO}_{\text{dipole}} - \text{HOMO}_{\text{dipolarophile}} \) interactions. As Figure 1 illustrates, the \( \text{LUMO}_{\text{dipole}} \) has the largest coefficient at the carbon atom of the nitrone and the \( \text{HOMO}_{\text{dipolarophile}} \) has the largest amplitude at the []-carbon of the alkene; thus the two components combine to favor formation of the 5-substituted cycloadduct. This phenomenon is reinforced by steric factors, since the sterically demanding end of the alkene is being placed away from the more bulky C-substituent on the nitrone.

In contrast, the cycloaddition of nitrones and electron-deficient alkenes is primarily controlled by \( \text{HOMO}_{\text{dipole}} - \text{LUMO}_{\text{dipolarophile}} \) interactions. Since the largest orbital coefficients are on the oxygen atom of the \( \text{HOMO}_{\text{dipole}} \) and the []-carbon on the \( \text{LUMO}_{\text{dipolarophile}} \) these “normal electron demand” cycloadditions electronically favor formation of the 4-substituted product. These interactions are enhanced when a Lewis
Acid is used to activate the alkene component of the reaction, thus creating an even larger electronic bias for forming the 4-substituted cycloadduct. When terminal alkenes are used, steric factors oppose the electronic bias of the reaction, which frequently results in the formation of a mixture of regioisomers in the non-Lewis acid catalyzed reaction. However, in the reaction of nitrones with 1,2-disubstituted electron deficient alkenes, the steric factor is eliminated, thus resulting in the FMO-controlled formation of the 4-EWG-substituted isomer as the sole product.

**Figure 1.** Control of regiochemistry in the [3+2] cycloaddition of nitrones and alkenes

The formation of diastereomers also has to be considered in the 1,3-dipolar cycloaddition reaction of nitrones and alkenes. In these reactions, the nitrone can approach the alkene in an *endo* or *exo* fashion, giving rise to two different diastereomers. This *endo/exo* nomenclature is borrowed from the Diels-Alder reaction, where the *endo* isomer arises though a transition state that is stabilized by secondary \( \pi \)-orbital interactions (Figure 2). Similarly, the *endo* isoxazolidine isomer is formed in a normal electron demand cycloaddition reaction though a transition state where the nitrogen atom of the nitrone is oriented towards the electron withdrawing group on the alkene.
However the actual interaction between the \( N \)-nitrone \( p_z \) orbital and the vicinal \( p_z \) orbital on the alkene is small, and thus this interaction contributes very little to electronically stabilizing the *endo* transition state. The *endo/exo* selectivity in the 1,3-dipolar cycloaddition reaction is therefore largely controlled by the structure of the catalyst and substrates.

**Figure 2.** Diastereoselectivity in the [3+2] cycloaddition of nitrones and alkenes

When dealing with achiral starting materials, the issue of enantioselectivity must also be considered. The development and application of *catalytic* asymmetric 1,3-dipolar cycloaddition reactions is a relatively new area. In contrast to its Diels-Alder counterpart, which has evolved since the mid-1980’s, the use of enantioselective catalysts in asymmetric 1,3-dipolar cycloadditions remained almost completely unexplored until 1993. Specifically, the asymmetric catalytic [3+2] cycloaddition of nitrones and alkenes has received considerable attention over the last 5 to 6 years; some of these advancements will be covered in the following section.
B. Asymmetric 1,3-Dipolar Cycloadditions of Nitrones and Alkenes

The diastereoselective 1,3-dipolar cycloaddition reaction of nitrones and alkenes is the most widely used method of inducing asymmetry in these reactions. The most common diastereoselective reactions are those involving the use of chiral nitrones, chiral dipolarophiles, or both (which is usually in the form of intramolecular cyclizations) to relay stereochemistry to the newly formed stereocenters on the isoxazolidine ring system. A variety of removable chiral auxiliaries have also been utilized for the asymmetric synthesis of isoxazolidines. In these cases, the auxiliary is most frequently attached to the dipolarophile in the form of an unsaturated ester or amide; however there are also a few cases where it is tethered from the dipole. The literature on diastereoselective 1,3-dipolar cycloadditions is vast, and since there have been excellent reviews published on these areas, they should be referred to for further details on these topics.2-4

The field of asymmetric catalysis of 1,3-dipolar cycloaddition reactions involving nitrones is relatively young. The first study on enantioselective, catalytic, normal electron-demand5 1,3-dipolar cycloaddition of nitrones and alkenes was published in 1994 by Jørgensen and coworkers, in which the authors examined a series of chiral TiCl₂-TADDOLates in the reaction of 3-N-alk-2-enoyloxazolidinones 5 with nitrones 6 (eq. 3).6 Ultimately they found that catalyst 7a was most effective, catalyzing the reaction of 5 and 6 to preferentially form exo cycloadduct 8 with selectivities that varied from poor to fair (1:1 to 9:1 exo/endo, 10-60% ee).

The authors were later able to improve on these results by switching to the more sterically demanding catalyst 7b.7 Treatment of alkenes 5 with N-aryl nitrones 6 in the
presence of 50 mol% 7b reversed the diastereoselectivity of the reaction, providing \emph{endo} products with good selectivities (eq. 4). This methodology was also extended to include acrylate derivatives.\(^8\) Reaction of acrylimides 5 (R\(^1\)=H) with nitrones 6 produced isoxazolidine cycloadducts with high \emph{endo} selectivity, but only moderate enantioselectivities (48-70\% ee). Although selectivities using these Ti-TADDOLate catalysts were relatively modest, these studies represent the first foray into the development of reactions of these types and helped to establish an interest in the development of asymmetric catalytic variants.

The Jørgensen group has also published on the use of chiral bisoxazoline (BOX) magnesium complexes as catalysts for the 1,3-dipolar cycloaddition of nitrones and alkenes (eq. 5). In the presence of 4Å molecular sieves (MS), magnesium complex 13 was found to serve as an effective catalyst in the reaction of oxazolidinone 11 with nitrone 10, catalyzing the reaction with 73:27 \emph{endo}/\emph{exo} selectivity and 82\% ee (\emph{endo}).\(^9\) Interestingly, these reactions exhibited the \emph{reverse} mode of enantioselectivity when they were run in the absence of 4Å MS (Table 1). In fact, these selectivities appeared to be dependent on the amount of 4Å MS used since reactions run in the presence of 50 mg of 4Å MS produced cycloadducts with ee’s nearly two times higher than those run with 10 mg of 4Å MS. Experimental results suggested that the sieves were not simply serving as a dehydrating agent since reactions run in the presence of magnesium sulfate were ineffective as reversing selectivity. Based on these results, the authors speculated that the MS are integrally involved in the catalytic cycle, potentially through the binding of the magnesium (II)-(\(R,R\))-bisoxazoline alkenoyloxazolidinone intermediate to the sieve’s surface.
In 1997, two independent research groups reported the development of two different chiral ytterbium catalysts for the asymmetric 1,3-dipolar cycloaddition reaction. The Jørgensen group (eq. 6a) reported the use of Yb(OTf)$_2$-pyridine-bisoxazoline complex 17 in the reaction of nitrones 14 with alkenoyloxazolidines 15 to preferentially produce endo cycloadducts with modest enantioselectivities (up to 73% ee).\(^{10}\) Kobayashi and coworkers separately described a 1,3-dipolar cycloaddition catalyzed by 20 mol% 18 in the presence of the achiral tertiary amine 19.\(^{11}\) Reaction of 14 with 15 (eq. 6b) produced isoxazolidine products with high endo selectivities and modest enantioselectivities (up to 78% ee). It was found, however, that when the reaction was run with 20 mol% 18 and 40 mol% of chiral amine 20, the enantioselectivities of the reaction were significantly increased; diastereoselectivities in this reaction for the substrates studied were generally high (c.a. 99:1 endo:exo) and enantioselectivities ranged from 79-96% ee.\(^{12}\) Interestingly, similar to the Mg(II)(BOX) catalyzed reactions, the absolute stereoselectivity of this reaction was also found to be influenced by the 4Å MS. The reaction catalyzed by complex 18 with 20 (eq. 6c) as an additive afforded endo-16 (R=Bn, R’=Me) in 96% ee in the presence of 4Å MS; in the absence of 4Å MS the opposite enantiomer was obtained in 50% ee.\(^{13}\)

**Table 1.** Effect of 4Å MS on Mg(BOX) catalyzed 1,3-dipolar cycloaddition

<table>
<thead>
<tr>
<th>Additive</th>
<th>endo/exo</th>
<th>% ee (endo)</th>
<th>Absolute Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Å MS (50 mg)</td>
<td>73:27</td>
<td>82</td>
<td>(S, 48)</td>
</tr>
<tr>
<td>4Å MS (10 mg)</td>
<td>77:23</td>
<td>42</td>
<td>(S, 48)</td>
</tr>
<tr>
<td>CaSO$_4$ (500 mg)</td>
<td>80:20</td>
<td>41</td>
<td>(S, 48)</td>
</tr>
<tr>
<td>none</td>
<td>100:0</td>
<td>48</td>
<td>(R, 48)</td>
</tr>
<tr>
<td>water (20%)</td>
<td>90:10</td>
<td>36</td>
<td>(R, 48)</td>
</tr>
<tr>
<td>MgSO$_4$ (50 mg)</td>
<td>96:4</td>
<td>52</td>
<td>(R, 48)</td>
</tr>
</tbody>
</table>
Furukawa and coworkers have recently reported the successful use of palladium, a relatively soft metal, in asymmetric catalytic 1,3-dipolar cycloadditions between nitrones 14 and alkene 21. Catalysis of the cycloaddition using complex 23 generally produced mixtures of endo-22 and exo-22, each in moderate to good enantioselectivities (54-91% ee endo, 34-93% ee exo). Transition state model 24 was proposed to account for the observed absolute enantioselectivities. In the enantiodetermining intermediate 24, the BINAP ligand and crotonoyl oxazolidinone substrate are arranged in a square planar fashion around the metal center; approach of the nitrone from the less sterically demanding si face of the alkene provides the observed product 22.

**Figure 3.** Pd(BINAP) catalyzed 1,3-dipolar cycloaddition reaction
Finally, Kanemasa and coworkers have reported the successful application of their dibenzofuranyl 2,2’-bisoxazoline (DBFOX) ligand to the 1,3-dipolar cycloaddition reaction. Treatment of aryl and alkyl nitrones 25 with crotonoyloxazolidinone 21 in the presence of 4Å MS and aqua Ni-DBFOX complex 27 produces isoxazolidines 26 with excellent diastereo- and enantiocontrol (eq. 7). Molecular sieves also had a marked effect on the diastereo- and enantioselectivities in this reaction. In contrast to the Mg(II)(BOX) and Yb(BINOL) catalyst systems, experiments suggested that the MS were serving simply as a dehydrating agent in this case. The authors proposed that the coordination of water to the Ni(DBFOX) complex forces the ligands to orient around the metal in an octahedral geometry. This octahedral transition state structure provides inferior π-facial coverage of the crotonoyloxazolidinone olefin than does the dehydrated trigonal bipyramidal transition state structure, thereby leading to poorer selectivities in the absence of 4Å MS. This catalyst system was one of the most selective metal catalyst to date for normal electron-demand 1,3-dipolar cycloaddition reaction between nitrones and alkenes.

\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

C. Organocatalysis vs. metal catalysis of 1,3-dipolar cycloadditions

As the examples in the previous section illustrate, significant advances have been made over the last 10 years in the field of asymmetric catalytic 1,3-dipolar cycloaddition reactions of nitrones and electron-deficient alkenes. However there are noticeable shortcomings in these systems that we felt an organocatalytic variant of this reaction could address. Prior to the publication of the organocatalytic work described below, all normal electron-demand enantioselective catalytic 1,3-dipolar cycloadditions required the use of an achiral oxazolidinone auxiliary. This is because monodentate α,β-unsaturated carbonyl compounds, such as aldehydes and ketones, are poor substrates for metal
catalyzed nitrone cycloadditions, presumably due to the preferential coordination of Lewis acids to nitrone oxides (28) over monodentate carbonyls (29) (Figure 4). In order to activate an $\alpha,\beta$-unsaturated carbonyl compound towards cycloaddition, the equilibrium must be shifted towards the desired Lewis acid-carbonyl complex 29. Furthermore, any of the Lewis acid-carbonyl adduct 29 that might be formed possesses poor organizational control, since there is potential for free rotation around the Lewis acid-carbonyl bond (generating 30). This lack of structural rigidity generally leads to poor enantiocontrol.

In all the metal catalyzed systems discussed in the previous section, this equilibrium shift was accomplished though the use of bidentate chelating oxazolidinones 31 with metal catalysts that favor this type of bidentate coordination. The resultant complex 32 contains the aforementioned requisite structural rigidity that 29/30 does not, therefore potentially allowing for good levels of enantiocontrol.

**Figure 4.** Alkene substrate choice in Lewis acid catalyzed cycloadditions

A new asymmetric organocatalytic variant of the nitrone cycloaddition reaction was chosen for development because we felt that our new technology would be able to address some of the shortcomings of the metal mediated processes. Although these oxazolidinone auxiliaries can be used to overcome the reactivity and selectivity issues discussed above, they have to be removed with additional steps subsequent to the cycloaddition reaction. An organocatalytic variant of this reaction would allow for direct access to a desirable aldehyde functionality, thereby obviating the need for extra steps following the completion of the reaction. Furthermore, since the mechanism of
iminium-activation differs from metal-mediated catalysis, our organocatalysis strategy could allow us to overcome functional-group compatibility issues associated with metal catalysis.

In contrast to metal catalysts, we expected our chiral amine catalysts to be inert to nitrone association, thereby enabling $\alpha,\beta$-unsaturated aldehydes to undergo iminium activation and subsequent [3+2] cycloaddition (eq. 8). Additionally, since the amine catalyst is bound to the alkene substrate though a rigid double bond, iminium intermediate (eq. 8, boxed) would be expected to possess the structural rigidity necessary to enforce organizational control and provide cycloadducts with high enantioselectivities.

![Diagram of reaction](image)

Thus, we became interested in developing an organocatalytic variant of the nitrone cycloaddition reaction. This methodology would not only extend the scope of the reaction by providing access to the first enantioselective catalytic 1,3-dipolar cycloaddition between nitrones and $\alpha,\beta$-unsaturated aldehydes, but would also demonstrate the broad utility of our new organocatalytic strategy.

It should be noted that subsequent to the publication of this work, three different groups independently reported the development of four metal-based catalyst systems capable of catalyzing the [3+2] cycloaddition between nitrones and $\alpha,\beta$-unsaturated aldehydes with varying degrees of success. Kanemasa and coworkers have used pinhole aluminum catalysts\textsuperscript{16} and chiral DBFOX/ Ph-Zn or Ni catalysts\textsuperscript{17} to effect the desired transformation, while Kundig and coworkers have applied their single coordinate (CpRu-BIPHOP-F) and (CpFe-BIPHOP-F) catalysts to the [3+2] cycloaddition of nitrones to $\alpha$-methyl substituted enals.\textsuperscript{18} Most recently, Yamada and coworkers have reported the use of cationic cobalt (III) complexes to catalyze the formation of the desired aldehyde-functionalized isoxazolidines.\textsuperscript{19}
II. Results and Discussion

Our iminium-activation strategy (Chapter 1) was first tested by Kateri Ahrendt, who began by examining the capacity of (S)-proline methyl ester (33) to enantioselectively catalyze the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene. She found that the introduction of 20 mol% 33 to the reaction resulted in formation of the bicyclic Diels-Alder adduct in 81% yield and more importantly 48% ee (endo) (eq. 9). Exposure of the a,b-unsaturated aldehyde to diene in the absence of the amine resulted only in recovery of starting materials. These initial results indicated that iminium-activation strategy was indeed viable. We became interested in developing a new enantioselective amine catalyzed variant of the 1,3-dipolar cycloaddition between nitrones and a,b-unsaturated aldehydes (eq. 1).

A. Initial Optimization of Reaction Conditions

Our catalytic [3+2] cycloaddition strategy was first evaluated using N-benzylidenebenzylamine N-oxide 34 with (E)-crotonaldehyde 35 (eq. 10). Reaction conditions were initially optimized using 20 mol% (S)-proline methyl ester (33), since this catalyst had been found by Kateri to be effective in the Diels-Alder reaction. A variety of reaction conditions were surveyed, and two reaction variables were found to have a dramatic effect on the rate, yields, and selectivities of the reaction: solvent and water.

A survey of a variety of solvents with dielectric constants varying from 7.6 to 47 revealed that aprotic, polar solvents work best at promoting the desired [3+2]
cycloaddition reaction. These effects can be rationalized by examining the catalytic cycle of the reaction, shown in Figure 5. (See Chapter 1 for discussion of catalytic cycle.) Polar solvents are perhaps most effective at promoting the desired cycloaddition reaction due to their ability to stabilize the positive charge in iminium 38, a key intermediate along this catalytic pathway. Furthermore, protic solvents appeared to facilitate an acid catalyzed decomposition of nitrone 34 through a disproportionation reaction with crotonaldehyde 35 to produce benzaldehyde 41 and the conjugated, but unreactive nitrone 40. This side reaction generally leads to lower conversions and yields for reactions run in protic media. Based on these observations, nitromethane was ultimately chosen as the optimal reaction solvent, providing the cycloadduct 36 in 43% ee (endo) and 35% conversion after 12 hours.

Table 2. Solvent screena

<table>
<thead>
<tr>
<th>solvent</th>
<th>dielectric constant</th>
<th>% conv (12h)b</th>
<th>% ee (cyclo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>7.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CH₃Cl₂</td>
<td>9.1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>12.5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>EtOH</td>
<td>24.3</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>MeOH</td>
<td>32.6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CH₃NO₂</td>
<td>36.0</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>37.5</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>DMSO</td>
<td>47.0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

aOptimized based on the reaction in eq. 10; bConversion based on nitrone 34 starting material.

Figure 5. Catalytic cycle of the amine catalyzed [3+2] cycloaddition
One of the benefits of organocatalysis is that these reactions do not need to be run under the strict exclusion of water since the chiral amine catalysts are not particularly sensitive to water or oxygen. In fact, since it plays an integral role in the catalytic cycle, water can have a marked effect on the rate of the reaction, and therefore this reaction parameter was also optimized. Since water participates at two separate steps in the catalytic cycle (highlighted in green in Figure 5), enough H₂O has to be added to facilitate catalyst turnover (converting 39 to 36) without hindering the formation of iminium intermediate 38 from crotonaldehyde 35 and catalyst 37. A study of the effect of water, summarized briefly in Table 3, found that 3 equivalents of H₂O was an appropriate amount for this reaction. Thus these optimized conditions provided the desired cycloadduct in 42% ee, 1.3:1 endo/exo, with 46% conversion after 12 hours.

### Table 3. Water screen

<table>
<thead>
<tr>
<th>equiv H₂O</th>
<th>% conv (12h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
</tr>
</tbody>
</table>

*Optimized based on the reaction in eq. 10. *Conversion based on nitrene 34 starting material.

### B. Catalyst Development

With these reaction conditions in hand, a variety of chiral amines were surveyed to assess the reactivity and enantioselectivity potential of various structural frameworks. As Table 4 illustrates, these studies revealed that the general catalyst structure had a large influence on the reactivity of the [3+2] cycloaddition. Relatively basic acyclic and cyclic amines, such as those illustrated in entries 1 and 2, were generally poor catalysts in terms of efficiency. In contrast, acyclic amines containing a proximal electron withdrawing group, like an α-carbonyl moiety, provided moderate levels of reactivity (entries 3, 6 22-42% conv.). The most reactive catalysts, however, were cyclic amines proximal to an electron withdrawing group (entries 4, 5 70-75% conv.). The success of these catalysts can presumably be attributed to their ability to balance the nucleophilicity of the amine...
with the reactivity of the iminium ion. The increased nucleophilicity of the cyclic amines compared to their acyclic counterparts facilitates the formation of the reactive iminium intermediate 38 (Figure 5), while the proximal electron withdrawing group assists in further lowering the LUMO of 38, making this intermediate more reactive. The combination of these effects leads to highly reactive amine catalysts.

Table 4. [3+2] nitrore cycloaddition with representative amine catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst Structure</th>
<th>ee (%) Conv (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1" alt="Catalyst Image" /></td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td><img src="2" alt="Catalyst Image" /></td>
<td>63% (&gt;10% conv)</td>
</tr>
<tr>
<td>3</td>
<td><img src="3" alt="Catalyst Image" /></td>
<td>25% (22% conv)</td>
</tr>
<tr>
<td>4</td>
<td><img src="4" alt="Catalyst Image" /></td>
<td>42% ee (75% conv)</td>
</tr>
<tr>
<td>5</td>
<td><img src="5" alt="Catalyst Image" /></td>
<td>58% ee (70% conv)</td>
</tr>
<tr>
<td>6</td>
<td><img src="6" alt="Catalyst Image" /></td>
<td>75% ee (42% conv)</td>
</tr>
</tbody>
</table>

This survey also identified three catalysts that showed promising enantioselectivities with reasonable reactivity (entries 4, 5, 6). Most interestingly, N-methyl tryptophan methyl ester • HCl (Entry 6, 42) salt was able to catalyze the desired reaction in 75% ee (endo). However, efforts to improve these enantioselectivities through the derivatization of these catalysts were met with very little success.

In an effort to understand the origins of the observed enantioselectivities, computational models of the iminium ion structures were examined (Figure 6). Condensation of crotonaldehyde with N-methyl tryptophan methyl ester 42 results in the formation of two different iminium ion isomers: one where the olefin is oriented cis to the catalyst (43) and one where the alkene is oriented trans to the chiral center (44). As MM3-43 and MM3-44 illustrate, the indole ring of the catalyst effectively shields one -face of the olefin in both cases. However, these models suggest that the asymmetric environment associated with each iminium isomer will induce the opposite sense of
enantioselectivity during the course of the cycloaddition reaction. Whereas in MM3-43 it is the *si*-face that is left open to attack by the nitrone, leading to formation of the cycloadduct (+)-*endo*-36, it is the *re*-face that is left open in the case of MM3-44 which ultimately leads to the formation of the (−)-*endo*-36 adduct (the *enantiomer* of adduct formed via MM3-43). There is an energetic difference of only about 3 kJ/mol¹⁻¹ between the *cis* MM3-43 and *trans* MM3-44 iminium ion geometries, suggesting that both iminium ion geometries are operational (Figure 6). Catalysts that achieve poor levels of iminium geometry control exhibit diminished enantiocontrol. In order to improve the selectivity of the reaction, iminium ion geometry has to be controlled.

**Figure 6.** Comparison of the *cis* and *trans* iminium ion intermediates

One method for controlling iminium geometry is through C₂-symmetry. Condensation of an enal with a C₂ symmetric catalyst, such as 45, results in an iminium ion with only one possible geometry 46, since the two iminium isomers are degenerate. Thus a C₂ symmetric (2S,5S)-proline bismethyl ester 45 catalyst was synthesized²³ and found to catalyze the [3+2] nitrone cycloaddition (eq. 11) in 78% ee, and marked improvement from the analogous C₁ symmetric proline catalyst 33 (42% ee). Although subsequent efforts to increase selectivities though derivatization of the ester moiety proved unsuccessful, these experimental results corroborate the theoretical importance of iminium geometry control.
Ultimately, it was determined that catalysts that utilize steric elements to control iminium geometry are most effective. The benzylidimethyl imidazolidinone (47) architecture, which was first developed by Seebach and coworkers\textsuperscript{24-27} for use in chirality transfer reactions, was found to be an extremely effective organic catalyst. Initial results in the Diels-Alder reaction\textsuperscript{28} found that catalyst 47 was capable of catalyzing the reaction of cinnamaldehyde and cyclopentadiene (eq. 9) to generate the bicyclic product in excellent yields and enantioselectivities (93% ee (endo), 1.3:1 exo:end0, 99% yield). The success of catalyst 47 is due to several factors. In terms of catalyst architecture, the imidazolidinone system contains both characteristics that were found earlier to be important to catalyst reactivity: (1) the amino functionality is proximal to an electron withdrawing carbonyl group, and (2) the amine is integrated into a five-membered ring infrastructure. The observed levels of enantiocontrol originate from the selective formation of the \((E)\)-iminium isomer cis-48 to avoid non-bonding steric interactions between the substrate olefin and the geminal methyl substituents (Figure 7). These steric clashes are nontrivial. MM3 calculations place cis-48 almost 10 kJ/mol\textsuperscript{-1} lower in energy than trans-48, a significantly larger cis/trans energy difference than in the case of tryptophan 42. The use of these steric control elements to manipulate iminium ion geometry ultimately translates into excellent levels of enantioselectivity. Finally this catalyst architecture benefits from the practical convenience of being readily accessed in large quantities as a bench stable solid from an \(-\)-amino ester, acetone, and methyl amine.

\textbf{Figure 7.} Analysis of imidazolidinone catalyst framework
The potential of the imidazolidinone catalyst framework in the [3+2] nitrone cycloaddition was evaluated using a series of chiral imidazolidinone • HCl salts. As revealed in Table 5, this reaction was successfully catalyzed by a number of imidazolidinones containing a variety of chiral substituents (entries 1–7, yield >80%, 45-91% ee) in CH$_3$NO$_2$–H$_2$O at +4 °C. A survey of catalyst architecture reveals that incorporation of benzylic substituents at the 3 position on the imidazolidinone framework provides the highest levels of diastereo- and enantiofacial discrimination (47, R = CH$_2$Ph, 94% ee; 51, R = CH$_2$-2-naphthyl, 86% ee; 53, R = CH$_2$-4-MeOPh, 89% ee), while the 3-phenyl and 3-ethylphenyl substituted catalysts (entries 2 and 3) were substantially less stereoselective. These effects can be rationalized by examining the model of the benzyl catalyst complexed with crotonaldehyde, MM3-48$^{29}$. One methylene unit situates the aryl ring at an appropriate distance away from the five membered ring so that aryl moiety can effectively shield one p-face of the olefin. Furthermore, the superior performance of the aryl groups can potentially be attributed to p-stacking interactions that help orient the aryl ring in a parallel geometry relative to the olefin, therefore effectively shielding that p-face of the alkene. Ultimately, in accord with the Diels–Alder studies, the phenylalanine derived catalyst 47 was found to be most general with respect to reaction substrates (vide infra).

**Table 5.** Effect of catalyst structure on the dipolar cycloaddition between crotonaldehyde and nitrone 34.$^c$

<table>
<thead>
<tr>
<th>entry</th>
<th>R–(catalyst)</th>
<th>Time (h)</th>
<th>% yield</th>
<th>endo:endo$^a$</th>
<th>% ee (endo)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Ph (47)</td>
<td>72</td>
<td>70</td>
<td>88:12</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Ph (48)</td>
<td>70</td>
<td>73</td>
<td>78:22</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr (49)</td>
<td>60</td>
<td>68</td>
<td>58:32</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu (50)</td>
<td>70</td>
<td>45</td>
<td>33:66</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$-2-naphthyl (51)</td>
<td>48</td>
<td>62</td>
<td>78:22</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$-4-MeOPh (52)</td>
<td>48</td>
<td>77</td>
<td>79:21</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>CH$_3$CH$_2$Ph (53)</td>
<td>48</td>
<td>72</td>
<td>50:50</td>
<td>69</td>
</tr>
</tbody>
</table>

$^a$ Product ratios determined by HPLC using a Chiral OD-H column after reduction of the formyl group with NaBH$_4$. $^b$ Absolute and relative configurations assigned by chemical correlation or by analogy. (Supporting Information). $^c$ Done in collaboration with J. J. M. Wiener.
Surprisingly, during the course of reaction optimization using catalyst 47, it was discovered that a small, but significant amount of a side product was being formed in the [3+2] cycloaddition reaction. This product was isolated and identified to be 54, the result of a Henry reaction (eq. 12). This 1,4-addition product presumably arises from the mechanism detailed in Scheme 1. The discovery of this alternate reaction pathway was particularly notable, since this represented a new reaction manifold that was susceptible to organocatalysis, thus reasserting our belief that this methodology could be extended to a broad range of chemical transformations.

Scheme 1. Henry side reaction: Formation of 1,4-addition product 54 and proposed catalytic cycle

C. Substrate Scope

Since these reaction conditions generated the desired crotonaldehyde-derived cycloadduct 36 with good selectivities, other \( \alpha, \beta \)-unsaturated aldehydes were examined in an effort to expand the aldehyde substrate scope of the reaction. John Wiener, who subsequently joined the project, continued to investigate the potential of crotonaldehyde to reaction with other \( N \)-benzyl \( C \)-aryl nitrones.
A variety of \(\beta,\beta\)-unsaturated aldehydes were examined, and one enal that was found to generate cycloadducts with good selectivities was acrolein (eq 13). Unfortunately optimization of reaction conditions around the HCl salt 47 consistently produced cycloadducts with good selectivities (91% ee \((\text{endo}), 4:1 \text{endo/exo}\)) but poor yields (36% yield). In an effort to increase the reaction efficiency, the Brønsted acid component of the benzyl imidazolidinone catalyst was examined (Table 6). A number of imidazolidinone acid salts were found to catalyze the formation of isoxazolidine \((4S)-56\) in good yield and in greater than 87% ee (entries 1-6). Most notably, the choice in cocatalyst appeared to have a dramatic effect on reaction efficiency. Aside from the HCl derived catalyst 47, imidazolidinone salts derived from more acidic co-catalysts, such as 59 and 60, produced higher isolable yields than their less acidic counterparts.

Table 6. Effect of the Brønsted acid cocatalyst on the dipolar cycloaddition between acrolein and nitrone 34

<table>
<thead>
<tr>
<th>entry</th>
<th>HX co-catalyst</th>
<th>pK\textsubscript{a} (H\textsubscript{2}O)</th>
<th>(\text{endo:exo})</th>
<th>% cc ((\text{endo}))\textsuperscript{a}</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA (57)</td>
<td>-0.25</td>
<td>50:50</td>
<td>90</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>HCl (47)</td>
<td>-8.0</td>
<td>79:21</td>
<td>91</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>HBr (58)</td>
<td>-9.0</td>
<td>71:29</td>
<td>87</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>HClO\textsubscript{2} (59)</td>
<td>-10</td>
<td>80:20</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>TIOH (60)</td>
<td>-14</td>
<td>84:16</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>TIOH (-18 °C) (60)</td>
<td>-14</td>
<td>86:14</td>
<td>92</td>
<td>82</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with NaBH\textsubscript{4}

Mechanistic studies suggest that catalyst salts derived from acidic co-catalysts engender higher equilibrium concentrations of the active iminium species \((48)\). Presumably, higher concentrations of the reactive iminium ion \((48)\) allows the desired \([3+2]\) cycloaddition to out-compete the undesired nitrone decomposition pathway (Figure 5), while generally increasing reaction rates. Preliminary investigations also suggest that the observed variation in enantioselectivity as a function of co-catalyst can be attributed to the extent of iminium activation in preference to achiral Brønsted acid promotion. As
such, it is important to note that the TFA-, HClO₄-, and TfOH-derived catalysts successfully partition the [3+2] cycloaddition toward the iminium pathway with ≥90% selectivity (giving ≥90% ee). The superior levels of asymmetric induction and diastereoccontrol exhibited by the TfOH salt 60 to afford isoxazolidine (4S)-56 in 92% ee, 86:14 dr, and 82% yield (20 mol% catalyst, −18 °C) prompted us to select this catalyst for further exploration with acrolein. A similar study conducted with crotonaldehyde in lieu of acrolein revealed that the HClO₄ salt 59 was most appropriate for reactions with run with that enal substrate (94% ee, 94:6 dr, 98% yield with 20 mol% catalyst, −20 °C).

Table 7. Organocatalyzed dipolar cycloadditions between representative nitrones and dipolarophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>Z</th>
<th>R</th>
<th>R₁</th>
<th>endo:exo</th>
<th>yield %</th>
<th>ee (endo) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>Ph</td>
<td>Me</td>
<td>96:4</td>
<td>98</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Allyl</td>
<td>Ph</td>
<td>Me</td>
<td>93:7</td>
<td>73</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>95:5</td>
<td>66</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>4-PbCl</td>
<td>Me</td>
<td>92:8</td>
<td>78</td>
<td>95&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>4-PbCl</td>
<td>Me</td>
<td>93:7</td>
<td>76</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>4-MeO Ph</td>
<td>Me</td>
<td>98:2</td>
<td>93</td>
<td>91&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>4-MePh</td>
<td>Me</td>
<td>93:7</td>
<td>82</td>
<td>97&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>2-maph</td>
<td>Me</td>
<td>95:5</td>
<td>98</td>
<td>93&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>c-hex</td>
<td>Me</td>
<td>99:1</td>
<td>70</td>
<td>99</td>
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<td>10</td>
<td>Bn</td>
<td>Ph</td>
<td>H</td>
<td>81:19</td>
<td>72</td>
<td>90</td>
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<td>11</td>
<td>Bn</td>
<td>Ph</td>
<td>H</td>
<td>86:14</td>
<td>80</td>
<td>92&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>4-PbMe</td>
<td>H</td>
<td>85:15</td>
<td>80</td>
<td>90&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>4-PbCl</td>
<td>H</td>
<td>80:20</td>
<td>80</td>
<td>91&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>Bn</td>
<td>2-maph</td>
<td>H</td>
<td>81:19</td>
<td>82</td>
<td>90&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>Bn</td>
<td>4-MeO Ph</td>
<td>H</td>
<td>91:9</td>
<td>83</td>
<td>90&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Product ratios determined by HPLC using a Chiralcel OD-H column after reduction of the formyl group with NaBH₄.<br><sup>b</sup> Absolute and relative configurations assigned by chemical correlation or by analogy (see supporting information).<br><sup>c</sup> Reactions conducted with catalyst 60.<br><sup>d</sup> Reactions run by J.J.M. Wiener. Please refer to his thesis for any additional details on these substrates.

The scope of the organocatalytic 1,3-dipolar cycloaddition between a,b-unsaturated aldehydes and various nitrones has been investigated (Table 7). The reaction appears quite general with respect to the nitrone structure (entries 1–8, 66–98% yield, 92:8 to 98:2 endo:exo, 91–99% ee). Variation in the N-alkyl group (R₁ = Me, Bn, allyl, entries 1–3) is possible without loss in enantioselectivity (endo 94–99% ee). As revealed
with 4-chlorophenyl- and 4-methoxyphenyl-substituted nitrones (entries 4–6), the reaction is tolerant to a range of aromatic substituents on the dipole (76–93% yield, 92:8 to 98:2 endo:exo, 91–95% ee). Moreover, excellent levels of diastereo- and enantioselectivity can be achieved with alkyl-substituted nitrones (entry 9, 96:4 endo:exo, 99% ee).

To demonstrate the preparative utility, the addition of nitrone 3 to crotonaldehyde was performed on a 25 mmol scale with catalyst 8 to provide (R)-4 (94% ee, 94% yield). Per the previous discussion, structural variation in the dipolarophile can also be accommodated, as acrolein has been shown to react with a range of nitrones to generate the isoxazolidine products in good yields and selectivities (entries 10-15, 90-92% ee, 80% yield).

Although this methodology was found to be compatible with a variety of nitrone and α, β-unsaturated aldehyde substrates, there were a few limitations to this methodology. Attempts to react N-benzyl-C-phenyl nitrone 34 with cinnamaldehyde (61), and a few β-alkyl substituted enals (62, 63) were largely unsuccessful due to the sluggish nature of these reactions. Presumably, the lack of reactivity observed with cinnamaldehyde can be attributed to the highly stabilized nature of the resultant iminium ion, thus making it reluctant to undergo the desired cycloaddition.

**Figure 8.** Substrates not able to participate in the [3+2] cycloaddition
In an attempt to probe the limitations of the reaction with respect to the nitrone component, a few nitrones (e.g., 64, 65, 68) with different structural motifs were also examined, although with limited success. Cyclic nitrones such as 64 generally produced unidentifiable complex mixtures of products. Since a C-alkyl nitrone had been met with a high level of success (Table 7, entry 9, 99:1 endo:exo, 99% ee), several other nitrones of this type were also tested. However, less hindered nitrone substrates, such as 68, would decompose via the aforementioned (Figure 5) disproportionation pathway to generate the more stable, conjugated nitrone 40 before they would react with the enal. These conjugated nitrones were generally unreactive under these reaction conditions, but attempts were made to optimize conditions around the cinnamyl derived nitrone 67. As expected, these substrates were not susceptible to the disproportionation decomposition pathway, and thus afforded the desired functionalizable isoxzolidine 68 with moderate levels of selectivity and consistently low yields under partially optimized reaction conditions. It is notable, however, that although these substrates were greeted with limited amounts of success using these 2-dimethyl-4-benzylimidazolidinone catalysts, a more reactive and more selective second generation catalyst has been developed (see next chapter); it is potentially within the capacity of this new catalyst to promote the desired cycloaddition with these substrates.

Finally, one of the benefits of this organocatalytic methodology is that it is easily modeled using currently available calculation methods, and thus can be used to accurately predict selectivities in these amine catalyzed reactions. The sense of asymmetric induction and diastereoselectivity observed in all cases involving catalysts 59 and 60 are consistent with the calculated iminium model MM3-48 (see experimental information for stereochemical proofs). By inspection, it is evident that enforced formation of the (E)-iminium isomer and the position of the benzyl group on the catalyst framework effectively promote cycloaddition from the si-face of the dipolarophile. Furthermore, cycloaddition through an endo-topography effectively alleviates nonbonding interactions between the nitrone phenyl group and the neopentyl methyl substituent on the catalyst framework.
III. Conclusion

The first asymmetric, catalytic 1,3-dipolar cycloaddition between nitrones and \( \text{a,b-unsaturated aldehydes} \) has been described. Using a chiral imidazolidinone salt, we can access aldehyde-functionalized isoxazolidine cycloadducts in good yields and with excellent selectivities. This methodology not only demonstrates the ability of this new organocatalytic strategy to be extended to chemical processes other than the Diels-Alder reaction, but also highlights its ability for accessing chemical transformations not attainable though traditional Lewis acid catalysis.
References

5. The topic of asymmetric inverse-electron demand 1,3-dipolar cycloaddition reactions is slightly beyond the context of this work and therefore is not being reviewed here. This topic is covered in the review referred to in reference 2.
21. Catalyst development work was done in conjunction with Kateri Ahrendt and Christopher Borths, who were simultaneously working on developing the organocatalytic Diels-Alder reaction.
22. A Monte Carlo simulation, MM3 force-field; Macromodel V6.5
23. The C2 symmetric catalyst proline methyl ester catalyst was synthesized by Christopher Borths
29. Monte Carlo simulation, MM3 force-field; Macromodel V6.5
30. This particular reaction was later handed off to Catharine Larsen, who optimized this the reaction to produce the henry product in 66% ee, and about 20% conversion.
**Experimental**

**General Information.** Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.¹ Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.² Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by florescence quenching or KMnO₄ stain.

¹H NMR and ¹³C NMR spectra were recorded on Bruker AM-400 (400 MHz and 100 MHz, respectively), Bruker DRX-500 (500 MHz and 125 MHz, respectively), Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ¹H NMR are reported with chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ¹³C NMR are reported with chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). Optical Rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Gas Chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex [–]-TA (30 m x 0.25 mm) column. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

**(5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt (60).** Prepared from the hydrochloride salt 1a³ by treatment with saturated aq.

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NaHCO₃ (100 mL) and extraction of the free amine with CHCl₃ (3 x 100 mL). The solution was dried over Na₂SO₄, filtered, and concentrated. The residue was taken up in Et₂O and trifluoromethanesulfonic acid was added to precipitate 5. The precipitate was recrystallized from 2-propanol to provide the title compound as colorless crystals. IR (CH₂Cl₂) 2363, 1730, 1290, 1182 cm⁻¹; ¹H NMR (300 MHz, d₆-DMSO) □ 10.35 (br s, 1H, "NH₂), 9.27 (br s, 1H, "NH₂), 7.19–7.38 (m, 5H, C₆H₅), 4.67 (br d, J = 8.6 Hz, 1H, COCH), 3.30 (dd, J = 3.3, 15.4 Hz, 1H, CH₂C₆H₅), 2.93 (dd, J = 11.0, 15.4 Hz, 1H, CH₂C₆H₅), 2.79 (s, 3H, CH₃NCO), 1.62 (s, 3H, CH₃), 1.48 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) □ 166.8, 136.6, 129.7, 129.3, 127.8, 77.5, 57.9, 34.4, 25.7, 24.6, 22.5; LRMS (CI) m/z 219 (MH⁺); HRMS (CI) exact mass calcd for (C₁₇H₁₉N₂O)⁺ requires m/z 219.1497, found m/z 219.1497; [□]D = −58.8 (c = 1.0, CH₃OH).

(5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one trifluoroacetic acid salt (57). Prepared from the hydrochloride salt 1a by treatment with saturated aq. NaHCO₃ (100 mL) and extraction of the free amine with CHCl₃ (3 x 100 mL). The solution was dried over Na₂SO₄, filtered, and concentrated. The residue was taken up in Et₂O and trifluoroacetic acid was added to precipitate the title compound as white crystals. IR (film) 3437, 2920, 2742, 2518, 2418, 1722, 1653, 1491, 1429, 1398, 1274, 1182, 1074, 834, 695 cm⁻¹; ¹H NMR (300 MHz, d₆-DMSO) □ 9.97 (br s, 1H, "NH₂), 7.22–7.37 (m, 5H, C₆H₅), 4.53 (br d, J = 7.1 Hz, 1H, COCH), 3.27 (dd, J = 3.3, 14.8 Hz, 1H, CH₂C₆H₅), 3.00 (dd, J = 10.2, 14.8 Hz, 1H, CH₂C₆H₅), 2.76 (s, 3H, CH₃NCO), 1.59 (s, 3H, CH₃), 1.46 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) □ 167.6, 136.9, 129.8, 129.3, 127.5, 77.2, 58.0, 34.7, 25.6, 24.7, 22.8; LRMS (EI) m/z 218 (M⁺); HRMS (EI) exact mass calcd for (C₁₇H₁₉N₂O)⁺ requires m/z 218.1419, found m/z 218.1424; [□]D = −63.2 (c = 1.0, CHCl₃).

(5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrobromide (58). Prepared from the hydrochloride salt 1a by treatment with saturated aq. NaHCO₃ (100 mL) and extraction of the free amine with CHCl₃ (3 x 100 mL). The solution was dried over Na₂SO₄, filtered, and concentrated. The residue was taken up in Et₂O and hydrobromic acid was added to precipitate the title compound as white crystals. IR (film) 3414, 2912, 2711, 2557, 1707, 1607, 1390, 1274, 1197, 1159, 1058, 989, 703 cm⁻¹; ¹H
NMR (300 MHz, $d_6$-DMSO) \( \delta \) 10.41 (brs, 1H, $^1$NH$_2$), 9.69 (br s, 1H, $^1$NH$_2$), 7.24–7.43 (m, 5H, C$_6$H$_5$), 4.69 (br d, $J = 7.1$ Hz, 1H, COCH), 3.28 (dd, $J = 3.0$, 15.1 Hz, 1H, CH$_2$C$_6$H$_5$), 3.15 (dd, $J = 10.4$, 14.8 Hz, 1H, CH$_2$C$_6$H$_5$), 2.77 (s, 3H, CH$_3$NCO), 1.67 (s, 3H, CH$_3$), 1.49 (s, 3H, CH$_3$); $^1$C NMR (75 MHz, CDCl$_3$) \( \delta \) 166.8, 136.7, 129.9, 129.2, 127.7, 77.6, 58.1, 33.9, 25.8, 24.5, 22.6; LRMS (EI) $m/z$ 218 (M$^+$); HRMS (EI) exact mass calcd for (C$_{15}$H$_{18}$N$_2$O)$^+$ requires $m/z$ 218.1419, found $m/z$ 218.1420; $[\alpha]_D = -21.3$ (c = 1.0, CHCl$_3$).

**(S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (59).** Prepared from the hydrochloride salt 1a by treatment with saturated aq. NaHCO$_3$ (100 mL) and extraction of the free amine with CHCl$_3$ (3 x 100 mL). The solution was dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was taken up in Et$_2$O and perchloric acid was added to precipitate the title compound as white crystals. IR (film) 3514, 3059, 2927, 2850, 1707, 1607, 1398, 1267, 1097, 927. 703 cm$^{-1}$; $^1$H NMR (300 MHz, $d_6$-DMSO) \( \delta \) 10.37 (br s, 1H, $^1$NH$_2$), 9.25 (br s, 1H, $^1$NH$_2$), 7.26–7.43 (m, 5H, C$_6$H$_5$), 4.66 (br d, $J = 8.8$ Hz, 1H, COCH), 3.33 (dd, $J = 3.3$, 15.1 Hz, 1H, CH$_2$C$_6$H$_5$), 2.94 (dd, $J = 10.7$, 15.1 Hz, 1H, CH$_2$C$_6$H$_5$), 2.78 (s, 3H, CH$_3$NCO), 1.62 (s, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$); $^1$C NMR (75 MHz, CDCl$_3$) \( \delta \) 166.8, 136.5, 129.7, 129.3, 127.8, 77.6, 58.0, 34.4, 25.7, 24.6, 22.5; LRMS (EI) $m/z$ 218 (M$^+$); HRMS (CI) exact mass calcd for (C$_{15}$H$_{18}$N$_2$O)$^+$ requires $m/z$ 218.1419, found $m/z$ 218.1428; $[\alpha]_D = -61.1$ (c = 1.0, CH$_3$NO$_2$).

**General Procedure A.** A flask containing nitrone and imidazolidinone catalyst was charged with CH$_3$NO$_2$, then treated with the appropriate amount of H$_2$O. After cooling the solution to the desired temperature, an unsaturated aldehyde was added drop wise to the flask. After the appropriate reaction time, the resulting solution was passed through a silica gel column with ethyl acetate. Removal of volatiles resulted in an oily residue, which was purified by silica gel chromatography to afford the title compounds.

**General Procedure B.** A flask containing nitrone and imidazolidinone catalyst was charged with CH$_3$NO$_2$, then treated with the appropriate amount of H$_2$O. After
cooling the solution to the desired temperature, an unsaturated aldehyde was added drop wise to the flask. Additional aldehyde was added to the reaction mixture at 24 h intervals until the specified reaction time was reached. The resulting solution was passed through a silica gel column with ethyl acetate. Removal of volatiles resulted in an oily residue, which was purified by silica gel chromatography to afford the title compounds.

**General Procedure C: The Reduction of Isoxazolidine Products.** To a solution of the isoxazolidine aldehyde in absolute ethanol (1ml) were added 3 equivalents of NaBH₄. After 0.5 hours, the reaction mixture was quenched with H₂O, and extracted with 2 x 10mL of CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the resultant residue by silica gel chromatography provided the corresponding primary alcohol.

**(3R,4S,5R)-2-Benzyl-4-formyl-5-methyl-3-phenylisoaxzolidine (Table 7, entry 1).** Prepared according to general procedure B from (Z)-N-benzylidenebenzylamine N-oxide (63 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.06 mmol), crotonaldehyde (100 mL, 1.2 mmol followed by 5 x 75 mL, 0.90 mmol over 24 h intervals) and H₂O (16 mL, 0.90 mmol) in CH₂NO₂ (3.0 ml) at –20 °C over the course of 144 h. The resulting solution was passed through a silica gel column with CH₂Cl₂ to provide the title compound as an oil in 94% yield (79 mg); 96:4 *endo:exo*. *Endo* isomer: IR (CH₂Cl₂) 2853, 1722, 1494, 1455, 1374 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, J = 2.4 Hz, 1H, CHO), 7.24–7.58 (m, 1H, CH₃H₅ and CH₂CH₃), 4.57 (dq, J = 6.1, 12.2 Hz, 1H, CHCH₃), 4.21 (d, J = 7.8 Hz, 1H, CH₃CH₂), 4.02 (d, J = 14.4 Hz, 1H, CH₂CH₃), 3.84 (d, J = 14.3 Hz, 1H, CH₂CH₃), 3.15 (m, 1H, CHCHO), 1.52 (d, J = 6.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 198.5, 138.4, 137.3, 129.0, 128.6, 128.3, 128.2, 127.5, 127.1, 73.4, 71.5, 71.1, 59.5, 21.2; LRMS (CI) m/z 281 (M⁺); HRMS (CI) exact mass calcld for C₁₉H₁₉NO₂ requires m/z 281.1418, found m/z 281.1413 (M⁺); [δ]D = +82.5 ° (c = 1.0, CHCl₃). Diastereomeric ratios were determined by ¹H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30%}

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⁴ Run by J. J. M. Wiener.
EtOAc/hex) for the determination of enantiomeric purity; \textit{endo} 94\% ee. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.22–7.47 (m, 10H, ArH), 4.22–4.24 (m, 1H, CHON), 4.00 (d, $J = 14.6$ Hz, 1H, CH$_2$C$_6$H$_3$), 3.81 (d, $J = 14.6$ Hz, 1H, CH$_2$C$_6$H$_3$), 3.74–3.75 (m, 2H, CH$_2$OH), 3.65 (d, $J = 8.3$ Hz, 1H, CHC$_6$H$_3$), 2.36–2.42 (m, 1H, CHCH$_2$OH), 1.46 (d, $J = 6.4$ Hz, 3H, CH$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (2.5\% iPrOH/hex, 1 mL/min flow rate); \textit{endo} isomers $t_r = 59.3$ min and 76.3 min.

(3R,4S,5R)-2-Allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 7, entry 2). Prepared according to general procedure B from (Z)-N-benzylideneallylamine N-oxide (63 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.08 mmol), crotonaldehyde (133 $\mu$L, 1.6 mmol followed by 5 x 75 $\mu$L, 1.2 mmol over 24 h intervals) and H$_2$O (22 $\mu$L, 1.2 mmol) in CH$_3$NO$_2$ (4.0 ml) at $–20^\circ$C over the course of 132 h to provide the title compound as a colorless oil in 73\% yield (68 mg); 93:7 \textit{endo}:\textit{exo}. \textit{Endo} isomer: IR (CH$_2$Cl$_2$) 2981, 2842, 1722, 1645, 1498, 1376 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.77 (d, $J = 2.2$ Hz, 1H, CHO), 7.14–7.24 (m, 5H, C$_6$H$_5$), 5.84–5.98 (m, 1H, CH$_2$=CHCH$_2$), 5.06–5.28 (m, 2H, CH$_2$=CH), 4.51 (dq, $J = 6.0$, 6.0 Hz, 1H, CHCH$_3$), 4.10 (d, $J = 7.7$ Hz, 1H, CHC$_6$H$_5$), 3.46 (dd, $J = 5.5$, 14.3 Hz, 1H, CH$_2$=CHCH$_2$N), 3.31 (dd, $J = 6.6$, 14.3 Hz, 1H, CH$_2$=CHCH$_2$N), 3.09 (ddd, $J = 2.5$, 5.8, 8.0 Hz, 1H, CHCHO), 1.50 (d, $J = 6.0$ Hz, 3H, CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.7, 138.6, 133.9, 129.1, 128.4, 127.8, 118.1, 73.7, 71.9, 71.3, 59.1, 21.3; LRMS (CI) $m/\epsilon$ 231 (M$^+$); HRMS (Cl) exact mass calcd for (C$_{14}$H$_{15}$NO$_2$) requires $m/\epsilon$ 231.1259, found $m/\epsilon$ 231.1256 (M$^+$); $[\alpha]_D = +63.8$ ° (c = 1.0, CHCl$_3$). Diastereomeric ratios were determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30\% EtOAc/hex) for the determination of enantiomeric purity; \textit{endo} 98\% ee. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.13–7.41 (m, 5H, C$_6$H$_5$), 5.83–5.97 (m, 1H, CH$_2$=CHCH$_2$), 5.08–5.22 (m, 2H, CH$_2$=CH), 4.21 (dq, $J = 6.4$, 6.4 Hz, 1H, CHCH$_3$), 3.64–3.83 (br s, 2H, CH$_2$OH), 3.57 (d, $J = 8.0$ Hz, 1H, CHC$_6$H$_5$), 3.44 (dd, $J = 5.2$, 14.3 Hz, 1H, CH$_2$=CHCH$_2$N), 3.28 (dd, $J = 6.6$, 14.3 Hz, 1H, CH$_2$=CHCH$_2$N), 2.34 (m, 1H, CHCH$_2$OH), 1.44 (d, $J = 6.1$ Hz, 3H, CH$_3$). Enantiomeric ratios were determined by
HPLC with a Chiralcel AD column and AD guard column (3% EtOH/hex, 1 mL/min flow rate); *endo* isomers t<sub>e</sub> = 18.2 min and 24.2 min.

**(3R,4S,5R)-2,5-Dimethyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 3).** Prepared according to general procedure B from (Z)-N-benzylideneethylamine N-oxide (54.1 mg, 0.40 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (26 mg, 0.08 mmol), crotonaldehyde (133 mL, 1.6 mmol followed by 5 x 100 mL, 1.2 mmol, over 24 h intervals) and H<sub>2</sub>O (22 mL, 1.2 mmol) in CH<sub>3</sub>NO<sub>2</sub> (4.0 ml) at −20 °C over the course of 132 h to provide the title compound as a colorless oil in 66% yield (54 mg); 95:5 *endo*:exo. *Endo* >99% ee *Endo* isomer: IR (CH<sub>2</sub>Cl<sub>2</sub>) 2974, 2873, 1722, 1552 cm<sup>−1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.74 (d, J = 2.5 Hz, 1H, CHO), 7.26–7.39 (m, 5H, C<sub>6</sub>H<sub>5</sub>), 4.54 (dq, J = 6.0, 12.3 Hz, 1H, CHCHO), 3.83 (br s, 1H, CHC<sub>6</sub>H<sub>5</sub>), 3.09 (m, 5H, CHCHO), 2.60 (s, 3H, NCH<sub>3</sub>), 1.50 (d, J = 6.3 Hz, 3H, CHCH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 198.6, 137.8, 129.1, 128.5, 127.8, 73.5, 72.2, 66.3, 43.6, 21.9; LRMS (Cl) m/z 205 (M)<sup>+</sup>; HRMS (Cl) exact mass calcd for (C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>) requires m/z 205.1103, found m/z 205.1100 (M)<sup>+</sup>; [α]<sub>D</sub> = +77.2 ° (c = 1.0, CHCl<sub>3</sub>). Diastereomeric ratios were determined by <sup>1</sup>H NMR analysis. Enantiomeric ratios were determined by GLC with a Bodman ↓-PH column (100 °C, 23 psi); *endo* isomers t<sub>e</sub> = 38.0 min and 39.8 min.

**(3R,4S,5R)-2-Benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine (Table 7, entry 4).<sup>5</sup>** Prepared according to general procedure B from (Z)-N-para-chlorobenzylideneethylamine N-oxide (74 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.06 mmol), crotonaldehyde (100 mL, 1.2 mmol followed by 7 x 75 mL, 0.90 mmol, over 24 h intervals) and H<sub>2</sub>O (16 mL, 0.90 mmol) in CH<sub>3</sub>NO<sub>2</sub> (3.0 ml) at −20 °C over the course of 160 h. The resulting solution was passed through a silica gel column with CH<sub>2</sub>Cl<sub>2</sub> to provide the title compound as an oil in 78% yield (74 mg); 92:8 *endo*:exo. *Endo* isomer: IR (film) 3429, 3066, 2981, 2873, 2835, 2726, 1722, 1599, 1491, 1452, 1375, 1089, 1020, 819, 734, 703 cm<sup>−1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.79 (d, J = 2.2 Hz, 1H, CHO), 7.24–7.38 (m, 9H, C<sub>6</sub>H<sub>5</sub>Cl and CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 4.55 (m, 1H, CHCH<sub>3</sub>), 4.16 (d, J = 7.7 Hz, 1H, CHCH<sub>3</sub>), 3.97

<sup>5</sup> Run by J. J. M. Wiener.
(d, J = 14.0 Hz, 1H, CH$_3$C$_6$H$_5$), 3.84 (d, J = 14.3 Hz, 1H, CH$_2$C$_6$H$_5$), 3.06 (ddd, J = 7.4, 5.5, 2.2 Hz, 1H, CHCHO), 1.50 (d, J = 6.0 Hz, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.6, 137.5, 137.2, 129.8, 129.6, 129.4, 129.1, 128.8, 128.6, 127.6, 21.3; LRMS (Cl) m/z 315 (M)$^+$; HRMS (Cl) exact mass calcd for (C$_{15}$H$_{18}$NClO$_2$) requires m/z 315.1026, found m/z 315.1023 (M)$^+$; $[\alpha]_D$ = +69.8 (c = 1.0, CHCl$_3$). Diastereomeric ratios were determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 95% ee. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.24–7.39 (m, 9H, ArH), 4.23 (m, 1H, CHON), 3.97 (d, J = 14.2 Hz, 1H, CH$_3$C$_6$H$_5$), 3.84 (d, J = 14.2 Hz, 1H, CH$_2$C$_6$H$_5$), 3.73–3.81 (m, 2H, CH$_2$OH), 3.67 (d, J = 7.8 Hz, 1H, CHC$_6$H$_5$Cl), 2.31–2.33 (m, 1H, CHCH$_2$OH), 1.44 (d, J = 6.4 Hz, 3H, CH$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (2.4% EtOH/hex, 1 mL/min flow rate); endo isomers $t_r$ = 47.7 min and 83.6 min.

(3R,4S,5R)-2,5-Dimethyl-4-formyl-3-(4-chlorophenyl) isoxazolidine (Table 3, entry 5).

Prepared according to general procedure B from (Z)-N-para-chlorobenzylidene-N,N-dimethylamine $\cdot$ 0.5H$_2$O (55 mg, 0.40 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (26 mg, 0.08 mmol), crotonaldehyde (133 $\mu$L, 1.6 mmol followed by 8 x 100 $\mu$L, 1.20 mmol, over 24 h intervals) and H$_2$O (22 $\mu$L, 1.20 mmol) in CH$_3$NO$_2$ (4.0 ml) at −20 °C over the course of 160 h. The resulting solution was passed through a silica gel column with CH$_2$Cl$_2$ to provide the title compound as an oil in 76% yield (73 mg); 93:7 endo:exo. Endo isomer: IR (film) 3429, 2974, 2927, 2850, 2781, 2734, 1908, 1722, 1599, 1490, 1460, 1375, 1344, 1298, 1205, 1089, 1020, 911.4, 818.7, 679.7 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.74 (d, J = 2.3 Hz, 1H, CHO), 7.25–7.33 (m, 4H, ArH), 4.51 (dq, $J_d$ = 5.9, $J_q$ = 6.1 Hz, 1H, CHCH$_3$), 3.82–4.01 (m, 1H, CHC$_6$H$_5$Cl), 3.02 (ddd, $J = 8.0$, 5.5, 2.3 Hz, 1H, CHCHO), 2.59 (s, 3H, NCHO), 1.55 (d, J = 6.2 Hz, 3H, CHCH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.3, 136.7, 134.3, 129.6, 129.5, 129.3, 129.1, 73.5, 73.1, 72.2; LRMS (FAB) m/z 239 (M)$^+$; HRMS (FAB) exact mass calcd for (C$_{12}$H$_{14}$NClO$_2$) requires m/z 239.0713, found m/z 239.0707

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$^a$ Run by J. J. M. Wiener.
Diastereomeric ratios were determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the determination of enantiomeric purity; endo 94% ee. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24-7.38 (m, 4H, ArH), 3.40 (dq, $J_d = 6.2$, $J_q = 6.0$, 1H, CHON), 3.66-3.75 (m, 2H, CH$_2$OH), 3.35 (d, $J = 8.52$ Hz, 1H, CHC$_6$H$_4$Cl), 2.28-2.34 (m, 1H, CHCH$_2$OH), 1.43 (d, $J = 6.3$ Hz, 3H, CH$_3$). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (3.0% iPrOH/hex, 1 mL/min flow rate); endo isomers $t_r = 29.0$ min and 45.3 min.

(3R,4S,5R)-2-Benzyl-4-formyl-5-methyl-3-(4-methoxyphenyl) isoxazolidine

(Table 7, entry 6). Prepared according to general procedure B (Z)-N-$para$-methoxybenzylidenebenzylamine N-oxide (72 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.06 mmol), crotonaldehyde (100 $\mu$L, 1.2 mmol followed by 5 x 75 $\mu$L, 0.90 mmol, over 24 h intervals) and H$_2$O (16 $\mu$L, 0.90 mmol) in CH$_3$NO$_2$ (3.0 ml) at $-20\,^\circ$C over the course of 136 h. The resulting solution was passed through a silica gel column with CH$_2$Cl$_2$ to provide the title compound as an oil in 93% yield (86 mg); 98:2 endo:exo. Endo isomer: IR (film) 3429, 3035, 2974, 2935, 2835, 2726, 1722, 1614, 1514, 1452, 1375, 1298, 1251, 1174, 1035, 826, 734, 703 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.76 (d, $J = 2.5$ Hz, 1H, CHO), 7.23-7.38 (m, 7H, ArH), 6.87-6.91 (m, 2H, ArH), 4.52 (m, 1H, CHCH$_3$), 4.06 (d, $J = 8.2$ Hz, 1H, CHC$_6$H$_4$OCH$_3$), 3.99 (d, $J = 14.3$ Hz, 1H, CH$_3$C$_6$H$_5$), 3.80 (s, 3H, OCH$_3$), 3.76 (d, $J = 14.6$ Hz, 1H, CH$_3$C$_6$H$_5$), 3.08 (ddd, $J = 8.0$, 5.5, 2.5 Hz, 1H, CHCHO), 1.50 (d, $J = 6.3$ Hz, 3H, CHCH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 199.1, 159.8, 137.7, 130.1, 129.1, 128.7, 128.5, 137.4, 114.6, 73.6, 71.8, 71.2, 59.5, 55.6, 21.5; LRMS (Cl) $m/z$ 311 (M)$^+$; HRMS (Cl) exact mass calc for (C$_{19}$H$_{21}$NO$_3$) requires $m/z$ 311.1521, found $m/z$ 311.1514 (M)$^+$; $[\alpha]_D^{20} = +71.8$ ° (c = 1.0, CHCl$_3$). Diastereomeric ratios were determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 91% ee. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.17-7.41 (m, 7H, ArH), 6.86-6.93 (m, 2H, ArH), 4.17 (dq, $J_d = 5.9$, $J_q =
Enantiomeric determination of \( \text{calcd} \; 128.0, 6.3 \); \( \text{8.4}, 1 \) compound \( (133 \text{ trimethylimidazolidin-4-one methylbenzylidenemethylamine} \) Prepared in 69.5 min.

Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (3.0% EtOH/hex, 1 mL/min flow rate); \textit{endo} isomers \( t_e = 37.7 \) min and 69.5 min.

\[ (3R,4S,5R)-2,5-Dimethyl-4-formyl-3-(4-tolyl) isoazolidine \] (Table 7, entry 7).

Prepared according to general procedure B from \((Z)-N\)-para-methylbenzylidenemethylamine \( N\)-oxide (60 mg, 0.40 mmol), \((5S)\)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (26 mg, 0.08 mmol), crotonaldehyde (133 \( \mu \)L, 1.6 mmol followed by 7 x 100 \( \mu \)L, 1.20 mmol, over 24 h intervals) and \( \text{H}_2\text{O} \) (22 \( \mu \)L, 1.20 mmol) in \( \text{CH}_3\text{NO}_2 \) (4.0 ml) at \(-20^\circ \text{C} \) over the course of 160 h. The resulting solution was passed through a silica gel column with \( \text{CH}_2\text{Cl}_2 \) to provide the title compound as an oil in 82% yield (72 mg); 93:7 \textit{endo:exo}. \textit{Endo} isomer: IR (film) 3429, 2974, 2927, 2873, 2726, 1722, 1514, 1452, 1375, 1344, 1112, 1066, 911, 811, 687 cm\(^{-1}\); \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.74 (d, \( J = 2.5 \) Hz, 1H, CHO), 7.12-7.26 (m, 4H, ArH), 4.53 (dq, \( J_d = 5.9, J_q = 6.3 \) Hz, 1H, CHCH\(_3\)), 3.78 (bs, 1H, CHC\(_6\)H\(_4\)CH\(_3\)), 3.09 (ddd, \( J = 8.4, 5.4, 2.5 \) Hz, 1H, CHCHO), 2.59 (s, 3H, NCH\(_3\)), 2.34 (s, 3H, C\(_6\)H\(_4\)CH\(_3\)), 1.51 (d, \( J = 6.3 \) Hz, 3H, CHCH\(_3\)); \( ^{13}\text{C} \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 198.7, 138.3, 134.5, 130.0, 129.6, 128.0, 127.5, 73.6, 72.2, 43.7, 21.6; LRMS (CI) \( m/z \) 219 (M\(^+\)); HRMS (CI) exact mass calcld for \( (\text{C}_{13}\text{H}_{13}\text{NO}_2) \) requires \( m/z \) 219.1259, found \( m/z \) 219.1262 (M\(^+\); \( [\theta]_D \) = +67.9° (c = 1.0, CHCl\(_3\)). Diastereomeric ratios were determined by \( ^1\text{H} \) NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; \textit{endo} 97% ee. \( ^1\text{H} \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.13-7.26 (m, 4H, ArH), 4.20 (dq, \( J_d = 6.2, J_q = 6.0 \) Hz, 1H, CHON), 3.63-3.71 (m, 2H, CH\(_2\)OH), 3.29 (d, \( J = 7.7 \) Hz, 1H, CHC\(_6\)H\(_4\)CH\(_3\)), 2.55 (s, 3H, NCH\(_3\)), 2.33 (s, 3H, C\(_6\)H\(_4\)CH\(_3\)), 2.31-2.39 (m, 1H, CHC\(_6\)H\(_4\)OH), 1.44 (d, \( J = 6.0 \) Hz, 3H, CHCH\(_3\)). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD
guard column (3.0% iPrOH/hex, 1 mL/min flow rate); *endo* isomers \( t_c = 40.2 \) min and 47.6 min.

\((3R,4S,5R)-2\)-Benzyl-4-formyl-5-methyl-3-(2-napthyl) isoxazolidine (Table 7, entry 8).

Prepared according to general procedure B from (Z)-N-2-naphthylidenebenzylamine N-oxide (78 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.06 mmol), crotonaldehyde (100 \( \mu \)L, 1.2 mmol followed by 5 x 75 \( \mu \)L, 0.90 mmol, over 24 h intervals) and \( \text{H}_2\text{O} \) (16 \( \mu \)L, 0.90 mmol) in \( \text{CH}_3\text{NO}_2 \) (3.0 ml) at -20 °C over the course of 138 h. The resulting solution was passed through a silica gel column with \( \text{CH}_2\text{Cl}_2 \) to provide the title compound as an oil in 98% yield (97 mg); 95:5 *endo*:exo. *Endo* isomer: IR (film) 3429, 3059, 2981, 2927, 2866, 2726, 1954, 1722, 1607, 1498, 1452, 1375, 1313, 1120, 819, 742, 703 cm\(^{-1}\); \(^1\)H NMR (400 MHz, \( \text{CDCl}_3 \)) \([ \delta ] = 9.83 \text{ (d,} J = 2.3 \text{ Hz,} 1\text{H,} \text{CHO})\), 7.84-7.89 (m, 5H, ArH), 7.61 (dd, \( J = 1.6 \) Hz, 1H, ArH), 7.49-7.52 (m, 2H, ArH), 7.24-7.38 (m, 2H, ArH), 4.61 (dq, \( J_d = 5.9 \), \( J_q = 6.1 \) Hz, 1H, CHCH\(_3\)), 4.35 (d, \( J = 7.7 \) Hz, 1H, CHNapth), 4.06 (d, \( J = 14.3 \) Hz, 1H, CH\(_2\)C\(_6\)H\(_5\)), 3.89 (d, \( J = 14.3 \) Hz, 1H, CH\(_2\)C\(_6\)H\(_5\)), 2.20 (ddd, \( J = 7.8 \), 5.5, 2.3 Hz, 1H, CHCHO), 1.55 (d, \( J = 6.2 \) Hz, 3H, CHCH\(_3\)\)); \(^{13}\)C NMR (125 MHz, \( \text{CDCl}_3 \)) \([ \delta ] = 198.8, 137.5, 136.0, 133.5, 133.4, 129.1, 128.7, 128.4, 128.1, 127.9, 137.4, 127.1, 126.6, 126.5, 125.1, 73.8, 71.6, 71.5, 59.8, 21.3; LRMS (CI) \( m/z \) 331 (M\(^+\)); HRMS (FAB) exact mass calcd for (C\(_2\)H\(_3\)N\(_2\)O\(_2\)) requires \( m/z \) 331.1572, found \( m/z \) 331.1567 (M\(^+\)); \([ \delta ]_D = +53.1 \) ° (c = 1.0, \( \text{CHCl}_3 \)). Diastereomeric ratios were determined by \(^1\)H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; *endo* 93% ee. \(^1\)H NMR (500 MHz, \( \text{CDCl}_3 \)) \([ \delta ] = 7.84-7.86 \text{ (m,} 4\text{H,} \text{ArH})\), 7.66-7.67 \text{ (m,} 1\text{H,} \text{ArH})\), 7.48-7.52 \text{ (m,} 2\text{H,} \text{ArH})\), 7.20-7.40 \text{ (m,} 5\text{H,} \text{ArH})\), 4.28 (dq, \( J_d = 6.1 \), \( J_q = 5.9 \) Hz, 1H, CHON), 4.04 (d, \( J = 14.2 \) Hz, 1H, CH\(_2\)C\(_6\)H\(_5\)), 3.75-3.87 (m, 4H, CH\(_2\)C\(_6\)H\(_5\), CHOH, CHNapth), 2.46-2.51 (m, 1H, CHCH\(_2\)OH), 1.50 (d, \( J = 5.9 \) Hz, 3H, CH\(_3\)). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (2.5% EtOH/hex, 1 mL/min flow rate); *endo* isomers \( t_c = 57.7 \) min and 107.6 min.

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\(^7\) Run by J. J. M. Wiener.
**3R,4S,5R)-2-Benzyl-4-formyl-5-methyl-3-cyclohexyl isoxazolidine (Table 7, entry 9).** Prepared according to general procedure B from (Z)-N-cyclohexylmethylidenebenzylamine N-oxide (65 mg, 0.30 mmol), (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one perchloric acid salt (8) (19 mg, 0.06 mmol), crotonaldehyde (200 mL, 2.4 mmol followed by 2 x 75 mL, 0.90 mmol, over 24 h intervals) and H2O (16 mL, 0.90 mmol) in CH3NO2 (3.0 mL) at −20 °C over the course of 72 h. The resulting solution was passed through a silica gel column with CH3Cl2 to provide the title compound as an oil in 63% yield (54 mg); 96:4 endo:exo. Endo isomer: IR (film) 2927, 2858, 2719, 1722, 1498, 1452, 1383, 1328, 1074, 973, 703 cm−1; 1H NMR (300 MHz, CDCl3) δ 9.80 (d, J = 3.0 Hz, 1H, CHO), 7.23-7.40 (m, 5H, ArH), 4.57-4.64 (dq, Jd = 7.7, Jq = 6.1 Hz, 1H, CHON), 4.08 (d, J = 13.5 Hz, 1H, CH2C6H5), 3.82 (d, J = 13.2 Hz, 1H, CH2C6H5), 3.05 (dd, J = 7.7, 5.5 Hz, 1H, CH−chex), 2.86-2.91 (m, 1H, CHCHO), 1.35 (d, J = 6.1 Hz, 3H, CHCH3), 0.70-2.03 (m, 11H, chex-H); 13C NMR (75 MHz, CDCl3) δ 73.6, 72.8, 67.2, 62.0, 42.6, 30.9, 29.8, 26.7, 26.3, 26.2, 18.1; LRMS (EI) m/z 287 (M)+; HRMS (EI) exact mass calcld for (C18H25NO2) requires m/z 287.1885, found m/z 287.1881 (M)+; [α]D = +48.6 ° (c = 1.0, CHCl3). Diastereomeric ratios were determined by 1H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 99% ee. 1H NMR (300 MHz, CDCl3) δ 7.32-7.41 (m, 5H, ArH), 4.32-4.34 (m, 1H, CHON), 4.14 (d, J = 12.7 Hz, 1H, CH2C6H5), 3.88 (d, J = 13.2 Hz, 1H, CH2C6H5), 3.73-3.84 (m, 2H, CH2OH), 2.58 (dd, J = 6.1, 5.4 Hz, 1H, CH−chex), 2.14-2.18 (m, 1H, CHCH2OH), 1.34 (d, J = 6.4 Hz, 3H, CHCH3), 0.82-1.74 (m, 11H, chex-H). Enantiomeric ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (3.0% iPrOH/hex, 1 mL/min flow rate); endo isomers tR = 22.9 min and 26.7 min.

**3R,4S)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 11).** Prepared according to general procedure A from (Z)-N-benzylidenebenzylamine N-oxide (63 mg, 0.30 mmol), (5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one
trifluoromethanesulfonic acid salt (5) (22 mg, 0.06 mmol), acrolein (71 \[L, 1.2 \text{ mmol}\) and H$_2$O (16 \[L, 0.90 \text{ mmol}\) in CH$_3$NO$_2$ (3.0 ml) at –10 °C over the course of 35 h to provide the title compound as a colorless oil in 80% yield (63 mg); 86:14 endo:exo. Endo isomer: IR (CH$_2$Cl$_2$) 2873, 1722, 1498, 1452, 1050 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.80 (d, $J = 2.1$ Hz, 1H, CHO), 7.27–7.51 (m, 10H, C$_6$H$_5$ and CH$_2$C$_6$H$_5$), 4.27–4.30 (m, 2H, CH$_2$ON), 4.07 (d, $J = 7.1$ Hz, 1H, CHC$_6$H$_5$), 3.99 (d, $J = 14.2$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.78 (d, $J = 14.2$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.44 (m, 1H, CHCHO); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.4, 138.1, 137.1, 128.9, 128.6, 128.3, 128.2, 127.8, 127.3, 70.6, 65.8, 64.3, 59.6; LRMS (CI) m/z 267 (M)$^+$; HRMS (Cl) exact mass calcd for (C$_{17}$H$_{17}$NO$_2$) requires m/z 267.1259, found m/z 267.1268; $[\alpha]_D^1 = +43.4$ ° (c = 1.0, CHCl$_3$). Diastereomeric ratios were determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 90% ee. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.19–7.51 (m, 10H, C$_6$H$_5$ and CH$_2$C$_6$H$_5$), 4.19 (dd, $J = 8.2, 8.2$ Hz, 1H, CH$_2$ON), 3.94 (d, $J = 14.3$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.88–3.92 (dd, $J = 4.4, 8.2$ Hz, 1H, CH$_2$ON), 3.65–3.83 (m, 2H, CH$_2$OH), 3.70 (d, $J = 14.0$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.47 (d, $J = 7.7$ Hz, 1H, CHC$_6$H$_5$), 2.72–2.83 (m, 1H, CHCH$_2$OH). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column (4% EtOH/hex, 1 mL/min flow rate); endo isomers $t_r = 15.8$ min and 20.4 min.

(3R,4S)-2-Benzyl-4-formyl-3-(4-methylphenyl)isoxazolidine (Table 7, entry 12). Prepared according to general procedure B from (Z)-N-para-methylbenzyldenebenzylamine N-oxide (72 mg, 0.30 mmol), (5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonylic acid salt (5) (22 mg, 0.06 mmol), acrolein (71 \[L, 1.2 \text{ mmol}\) followed by 4 x 36 \[L, 0.60 \text{ mmol, over 24 h intervals}\), H$_2$O (16 \[L, 0.90 \text{ mmol}\), and in CH$_3$NO$_2$ (3.0 ml) at –18 °C over the course of 112 h to provide the title compound as a colorless oil in 80% yield (66 mg) after silica gel chromatography (17% EtOAc/hex); 85:15 endo:exo. Endo isomer: IR (CH$_2$Cl$_2$) 2873, 1722, 1514, 1050 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.77 (d, $J = 2.2$ Hz, 1H, CHO), 7.19–7.47 (m, 7H, C$_6$H$_4$CH$_3$ and CH$_2$C$_6$H$_5$), 4.24–4.28 (m, 2H, CH$_2$ON), 3.97–4.02 (m, 2H, CHNO and CH$_2$C$_6$H$_5$), 3.75 (d, $J = 14.0$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.38–3.46 (m, 1H,
CHCHO), 2.39 (s, 3H, C₆H₅CH₃); ¹³C NMR (100 MHz, CDCl₃)  [199.1, 138.4, 137.5, 135.0, 129.9, 128.9, 128.5, 128.0, 127.5, 70.9, 66.2, 64.6, 59.9, 21.6; LRMS (CI) m/z 281 (M)⁺; HRMS (CI) exact mass calcd for (C₁₈H₁₆NO₂) requires m/z 281.1416, found m/z 281.1415; [θ]D = +39.8 ° (c = 1.0, CHCl₃). Diastereomeric ratio was determined by ¹H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 90% ee. ¹H NMR (300 MHz, CDCl₃)  [7.16–7.37 (m, 9H, C₆H₅CH₃ and CH₂C₆H₅), 4.18 (dd, J = 8.2, 8.2 Hz, 1H, CH₂ON), 3.94 (d, J = 14.8 Hz, 1H, CH₂C₆H₅), 3.87-3.91 (dd, J = 4.3, 8.1 Hz, 1H, CH₂ON), 3.67–3.82 (m, 2H, CH₂OH), 3.65 (d, J = 14.3 Hz, 1H, CH₂C₆H₅), 3.44 (d, J = 7.7 Hz, 1H, CHC₆H₄CH₃), 2.70–2.81 (m, 1H, CHCH₂OH), 2.35 (s, 3H, C₆H₅CH₃). Enantiomeric ratios were determined by HPLC with Chiralcel AD column and AD guard column (10% EtOH/hex, 1 mL/min flow rate); endo isomers tₚ = 9.1 min and 10.0 min.

(3R,4S)-2-Benzyl-4-formyl-3-(4-chlorophenyl)isoxazolidine (Table 7, entry 13). Prepared according to general procedure B from (Z)-N-para-chlorobenzylidenebenzylamine N-oxide (74 mg, 0.30 mmol), (S,S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt (5) (22 mg, 0.06 mmol), acrolein (71 mmol, 1.2 mmol followed by 3 x 36 mmol, 0.60 mmol, over 24 h intervals) and H₂O (16 mmol, 0.90 mmol) in CH₃NO₂ (3.0 ml) at −18 °C over the course of 96 h to provide the title compound as a colorless oil in 80% yield (70 mg) after silica gel chromatography (20% EtOAc/hex); 80:20 endo:exo. Endo isomer: IR (CH₂Cl₂) 2881, 1722, 1599, 1491 cm⁻¹; ¹H NMR (400 MHz, CDCl₃)  [9.78 (d, J = 2.0 Hz, 1H, CHO), 7.26–7.44 (m, 9H, C₆H₅Cl and CH₂C₆H₅), 4.27–4.29 (m, 2H, CH₂ON), 4.08 (d, J = 7.0 Hz, 1H, CHC₆H₄Cl), 3.96 (d, J = 14.0 Hz, 1H, CH₂C₆H₅), 3.80 (d, J = 14.2 Hz, 1H, CH₂C₆H₅), 3.34–3.40 (m, 1H, CHCHO); ¹³C NMR (100 MHz, CDCl₃)  [198.4, 136.8, 134.0, 136.7, 129.1, 128.7, 128.2, 127.4, 129.1, 69.6, 65.8, 64.3, 59.7; LRMS (CI) m/z (M); HRMS (CI) exact mass calcd for (C₁₇H₁₆ClNO₂) requires m/z 301.0870 (M)⁺, found m/z 301.0862; [θ]D = +45.8 ° (c = 1.0, CHCl₃). Diastereomeric ratios were determined by ¹H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the
determination of enantiomeric purity; endo 91% ee. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.04–7.42 (m, 9H, C\(_6\)H\(_4\)Cl and CH\(_2\)C\(_6\)H\(_4\)), 4.17 (dd, \(J = 8.2, 8.2\) Hz, 1H, CH\(_2\)ON), 3.91 (d, \(J = 14.0\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.86–3.90 (dd, \(J = 4.7, 8.2\) Hz, 1H, CH\(_2\)ON), 3.72–3.78 (m, 2H, CH\(_2\)OH), 3.72 (d, \(J = 14.0\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.49 (d, \(J = 7.7\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)Cl), 2.68–2.76 (m, 1H, CHCH\(_2\)OH). Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (5% iPrOH/hex, 1 mL/min flow rate); endo isomers \(t_r = 20.7\) min and 23.5 min.

(3R,4S)-2-Benzyl-4-formyl-3-naphthylisoxazolidine (Table 7, entry 14). Prepared according to general procedure A from (Z)-N-2-naphthylidenebenzylamine N-oxide (78 mg, 0.30 mmol), (5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt (5) (22 mg, 0.06 mmol), acrolein (71 \(\mu\)L, 1.2 mmol), H\(_2\)O (16 \(\mu\)L, 0.90 mmol), and in CH\(_2\)NO\(_2\) (3.0 ml) at \(-18^\circ\)C over the course of 112 h to provide the title compound as a colorless oil in 80% yield (75 mg) after silica gel chromatography (25% EtOAc/hex); 86:14 endo:exo. Endo isomer: IR (CH\(_2\)Cl\(_2\)) 3059, 2835, 1722, 1498, 1607 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.83 (d, \(J = 2.0\) Hz, 1H, CHO), 7.27–7.95 (m, 12H, C\(_{10}\)H\(_7\) and CH\(_2\)C\(_6\)H\(_4\)), 4.32–4.36 (m, 2H, CH\(_2\)ON), 4.28 (d, \(J = 7.0\) Hz, 1H, CHC\(_{10}\)H\(_7\)), 4.01 (d, \(J = 14.1\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.85 (d, \(J = 14.2\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.53 (m, 1H, CHCHO); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.7, 137.1, 135.4, 133.3, 133.2, 128.9, 128.7, 128.2, 127.9, 127.8, 127.7, 127.3, 127.2, 126.4, 126.3, 125.0, 110.4, 70.8, 65.9, 64.2, 59.7; LRMS (Cl) \(m/z\) 317 (M\(^+\)); HRMS (Cl) exact mass caled for (C\(_3\)H\(_{10}\)NO\(_2\)) requires \(m/z\) 317.1416, found \(m/z\) 317.1416; [\(\alpha\)]\(_D\) = +20.3° (c = 1.0, CHCl\(_3\)). Diastereomeric ratio was determined by \(^1\)H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; endo 89% ee. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.21–7.89 (m, 12H, C\(_{10}\)H\(_7\) and CH\(_2\)C\(_6\)H\(_4\)), 4.26 (dd, \(J = 8.2, 8.2\) Hz, 1H, CH\(_2\)ON), 3.98 (d, \(J = 14.0\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.93–3.98 (dd, \(J = 4.6, 8.2\) Hz, 1H, CH\(_2\)ON), 3.75 (d, \(J = 14.0\) Hz, 1H, CH\(_2\)C\(_6\)H\(_4\)), 3.72–3.83 (m, 2H, CH\(_2\)OH), 3.67 (d, \(J = 7.7\) Hz, 1H, CHC\(_{10}\)H\(_7\)), 2.82–2.93 (m, 1H, CHCH\(_2\)OH). Enantiomeric ratios were determined by HPLC with Chiralcel AD column.
and AD guard column (10% EtOH/hex, 1 mL/min flow rate); endo isomers $t_r = 12.7$ min and 17.5 min.

**(3R,4S)-2-Benzyl-4-formyl-3-(4-methoxyphenyl)isoxazolidine (Table 7, entry 15).**

Prepared according to general procedure B from (Z)-N-para-methoxybenzylidenebenzylamine $N$-oxide (72 mg, 0.30 mmol), (5S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one trifluoromethanesulfonic acid salt (5) (22 mg, 0.06 mmol), acrolein (71 mL, 1.2 mmol followed by 3 x 36 mL, 0.60 mmol, over 24 h intervals), H$_2$O (16 mL, 0.90 mmol), and in CH$_3$NO$_2$ (3.0 ml) at $-18 \, ^\circ$C over the course of 87 h to provide the title compound as a colorless oil in 83% yield (73 mg) after silica gel chromatography (30% EtOAc/hex); 91:9 endo:exo. Endo isomer: IR (CH$_2$Cl$_2$) 2935, 1722, 1614, 1514, 1460, 1251 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.77 (d, $J = 2.1$ Hz, 1H, CHO), 7.26–7.42 (m, 7H, C$_6$H$_4$OCH$_3$ and CH$_2$C$_6$H$_5$), 6.94 (d, $J = 8.7$ Hz, 2H, ortho C$_6$H$_4$OCH$_3$), 4.22–4.28 (m, 2H, CH$_2$ON), 3.96–4.00 (m, 2H, CHNO and CH$_2$C$_6$H$_5$), 3.82 (s, 3H, OCH$_3$), 3.73 (d, $J = 14.2$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.40 (m, 1H, CHCHO); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.9, 159.6, 137.3, 129.6, 129.0, 128.6, 128.2, 127.2, 114.3, 70.3, 65.8, 64.1, 59.4, 55.2; LRMS (CI) $m/z$ 297 (M$^+$); HRMS (CI) exact mass calcd for (C$_{18}$H$_{19}$NO$_3$) requires $m/z$ 297.1365, found $m/z$ 297.1361. [\%]$_D$ = +31.9 ° (c = 1.0, CHCl$_3$)

Diastereomeric ratio was determined by $^1$H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (40% EtOAc/hex) for the determination of enantiomeric purity; endo 90% ee. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.19–7.40 (m, 7H, C$_6$H$_4$OCH$_3$ and CH$_2$C$_6$H$_5$), 6.92 (d, $J = 1.9$ Hz, 2H, C$_6$H$_4$OCH$_3$), 4.16 (dd, $J = 8.2, 8.2$ Hz, 1H, CH$_2$ON), 3.90 (d, $J = 14.3$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.87 (dd, $J = 4.4, 8.2$ Hz, 1H, CH$_2$ON), 3.81 (s, 3H, C$_6$H$_4$OCH$_3$), 3.66–3.79 (m, 2H, CH$_2$OH), 3.65 (d, $J = 14.3$ Hz, 1H, CH$_2$C$_6$H$_5$), 3.42 (d, $J = 7.6$ Hz, 1H, CHC$_6$H$_4$OCH$_3$), 2.69–2.80 (m, 1H, CHCH$_2$OH).

Enantiomeric ratios were determined by HPLC with Chiralcel AD column and AD guard column (8% iPrOH/hex, 1 mL/min flow rate); endo isomers $t_r = 15.4$ min and 17.0 min.
Determination of Absolute and Relative Stereochemistry through Chemical Correlation and X-Ray Crystal Structure

\[
\begin{align*}
\text{Bn} & \quad + \quad \text{Me} \\
\text{Me}O & \quad \text{Ph} \quad \text{N} \quad \text{O} \\
20 \text{ mol\%}, 25 \degree \text{C}, & \quad \text{CH}_3\text{NO}_2-\text{H}_2\text{O} \\
20 \text{ mol\%}, -20 \degree \text{C}, & \quad \text{CH}_3\text{NO}_2-\text{H}_2\text{O} \\
\text{HClO}_4 & \quad \text{HClO}_4 \\
1. \text{NaClO}_2, \text{NaH}_2\text{PO}_4, & \quad 1. \text{NaClO}_2, \text{NaH}_2\text{PO}_4, \\
2\text{-methyl-2-butene,} & \quad 2\text{-methyl-2-butene,} \\
\text{H}_2\text{O,} & \quad \text{H}_2\text{O,} \\
\text{iBuOH} & \quad \text{iBuOH} \\
2. \text{DCC, DMAP,} & \quad 2. \text{DCC, DMAP,} \\
\text{iPrOH} & \quad \text{iPrOH} \\
\text{CH}_2\text{Cl}_2 & \quad \text{CH}_2\text{Cl}_2 \\
\text{NaBH}_4, & \quad \text{NaBH}_4, \\
\text{EtOH} & \quad \text{EtOH} \\
\text{HPLC:} \ t_1 = 59.3 & \quad \text{HPLC:} \ t_1 = 59.3 \\
\text{(minor enantiomer)} & \quad \text{(minor enantiomer)} \\
\text{t}_2 = 76.3 & \quad \text{t}_2 = 76.3 \\
\text{(major enantiomer)} & \quad \text{(major enantiomer)}
\end{align*}
\]

Determination of the Absolute Configuration of \((3\text{R},4\text{S},5\text{R})\)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 7, entry 1) by Correlation with \((3\text{R},4\text{S},5\text{R})\)-2-benzyl-5-methyl-3-phenylisoxazolidine-4-carboxylic acid isopropyl ester.

\((3\text{S},4\text{R},5\text{S})\)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine was prepared according to general procedure B from \((Z)\)-\(N\)-benzylidenebenzylamine \(N\)-oxide (105.6 mg, 0.50 mmol), \((2\text{S})\)-proline methyl ester hydrochloric acid salt\(^3\) (20.3 mg, 0.10 mmol), crotonaldehyde (0.13 mL, 1.50 mmol) and \(\text{H}_2\text{O}\) (5.0 mL, 0.09 mmol) in \(\text{CH}_3\text{NO}_2\) (5.0 mL) over the course of 24 h. The resulting solution was passed through a silica gel column with \(\text{CH}_2\text{Cl}_2\) to provide an oil. A portion of the product was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex) for the determination of enantiomeric purity; \textit{endo} 41% ee. Enantiomeric
ratios were determined by HPLC with a Chiralcel OD-H column and OD guard column (2.5% iPrOH/hex, 1 mL/min flow rate); *endo* isomers $t_1 = 59.3$ min (minor enantiomer) and 76.3 min (major enantiomer). The remainder of the product (59.4 mg, 0.21 mmol) was dissolved in tert-butanol (4.4 mL). To this solution was added 2-methyl-2-butene (1 mL, 90 mmol) and, dropwise, a solution of NaClO$_2$ (175 mg, 1.93 mmol) and NaH$_2$PO$_4$ (203 mg, 1.47 mmol) in H$_2$O (1.8 mL). The biphasic solution was stirred for 11h. The reaction was concentrated, diluted with H$_2$O, and washed with hexanes. The aqueous layer was acidified with 1N HCl to pH 2, and extracted twice with Et$_2$O. The combined organic layers were washed with cold H$_2$O, dried (Na$_2$SO$_4$), and concentrated. To this oil was added CH$_2$Cl$_2$ (0.75 mL), 4-dimethylamino-pyridine (1.0 mg, 0.008 mmol), and 2-propanol (0.023 mL, 0.3 mmol). This solution was added to dicyclohexylcarbodiimide (19.3 mg, 0.09 mmol) and the reaction was stirred for 2h at which time it was filtered, concentrated, dissolved in CH$_2$Cl$_2$, and filtered. The filtrate was washed sequentially with 0.5M HCl and sat. aq. NaHCO$_3$, dried (Na$_2$SO$_4$), and concentrated. The resulting oil was purified by silica gel chromatography (10% EtOAc/hex) to afford an oil with spectral data identical to those reported for (3S,4R,5S)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine isopropyl ester;\footnote{Gothelf, K. V., Thomsen, I., Jørgensen, K. A., *J. Am. Chem. Soc.*, 1996, 118, 59-64.} \([\delta]_D^0\) (literature) = -28.1° (c = 1.0, CHCl$_3$); \([\delta]_D^0\) (found) = -7.4° (c = 1.0, CHCl$_3$).

**Determination of the Absolute Configuration of (3R,4S,5R)-2-allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 7, entry 2) by Correlation with (2R)-[1-((R)-allyl-benzyl-amino)-phenyl-methyl]-butane-1,(3R)-diol.**

(2R)-[(R)-Benzylamino-phenyl-methyl]-butane-1,(3R)-diol, of known absolute configuration (*vida infra*) (23.0 mg, 0.08 mmol), and K$_2$CO$_3$ (44.8 mg, 0.32 mmol) were dissolved in 1 : 1 H$_2$O : CH$_2$CN (0.5 mL : 0.5 mL). To the solution was added allyl bromide (0.05 mL, 0.32 mmol) and the reaction was stirred for 63h. The reaction was extracted with Et$_2$O. The organic layer was dried (Na$_2$SO$_4$) and concentrated. The resulting oil was purified by silica gel chromatography (40% EtOAc/hex) to afford (2R)-[1-((R)-allyl-benzyl-amino)-phenyl-methyl]-butane-1,(3R)-diol: $^1$H NMR (500 MHz, CDCl$_3$) \[7.45–7.21\] (m, 10H, C$_6$H$_5$), 5.93–5.87 (m, 1H, CH$_2$=CHCH$_2$), 5.25–5.21 (m,
2H, CH=CH, 4.17-4.10 (m, 1H, CHCH₃), 4.07 (d, J = 11.2 Hz, 1H, NCH₂CH₃), 4.02 (d, J = 13.7 Hz, 1H, CH₂CH₃), 3.55-3.49 (m, 2H, CH₂OH, CH₂=CHCH₂N), 3.31 (dd, J = 3.4, 11.3 Hz, 1H, CH₂OH), 2.95 (d, J = 13.7 Hz, 1H, CH₂CH₃), 2.55 (dd, J = 8.8, 13.2 Hz, 1H, CH₂=CHCH₂N), 2.26-2.22 (m, 1H, CHCH₂OH), 1.33 (d, J = 6.3 Hz, 3H, CH₃);

¹³C NMR (125 MHz, CDCl₃) [δ 138.5, 135.7, 133.9, 130.1, 129.4, 128.9, 128.5, 128.0, 127.6, 119.1, 70.2, 65.0, 61.8, 54.4, 53.1, 46.1, 21.2; [α]D = +74.3° (c = 1.0, CHCl₃).

A solution of (3R,4S,5R)-2-allyl-4-formyl-5-methyl-3-phenylisoxazolidine (Table 3, entry 2), (51.0 mg, 0.22 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil (24.8 mg, 0.11 mmol) was dissolved in EtOH (3.5 mL) and heated to reflux. Sodium metal (150 mg, 6.52 mmol) was added in 25 mg portions to the solution. After 3 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH₄Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na₂SO₄), and concentrated. Purification of the resulting oil by silica gel chromatography (4% Et₃N/EtOAc) afforded a white solid. The solid (5.4 mg, 0.023 mmol) was dissolved in CH₃CN (1.0 mL). To the stirring solution was added benzyl bromide (3.0 mL, 0.025 mmol) and K₂CO₃ (5.7 mg, 0.041 mmol). The reaction was heated to reflux for 12 hours. The solution was filtered and concentrated. The resulting oil was purified by silica gel chromatography (50% EtOAc/hex) to afford a clear oil with ¹H and ¹³C NMR spectra identical to those of (2R)-[1-((R)-allyl-benzyl-amino)-phenyl-methyl]-butane-1,(3R)-diol above; [α]D = +72.1° (c = 1.0, CHCl₃).

**Determination of the Absolute Configuration of (3R,4S,5R)-2,5-dimethyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 3) by Correlation with (2R)-[1-((R)-benzyl-methyl-amino)-phenyl-methyl]-butane-1,(3R)-diol.**

(2R)-[(R)-Benzylamino-phenyl-methyl]-butane-1,(3R)-diol, of known absolute configuration (vide infra) (26.8 mg, 0.09 mmol), and K₂CO₃ (52.0 mg, 0.38 mmol) were suspended in CH₃CN (1.5 mL). To the suspension was added iodomethane (5.8 mL, 0.09 mmol) and the reaction was stirred for 48h. The reaction was diluted with H₂O and extracted with EtOAc. The organic layer was dried (Na₂SO₄) and concentrated. The
resulting oil was purified by silica gel chromatography (50% EtOAc/hex) to afford (2R)-[1-((R)-benzyl-methyl-amino)-phenyl-methyl]-butane-1,(3R)-diol; 

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.45–7.22 (m, 10H, C$_5$H$_5$), 4.24 (dq, $J = 2.4, 6.4$ Hz, 1H, CH$_2$), 4.14 (d, $J = 11.2$ Hz, 1H, NCH$_2$C$_6$H$_5$), 3.61 (dd, $J = 2.4, 11.8$ Hz, 1H, CH$_3$OH), 3.48 (m, 2H, NCH$_2$C$_6$H$_5$), 3.37 (dd, $J = 3.9, 11.7$ Hz, 1H, CH$_2$OH), 2.20–2.13 (m, 1H, CHCH$_2$OH), 2.12 (s, 3H, NCH$_3$), 1.38 (d, $J = 6.4$ Hz, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.1, 133.5, 130.1, 129.3, 128.9, 128.5, 128.1, 127.7, 70.3, 69.9, 61.7, 60.0, 45.9, 37.0, 21.9; $[\alpha]_D = -10.3^\circ$ (c = 1.0, CHCl$_3$).

A solution of (3R,4$S$,5$R$)-2,5-dimethyl-4-formyl-3-phenylisoxazolidine (Table 3, entry 3), (51.0 mg, 0.25 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (5.0 mL) and heated to reflux. Sodium metal (180 mg, 7.83 mmol) was added in 25 mg portions to the solution. After 4 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH$_4$Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na$_2$SO$_4$), and concentrated. Purification of the resulting oil by silica gel chromatography (10% Et$_3$N/EtOAc) afforded a white solid. The solid (9.1 mg, 0.047 mmol) was dissolved in CH$_3$CN (1.0 mL). To the stirring solution was added benzyl bromide (5.8 mL, 0.048 mmol) and K$_2$CO$_3$ (12.0 mg, 0.086 mmol). The reaction was heated to reflux for 14h hours. The solution was filtered and concentrated. The resulting oil was purified by silica gel chromatography (65% EtOAc/hex) to afford a clear oil with $^1$H and $^{13}$C NMR spectra identical to those of (2R)-[1-((R)-benzyl-methyl-amino)-phenyl-methyl]-butane-1,(3R)-diol above; $[\alpha]_D = -8.4^\circ$ (c = 1.0, CHCl$_3$).

**Determination of the Absolute Configuration of (3R,4$S$,5$R$)-2-benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine (Table 7, entry 4) by Correlation with (2R)-[(R)-benzylamino-phenyl-methyl]-butane-1,(3R)-diol**

(3R,4$S$,5$R$)-2-Benzyl-4-formyl-5-methyl-3-phenylisoxazolidine, of known absolute configuration (Table 3, entry 1) (25.0 mg, 0.09 mmol), was reduced to the

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9 Experiment run by J. J. M. Wiener.
corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (1.2 mL) and heated to reflux. Sodium metal (180 mg, 7.83 mmol) was added in 25 mg portions to the solution. After 2.5 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH₄Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na₂SO₄), and concentrated. Purification of the resulting oil by silica gel chromatography (2.5% Et₃N/EtOAc) afforded (2R)-[(R)-benzylamino-phenyl-methyl]-butane-1,(3R)-diol as a white solid: ¹H NMR (300 MHz, CDCl₃) [J 7.42–7.20 (m, 10H, C₆H₆), 4.07 (dq, J = 2.2, 6.0 Hz, 1H, CHCH₃), 3.99 (d, J = 9.3 Hz, 1H, NCH₂CH₃), 3.60 (d, J = 12.6 Hz, 1H, CH₂C₆H₅), 3.54 (d, J = 12.6 Hz, 1H, CH₂C₆H₅), 3.52 (dd, J = 3.9, 11.3 Hz, 1H, CH₂OH), 3.19 (dd, J = 3.3, 11.3 Hz, 1H, CH₂OH), 1.74-1.66 (m, 1H, CHCH₂OH), 1.25 (d, J = 6.3 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) [J 141.4, 139.0, 129.1, 128.8, 127.9, 127.6, 127.5, 69.6, 64.9, 61.6, 51.9, 51.7, 22.3; [ŋ]₁ᵣ = +41.5 ° (c = 1.0, CHCl₃).

A solution of (3R, 4S,5R)-2-benzyl-4-formyl-5-methyl-3-(4-chlorophenyl) isoxazolidine, (25.0 mg, 0.08 mmol) was reduced to the corresponding primary alcohol (general procedure C) and purified by silica gel chromatography (30% EtOAc/hex). The resulting oil was dissolved in EtOH (1.2 mL) and heated to reflux. Sodium metal (180 mg, 7.82 mmol) was added in 25 mg portions to the solution. After 2 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH₂Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na₂SO₄), and concentrated. Purification of the resulting oil by silica gel chromatography (2.5% Et₃N/EtOAc) afforded a white solid oil with ¹H and ¹³C NMR spectra identical to those of (2R)-[(R)-benzylamino-phenyl-methyl]-butane-1,(3R)-diol above; [ŋ]₁ᵣ = +35.5 ° (c = 1.0, CHCl₃).

**Determination of the Absolute Configuration of (3R,4S)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 11) by Correlation with (S)-3-Benzylamino-3-phenyl-propan-1-ol.** To Wilkinson's catalyst (72.2 mg, 0.078 mmol) was added a
solution of (3R,4S)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 3, entry 11) (20.4 mg, 0.078 mmol) in degassed benzene (3.5 mL). The stirring solution was heated to reflux under a nitrogen atmosphere. After 20h, the reaction was cooled to room temperature and H$_2$O was added. The mixture was extracted with Et$_2$O, dried (Na$_2$SO$_4$), and concentrated to give a red oil which was purified by silica gel chromatography (10% EtOAc/hex). The resulting oil was dissolved in EtOH (2 mL) and heated to reflux. Sodium metal (120 mg, 5.22 mmol) was added in 25 mg portions to the solution. After 4 hours at reflux, when a white solid had formed, the reaction was cooled to room temperature and quenched with water. The mixture was diluted with EtOAc, washed with NH$_4$Cl, and extracted with EtOAc. The organic extracts were combined, dried (Na$_2$SO$_4$), and concentrated. Purification of the resulting oil by silica gel chromatography (EtOAc) afforded an oil with $^1$H and $^{13}$C NMR spectra identical to those reported for (S)-3-Benzylamino-3-phenyl-propan-1-ol; $^5$ [α]$_D$ (literature) = -28.1 ° (c = 1.0, CHCl$_3$); [α]$_D$ (found) = +26.2 ° (c = 1.0, CHCl$_3$).

**Determination of the Relative Configuration of (3R,4S)-2-Benzyl-4-formyl-3-phenylisoxazolidine (Table 7, entry 14) by X-ray Crystallography.** 2-Benzyl-4-formyl-3-phenylisoxazolidine (54 mg, 0.18 mmol) was dissolved in tert-butanol (3.9 mL). To this solution was added 2-methyl-2-butene (1 mL, 90 mmol) and, dropwise, a solution of NaClO$_2$ (152 mg, 1.69 mmol) and NaH$_2$PO$_4$ (178 mg, 1.29 mmol) in H$_2$O (1.7 mL). The biphasic solution was stirred for 12h. The reaction was then concentrated, diluted with H$_2$O and EtOAc and extracted twice with EtOAc. The combined organic layers were washed with cold H$_2$O, dried (Na$_2$SO$_4$), concentrated, and purified by silica gel chromatography (40% EtOAc/Hex). The resulting yellow oil was subsequently taken up in methanol (0.5 mL) and cooled to 0 °C. A solution of KOH (5 mg) in methanol (53 µL) was added to the reaction mixture. After stirring for 3 hours, the solution was concentrated and the resulting yellow solid was recrystallized from ethanol/THF to afford racemic crystals suitable for single crystal X-ray diffraction.

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Table 1. Crystal data and structure refinement for W3J01.

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

Table 2. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10⁴) for WS101. U(eq) is defined as the trace of the orthogonalized U tensor.

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Table 4: Bond lengths [Å] and angles [°] for WSJ301.
Table 5. Anisotropic displacement parameters ($\AA^2 \times 10^3$) for WSJ01. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [ h^2 a^* U_{11} + ... + 2 b k a^* b^* U_{12} ]$.

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Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\AA^2 \times 10^3$) for WSJ01.

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Table 7. Hydrogen bonds for WSJ01 [Å and °].

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

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Chapter 3

Enantioselective Organocatalytic Intramolecular Diels-Alder Reactions and Their Application toward the Asymmetric Total Synthesis of (–)-Solanapyrone D

I. Introduction

Since its discovery over 70 years ago,\(^1\) the Diels-Alder reaction has become one of the most widely used synthetic transformations in organic chemistry. Its ability to generate up to four stereocenters in a highly stereoselective and predictable fashion led to its widespread application in solving difficult synthetic challenges. The intramolecular version of this process, in which the diene and dienophile are tethered by a connecting chain, has similarly attracted a great deal of attention; numerous examples in the literature attest to its utility in generating stereochemically complex polycyclic ring systems from relatively simple starting materials.

In contrast to its bimolecular counterpart, of which there are a large number of documented asymmetric catalytic variants,\(^2\) there are relatively few examples in the literature of enantioselective catalytic intramolecular Diels-Alder (IMDA) reactions. Therefore, we began a program to address the utility of asymmetric organocatalysis to the intramolecular Diels-Alder cycloaddition, thus expanding the scope of this reaction. (eq. 1) Furthermore, the successful application of this methodology to an enantioselective synthesis of (–)-solanapyrone D is presented.

![](image)
A. Background

The IMDA reaction is one of the most efficient and elegant methods for constructing polycyclic ring systems in the synthetic chemist’s toolbox of transformations. In a single step, functionalized bicyclic ring systems possessing up to four contiguous stereocenters can be generated from relatively simple triene precursors. Since the reaction proceeds through a highly ordered transition state, excellent levels of regio- and diastereoselectivities are oftentimes observed.

The intramolecular Diels-Alder cycloaddition reaction can be broken down into two major classes, identified based on the point of connection between the diene and the dienophile (Figure 1). Type I IMDA reactions involve trienes with the dienophile tethered from the terminus of the diene, resulting in bicyclic products containing a fused ring junction. The stereo- and regioselectivities of these reactions are highly dependent on the nature of the diene, dienophile, and tether. Comprehensive reviews have been published on this topic, and therefore it will not be discussed here.\textsuperscript{3-7} Type II IMDA substrates, on the other hand, have the dienophile tethered from an internal position on the diene, resulting in the formation of bridged bicycles containing highly strained bridgehead double bonds (anti-Bredt olefin). This reaction is notably powerful since there are few methods for accessing these particularly complex frameworks, which are prevalent in a number of natural products families. Selectivity is also a potential concern in these reactions; however, predicting diastereoselectivity is somewhat simpler in these cases as compared to the type I IMDA. Substrates with bridging chains of three or four atoms cyclize exclusively to give syn products because the transition state leading to the anti diastereomer is prohibitively high in energy.\textsuperscript{8} Given the powerful nature of this reaction, it is interesting to note that there is no asymmetric catalytic type II intramolecular Diels-Alder variant reported in the literature to date.
B. Diastereoselective Intramolecular Diels-Alder Reactions

There are many examples in the literature of diastereoselective IMDA reactions, the most common type being where one or more stereocenters in the acyclic IMDA precursor is used to relay stereochemistry to the newly formed chiral centers (eq. 2). These reactions are extremely useful, although somewhat limiting; since the stereocontrol element is not easily removed in most cases, these reactions are only useful when that chiral element is present in the target of interest.

A more general approach for accessing enantioenriched IMDA cycloadducts is through the use of chiral auxiliaries, which can removed upon completion of the cycloaddition reaction. Mukaiyama was the first to publish on such a system in his synthesis of sesquiterpene (+)-farnesiferol (eq. 3). Intramolecular cycloaddition of furanyl diene 4 with the phenyl glycinol-derived unsaturated amide provided the desired cycloadduct 6 in moderate yields and selectivities. The authors speculated that the reaction proceeded through the conformationally locked intermediate 5 which favored
approach of the diene from the re-face of the dienophile; this therefore led to the preferential formation of the desired diastereomer. This example is a rare case of an “internal” auxiliary (where the removable chiral element is embedded within the tether); subsequent excision of the chiral auxiliary necessarily leads to the cleavage of the bicycle formed in the IMDA reaction.

![Image](image.png)

More commonly used are “external” chiral auxiliaries in which the auxiliary is connected to the terminus of the dienophile. In these cases, the polycyclic system formed in the IMDA reaction can be left intact upon removal of the chiral controlling element. To date, the two most successful chiral auxiliaries of this type are the acyl oxazolidinones 7\textsuperscript{11-14} and acyl sultams 8.\textsuperscript{15}

**Figure 2.** Models for asymmetric induction for imide and sultam auxiliaries
Both auxiliaries have been shown to confer higher levels of reactivity and selectivity on the IMDA reaction than any previously published auxiliaries (eq. 4, 5). The imide and sultam cycloadditions are believed to proceed through similar transition states. Evans speculates that addition of a Lewis acid to 7 produces ion pair 9 in which the si-face is left open to attack, leading to the observed product. Likewise, chelated intermediate 10 correctly predicts the stereochemistry of the sultam-mediated reaction. The utility of these auxiliaries has been demonstrated by their use in the synthesis of complex natural products. Evans and Black used a chiral imide-controlled IMDA reaction to access a highly functionalized bicyclic intermediate on the way to (+)-lepicidin. Morimoto and coworkers have also disclosed their use of a chiral oxazolidinone auxiliary to establish the key stereochemical relationships in the core of (−)-stenine.

C. Enantioselective Intramolecular Diels-Alder Reactions

In contrast to the bimolecular Diels-Alder reaction, of which there are hundreds of asymmetric catalytic variants, there are relatively few examples in the literature of enantioselective catalytic IMDAs. Furthermore, in a number of these examples, very few substrates have been examined, since they are treated mainly as an extension of the intermolecular Diels-Alder reaction, or substrate scope has been shown to be somewhat limited.

Yamamoto and coworkers were one of the first groups to report the successful use of a chiral Lewis acid to catalyze an asymmetric IMDA reaction. They found that treatment of triene 12 with chiral acyloxyborane complex (CAB) 11 produced the desired
[4.3.0] bicycle in good yields and with excellent diastereo- and enantiocontrol (eq. 6). However, it was also found that this catalyst system was not generally applicable to the IMDA reaction; cyclization of analogous trienal substrate 14 lacking a \( \beta \)-methyl group proceeded in only 46% ee.

This shortcoming was later addressed by Yamamoto with the introduction of their Brønsted acid-assisted chiral Lewis acid (BLA) 13.\(^{19,20}\) The reaction of \( \beta \)-unsubstituted decatrienal 14 in the presence of 13 produced the desired [4.3.0] bicycle as a single diastereomer in 95% yield and 80% ee (eq. 7). Although a number of intermolecular Diels-Alder substrates were studied, trienal 14 was the only IMDA substrate that was examined in this study.

A more extensive study of asymmetric IMDA reactions was carried out by Narasaka and coworkers, who found that Ti-TADDOL complex 15 was capable of catalyzing the IMDA reaction of a number of trienimides.\(^{21}\) Although nonatrieneimides reacted, decatrienimide reactions proceeded very slowly, or very poorly, and therefore required high catalyst loadings and extended reaction times (3-10 days, eq. 8). Reactivity could be increased (reaction times of 3-4.5 days) by modifying the substrates to incorporate a dithiane moiety on the tether, presumably due to Thorpe-Ingold acceleration.\(^{22}\) Narasaka later demonstrated the potential utility of this methodology in the elaboration of one of these IMDA cycloadducts into the hydronaphthalene core of the mevinic acid family of natural products.
One of the more extensive studies on asymmetric catalytic IMDA reactions was published recently by Evans and Johnson, who reported the successful application of their cationic $C_2$-symmetric Cu(II)-tert-butyl-bis(oxazoline) catalyst 16 to the IMDA reaction (eq. 10). Unsubstituted and phenyl-substituted trienimides were found to cyclize efficiently in the presence of 16 to afford [4.4.0] and [4.3.0] bicyclic ring products in good yields and with good selectivities (Table 1, with the exception of 19). The synthetic utility of this process was demonstrated in the subsequent conversion of IMDA cycloadduct 21b to the marine natural product (−)-isopulo’upone.

Although these studies have significantly advanced the field of asymmetric catalytic intramolecular Diels-Alder reactions, there are still improvements that can be made on the current technology. None of these studies explore a particularly wide substrate scope, and therefore it is difficult to draw conclusions as to the generality of these catalyst systems toward the IMDA reaction. Furthermore, the most useful systems currently employ the use of an achiral oxazolidinone auxiliary, which must be removed upon completion of the reaction. Since our organocatalytic methodology allows for direct access to aldehyde functionalities, we became interested in applying our enantioselective organocatalytic technology to the IMDA reaction, in the hopes of developing a broadly useful variant of the asymmetric, catalytic intramolecular Diels-Alder reaction.
Table 1. Cu(II) tert-butyl-bis(oxazoline) catalyzed IMDA reactions

<table>
<thead>
<tr>
<th>tricinimide</th>
<th>n</th>
<th>R</th>
<th>catalyst (mol%)</th>
<th>product</th>
<th>% yield</th>
<th>endocisio</th>
<th>% ee</th>
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<tr>
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<td>H</td>
<td>10</td>
<td>17b</td>
<td>89</td>
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<td>86</td>
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<tr>
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<td>1</td>
<td>Ph</td>
<td>5</td>
<td>18b</td>
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<td>H</td>
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<td>5</td>
<td>21b</td>
<td>&gt;99:1</td>
<td>&gt;99:1</td>
<td>96</td>
</tr>
</tbody>
</table>

II. Results and Discussion

A. Synthesis of Intramolecular Diels-Alder Reaction Substrates

The synthesis of tetraenal substrate 24 is outlined in Scheme 1. Known aldehyde 22 (prepared in one step from glutaric dialdehyde) was treated with a Wittig reagent formed from n-BuLi deprotonation of (2E,4E)-2,4-hexadiene-1-triphenylphosphonium bromide. The resulting ester was then reduced to the primary alcohol with DIBAL-H to give the tetraene as a 2:1 mixture of (2E, 7E, 9E, 11E)- to (2E, 7Z, 9E, 11E)- olefin isomers. Subjection of the alcohol to iodine olefin isomerization conditions produced 23 as a 6:1 mixture of olefin isomers, favoring the desired (2E, 7E, 9E, 11E)- isomer. Subjection of the primary alcohol to oxidation conditions afforded the desired tetraenal 24.
Synthesis of phenyl-substituted decatrienal 29 began with a one-pot DIBAL-H reduction/Wittig olefination of commercially available \( \delta \)-caprolactone to produce diene 30 as a 1:1 mixture of olefin isomers. Iodine mediated olefin isomerization equilibrated the mixture to a 5:1 mixture favoring the desired \((6E, 8E)\)-isomer. Subsequent oxidation of the alcohol to the aldehyde, followed by Wittig olefination with methyl (triphenylphosphoranylidene)acetate furnished ester 27 in good yields. DIBAL-H reduction of the ester followed by TPAP oxidation afforded trienal 29.

Finally, it should be noted that this project was carried out in collaboration with Rebecca Wilson, who originally began this work; one should refer to her thesis for the synthetic details of any substrates in the subsequent discussion that are not covered in this section.
B. Organocatalytic Intramolecular Diels-Alder Reactions

**Reaction Optimization.** Each of the IMDA substrates were individually studied and optimized to maximize yield and selectivity. There were four main side reactions that had to be considered during optimization, since it was these alternate reaction pathways that led to the degradation of product selectivity and yields.

First, polymerization of the starting materials under reaction conditions was frequently a problem, which is not surprising given the notorious instability of trienals and tetrenals. Second, acid catalyzed racemic background reactions were frequently a concern. Since the two reacting partners in the IMDA reaction (the diene and dienophile) are tethered to one another, simple dilution effects were generally ineffective at reducing racemic background. Because these background reactions proceed through an achiral transition state, the resulting products are racemic; this therefore led to a degradation in the optical purity (ee) of the bicyclic products.

Third, the products of the IMDA reaction were prone to epimerization at the aldehydic stereocenter (eq. 12). Given the somewhat acidic nature of the proton to the aldehyde, it was not surprising that that stereocenter was prone to epimerization in the presence of bases, such as the amine catalyst and conjugate base of the cocatalyst.

Finally, it was found that under certain reaction conditions, a considerable amount of aromatic side product 34 was formed. This presumably occurs though the dimerization mechanism outlined in Scheme 3. Condensation of the chiral amine catalyst with aldehyde 30 produces the iminium 31. Since the dienophile is now activated, the predicted course of action would be for the triene to cyclize to form the desired IMDA cycloadduct. However, the triene can also be deprotonated with the conjugate base of the acid cocatalyst (X⁻), to form dienamine 32. Subsequent intermolecular Diels-Alder cyclization of the electron deficient olefin in 31 with the very electron rich diene 32 produces cyclohexene 33. Hydrolysis of the iminium, followed by elimination and
oxidation provides the observed fully aromatized side product 34. Since this dimerization pathway lead to an undesired consumption of the IMDA substrate, this side reaction would result in a decrease in the yield for the desired IMDA reaction.

**Scheme 3.** Proposed mechanism for the dimerization side products observed in IMDA reactions

Since the extent to which each of these side reactions factored into the IMDA reaction was highly dependent on the inherent reactivity of the IMDA substrate being studied, each substrate had to be optimized on an individual basis. Several reaction variables were tuned to maximize yield and selectivity, and to minimize the aforementioned undesired side reactions.

One variable that seemed to consistently have a large effect on the reaction was the nature of the acid co-catalyst (Figure 3). It was generally found that more acidic co-catalysts (HClO₄, HCl) were effective at decreasing product epimerization and starting material dimerization. This result is not surprising, since both of these side reactions are base catalyzed pathways; decreasing the basicity of the co-catalyst’s conjugate base should decrease the amount of epimerization and dimerization.

On the other hand, use of less acidic co-catalysts generally led to a decrease in the acid promoted racemic background reaction and starting material polymerization reaction. These trends ultimately lead to the general use of less acidic co-catalysts (TFA, TCA) for more reactive substrates, while less reactive substrates generally required the
use of more acidic co-catalysts (TfOH, HClO₄). Substrates that cyclized more readily, such as nonatrienal 35, suffered mainly from an acid-catalyzed background reaction and substrate polymerization; thus, less acidic co-catalysts such as TFA were generally most appropriate. In contrast, less reactive substrates, such as decatrienal 36, were affected mainly by dimerization and epimerization side reactions, and hence co-catalysts such as TfOH were often used in these IMDA reactions. In general, less acidic co-catalysts (TFA) are used for more reactive substrates and more acidic co-catalysts (such as HClO₄) are used for less reactive substrates. The reactivity of most substrates lies somewhere between the two extremes discussed above; thus, the optimal co-catalyst must be independently determined for each substrate examined.

**Figure 3.** Effect of the nature of the Brønsted acid co-catalyst on IMDA reactions

Temperature also seemed to have a large effect on the yields and selectivities of the IMDA reactions (Figure 4). Generally, lower reaction temperatures led to less racemic background, epimerization, and dimerization, while often improving product diastereo- and enantioselectivities. However, higher reaction temperatures generally led to increased reaction yields by reducing starting material polymerization, since this side reaction occurs mainly when substrates do not undergo the desired IMDA cyclization. Therefore, less reactive substrates are generally run at higher reaction temperatures since they are unreactive at lower temperatures and simply polymerized. However substrates that are sufficiently reactive are generally run at lower temperatures, and thus benefited from less background, dimerization, epimerization, and improved selectivities.
Empirical results suggested that water and solvent play an important role in mediating the amount of polymerization, epimerization, and background reaction in the IMDA cyclization reactions. Acetonitrile, chloroform, isopropanol, and butanol were generally the best solvents. In particular, CH₃CN and CHCl₃ are effective at reducing substrate polymerization and increasing substrate and catalyst solubility. On the other hand, butanol and isopropanol appeared to be effective at minimizing the epimerization side reaction. In addition, a solvent:water ratio of about 98:2 was generally used to maximize the rate of catalyst turnover.

Finally, one of the most important reaction variables was choice in amine catalyst. In the time since the [3+2] cycloaddition project was completed, second generation imidazolidinone catalyst 2 was developed by Christopher Borths and Joel Austin. Amine 2 has been found to be a more effective catalyst than 1 in some cases, producing IMDA cycloadducts with better selectivities and yields and with reduced reaction times. These increases in reactivity and selectivity can be rationalized by examining the differences between the two catalysts (Figure 5). Whereas the amine lone pair is eclipsed by one of the geminal dimethyl groups in 1, catalyst 2 does not contain the same eclipsing interaction. The lone pair in 2 is therefore more sterically accessible; this leads to greater nucleophilicity and overall catalyst reactivity. Moreover, compounds reacting with the catalyst-1-derived iminium ion must encounter a retarding interaction with the illustrated methyl substituent, whereas the reactive enantioface of the catalyst-2-derived iminium ion is free from obstruction; this leads to increased reactivity for 2. Furthermore, the methyl group syn to the benzyl functionality in 1 has been replaced by a tert-butyl group in 2. This allows catalyst 2 to control iminium ion geometry, just as catalyst 1 does, thus allowing the benzyl group on the catalyst framework to effectively shield one ␣-face of the olefin. Due to its enhanced reactivity, catalyst 2 was particularly effective at
promoting the cyclization of relatively unreactive IMDA substrates. For many of the substrates (although not all), catalyst 2 performed better than 1.

**Figure 5.** Comparison of first generation catalyst 1 and second generation catalyst 2.

**IMDA Reaction Scope.** Using the aforementioned variables to tune the reaction conditions, a variety of IMDA substrates were studied, the results of which are summarized in Table 2. The reaction appears to tolerate variation in the diene, tether, and dienophile components of the IMDA substrates. Cycloadducts are generated in good yields and selectivities from IMDA substrates containing aryl (37, 85% yield, 93% ee), allyl (24, 75% yield, 93% ee), and substitution on the diene. Furthermore, the less reactive decatriene substrate 29, while unreactive with 1, reacts readily in the presence of 2 to afford the [4.4.0]-bicycle in excellent yield and selectivity (70% yield, 93% ee). Furthermore, we were able to access a bicyclic system containing a quaternary carbon stereocenter in excellent yield and enantioselectivity (cat. 1, 76% yield, 94% ee) from a trisubstituted (Z)-dienophile.

There have been no reports to date of an asymmetric IMDA in which the substrate contains a heteroatom in the tether, perhaps due to the incompatibility of some Lewis acids with the heteroatom functionality. Because organocatalysis does not suffer from the same functional group compatibility issues, we were able to generate ether cycladduct 44 in 84% yield and 93% ee.
Tetraene 24 was one of the more reactive substrates examined in this study, cyclizing in 12 hours with catalyst 2 at –20 °C to afford [4.3.0]-bicycle 39 in 94% ee (endo). This is not wholly unexpected, since the introduction of an electron releasing group should increase the energy of the diene HOMO and reduce the activation energy, thereby making the reaction more facile. Since the reaction was so facile, background reaction was somewhat of a problem. Similar to nonatrienal 37, 24 cyclized in the presence of catalyst 1 to produce cycloadducts with lower enantioselectivities. This is presumably due to the fact that 24 (and 37) are so reactive that there is a reasonable amount of background reaction taking place; the more reactive catalyst 2 is better able to out-compete the racemic background to produce cycloadducts in higher ee’s. Catalyst 2
was also superior to 1 in minimizing product epimerization of cycloadduct 39; efforts to improve product:epimer ratios beyond 2:1 using catalyst 1 were largely unsuccessful. Yields were also generally low using catalyst 1, presumably due to the inability of the catalyst to out-compete the decomposition of the somewhat unstable tetaene moiety (47% yield with catalyst 1).

The relative stereochemistry of bicycle 39 was determined through nOe analysis. Confirmation that 39 was indeed the endo isomer was accomplished by the observation of nOe enhancements between C-3 and C-4 methine protons, and the C-4 and C-6 protons (Figure 6).

Figure 6. Relative stereochemistry for IMDA product 39

Decatrienal 29 was examined to assess the ability of the organocatalytic IMDA reaction to accommodate the formation of [4.4.0]-bicycles. This substrate was noticeably less reactive than most other substrates, and efforts to optimize the reaction using catalyst 1 were largely unsuccessful. This was not unexpected given that IMDA cyclizations to form [4.4.0] systems are well documented to be slower than triene cyclizations to form [4.3.0] ring systems. Catalyst 2, however, was successful in increasing the rate of the reaction to useful levels while producing cycloadduct 45 with good diastereo- and enantioselectivities. In contrast to nonatrienal substrates 37 and 24, endo vs. exo selectivity was more of an issue in this reaction. This is also surprising since the steric requirements in the transition state leading to the formation of a decalin system are less than that for a hydridene system. Fortunately, reaction conditions could be carefully optimized to maximize the diastereoselectivity of the reaction.

The absolute and relative stereochemistry of 40 was established by chemical correlation to the known thioester 47 ([α]_D = -437.3 (c 1, CHCl₃)), whose absolute configuration was previously established (Scheme 4).
The Type II IMDA is one of the most efficient and elegant routes to these complex ring systems; thus it is notable that there have been no reported examples of an asymmetric Type II IMDA to date. Due to the success of the imidazolidinone catalysts in promoting a range of traditional Type I IMDA cyclizations, we sought to extend our organocatalytic strategy to the Type II IMDA. We were pleased to find that when triene 48 was treated with imidazolidinone catalyst 2, it reacted to afford the Type II cycloadduct 49 as a single isomer in good yields with excellent levels of enantioselectivity (72% yield, 98% ee). To our knowledge, this is the first reported example of an asymmetric, catalytic Type II intramolecular Diels-Alder reaction.

Again, one should refer to R.M. Wilson’s thesis for reaction details and analysis of any substrates not discussed in this section.

C. Asymmetric Total Synthesis of (−)-Solanapyrone D

**Background.** The phytotoxic polyketide natural product solanapyrone D (3) was isolated in 1989 by Oikawa and Ichihara from the fungus Altenaria solani as a side
product in the biosynthesis of solanapyrone A.\textsuperscript{28} Its biological activity has yet to be fully explored, although recent studies have shown that solanapyrone A is a selective inhibitor of mammalian DNA polymerase \([\text{II}]\) and \([\text{I}]\) suggesting that compounds of this type may find utility in cancer chemotherapy.\textsuperscript{29} The relationship between solanapyrones A and D suggested that the biosynthesis of these natural products could involve an enzyme capable of catalyzing a [4+2] cycloaddition reaction. Indeed, in 1998 Oikawa and Ichihara reported the first direct experimental evidence for the existence of a Diels-Alderase through their studies on the biosynthesis of solanapyrones A and D.\textsuperscript{28,30-33} Feeding experiments performed with labeled prosolanapyrone 50 allowed the authors to unambiguously establish that the solanapyrone natural products were formed via an enzymatically catalyzed \textit{exo}-selective intramolecular Diels-Alder reaction. Incubation of the achiral triene 50 in the crude enzyme extract from \textit{A. solani} provided solanapyrone A in 53\% yield and 98\% \textit{ee}.\textsuperscript{30}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{solanapyrene_natural_products.png}
\caption{Solanapyrone natural products}
\end{figure}

\begin{scheme}[h]
\centering
\includegraphics[width=0.8\textwidth]{biosynthetic_pathway.png}
\caption{Biosynthetic pathway for solanapyrones A and D}
\end{scheme}

The first, and only, total synthesis of solanapyrone D to date was recently accomplished by Hagiwara and coworkers in 19 steps \textit{via} a diastereoselective domino Michael reaction (Scheme 6).\textsuperscript{34} The key transformation in the synthesis involved a
diastereoselective domino Michael reaction between enantiopure known trimethylsilyl enol ether 51 and methyl crotonate, to produce the desired trans-fused bicycle 52 following base isomerization. This core was then elaborated over 13 steps to afford pyrone 53. Given the nontrivial nature of installing the final C-14 formyl group, the authors developed a new 4 step formylation protocol which ultimately allowed them to access solanapyrone D (3).\textsuperscript{35,36}

**Scheme 6.** Hagiwara's synthesis of (–)-solanapyrone D

Given the Diels-Alderase studies and the presence of an appropriately substituted trans-fused decalin system, we felt that solanapyrone D presented itself as an appropriate platform for demonstrating the utility of our enantioselective organocatalytic IMDA methodology. This target molecule would also allow us to further probe the scope of this IMDA reaction by testing the tolerance of catalyst 2 to alkyl substitution at the diene terminus in the formation of [4.4.0] bicyclic ring systems.

**Synthesis of (–)-Solanapyrone D.** The synthesis of cyclization precursor 57 was initiated by Wittig olefination of known aldehyde 55\textsuperscript{30} (synthesized in 2 steps from commercially available \( \epsilon \)-caprolactone) with methyl(triphenylphosphoranylidene) acetate to provide triene 56. Ester 56 was subjected to DIBAL-H reduction conditions and the derived alcohol was treated with TPAP/NMO to afford the desired IMDA precursor 57.

**Scheme 7.** Solanapyrone D: Synthesis of IMDA cyclization precursor

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Key: (a) methyl(triphenylphosphoranylidene)acetate, THF, 57%; (b) DIBAL-H, CH\(_2\)Cl\(_2\), –78 °C, 91%; (c) TPAP, NMO, 4Å MS, CH\(_2\)Cl\(_2\), rt, 59%.
With the requisite trienal in hand, the key organocatalytic IMDA reaction was attempted. Extensive optimization of the previously discussed reaction variables produced conditions that cyclized IMDA precursor 57 to [4.4.0] bicycle 58 as a single detectable isomer in 81% yield (eq. 14). The IMDA reaction proceeded with good enantioselectivity (90% ee) to introduce the bicyclic solanapyrone D core containing all four stereocenters in the required configuration.

![Reaction Scheme](image)

The target 3 required that the aldehyde functionality of 58 be converted to a pyrone moiety (Scheme 8). This was achieved by using the precedented work in Hagiwara’s synthesis as a guide. 34 58 was reacted with methyl acetoacetate bis(trimethylsilyl) enol ether in the presence of titanium tetrachloride to afford aldol adduct 59 (1:1 mixture of alcohol isomers). This hydroxyketoeester was subjected to Dess-Martin oxidation conditions, and subsequently cyclized with DBU at elevated temperatures to furnish pyrone 60 in 87% yield.

**Scheme 8.** Solanapyrone D: Conversion of IMDA cycloadduct to pyrone 60

![Conversion Scheme](image)

Conversion of 60 to the natural product 3 proved to be nontrivial. Although pyrone 60 is only two functional group transformations away from the target product 3, C-3 formylations of 4-hydroxypryones and 4-methoxypyrones (C-14 on 60) have been documented to be difficult. There are only a handful of methods for introducing this functionality in the context of the pyrone system; all but one require lengthy multi-step
sequences.\textsuperscript{37,38} The only one-step protocol requires harsh acidic conditions (TiCl$_4$, Cl$_2$CHOMe), and was found to be unsuitable in the context of this synthesis; subjection of 60 to these reaction conditions produced a complex mixture of products. Hagiwara developed a three-step sequence to address this shortcoming in his synthesis of solanapyrone D (four steps including the methylation of C-15 hydroxyl, Scheme 6).\textsuperscript{35} Given the dearth of efficient methods for formylating 4-oxypyrone, we became interested in developing an efficient protocol for effecting this transformation.

A variety of reaction conditions were examined in an effort to identify suitable conditions for formylating 4-hydroxypyrone (e.g. 60) and 4-methoxypyrone (e.g. 61). Extensive efforts were invested into finding Vilsmeier-Haack or Fries-type rearrangement conditions that could effect the desired transformation. Unfortunately, the former generally resulted in recovery of unreacted starting material, and the latter led to the formation of dimerization products. Attempts at directly condensing 60 and 4-methoxypyrone 61 resulted only in the formation of dimeric products under a variety of acidic and basic conditions. Finally, attempts were made to iodinate at C-14 on 60 and formylate with Pd(0)/CO/Bu$_3$SnH in a two-step protocol. This strategy was mildly successful on the model system 4-methoxy-6-methyl-pyran-2-one (c.a. 15% yield in the Pd(0) mediated coupling); however, iodination of 60 proved to be difficult because of the alkene present in the decalin system.

Attempts to generate and trap the C-14 carbanion were, however, greeted with success. Methylation of 60 with methyl p-toluenesulfonate afforded 61 in 81% yield, which was then subjected to n-BuLi to effect the ortho-lithiation of the pyrone moiety, generating intermediate 62. Subsequent addition of methyl formate then resulted in the formation of 3 in c.a. 20% yield. LDA was later identified to be a superior lithiation reagent; it increased yields while decreasing decomposition of starting material. Reaction conditions were ultimately optimized to provide the desired product 3 in 57% yield (91% yield based on recovered starting material). The $^1$H NMR, $^{13}$C NMR, IR, and HRMS data of the synthetic sample matched the literature data for 3.\textsuperscript{27} Furthermore, the optical rotation, $[\alpha]_D$ –227.8 (c 1, CHCl$_3$), had the same sign as the natural product, lit. $[\alpha]_D$ –148.7 (c 1, CHCl$_3$), there confirming the absolute and relative stereochemistry of the
synthetic product 3. Ultimately, the synthesis of (−)-solanapyrone D was achieved in 9 steps from known aldehyde 55, or 11 steps from commercially available e-caprolactone.

**Scheme 9.** Solanapyrone D: Completion of the asymmetric total synthesis

III. Conclusion

We have developed a new enantioselective organocatalytic intramolecular Diels-Alder reaction capable of cyclizing a variety of trienals in good yields and with excellent selectivities. This reaction has been found to tolerate variation in the diene, tether, and dienophile components of the IMDA substrate, thereby allowing access to range of substituted [4.3.0] and [4.4.0] bicyclic ring systems. This survey represents one of the most comprehensive substrate studies reported to date on the asymmetric catalytic IMDA reaction. Furthermore, we have successfully developed the first asymmetric Type II intermolecular Diels-Alder cyclization. Finally, asymmetric organocatalytic IMDA reaction comprised the pivotal bond construction in an efficient total synthesis of (−)-solanapyrone D. The desired decalin core containing all four contiguous stereocenters was introduced in a single step. In the course of this synthesis, an efficient new one-step protocol was developed for the formylation of 4-methoxylpyrones. This 9 step synthesis of (−)-solanapyrone D (compared to the previously published synthesis of 19 steps) effectively demonstrates the synthetic utility of this newly developed organocatalytic IMDA methodology.
References


Experimental

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by florescence quenching, anisaldehyde stain, or potassium permanganate stain.

$^1$H and $^{13}$C spectra were recorded on Bruker AM-400 (400 MHz and 100 MHz, respectively), Bruker DRX-500 (500 MHz and 125 MHz, respectively), Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for $^1$H are reported with chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for $^{13}$C are reported with chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm$^{-1}$). Optical Rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25°C). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Gas Chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex $\|-$TA (30 m x 0.25 mm) column, Bodman Chiraldex $\|-$DM (30 m x 0.25 mm) column or Bodman Chiraldex $\|-$PH (30 m x 0.25 mm) column. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

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Alcohol 23. To a suspension of (2E, 4E)-hexadiene-1-triphenylphosphonium bromide (1.9 g, 4.6 mmol) in 6.0 mL THF cooled to −30 °C was added 2.2 mL (4.6 mmol) nBuLi (2.13M in hexanes). The dark red suspension was stirred at −30 °C for 1 hour, after which 7-oxo-hept-2-enoic acid methyl ester (0.65 g, 4.2 mmol) was added in 6.0 mL THF. The solution was warmed to room temperature and stirred for an additional 1.5 hours. The reaction was quenched with H₂O, partitioned, and extracted with hexanes (3 x 30 mL). The organic extracts were combined and washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude ester 22a was taken immediately onto the next step without further purification.

To a solution of crude ester 22a in 42 mL CH₂Cl₂ cooled to −78 °C was added 1.7 mL (12.6 mmol) of DIBAL-H. The solution was allowed to stir for 15 minutes, after which the reaction was quenched with methanol (5 mL). Upon warming the reaction to room temperature, a saturated solution of sodium potassium tartrate was added (50 mL) and the mixture was stirred vigorously for 8 hours. The mixture was extracted with CH₂Cl₂ (3 x 40 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (1:4 EtOAc/Hexanes) to afford the title compound as a clear, colorless oil in 63% yield (0.51 g) as a 2.9:1 mixture of (2E,7E,9E,11E)- and (2E,7Z,9E,11E)- olefin isomers. The mixture was redissolved in 10 mL of CH₂Cl₂ and 50 mg (0.2 mmol) of I₂ was added. After 30 minutes, 10 mL of Na₂S₂O₃ (saturated) were added and the layers were partitioned. The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to provide the title compound as a

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5.5:1 (6E,8E):(6Z,8E) mixture of geometric isomers in 54% yield (2.1 g). Major isomer: IR (film) 3391, 3012, 2858, 1668, 1444, 996 cm\(^{-1}\); \(^1\)H NMR (300 mHz, CDCl\(_3\)) \[6.30-5.99 (m, 4H, CH=CH), 5.75-5.62 (m, 4H, CH=CH), 4.08 (d, \(J=7.1\) Hz, 2H, CH\(_2\)OH), 2.14-2.00 (m, 4H, CH\(_2\)CH=CH, HC=HCCH\(_2\)), 1.74 (d, \(J=6.6\) Hz, 3H, CH\(_3\)CH), 1.49-1.44 (tt, \(J=7.1,7.1\) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_2\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \[133.9, 133.03, 131.9, 131.1, 130.6, 129.4, 129.2, 125.9, 64.1, 32.6, 32.0, 29.0, 18.7; HRMS (EI) exact mass calcd for (C\(_{13}\)H\(_{20}\)O) requires \(m/z\) 192.1514, found \(m/z\) 192.1507.

**Aldehyde 24.** To a solution of 60 mg (0.31 mmol) of alcohol 23 in 3 mL of CH\(_2\)Cl\(_2\) was added 140 mg (0.33 mmol) of Dess-Martin periodinane and 79 mg (0.90 mmol) of sodium bicarbonate. The solution was stirred at room temperature for 20 minutes, after which 3 mL of 1:1 Na\(_2\)S\(_2\)O\(_3\)/NaHCO\(_3\) aq. solution was added. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL), and the combined extracts were washed with brine. The organic extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. Flash chromatography on florisil (10% EtOAc/hexanes) in the absence of light provided the title compound as a clear oil in 53% yield (32 mg). Due to compound instability, the aldehyde was used immediately without full characterization. \(^1\)H NMR (300 mHz, CDCl\(_3\)) \[9.50 (d, \(J=7.7\) Hz, 1H, CHO), 6.84 (dt, \(J=7.1,13.2\) Hz, 1H, CHCHCHO), 6.22-6.00 (m, 5H, CH=CH), 5.74-5.56 (m, 2H, CH=CH), 2.40-2.28 (m, 2H, CH\(_2\)CH=CHCHO), 2.18-2.11 (m, 2H, CH\(_2\)CH=CH), 1.76 (d, \(J=5.5\) Hz, 3H, CH\(_3\)CH), 1.64 (tt, \(J=6.6,6.6\) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_2\)); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \[194.2, 158.7, 133.3, 132.7, 131.8, 130.6, 130.4, 130.3, 129.6, 32.5, 32.4, 27.8, 18.7.
[4,3.0]-bicycle 39. Using imidazolidinone catalyst I. A flask containing tetraene 24 (20 mg, 0.22 mmol, 85% E,E-diene geometry) was charged with 0.40 mL of 2% v/v H₂O/CH₃CN and then cooled to −20°C. (5S)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one trifluoroacetic acid salt (6.5 mg, 0.02 mmol) was then added in one portion to the solution and the reaction was shaken for 72 hours. The mixture was then loaded onto a silica gel column and eluted with CH₂Cl₂. Removal of volatiles resulted in a oily residue that was purified by silica gel chromatography (5% EtOAc/hexanes) to afford the title compound as a clear oil in 47% yield (7.8 mg); 1.7:1:0.25 endo:endo epimer:exo. Endo isomer: IR (film) 3020, 2950, 2873, 1707, 1452, 965 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.63 (d, J=2.7 Hz, 1H, CHO), 5.88 (d, J=9.3, 1H, HC=CH), 5.56-5.29 (m, 3H, HC=CH), 3.36-3.27 (m, 1H, HC=CHCHCH=CH), 2.52 (ddd, J=2.7, 6.0, 10.8 Hz, 1H, CHOCH), 2.05-1.95 (m, 1H, CHCHCH₂), 1.89-1.69 (m, 5H, CHCHCH₂, CH₂CH₂CH₂), 1.25-1.01 (m, 2H, CH₂CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 205.0, 130.1, 130.0, 129.4, 128.5, 56.5, 45.3, 41.6, 39.9, 28.8, 27.8, 22.8, 18.3; HRMS (EI) exact mass calcd for (C₁₃H₁₈O) requires m/z 190.1358, found m/z 190.1356. [α]D = +196.2 (c=1.0, CHCl₃). Diastereomeric ratios were determined by ¹H NMR analysis. A portion of the title compound was converted to the (2R, 4R)-pentane-2,4-diol acetal for the determination of enantiomeric purity. 5.0 mg of the title compound was taken up in 1 mL of CH₂Cl₂. 4.0 mg of (2R, 4R)-pentane-2,4-diol and 0.5 mg of pTSA was added to the solution, and the reaction was stirred for 0.5 hour. NaHCO₃ solution (saturated) was then added, and the mixture was washed with brine, dried over Na₂SO₄, and filtered. The resultant filtrate was loaded onto a short silica plug, eluted with EtOAc, and concentrated, to provide the acetal of the title
compound; (endo) 87% ee. Enantiomeric excesses were determined by GC with a Chiralex ™-DM column (50 °C/10 min, 5 °C/min ramp, 200 °C /20 min); eno isomers t<sub>e</sub> = 41.9 min and 42.3 min.

[4.3.0]-bicycle 39. Using imidazolidinone catalyst 2. A flask containing tetraene 24 (42 mg, 0.22 mmol, 85% E,E-diene geometry) was charged with 1.5 mL of 2% v/v H<sub>2</sub>O/CH<sub>3</sub>CN and then cooled to −20 °C. (2S,5S)-5-Benzyl-2-tert-butyl-3-methylimidazolidin-4-one trifluoroacetic acid salt (11.8 mg, 0.03 mmol) was then added in one portion to the solution and the reaction was shaken for 12 hours. The mixture was then loaded onto a silica gel column and eluted with CH<sub>2</sub>Cl<sub>2</sub>. Removal of volatiles resulted in a oily residue that was purified by silica gel chromatography (5% EtOAc/hexanes) to afford a compound as a clear oil in 75% yield (26.7 mg) with spectral data identical to those reported for # above; 6.4:1:<0.2 endo:end isomer:exo. [α]<sub>D</sub> = +212.3 (c=1.0, CHCl<sub>3</sub>). Diastereomeric ratios were determined by ¹H NMR analysis. A portion of the title compound was converted to the (2R,4R)-pentane-2,4-diol acetal for the determination of enantiomeric purity. 5.0 mg of the title compound was taken up in 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. 4.0 mg of (2R,4R)-pentane-2,4-diol and 0.5 mg of pTSA was added to the solution, and the reaction was stirred for 1 hour. NaHCO<sub>3</sub> solution (saturated) was then added, and the mixture was washed with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The resultant filtrate was loaded onto a short silica plug, eluted with EtOAc, and concentrated, to provide the acetal of the title compound: 94% ee (endo).

![Chemical Structure]

Alcohol 26. To a solution of α-caprolactone (2.0 ml, 18.0 mmol) in 30 mL of THF cooled to −78 °C was added DIBAL-H (3.4 mL, 18.9 mmol) dropwise. The solution was stirred at −78 °C for 1.5 hours. In a separate flask, a suspension of cinnamyl triphenylphosphonium chloride in 30 mL THF was cooled to 0 °C. 7.6 mL (18.0 mmol) of nBuLi (2.35M in hexanes) was added to the Wittig reagent and the solution was stirred
at that temperature for 1 hour. The \( \text{-caprolactone/DIBALH} \) solution was then transferred via syringe into the flask containing the Wittig reagent, and the solution was warmed to room temperature and stirred for an additional 2 hours. The reaction was quenched with saturated sodium potassium tartrate solution and stirred for 8 hours. The mixture was then partitioned and the aqueous layer was washed with EtOAc (3 x 30 mL) The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (1:4 EtOAc/hexanes), providing the title compound as a 1:1 mixture of geometric isomers. The mixture was redissolved in 5 mL of CH\(_2\)Cl\(_2\) and 50 mg (0.2 mmol) of I2 was added. After 30 minutes, 5 mL of Na\(_2\)S\(_2\)O\(_3\) (saturated) were added and the layers were partitioned. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL), and the combined organics were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo to provide the title compound as a 4.5:1 (6E,8E):(6Z,8E) mixture of geometric isomers in 54% yield (2.1 g). Major isomer: IR (film) 3352, 3020, 2927, 2858, 1452,1058 cm\(^{-1}\); \(^1\)H NMR (300 mHz, CDCl\(_3\)) \( \square \) 7.31-7.07 (m, 5H, Ph-H), 6.67 (dd, J=10.5, 15.4 Hz, 1H, C8H), 6.34 (d, J=15.4 Hz, 1H, C9H), 6.11 (dd, J=10.9, 14.6 Hz, 1H, C7H), 5.72 (dt, J=7.2, 14.5 Hz, 1H, C6H), 3.52 (t, J=6.0 Hz, 2H, HOClH\(_2\)), 2.10-2.04 (m, 2H, C5H), 1.54-1.43 (m, 2H, CH\(_2\)CH\(_2\)), 1.42-1.26 (m, 4H, CH\(_2\)CH\(_2\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \square \) 137.7, 135.6, 130.8, 130.1, 129.5, 128.6, 128.6, 127.2, 126.2, 126.2, 62.7, 33.1, 32.9, 29.4, 25.7; HRMS (FAB) exact mass calcd for (C\(_{15}\)H\(_{30}\)O) requires m/z 216.1514, found m/z 216.1517.

**Aldehyde 26a.** To a solution of 26 (2.0 g, 9.3 mmol) in CH\(_2\)Cl\(_2\) (30 mL) was added N-methyl morpholine (2.2 g, 18.5 mmol), followed by 250 mg of 4Å molecular sieves. After stirring for 20 minutes, tetrapropylammonium perruthenate (65 mg, 0.19 mmol) was added the mixture. The reaction was worked up after an additional 30 minutes by loading the black colored mixture onto a silica column and eluting with CH\(_2\)Cl\(_2\). Removal of volatiles provided a clear crude oily residue which was purified though by silica gel chromatography (10% EtOAc/hexanes) to afford the title compound
as a clear oil in 50% yield (1.0 g): IR (film) 3228, 2935, 2866, 2726, 1722, 1452, 1120, 988 cm⁻¹; H NMR (300 MHz, CDCl₃) 9.73 (s, 1H, CHO), 7.45-7.18 (m, 5H, Ph-H), 6.76 (dd, J=10.5, 15.6 Hz, 1H, C8-H), 6.46 (d, J=15.3 Hz, 1H, C9-H), 6.21 (dd, J=10.5, 14.4 Hz, 1H, C7-H), 5.79 (dt, J=6.6, 14.4 Hz, 1H, C6-H), 2.42-2.37 (m, 2H, CHO), 2.19-2.12 (m, 2H, C5-H), 1.69-1.59 (m, 2H, C₆H₂CHO), 1.49-1.42 (m, 2H, C₆H₂CH₂); C NMR (75 MHz, CDCl₃) 202.5, 137.7, 135.1, 131.3, 130.5, 129.4, 128.8, 128.8, 127.4, 126.4, 126.4, 44.0, 32.9, 29.1, 22.0; HRMS (FAB) exact mass calcd for (C₁₅H₁₈O) requires m/z 214.1358, found m/z 214.1353.

**Ester 27.** The flask containing diene 26a (1.0 g, 4.7 mmol) was charged with 10 mL of THF, then treated with 1.8 g (5.2 mmol) of methyl (triphenylphosphoranylidene)acetate. The mixture was stirred for 12 hours, after which volatiles were removed in vacuo. The resulting solid was triturated with diethyl ether (3 x 30mL), filtered, and the filtrate concentrated. The resulting crude yellow oily residue was purified by silica gel chromatography (5% EtOAc/Hexanes) to afford the title compound as an oil in 96% yield (1.1 g): IR (film) 3355, 2926, 2854, 1448, 987, 745, 691 cm⁻¹; H NMR (300 MHz, CDCl₃) 7.43-7.17 (m, 5H, Ph-H), 6.75 (dd, J=10.4, 15.7 Hz, 1H, C10-H), 6.45 (d, J=15.7 Hz, 1H, C11-H), 6.20 (dd, J=10.2, 14.5 Hz, 1H, C9-H), 5.87-5.75 (m, 1H, C8-H), 5.70-5.64 (m, 2H, C2-H, C3-H), 4.09 (m, 2H, C1H₂OH), 2.17-2.12 (m, 2H, C7H₂), 2.07 (m, 2H, C4H₂), 1.45-1.42 (m, 4H, C5H₂, C6H₂); C NMR (75 MHz, CDCl₃) 137.7, 135.7, 133.3, 130.1, 129.4, 128.7, 128.6, 127.2, 126.2, 124.4, 64.0 33.0, 32.3, 29.1, 28.9; HRMS (EI) exact mass calcd for (C₁₇H₂₂O) requires m/z 242.1671, found m/z 242.1668.
**Alcohol 28.** To a cooled solution (78 °C) of ester 27 (2.1 g, 7.8 mmol) in CH₂Cl₂ (77 mL) was added 3.0 mL (17.1 mmol) of DIBAL-H. After 30 minutes, the reaction was quenched with methanol and allowed to warm slowly to room temperature. The mixture was then treated with 50 mL of saturated sodium potassium tartrate solution. After stirring 8 hours, the mixture was partitioned and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over Na₂SO₄, and concentrated *in vacuo* to afford 1.9 g (100%) of the title compound as a yellow oil, which was carried onto the next step without further purification. IR (film) 3355, 2926, 2854, 1148, 987, 745, 691 cm⁻¹; HNMR (300 MHz, CDCl₃) 7.43-7.17 (m, 5H, PhH), 6.75 (dd, J=10.4, 15.7 Hz, 1H, C3-H, C10-H), 6.45 (d, J=15.7 Hz, 1H, C11-H), 6.20 (dd, J=15.9 Hz, 1H, C9-H), 5.87-5.75 (m, 1H, C8-H), 5.70-5.64 (m, 2H, C2H₂, C3H₂), 4.09 (m, 2H, CH₂OH), 2.17-2.12 (m, 2H, C7H₂), 2.07 (m, 2H, C4-H₂), 1.45-1.42 (m, 4H, C5H₂, C6H₂); C NMR (75 MHz, CDCl₃) 137.7, 135.7, 133.3, 1130.1, 129.4, 128.7, 128.6, 127.2, 126.2, 124.4, 64.0, 33.0, 32.3, 29.1, 28.9; HRMS (EI) exact mass calcd for (C₁₁H₂₂O) requires m/z 242.1674, found m/z 242.1668.

![Chemical Structure](image)

**Aldehyde 29.** To a solution of 28 (100 mg, 0.55 mmol) in CH₂Cl₂ (1.9 mL) was added N-methyl morpholine (128 mg, 1.1 mmol), followed by 25 mg of 4Å molecular sieves. After stirring for 20 minutes, tetrapropylammonium perruthenate (10 mg, 0.03 mmol) was added the mixture. The reaction was worked up after an additional 30 minutes by loading the black colored mixture onto a silica column and eluting with CH₂Cl₂. Removal of volatiles provided a clear crude oily residue which was purified though by silica gel chromatography (5% EtOAc/hexanes) to afford the title compound as a clear oil in 62% yield (62 mg): IR (film) 3014, 2918, 2850, 1688, 1635, 989 cm⁻¹; HNMR (300 MHz, CDCl₃) 9.50 (dd, J=2.0, 8.1 Hz, 1H, CHO), 7.39-7.17 (m, 5H, PhH), 6.90-6.71 (m, 2H, C3-H, C10-H), 6.45 (d, J=15.9 Hz, 1H, C11-H), 6.26-6.08 (m, 2H, C9-H, C2-H), 5.80 (dt, J=6.9, 15.3 Hz, 1H, C8-H), 2.39-2.32 (m, 2H, C4H₂), 2.18 (dt, J=6.9, 6.9 Hz, 2H, C7H₂), 1.58-1.44 (m, 4H, C5H₂, C6H₂); C NMR (75 MHz, CDCl₃)
HRMS (EI) exact mass calcd for (C17H20O) requires m/z 240.1514, found m/z 240.1510.

(3R,4S,5R,6S)-Bicyclo[4.4.0]decene-3-phenyl-4-carbaldehyde 40. A flask containing triene 29 (188.8 mg, 0.78 mmol, 80% E,E-diene geometry) was charged with 7.8 mL of 2% v/v H2O/CH3CN and then cooled to 4 °C. (2R,5R)-5-Benzyl-2-tert-butyl-3-methylimidazolidin-4-one trifluoromethanesulfonic acid salt (38.5 mg, 0.15 mmol) was then added in one portion to the solution and the reaction was shaken for 16 hours. The mixture was then loaded onto a silica gel column and slowly eluted with 5% EtOAc/Hexanes. Fractions containing product were combined and concentrated, providing the title compound as a clear oil in 70% yield (106 mg); endo:exo:endo epimer 12:2:1. *Endo* isomer: IR (film) 3028, 2927, 2858, 1715, 1452 cm⁻¹; ¹H NMR (300 mHz, CDCl₃) δ 8.90 (d, J=5.5 Hz, 1H, CHO), 7.35-7.12 (m, 5H, PhH), 5.76 (d, J=9.6 Hz, 1H, CH=CH), 5.61 (m, 1H, CH=CH), 3.83 (m, 1H, CHPh), 2.48 (m, 1H, CHCHO), 1.92-0.92 (m, 10H, CH₂CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 207.4, 138.9, 133.4, 130.1, 128.6, 127.3, 127.0, 56.2 43.6, 41.9, 35.2, 33.4, 30.6, 27.0, 26.7; HRMS (EI) exact mass calcd for (C₁₇H₂₀O) requires m/z 240.1514, found m/z 240.1517; [α]D = +626.3 (c=1.0, CHCl₃). Diastereomeric ratios were determined by ¹H NMR analysis. A portion of the title compound was reduced to the corresponding primary alcohol for the determination of enantiomeric purity. To a solution of the title compound in absolute ethanol (1 mL) was added 3 equivalents of NaBH₄. After 0.5 hours, the reaction mixture was quenched with H₂O and extracted with 2 x 10 mL CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the resultant residue by silica gel chromatography provided the corresponding primary alcohol: *endo* 92% ee. ¹H NMR
(300 mHz, CDCl$_3$) $\Delta$ 7.35-7.19 (m, 5H, PhH), 5.68 (d, $J$=9.9 Hz, 1H, CH=CH), 5.61 (ddd, $J$=2.1, 3.9, 9.9 Hz, 1H, CH=CH), 3.75-3.64 (m, 2H, CH$_2$OH), 3.34 (m, 1H, CHPh), 1.98-0.86 (m, 11H, CHCH$_2$OH, CHCH$_2$, CH$_2$CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\Delta$ 141.5, 133.4, 130.3, 128.7, 128.6, 128.4, 128.3, 126.9, 62.6, 45.8, 44.63, 43.7, 37.0, 33.7, 29.6, 27.1, 27.0. Enantiomeric ratios were determined by HPLC with a Chiralcel AD column and AD guard column (5% EtOH/hex); $endo$ isomers, $t_r$ = 11.1 min, 13.4 min.

Proof of absolute stereochemistry of (3R,4S,5R,6S)-Bicyclo[4.4.0]decene-3-phenyl-4-carbaldehyde. $S$-Ethyl-(3R,4S,5R,6S)-Bicyclo[4.4.0]decene-3-phenyl-4-carbothioate 47. 32.1 mg (0.17 mmol) of 40 was dissolved in tert-butanol (2.9 mL). To this solution was added 2-methyl-2-butene (0.8 mL) and dropwise, a solution of NaClO$_2$ (139 mg, 1.5 mmol) and NaH$_2$PO$_4$ (162 mg, 1.2 mmol) in H$_2$O (1.6 mL). The biphasic solution was stirred for 12 hours. The reaction was then concentrated, diluted with H$_2$O, and washed with hexanes. The aqueous layer was acidified with 1N HCl to pH 2, and extracted with Et$_2$O. The combined organic layers were washed with cold H$_2$O, dried over Na$_2$SO$_4$, filtered, and concentrated to provide the corresponding carboxylic acid 46: $^1$H NMR (300 MHz, CDCl$_3$) $\Delta$ 7.44-7.12 (m, 5H, ArH), 5.71 (d, $J$=9.9 Hz, 1H, HC=CH), 5.60 (ddd $J$=2.4, 3.9, 9.9 Hz, 1H HC=CH), 3.81-3.74 (m, 1H, CHPh), 2.78 (dd, $J$=6.6, 12.0 Hz, 1H, CHCOOH), 2.20-1.15 (m, 10H, CH$_2$CH$_2$ and CHCH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\Delta$ 178.8, 140.2, 133.1, 129.5, 128.1, 127.2, 126.7, 51.3, 44.4, 41.9, 36.0, 32.9, 30.4, 27.2, 26.7.

To acid 46 was added 1 mL CH$_2$Cl$_2$, 4-dimethylamino-pyridine (1.2 mg, 0.01 mmol), ethanethiol (9 mL, 0.12 mmol) and dicyclohexylcarbodiimide (24.8 mg, 0.12 mmol). The reaction was stirred for 3 hours, after which time the mixture was filtered and 1N HCl solution (1 mL) was added to resulting filtrate. The layers were partitioned, and the aqueous extracts were washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The
resulting oily residue was purified by silica gel flash chromatography (5% EtOAc/hexanes) to afford compound in 71% yield (21 mg) with spectral data identical to hose reported for S-Ethyl-(3R,4S,5R,6S)-Bicyclo[4.4.0]decene-3-phenyl-4-carbothioate:[$\eta$]D (literature) = −290 (c=0.7, CHCl₃), [$\eta$]D = −437 (c=1, CHCl₃).

**Synthesis of Solanapyrone D**

![Synthesis of Solanapyrone D](image)

**Ester 56.** To a solution of (6E,8E)-6,8-decadienol⁷ (1.7g, 11.0 mmol) in CH₂Cl₂ (55mL) was added N-methyl morpholine (2.6 g, 22.0 mmol), followed by 300mg of 4Å molecular sieves. After stirring for 20 minutes, tetrapropylammonium perruthenate (77 mg, 0.22 mmol) was added the mixture. The reaction was worked up after an additional 30 minutes by loading the black colored mixture onto a silica column and eluting with CH₂Cl₂. Most of the solvent was removed in vacuo over an ice bath; due to the volatility of the aldehyde, the solution was not concentrated to dryness, and was immediately taken on to the next step.

The flask containing (6E,8E)-decadienal was charged with 20mL of THF, then treated with 3.8 g (10.6 mmol) of methyl (triphenylphosphoranylidene)acetate. The mixture was stirred for 12 hours, after which volatiles were removed in vacuo. The resulting solid was triturated with diethyl ether (3 x 100mL), filtered, and the filtrate concentrated. The resulting crude yellow oily residue was purified by silica gel chromatography (5% EtOAc/Hexanes)to afford the title compound as an oil in 52% yield over 2 steps (1.19 g): IR (film) 3020, 2935, 2858, 1722,1661, 1437, 1274, 1197; ¹H NMR (500 MHz, CDCl₃) δ 7.01-6.94 (m, 1H, CHCHCO₂Me), 6.06-6.01 (m, 2H, CH=CCH), 5.83 (d, J= 9.3 Hz, 1H, CO₂MeCH), 5.65-5.51 (m, 2H, CHCH₂,CHCH₃), 3.72 (s, 3H, OCH₃), 2.25-2.18 (m, 2H, MeO₂CCCH₂), 2.12-2.07 (m, 2H, CHCH₂), 1.73 (d, J=9.0 Hz, 3H, CHCH₃), 1.52-1.40 (m, 4H, CH₂CH₂, CH₂CH₂), ¹³C NMR (125 MHz, CDCl₃) δ

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167.4, 149.8, 131.8, 130.9, 129.6, 129.1, 121.2, 51.6, 32.8, 32.5, 32.3, 29.1, 27.8; HRMS (FAB+) exact mass calculated for \((\text{C}_{13}\text{H}_{21}\text{O}_2)\) requires \(m/z\) 209.1542, found \(m/z\) 209.1541.

**Alcohol 56a.** To a solution of 56 (1.08 g, 5.2 mmol) in 50 mL CH\(_2\)Cl\(_2\) cooled to −78 °C was added 2.2 mL (12.6 mmol) of DIBAL-H. The solution was allowed to stir for 15 minutes, after which the reaction was quenched with methanol (5 mL). Upon warming the reaction to room temperature, a saturated solution of sodium potassium tartrate was added (50 mL) and the mixture was stirred vigorously for 8 hours. The mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 40 mL), and the combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and filtered. Volatiles were removed *in vacuo* and the resultant crude oil was purified by silica gel chromatography (1:5 EtOAc/Hexanes) to afford the title compound as a clear, colorless oil in 91% yield (0.98 g): IR (film) 3344, 3020, 2927, 2858, 1444, 988 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.01-5.93 (m, 2H, CH=C\(\text{H}\)), 5.70-5.63 (m, 2H, CH=C\(\text{H}\)), 5.62-5.48 (m, 2H, CH=C\(\text{H}\)), 4.06 (d, \(J=9.2\) Hz, 2H, CH\(_2\)OH), 2.11-2.00 (m, 4H, CH\(\text{CH}_2\), CH\(\text{CH}_2\)), 1.72 (d, \(J=6.0\) Hz, 3H, CH\(_3\)CH), 1.46-1.33 (m, 4H, CH\(_2\)CH\(_2\), CH\(_2\)CH\(_2\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 133.4, 131.9, 131.8, 130.6, 129.1, 127.1, 64.1, 32.7, 32.4, 29.3, 29.0, 18.4; HRMS (FAB+) exact mass calcd for \([(\text{C}_{12}\text{H}_{19}\text{O})]\) requires \(m/z\) 179.1436, found \(m/z\) 179.1434.

**Aldehyde 57.** To a solution of 56a (75 mg, 0.42 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added \(N\)-methyl morpholine (97 mg, 0.83 mmol), followed by 25 mg of 4Å molecular sieves. After stirring for 20 minutes, tetrapropylammonium perruthenate (3.0 mg, 0.0080 mmol) was added the mixture. The reaction was worked up after an additional 30 minutes by loading the black colored mixture onto a silica column and eluting with CH\(_2\)Cl\(_2\). Removal of volatiles provided a clear crude oily residue which was purified though by silica gel chromatography to afford the title compound as a clear oil in 59%
yield (44 mg): IR (film) 3020, 2927, 2858, 2734, 1692, 1444, 1120, 980 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.47 (d, \(J=8.2\ Hz, 1H, CHO\)), 6.92 (dt, \(J=7.1, 15.4\ Hz, 1H, CHCHCHO\)), 6.07 (dd, \(J=7.8, 15.6\ Hz, 1H, CHCHO\)), 6.00-5.90 (m, 2H, CH=CH, CH=CH), 5.63-5.44 (m, 2H, CH\(_2\)CH, CH\(_3\)CH), 2.36-2.27 (m, 2H, CH\(_2\)CHCHCHO), 2.17-2.01 (d, \(J=6.0\ Hz, 3H, CH\(_3\)CH\)), 1.70 (d, \(J=6.0\ Hz, 3H, CH\(_3\)CH\)), 1.54-1.37 (m, 4H, CH\(_2\)CH\(_2\), CH\(_2\)CH\(_2\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 194.2, 158.9, 133.2, 131.6, 131.2, 131.0, 127.4, 32.9, 32.5, 29.2, 27.6, 18.4; HRMS (EI) exact mass calcd for (C\(_{12}\)H\(_{18}\)O) requires \(m/z\) 178.1358, found \(m/z\) 178.1351.

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\text{endo} \hspace{1cm} \text{exo} \hspace{1cm} \text{endo epimer}

\((3\text{R,4S,5R,6S})\)-Bicyclo[4.4.0]decene-3-methyl-4-carbaldehyde 58. A flask containing triene 57 (43.7 mg, 0.25 mmol, 84% \(E,E\)-diene geometry) was charged with 0.83 mL of 2\% v/v H\(_2\)O/CH\(_3\)CN and then cooled to \(-5^\circ\)C. \((2\text{R,5R})\)-5-Benzyl-2-\text{tert}-butyl-3-methylimidazolidin-4-one trifluoromethanesulfonic acid salt (19.4 mg, 0.050 mmol) was then added in one portion to the solution and the reaction was shaken for 48 hours. The mixture was then loaded onto a silica gel column and slowly eluted with 5\% EtOAc/Hexanes. Fractions containing product were combined and concentrated, providing the title compound as a clear oil in 71\% yield (26.1 mg); >20:1:1 \text{endo:exo:endo epimer}. \text{Endo} isomer: IR (film) 2927, 1715, 1452, 1267 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.73 (d, \(J=4.4\ Hz, 1H, CHO\)), 5.53 (ddd, \(J=2.1, 4.5, 9.9\ Hz, 1H, CH=CHCH\)), 5.40 (d, 9.9 Hz, 1H, CH=CHCH), 2.61-2.55 (m, 1H, CHCH\(_3\)), 2.37 (ddd, \(J=4.5, 6.3, 11.1\ Hz, 1H, CHCHO\)), 1.82-1.58 (m, 6H, CHCHCH\(_2\), CH\(_2\)CH\(_2\)), 1.42-1.20 (m, 4H, CH\(_2\)CH\(_2\)), 1.03 (d, \(J=7.2\ Hz, 3H, CH\(_3\)\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 207.1, 131.4, 131.1, 55.72, 42.4, 35.9, 33.3, 32.1, 30.5, 26.9, 26.8, 17.4; HRMS (CI) exact mass calcd for (C\(_{12}\)H\(_{18}\)O) requires \(m/z\) 178.1358, found \(m/z\) 178.1351; \([\alpha]\)\(_D\) = +168.0 (c=1.0, CHCl\(_3\)). Diastereomeric ratios were determined by \(^1\)H NMR analysis. A portion of the
title compound was converted to the (2\(R\), 4\(R\))-pentane-2,4-diol acetal for the determination of enantiomeric purity. 5.0 mg of the title compound was taken up in 1 mL of CH\(\text{2}\text{Cl}_2\). 4.0 mg of (2\(R\), 4\(R\))-pentane-2,4-diol and 0.5 mg of pTSA was added to the solution, and the reaction was stirred for 1 hour. NaHCO\(_3\) solution (saturated) was then added, and the mixture was washed with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\), and filtered. The resultant filtrate was loaded onto a short silica plug, eluted with EtOAc, and concentrated, to provide the acetal of the title compound: 90\% ee (endo). Enantiomeric ratios were determined by GC with a Bodman [-]-DM column (23 psi, assay: hold 50 °C for 10 min, ramp 5 °C/min to 200 °C); endo isomers \(t_e = 38.7\) min and 39.0.

**Methyl 5-hydroxy-5-[(1\(R\),2\(R\),4\(a\)R,8\(S\),8\(a\)R)-1,2,4\(a\),5,6,7,8,8\(a\)-octahydro-2-methylnaphthyl]-3-oxopentanoate 59.** To a \(-78\) °C solution of 143 mg (0.80 mmol) of aldehyde 58 in 15 mL of CH\(\text{2}\text{Cl}_2\) under nitrogen atmosphere was added a solution of methyl acetoacetate bis(trimethylsilyl)ether in 20 mL of CH\(\text{2}\text{Cl}_2\). This solution was then treated with 800 [\(\mu\)L (0.80 mmol) of TiCl\(_4\) (1M in CH\(\text{2}\text{Cl}_2\)) from a newly opened bottle. After stirring for 1 hour, the reaction was quenched with H\(_2\)O and extracted with CH\(\text{2}\text{Cl}_2\) (2 x 30 mL). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification of the resultant residue by silica gel chromatography (20% EtOAc/hexanes) afforded 175 mg (75\% yield) of the title compound as a clear oil whose spectral characteristics matched those previously reported.
Methyl 4-[(1R,2R,4aR,8S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthyl]-3,5-dioxobutanoate 59a. To a solution of 175 mg (0.60 mmol) of alcohol 59 in 6.0 mL of CH₂Cl₂ was added 254 mg (0.60 mmol) of Dess-Martin Periodinane. The solution was stirred at room temperature for 2 hours, after which 10 mL of 1:1 Na₂S₂O₅/NaHCO₃ aq. solution was added. The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL), and the combined extracts were washed with brine. The organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography on silica gel (10% EtOAc/hexanes) provided the title compound as a yellow oil in 71% yield (124 mg) whose spectral characteristics matched those previously reported.

\[
\text{Me} \quad \text{H} \quad \text{O} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{H} \quad \text{O} \quad \text{Me}
\]

4-Hydroxy-6-[(1R,2R,4aR,8S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthyl]-2H-pyran-2-one 60. To a solution of the diketoester 59a (67 mg, 0.23 mmol) in 2.5 mL of benzene was added DBU (67 μL, 0.46 mmol), upon which the solution immediately turned bright yellow in color. The flask was sealed, and the solution was stirred at 60 °C for 3 hours. The reaction was then quenched with the addition of 1N HCl (0.8 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts where then washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to afford the title compound as a bright yellow oil in 87% yield (58 mg) whose spectral characteristics matched those previously reported. 60 was taken on immediately to the next step without further purification.

\[
\text{Me} \quad \text{O} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{O} \quad \text{Me}
\]
4-Methoxy-6-[(1R,2R,4aR,8S,8aR)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-naphthyl]-2H-pyran-2-one 61. A suspension of 4-hydroxypyrone 60 (58 mg, 0.22 mmol), methyl p-toluenesulfonate (1.0 mmol), and potassium carbonate (1.0 mmol) in DMF (3 mL) was stirred at room temperature for 5 hours. The reaction was quenched with saturated NH₄Cl solution, and extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and filtered. Removal of volatiles under reduced pressure provided a yellow oily residue which was purified by silica gel flash chromatography (25% EtOAc/hexanes) to afford the title compound as a yellow oil in 81% yield (49 mg): IR (film) 2927, 2858, 1722, 1645, 1568, 1452, 1413, 1251, 1159; ¹H NMR (300 MHz, CDCl₃) δ 5.77 (d, J=2.4 Hz, 1H, CH=COC=O), 5.55 (ddd, J=2.7, 4.4, 10.5 Hz, 1H, CH=CHCH), 5.45-5.39 (m, 2H, CH=CHCH, O=CC₃HCOMe), 3.79 (s, 3H, OC₃H₃), 2.62 (dd, J=6.0, 11.4 Hz, 1H, CHCOC=O), 2.44-2.41 (m, 1H, CHCH₃), 2.39-2.22 (m, 1H, CHCHCH₂), 1.81-1.52 (m, 5H, CH₂CH₂, CH₂CH₃), 0.94 (d, J=6.9 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 165.2, 131.6, 131.4, 130.0, 101.9, 87.7, 56.1, 49.2, 43.4, 36.7, 35.4, 33.4, 30.4, 26.9, 26.8, 18.1; [α]D = -101.7 (c=1, CHCl₃); HRMS (FAB+) exact mass calculated for [(C₁₇H₂₂O₃)H]⁺ requires m/z 275.1647, found m/z 275.1640.

(-) Solanapyrone D 3. To a −78 °C solution of diisopropyl amine (11.4 mL, 0.082 mmol) in 0.2 mL THF was added 28 mL (0.070 mmol) of nBuLi (2.5M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 6.4 mg (0.023 mmol) of 4-methoxypyrone 61 was added in THF (2 x 0.1 mL). The solution was stirred for an additional 20 minutes, after which methyl formate (28 mL, 0.46 mmol, freshly distilled) was added. After stirring for an additional 2.5 hours, the reaction was quenched with saturated NH₄Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic extracts were
washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resultant crude yellow oily residue was purified by silica gel chromatography to afford Solanapyrone D as a yellow oil in 57% yield (3.9 mg, 91% yield based on recovered starting material): $[\alpha]_D = -201.1$ (c=1, CHCl$_3$); $[\alpha]_D$ literature$^8 = -148.7$ (c=1, CHCl$_3$); IR (film) 2930, 2862, 1728, 1686, 1615, 1520, 1375, 1265 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.16 (s, 1H, CHO), 6.12 (s, 1H, CHC(OMe)=C(CHO)), 5.57 (ddd, $J$=2.7, 4.2, 9.9 Hz, 1H, CH=CHC(Me)H), 5.45 (d, $J$=9.9 Hz, 1H, CH=CHCH), 4.07 (s, 3H, OCH$_3$), 2.75 (dd, $J$=6.0, 11.0 Hz, 1H, CHC(Me)H), 2.50 (m, 1H, CHC(Me)H), 1.59-1.85 (m, 5H, CHCH$_2$, CH$_2$CH$_2$), 1.40-1.25 (m, 2H, CH$_2$CH$_2$), 1.21-1.11 (m, 1H, CHCH$_2$CH$_2$), 0.99 (d, $J$=7.5, 3H, CHCH$_3$), 0.96-0.88 (m, 1H, CHCH$_2$CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 186.8, 176.3, 173.8, 162.2, 131.0, 130.7, 101.3, 96.0, 57.6, 50.8, 43.0, 36.5, 35.5, 30.2, 26.5, 26.3, 17.7; HRMS (FAB+) exact mass calcd for [(C$_{18}$H$_{22}$O$_4$)H]$^+$ requires m/z 303.1596, found m/z 303.1585.

Chapter 4

Progress toward the Total Synthesis of Guanacastepene A

I. Introduction

The diterpene antibiotic guanacastepene A (1) was first isolated by Clardy and coworkers in 2000 from an unclassified endophytic fungus CR115 in the Guanacaste Conservation Area in Costa Rica. Interest in this natural product initially arose from its promising biological activity; preliminary studies revealed that this compound exhibited excellent antibiotic activity against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*. Methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecalis* (VREF) are two of the most problematic drug-resistant pathogens, since these two antibiotics are often seen as the drug of last resort. Thus, its excellent activity against MSRA and VREF made 1 a potentially powerful therapeutic drug. However, subsequent studies by Singh and coworkers determined that it possessed only moderate activity against Gram-positive bacteria and poor activity against Gram-negative bacteria. Furthermore, experiments revealed that 1 exhibits hemolytic activity against human blood cells, thus suggesting nonspecific membrane lysis as its mode of action. Despite the discouraging implications of these results on its future as a therapeutic agent, guanacastepene A has maintained the interest of the synthetic community, largely due to its novel structure and the potential for studying the biological profile of related compounds.
The guanacastane skeleton, which had not been reported previous to Clardy’s communication, is closely related to the marine-derived dolabellane family of natural products. The dolabellane ring system, which is characterized by an unusual trans-bicyclo-[9.3.0] tetradecone nucleus, occupies a pivotal position in the biogenesis of several novel diterpene skeletons, including the dolastanes and neodolabellanes (Figure 2). Although close to 150 dolabellanes have been reported, guanacastepene A is the first in the guanacastane to be identified.

Figure 2. The relationship between the dolabellanes and related diterpene natural products

The structure of 1 was elucidated though single-crystal X-ray diffraction techniques, and the resultant crystal structure (which defines only the relative configuration of the natural product) reveals that guanacastepene A consists of a 5-7-6 tricyclic ring system with one highly oxidized edge and a hydrophobic opposite edge. The natural product exists as two conformers in a dynamic equilibrium at room temperature, thus making the $^1$H and $^{13}$C NMR spectra complex and difficult to interpret. Clardy speculates that the observed NMR anomalies could result from flexibility in the C9-C10 region of the central cycloheptane ring. MM2 force field calculations identified two gauche butane-like conformers around the C9-C10 bond that differ by 0.14 kcal/mol and are separated by a 15 kcal/mol energy barrier. The slow interconversion of the two conformers on the NMR time scale at room temperature would account for the observed irregularity found in the NMR spectra of 1.
More recently, the same research group reported their findings that the endophytic fungus CR115 produces not only 1, but also a family of related, structurally diverse metabolites. Structural elucidation of guanacastepenes B-O (some of which are shown in Figure 3) was also accomplished by X-ray crystallography, and the absolute configuration of guanacastepenes E and L (as drawn) were determined by using anomalous dispersion from the C-5 p-bromobenzoyl derivative of each natural product. Clardy and coworkers speculate that the chemical diversity of the guanacastepenes arises from multiple biosynthetic pathways working in concert or as a single highly branched biosynthetic grid, both of which are analogous to our methods for synthesizing libraries of natural product-like compounds (e.g. parallel synthesis or split/pool synthesis). Preliminary studies indicate that guanacastepene I is the only member of this newly characterized family of natural products that exhibits pronounced antibacterial activity in agar diffusion assays against S. aureus. However, it is possible that others may be active at higher concentrations or in other assays, since their studies were limited by the small supplies of the natural products available for testing.

![Figure 3. Selected members of the guanacastane family of natural products](image)

To date there has been only one reported total synthesis of (+) guanacastepene A, which was published by Danishefsky and coworkers in late 2002. In addition, over 10 different groups have published on their synthetic strategies towards 1, testifying to
the continuing interest that the synthetic community has in this family of natural products. Interestingly, the cultured fungus CR115 no longer produces guanacastepene A,\(^7\) and therefore any further production of this natural product for biological studies must be manufactured through synthetic means.

II. Results and Discussion

A. General Synthetic Plan

Our initial interest in guanacastepene A derived from the challenge of devising a novel, convergent route to its stereochemically dense 5-7-6 fused ring system. Examination of its structure reveals several key synthetic challenges that should be addressed during the course of a planned synthesis: (1) the western portion of the molecule contains a fully functionalized cyclopentane ring with nontrivial stereochemical relationships between its substituents, (2) the central cycloheptene ring includes two quaternary carbon stereocenters, and (3) the six-membered ring contains an oxygenated stereocenter remote to much of the other functionality in the molecule.

Our retrosynthetic analysis suggested that these issues could be addressed through the plan detailed in Scheme 1. We felt that guanacastepene A could be derived from intermediate 2 through a selective hydrogenation and protecting group manipulations. In turn, tricycle 2 could be accessed though an intramolecular Diels-Alder (IMDA) cyclization of cyclopentanone 3, thus establishing two stereocenters, one of which is quaternary, and two of the three ring systems all in one step. Although examples of IMDA mediated formation of 7,6-fused ring systems are not common, there are several notable examples.\(^{26}\) Thus, we felt that the favorable electronics and structural preorganization in this IMDA substrate merited its exploration. It also seemed that IMDA precursor 3 could be efficiently accessed though a potential one-pot 3-component coupling of cyclopentenone 4, diene 5, and commercially available aldehyde 6. This strategy would allow for extremely rapid access to the elaborated tricyclic core of guanacastepene A in a highly convergent manner.
B. Synthesis of Cyclopentene Fragment 4

Asymmetric Catalytic Approach. Since our synthetic approach allowed for the stereochemical information of the two stereocenters in fragment 4 to be relayed to subsequently formed stereocenters in the molecule, our initial strategy involved the asymmetric synthesis of cyclopentenone 4. As Scheme 2 illustrates, we felt that 4 could be derived from the acyclic enone 7 though an olefin metathesis reaction. Although this substrate was both sterically and electronically challenging, recent advances in metathesis technology suggested that this enone could potentially cyclize under proper conditions. In turn, we felt that the stereochemical relationship between the benzyloxy and isopropyl substituents in enone 7 could be accessed via a Claisen rearrangement. Recent work in the Macmillan group by Tehshik Yoon revealed that magnesium complex 11 could be used to promote the asymmetric acyl-Claisen rearrangement of [oxygenated acid chlorides and allylic morpholine amines to generate amide Claisen adducts in good yields and with excellent enantioselectivities. Therefore, we became interested in utilizing this methodology to access the desired stereochemical array; this took us back to the allylic amine 9 and commercially available acid chloride 10.
The desired amine 9 was accessed in two steps from the known ester 12. Dibal-H reduction of 12 provided the desired alcohol in 92% yield. Subsequent in situ conversion of the alcohol moiety to the bromide through treatment with NBS/PPh₃ followed by displacement with morpholine afforded the necessary allylic amine 9 in 54% yield. Amine 9 was reacted with commercially available acid chloride 10 in the presence of magnesium complex 11 under a variety of reaction conditions (varying temperature, stoichiometries, concentrations); however, none of the desired rearrangement adduct 8 was ever observed. Attempts to catalyze the reaction racemically with TiCl₄ • 2THF were also unsuccessful. This result is not completely surprising; as transition state structure 14 illustrates, the large isopropyl moiety occupies a pseudo-axial position in the Claisen chair transition state, thus hindering the ability of this intermediate to undergo the desired 3,3-sigmatropic rearrangement.
Re-examination of the desired Claisen adduct 8 revealed that the acyl-Claisen rearrangement substrate could be modified to decrease the steric bulk in the axial positions of the Claisen transition state, potentially increasing the likelihood that the acyl-ammonium intermediate would undergo the desired rearrangement. As Scheme 4 illustrates, amide 8 can be derived from \( \text{[unsaturated amide 15] though a hydrogenation and Wittig olefination. Since there is a syn relationship between the benzyloxy and ketone functionalities in 15, this [unsaturated amide can be derived from an acyl-Claisen rearrangement of acid chloride 10 and (E)-olefin 16. In this case, the ketone occupies a more favorable equatorial position in the Claisen chair-transition state (17), thereby reducing the number of undesirable 1,3-diaxial interactions relative to the unsuccessful intermediate 14. Furthermore, Tehshik had found that electron deficient allylic amines were excellent substrates for the asymmetric acyl-Claisen reaction, whereas electron-rich or neutral olefins generally reacted poorly. Thus the inclusion of an electron-withdrawing ketone moiety in the amine substrate should favor the reaction the desired rearrangement.
Allyl amine 16 was synthesized (see experimental section) and subjected to a variety of asymmetric (using complex 11) and racemic (TiCl₄ • 2THF, MgBr₂ • Et₂O) acyl-Claisen conditions, although none of them produced the desired rearrangement product 15. Instead, von Braun fragmentation product 16 was isolated as the major product in these reactions. This result was initially surprising, since Tehshik had found that these types of von Braun fragmentation side products were only observed when electron rich/neutral allyl amines were subjected to asymmetric acyl-Claisen conditions. However, subjection of the ketone substrate 16 to acyl-Claisen conditions probably results in initial soft enolization of the ketone moiety, thus making the adjacent olefin electron rich. This then makes the acyl ammonium intermediate 19 prone to S₉2-type nucleophilic attack, therefore generating the observed morpholine amide 18.
Racemic Approach. Although the asymmetric acyl-Claisen approach could be modified to circumvent the undesired von Braun fragmentation side reaction (e.g. replacement of the ketone with an ester), we felt that the number of synthetic manipulations in this route was becoming unnecessarily high. Therefore we chose to pursue a more efficient racemic route in the interest of producing the necessary material to test the subsequent key steps. As Scheme 6 illustrates, acid 20, which contains the necessary stereochemical relationships to be elaborated into the desired 4 though olefin methathesis of the corresponding enone, can be obtained from an Ireland-Claisen rearrangement of the appropriately acetylated derivative of alcohol 13. This modified Ireland-Claisen route is not dependent on synthesizing large amounts of chiral magnesium complex 11, and therefore would allow for more efficient access to greater quantities of the desired cyclopentenone 4.

Scheme 6. Modified Ireland-Claisen strategy to cyclopentenone 4

Although this modified strategy would produce racemic products, it is potentially amenable to asymmetric synthesis in the future. An enantiomerically pure chiral secondary alcohol, such as 21 (obtained though an asymmetric Noyori hydrogenation of the corresponding methyl ketone), could be used to relay stereochemistry in the Claisen rearrangement (via transition state 22) to the two newly formed stereocenters in 23. The extra methyl group (highlighted in blue) is excised in the course of the olefin metathesis reaction of 24, thus providing cyclopentenone 4 in an enantioenriched form.

Using the racemic Ireland-Claisen route, the synthesis of cyclopentenone 4 began with the acylation of alcohol 13 with [p]-benzyloxy acid chloride 10, providing rearrangement precursor 25 in 85% yield. Gratifyingly, subjection of ester 25 to initial Claisen-rearrangement conditions (LDA, TBSCI) afforded the desired adduct 26, although in only 23% yield and with 4:1 anti:syn selectivity. These conditions were eventually optimized (through varying temperature, silylating agent, and additives) to provide acid 26 in an acceptable 80% yield and 6:1 anti:syn selectivity. Conversion of 26
to the Weinreb amide 27 proceeded in 80% yield in the presence of MeHNOMe and BOP.

**Scheme 7.** Ireland-Claisen strategy is amenable to asymmetric synthesis

Addition of vinyl grignard to 26 produced the desired enone 28, although in only 47% yield. The major product formed was instead ketone 29, where the amine byproduct NHMe(OMe) had added in a 1,4-fashion into the enone 28. Experiments determined that side product 29 was formed upon workup (with aqueous acid or on contact with the TLC plate) therefore suggesting that the metal chelated intermediate 27 remained intact until the reaction was quenched. Therefore we speculated that yields of 28 could be increased by revising the workup procedure to ensure that aqueous acid was always in excess;
under these conditions any liberated HNMe(OMe) formed upon workup would be immediately protonated and thus unable to add into 28. Indeed, slowly adding the reaction mixture to a saturated NH₄Cl solution in the workup increased the isolated yields of the desired enone dramatically; ultimately this procedure afforded the metathesis precursor 28 in an acceptable 83% yield.

Olefin metathesis precursor 28 was subjected to ring-closing metathesis conditions in hopes that 28 would cyclize to produce the desired cyclopentenone 4. This cyclization appeared to be nontrivial, since it involved the metathesis of two olefins of low to moderate reactivity. The terminally disubstituted olefin was adjacent to a sterically demanding isopropyl group, thus making it potentially difficult to access. Furthermore, olefins conjugated to ketones have been traditionally difficult to cyclize. However with the recent development of more active metathesis catalysts (such the second generation Grubbs ruthenium catalyst, 30) these substrates have been deemed viable substrates for metathesis to varying extents. Gratifyingly, treatment of enone 28 with the Grubbs catalyst 30 produced the desired cyclopentenone 4 in good yields (Scheme 9). nOe analysis confirmed that the major diastereomer formed in the reaction was indeed the syn-4 diastereomer. Interestingly, the metathesis appeared to be diastereoselective; cyclization of anti-28 proceeded faster than syn-28 under these metathesis conditions, resulting in the formation of a product (4) with higher isomeric ratios than the starting material (28).

**Scheme 9.** Ring closing metathesis of 28
C. Synthesis of Diene Fragment 5

Examining diene 5, we felt that the main challenge in synthesizing this fragment would be in controlling the geometry around the tri-substituted olefin and enol ether. In considering the various approaches to the synthesis of this diene piece, we settled on a strategy that would rely on using olefin isomerization chemistry developed by Shibasaki to establish the desired olefin geometries. In 1990, Shibasaki and coworkers reported the development of a chromium(0) mediated diene isomerization reaction capable of synthesizing silyl dienol ethers of the type 35 in a stereocontrolled manner from (1Z)-1-[(silyloxy)methyl]butadiene derivatives such as 33. Coordination of the cisoid diene to “Cr(CO)₃” followed by hydrogen abstraction results in the U-shaped [3]-intermediate 34, which eventually leads the observed (1E, 3Z)-diene. The high stereoselectivity of this process arises from the preferential formation of intermediate 34 because of the unfavorable steric interactions in the other chromium-bound isomer 36.

Scheme 10. Synthetic plan for diene 5

![Scheme 10](image)

Cuprate 5 could then be accessed from intermediate 31, which Shibasaki’s methodology permits us to obtain from the terminal diene 32. This molecule, in turn,
could be made though a Pd(0) mediated coupling to two simpler olefinic compounds. Of the various options for synthesizing compound 32, a route involving a Sonogashira coupling followed by syny-reduction was chosen over a Suzuki or Stille coupling, mainly due to the ease with which intermediates in the former route could be handled.

The synthesis of fragment 5 began with the conversion of commercially available 3-butyn-1-ol to vinyl iodide 39 as a single regioisomer under in situ “HI” generated conditions (Scheme 10). Subjection of the resultant iodide to Sonagashira coupling conditions with alkyne 40 afforded the desired enyne 41. A variety of palladium sources, amines and solvents were screened, and ultimately Cl₂Pd(PPh₃)₂, NEt₃, and THF were found to be optimal, providing enyne 41 in 70% yield. Initial attempts to reduce enyne 41 to Z-diene 32 with Lindlar’s catalyst were unsuccessful; instead these conditions produced complex mixtures of olefin isomers and over-reduced products. Catalyst poisoning additives (quinoline, pyridine) were also applied in an effort to attenuate the reactivity of the palladium catalyst, but these reactions also lead to the over-reduction of the alkyne.³⁰,³¹ Ultimately, we found that potassium-activated Reike Zinc/methanol/water conditions were highly effective at providing the desired diene 32 cleanly and in good yields without any sign of over-reduction or olefin isomerization.

Scheme 11. Synthesis of alkyl iodide 33
Isomerization of terminal diene \(32\) with catalytic amounts of (naphthalene)Cr(CO)\(_3\) yielded silyoxy-diene \(42\) in excellent yields (92%) and as a single isomer. nOe analysis revealed that the geometric isomer formed was indeed the desired \((1E, 3E)\)-diene \(42\). Alcohol \(42\) was converted to alkyl iodide \(31\) using standard conditions, taking care to pre-form the active I-PPh\(_3^+\) species prior to addition of the alcohol \(42\) to prevent I\(_2\) mediated decomposition of the diene. Not surprisingly, cuprate precursor \(31\) was relatively unstable and was typically generated just prior to use in the subsequent step.

**D. Synthesis of the IMDA precursor via a conjugate addition/aldol reaction**

Because of the scientific community’s interest in the prostaglandins during the 1970s and 1980s, a wealth of literature has been published on the synthesis of these biologically relevant natural products.\(^{32}\) One of the most popular and efficient strategies for accessing these molecules was a one-pot, 3-component coupling approach, which generally involved the 1,4-conjugate addition of a cuprate species into a cyclopentenone followed by trapping of the resultant enolate with an aldehyde or alkyl halide. We initially looked to this body of literature in hopes of finding reaction conditions that would produce the desired 3-component coupling. Unfortunately, attempts at generating the desired IMDA precursor \(43\) were unsuccessful using these (or variants of these) protocols (eq. 1).\(^{33-37}\) This, however, was not surprising. These reported procedures used lower-order organocuprates or organozinc-cuprates to add conjugately into \(\text{-mono-}\) substituted enones; our system, however, involved the 1,4-addition of a nucleophile into a \(\text{-di-}\) substituted enone. Copper mediated conjugate additions into these more sterically demanding substrates are documented to be difficult, and lower-order organocuprates or organozinc-cuprates are often not reactive enough to add to these substrates. In fact, no conjugate addition product was isolated in these attempted 3-component coupling reactions, lending credence to the idea that a more appropriate copper nucleophile needed to be found.
We elected to redirect our focus towards first finding an organocopper species that could effect the desired 1,4-conjugate addition. We looked towards using more reactive organocuprates such as the higher order cyanocuprate \( \text{R}_2\text{Cu(CN)Li}_2 \). Lipshutz and coworkers had success adding these cuprates into \( \beta,\beta \)-disubstituted enones,\(^{38-40}\) and therefore we felt that this organocopper species might be more effective. Indeed, lithium-halogen exchange of iodide 31, followed by addition of CuCN resulted in the \textit{in situ} formation of the higher order cyanocuprate; this mixture was treated with cyclopentenone 4 which, upon workup, provided the desired conjugate addition product 44 in 88% yield as a single diastereomer. The excellent diastereoselectivity observed in this reaction can be attributed to a large preference for the cuprate reagent to approach the enone from the face opposite that with the benzyloxy functionality and sterically demanding isopropyl group (Figure 5). Treatment of cyclopentanone 44 with aldehyde 6 under optimized aldol conditions produced IMDA precursor 43 in 56% yield, again, as a single isomer.

**Scheme 12.** Synthesis of IMDA precursor \textit{via} a conjugate addition/aldol reaction

Nuclear Overhauser effect analysis confirmed the relative stereochemistry around the cyclopentanone ring to be as drawn in Scheme 12 (see experimental details). The selectivity in this case can be rationalized by examining the transition state shown in Figure 5. The aldehyde favors approach from the face opposite the cyclopentanone ring.
and large isopropyl group in the 6-member chelated transition state, thus preferentially forming diastereomer 43.

**Figure 4.** Stereochemical rationale for cuprate addition and aldol reaction

![Cuprate Addition Diagram](image)

![Aldol Reaction Diagram](image)

A few attempts were made to use the higher order cyanocuprate in a 3-component coupling reaction. Unfortunately, the resultant cyanocupper enolate 45 is much less nucleophilic than it’s lower order organocupper counterpart. Efforts were made to transmetallate enolate 45 to the more reactive zinc enolate with reagents such as Me₂ZnLi, but the desired 3-component coupling product 43 was never isolated (eq. 2).

**E. Attempted Intramolecular Diels-Alder Cyclizations**

With the key intermediate in hand, attempts were made to cyclize the dienyne 43 into the desired tricyclic guanacastepene core 46 with a variety of thermal, oxocarbenium- and iminium- accelerated intramolecular Diels-Alder conditions (Table 1). Unfortunately none of these produced the desired cycloadduct 46; the diene moiety was prone to decomposition under some of these conditions, and in all the other cases
none of the desired product was observed. Attempts were also made to deprotect the acetal protecting group; not surprisingly, the diene moiety was incompatible since all acidic deprotection conditions used to effect this transformation either caused decomposition of the diene moiety, (initiated by cleavage of the silyl group) or failed to deprotect the acetal.

Since formation of the electron-withdrawing group in situ was unsuccessful (in the form of an iminium or oxocarbenium group), derivatives of 43 where the electron withdrawing group was in place (48 and 49) were synthesized via the same aldol route. Subjection of these compounds to a variety of thermal and Lewis acid conditions also did not produce any of the desired adduct 46a. Attempts were also made to bring in a masked aldehyde in the form of a protected alcohol (50). Unfortunately attempts to oxidize the alcohol to the aldehyde were met with little success; most conditions caused decomposition of the silyl-oxy diene moiety.

Table 1. Conditions attempted for the IMDA cyclization of 43 to 46

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>entry</th>
<th>conditions</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>LiClO₄, CH₃NO₂</td>
<td>8</td>
<td>InCl₃, CH₃NO₂</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OH)₃, CH₂Cl₂</td>
<td>9</td>
<td>Me₂AlCl, CH₂Cl₂, r.t.</td>
</tr>
<tr>
<td>3</td>
<td>HBF₄·OMe₂, CH₂Cl₂</td>
<td>10</td>
<td>47·TFA, CH₃CN, r.t.</td>
</tr>
<tr>
<td>4</td>
<td>LiClO₄, CSA, Et₃O</td>
<td>11</td>
<td>47·TFA, CH₃CN, Δ</td>
</tr>
<tr>
<td>5</td>
<td>TMSOTf, CH₂Cl₂</td>
<td>12</td>
<td>LiBF₄, H₂O, CH₃CN</td>
</tr>
<tr>
<td>6</td>
<td>110 °C, xylenes</td>
<td>13</td>
<td>47·HOTf, CH₃CN, r.t.</td>
</tr>
<tr>
<td>7</td>
<td>LiBF₄, H₂O, CH₃CN, Δ</td>
<td>14</td>
<td>160 °C, xylenes</td>
</tr>
</tbody>
</table>

Given the lack of success at cyclizing these alkyne-containing substrates, models of the IMDA precursors were examined in hopes of learning why they were reluctant to undergo the desired cycloaddition reaction. As the model in Figure 6 illustrates, the orbital overlap between the diene and alkyne dienophile in the IMDA transition state of
49 is non-ideal (51), thus making it difficult for this substrate to undergo the expected cycloaddition. We speculated that by converting the dienophile to an alkene, as in ester 52 the transition state of the IMDA cyclization (53) would look more product-like, thus improving the π-orbital overlap between the diene and dienophile and hopefully making the desired cycloaddition more facile.

**Figure 5.** Comparison of IMDA transition states for alkyne and alkene dienophiles

Therefore alkene 52 was synthesized via an aldol reaction from cyclopentanone 44. However, subjection of the IMDA substrate 52 to a variety of thermal and Lewis acid conditions did not produce any of the desired cycloadduct 54 (eq. 5).
In an effort to make the transition state of the IMDA reaction even more product-like, substrate 56, which contains an olefin adjacent to the alkene dienophile, was synthesized. This cyclization precursor also possesses electronic properties favorable to the IMDA; the dienophile is doubly activated and therefore more electron deficient than it’s predecessors since it is conjugated to both the ester and the ketone. Interestingly 56, which was synthesized though an LDA mediated aldol condensation between cyclopentanone 44 and aldehyde 55, was found to cyclize under mild conditions to produce the tricycle 57. This unusual product presumably arises from the reaction of the enone olefin with the trisubstituted alkene of the diene, ostensibly though a stepwise mechanism. Attempts were made to utilize 57 in a productive fashion towards the desired IMDA cycloadduct though a retro-[2+2]/[4+2] cyclization, but these efforts were not greeted with any success.

Scheme 13. Cyclization of IMDA precursor 56 to produce the unusual tricycle 57

Although tetraene 56 readily cyclized to tricycle 57, it did not eliminate the possibility that 56 contained the structural elements (such as good π-orbital overlap) necessary for the substrate to undergo the desired IMDA reaction. It was speculated that the nominal [2+2] reaction was out-competing the [4+2] cycloaddition because of the highly electron-deficient nature of the reactive enone olefin. Therefore we felt that the formal [2+2] reaction could be prevented by adjusting the electronics of that alkene to be less electron deficient. Specifically, diketone 58 appeared to possess these desirable traits. Similar to 56, the dienophile olefin in 58 is conjugated to both the ester and a ketone, thus electronically activating it towards the desired IMDA reaction. Furthermore, it is postulated that the diketone exists mainly in the enolic, fully conjugated form 58b. In this case, the enol is not as electron deficient as the enone olefin in 56, and therefore should be less likely to participate in an analogous [2+2] reaction. In addition, similar to
tetraene 56, 58b is able to provide access to the desired conformation that allows for optimal \[\pi\]-overlap between the diene and dienophile. And finally, in contrast to 56, 58b should provide excellent control over the enolic olefin geometry, since 1,3-diketones are well documented to exist in the geometry shown in 58b due to hydrogen bonding. It is for these reasons that we felt that diketone 58 contained electronic and structural features that would allow it to undergo the desired [4+2] cycloaddition in lieu of the [2+2] reaction.

**Figure 6.** Comparison of tetraene 56 and 1,3-diketone 58

LDA mediated acylation of ketone 44 with acid chloride 59 afforded the desired diketone 58 as a single isomer; as expected, NMR chemical shifts suggested that the compound existed predominantly in the enolic form 58b. Exposure of 58 to a variety of thermal and Lewis acid conditions, however, did not produce and of the desired cycloadduct 60. Interestingly, no [2+2] adduct was observed, suggesting that perhaps electronics did play a large role in the formation of tricycle 57.

**Scheme 14.** Attempted IMDA cyclization of diketone 58
F. Revised Route: Using an Intermolecular Diels-Alder Reaction

Since attempts to build the 5,7,6-tricycle core of guanacastepene though an IMDA reaction were unsuccessful, we were interested in determining whether this phenomenon was due to the unreactive nature of the silyoxy-diene moiety, or the inability of the reaction to accommodate the formation of the seven-membered ring. In the interest of seeing whether the silyoxy-diene moiety was reactive enough to undergo the Diels-Alder reaction, the protected diene 61 was exposed to a highly reactive dienophile, maleic anhydride (62) under thermal conditions. Gratifyingly, this produced the desired cycloadduct 63 as a single diastereomer whose relative stereochemistry was confirmed to be as shown in eq. 6 by nOe analysis. This suggested to us that it was the formation of the seven-membered ring in the IMDA reaction that prevented the desired cyclization. It is of note that the Kwon group recently revealed that they pursued a similar synthetic strategy to guanacastepene A involving an IMDA cyclization reaction. They too found the heptacycle-forming IMDA reaction to be intractable.

![Image](image_url)

However, this result was promising and was used to revise our synthetic plan towards guanacastepene A. Efforts have been directed towards converting 63 into iodide 65. Conjugate addition of the corresponding cuprate into cyclopentenone 4 would produce ester 66. Dieckmann condensations have been used extensively in the preparation of seven-membered carbocycles, and therefore treatment of 66 with base should produce the core of guanacastepene A 67 in a relatively efficient manner. In the event that these efforts are successful, an asymmetric route to 65 would be devised, thus leading to an efficient, asymmetric synthesis of guanacastepene A.
III. Conclusion

Progress has been made towards the total synthesis of guanacastepene A. Significant efforts were directed towards pursuing a 3-component coupling/intramolecular Diels-Alder approach towards the natural product. IMDA precursors were synthesized in an efficient and convergent manner. It was found, however, that these substrates were unable to undergo the desired cyclization. By modifying our synthetic approach towards guanacastepene A, we found that the stereochemically complex eastern cyclohexene portion of the natural product could be synthesized via an intermolecular Diels-Alder. Therefore recent efforts have been directed towards pursuing a more convergent intermolecular Diels-Alder/conjugate addition/Dieckmann condensation strategy towards guanacastepene A.
References

30. Subsequent to these experiments, Campos and coworkers published on their observations that Lindlar's catalyst consistently over-reduced alkynes with a primary amino group in close proximity. They speculate that this phenomenon can be attributed to preassociation of the amine functionality to the catalyst surface, thereby increasing reaction rates and the propensity of the alkyne to be over reduced to the alkane. It is possible that a similar phenomenon is being observed here in the case of enyne 40. With two hydroxyl groups proximal to the alkyne, the substrate could be highly associated with the catalyst, thus leading to over-reduction. Please see the following reference by Campos et. al.
Experimental

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or KMnO₄ stain.

¹H NMR and ¹³C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ¹H NMR are reported with chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ¹³C NMR are reported with chemical shift. IR spectra were recorded on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). Mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

Synthesis of Cyclopentenone 4.

Alcohol 13. To a solution of ester 12 (3.3g, 23.0 mmol) in 175 mL CH₂Cl₂ cooled to −78 °C was added 9.0 mL (50.0 mmol) of DIBAL-H. The solution was allowed to stir for 15 minutes, after which the reaction was quenched with methanol (15 mL). Upon warming the reaction to room temperature, a saturated solution of sodium

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potassium tartrate was added (200 mL) and the mixture was stirred vigorously for 8 hours. The mixture was extracted with CH₂Cl₂ (3 x 100 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (15% EtOAc/Hexanes) to afford the title compound as a clear, colorless oil in 92% yield (2.4 g): IR (film) 3406, 2958, 2873, 1460, 1383, 1267 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.12 (br d, J=9.6 Hz, 1H, CHCH=C(Me)CH₂OH), 4.14 (s, 2H, CH₂OH), 2.66-2.54 (m, 1H, CH(CH₃)₂), 1.77 (d, 3H, J=1.5 Hz, CH₃CH=CH), 0.95 (d, J=6.6, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 136.3, 133.6, 131.9, 61.6, 26.8, 23.5, 21.1; HRMS (CI) exact mass calculated for (C₁₁H₁₄O) requires m/z 114.1045, found m/z 114.1049.

**Amine 9.** To a cooled (0°C) solution of alcohol 13 (300 mg, 2.65 mmol) and triphenylphosphine (0.70 g, 2.65 mmol) in 2.5 mL THF was added N-bromosuccinimide (NBS, 472 mgs, 2.65 mmol) in portions. Morpholine (0.56 mL, 6.36 mmol) was then added by syringe to the yellow heterogeneous mixture. The mixture was heated to reflux for 5 hours, then filtered though celite. The filtrate was acidified with 1N HCl, and then washed with Et₂O. The aqueous extracts were then basified with 1N NaOH, and then extracted with 2 x 30 mL Et₂O. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (20% Et₂O/Pentane) to afford the title compound as an oil in 54% yield (0.26 g): IR (film) 2958, 2866, 2811, 1452, 1367, 1298, 1120, 1004 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.09 (d, J=9.3 Hz, 1H, CHCH=C(Me)CH₂N), 3.64 (m, 4H, O(CH₂)₂(CH₂)₂N), 2.87 (s, 2H, (Me)CCH₂N), 2.65-2.50 (m, 1H, CH(CH₃)₂), 2.32 (m, 4H, O(CH₂)₂(CH₂)₂N), 1.66 (d, 3H, J=1.5 Hz, CH₃CH=CH), 0.87 (d, J=6.6, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 137.6, 129.1, 67.3, 59.3, 53.7, 26.8, 23.5, 23.2; HRMS (CI) exact mass calculated for (C₁₁H₂₁NO) requires m/z 183.1625, found m/z 183.1623.
**Amine 16.** To a solution of methyl 3,3-dimethyl acrylate (0.68 g, 6.0 mmol) in CCl₄ was added NBS (1.1 g, 6.0 mmol), followed by benzoyl chloride (8.7 mgs, 0.036 mmol). The solution was heated to reflux for 1.5 hours, after which the mixture was filtered. The clear filtrate was added morpholine(0.51 mL, 6.0 mmol), and the mixture was stirred for another 1.5 hours. Volatiles were removed in vacuo, and 1N NaOH solution was added. The mixture was partitioned and the organic layer was acidified with 1N HCl and washed with water. The aqueous layer was then basified with 1N NaOH, and washed with diethyl ether. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (20% EtOAc/hexanes) to separate the isomers. The desired trans isomer of the title compound was isolated as a red oil in 12% yield (0.14 g): IR (film) 2950, 2858, 2811, 1715, 1653, 1437, 1290, 1220, 1035 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.80-5.79 (s, 1H, C=CH₂CO₂Me), 3.581 (m, 7H, CO₂Me and O(CH₂)₂(CH₂)₂N), 2.84 (s, 2H, (Me)CH=CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 166.9, 155.7, 116.8, 67.1, 53.9, 51.1, 17.6; HRMS (Cl) exact mass calculated for (C₁₁H₂₂NO) requires m/z 184.1701, found m/z 184.0963.

**Ester 25.** To a solution of alcohol 13 (1.8 g, 16.1 mmol) in 32 mL of CH₂Cl₂ was sequentially added pyridine (1.6 mL, 19.3 mmol), 4-dimethylaminopyridine (99 mg, 0.81 mmol), and (|-benzyloxy)-acetyl chloride (3.0 mL, 19.3 mmol). After stirring 8 hours at room temperature, the reaction was quenched by the addition of saturated NaHCO₃ solution (30 mL) was added. The mixture was partitioned and the aqueous layer was
washed with 3 x 40 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (20% EtOAc/Hexanes) to afford the title compound as a clear, colorless oil in 79% yield (3.3 g): IR (film) 2958, 2873, 1753, 1460, 1390, 1267 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.43-7.30 (m, 5H, ArH), 5.28 (dd, J=0.60, 9.6 Hz, 1H, CHCH=C(Me)CH₂OR), 4.73 (s, 2H, CH₂OBn), 4.69 (s, 2H, CHCH=C(Me)CH₂O), 4.16 (s, 2H, O₂CCH₂OBn), 2.69-2.62 (m, 1H, CH(CH₃)₂), 1.76 (d, J=2.5 Hz, 3H, CH₃CH=CH), 0.99 (d, J=5.4 Hz, 6H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) 170.5, 139.2, 137.2, 128.5, 128.1, 128.0, 126.9, 73.3, 67.2, 63.7, 27.2, 23.3, 21.4; HRMS (Cl) exact mass calculated for (C₁₆H₂₀O₃) requires m/z 263.1647, found m/z 263.1644.

**Acid 20.** To a -78 °C solution of diisopropyl amine (6.4 mL, 45.8 mmol) in 150 mL THF was added 16.7 mL (42.0 mmol) of nBuLi (2.53M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to -100 °C, and 10.0 g (0.023 mmol) of ester 25 were added in 2 x 20 mL of THF. The reaction was stirred at that temperature for 1 hour, after which 6.3 mL (50.0 mmol) of freshly distilled trimethylsilylchloride was added dropwise. After stirring for an additional hour at -100 °C, the solution was slowly warmed to room temperature and stirred for 12 hours. The reaction was quenched with the addition of 1N NaOH (60 mL). After stirring for 20 minutes to deprotect the trimethylsilyl ester, the volatiles were removed in vacuo. The resultant aqueous residue was washed with Et₂O (1 x 100 mL), then cooled to 0 °C and acidified to pH 1 with 1N HCl. This aqueous solution was then washed with 3 x 70 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (10-20% EtOAc/Hexanes gradient) to afford the title compound as a oil in 81% yield (8.1 g): 6:1 mixture of (desired) syn:anti
diastereomers. IR (film) 3035, 2966, 2873, 1715, 1452, 1383 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[ 7.41-7.30 \text{ (m, 5H, ArH), 4.83 (m, 1H, H\(_2\)C=C), 4.78 (d, J=11.3 Hz, 1H OCH\(_2\)Ph), 4.75 (m, 1H, H\(_2\)C=C), 4.36 (d, J=11.4 Hz, 1H, OCH\(_2\)Ph), 4.33 (d, J=3.6 Hz, 1H, HO\(_2\)CHOBn), 2.15 (dd, J=3.5, 9.0 Hz, 1H, CHCH(CH\(_3\))\(_2\)), 2.10-2.07 (m, 1H, CHCH(CH\(_3\))\(_2\)), 1.77 (s, 3H, CH\(_3\)C=CHH), 0.88 (d, J=6.0 Hz, 3H, CH(CH\(_3\))\(_2\)), 0.84 (d, J=6.0 Hz, 3H, CH(CH\(_3\))\(_2\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \[ 178.1, 144.3, 137.6, 128.6, 128.1, 127.9, 115.4, 80.0, 73.5, 57.7, 26.5, 21.6, 21.3, 20.7; HRMS (CI) exact mass calculated for (C\(_{16}\)H\(_{23}\)O\(_5\)) requires m/z 263.1647, found m/z 263.1640.

Amide 26. To a solution of acid 20 (2.82 g, 10.8 mmol) in 36 mL of CH\(_2\)Cl\(_2\) was added N,O-dimethylhydroxylamine hydrochloride (2.64 g, 27.0 mmol), followed by diisopropylethylamine (7.75 mL, 43.2 mmol) and Benzotriazol-ylloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 5.0 g, 11.3 mmol). The mixture was stirred for 6 hours, after which volatiles were concentrated in vacuo. The resultant reside was taken up in EtOAc (100 mL) and washed with 1M NaHSO\(_4\) (50 mL), brine, dried over Na\(_2\)SO\(_4\), and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (10-20% EtOAc/Hexanes gradient) to afford the title compound as a oil in 77% yield (2.52 g), which was taken directly on to the next step without full characterization: IR (film) 2958, 1676, 1460, 1375 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[ 7.40-7.21 \text{ (m, 5H, ArH), 4.78-4.76 (br s, 1H, H\(_2\)C=C), 4.73 (d, J=11.4 Hz, 1H, OCH\(_2\)Ph), 4.60-4.55 (br s, 1H, H\(_2\)C=C), 4.48-4.45 (d, J=5.3 Hz, 1H, O=CCHOBn), 4.25 (d, J=11.4 Hz, 1H, OCH\(_2\)Ph), 3.63 (s, 3H, NO(CH\(_3\)), 3.19 (s, 3H, N(CH\(_3\))), 2.22-2.28 (dd, J=5.0, 11.3 Hz, 1H, CHCH(CH\(_3\))\(_2\)), 2.12-1.98 (m, 1H, CHCH(CH\(_3\))\(_2\)), 1.79 (s, 3H, CH\(_3\)C=CHH), 0.77 (d, J=7.5 Hz, 3H, CH(CH\(_3\))\(_2\)), 0.71 (d, J=7.5 Hz, 3H, CH(CH\(_3\))\(_2\)).
Enone 28. To a cooled (%78 °C) solution of amide 26 (0.84 g, 2.7 mmol) in 27 mL of THF was added vinyl grignard (1M in THF, 6.8 mL, 6.8 mmol) dropwise. After stirring 10 minutes at %78 °C, the cold bath was removed and the reaction was warmed to room temperature. After stirring an addition 2 hours, the reaction was quenched by pouring the reaction mixture into 20 mL of 1M NaHSO₄ solution. The mixture was washed with 3 x 20 mL EtOAc, and the combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (4% EtOAc/Hexanes) to afford the title compound as a oil in 84% yield (0.62 g): IR (film) 2966, 1699, 1614, 1460 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 5H, ArH), 6.76 (ddd, J=1.0, 10.5, 17.1 Hz, 1H, HHC=CH=O), 6.36 (ddd, J=1.2, 1.8, 17.1 Hz, HHC=CH=O), 5.70 (ddd, J=1.2, 1.8, 10.5 Hz, 1H, HHC=CH=O), 4.73 (m, 1H, H₂C=CMe), 4.68 (d, J=11.4 Hz, 1H, OCH₂Ph), 4.66 (m, 1H, H₂C=CMe), 4.33 (d, J=11.4 Hz, 1H, OCH₂Ph), 4.27 (d, J=3.9 Hz, 1H, O=CC=OBn), 2.21-2.05 (m, 2H, CHCH(CH₃)₂ and CHCH(CH₂)₂), 1.80 (s, 3H, CH₃C=CHH), 0.94 (d, J=6.0 Hz, 3H, CH(CH₃)₂), 0.88 (d, J=6.0 Hz, 3H, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 202.1, 143.8, 137.9, 132.1, 128.4, 128.0, 127.7, 127.6, 115.4, 85.4, 72.9, 57.5, 26.5, 26.5, 21.3, 20.9, 20.6.

Cyclopentenone 4. To a solution of enone 28 (15.4 mg, 0.054 mmol) in 5 mL of toluene was added 2.3 mg (0.0027 mmol) of Grubbs second generation ruthenium methathesis catalyst 30. The solution was refluxed for 36 hours, after which the reaction

was cooled to room temperature and volatiles were removed in vacuo. The resultant brown solid was purified by silica gel chromatography (5-10-15% EtOAc/Hexanes gradient) to afford the title compound as a mixture of separable isomers in 61% yield (8.5 mg, 91% yield based on recovered starting material): IR (film) 2966, 1715, 1614, 1460, 1383, 1174 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[\text{7.40-7.25 (m, 5H, ArH), 6.00-5.99 (m, 1H, O=CC=CHMe), 4.99 (d, J=12.4 Hz, 1H, OCH\(_2\)Ph), 4.77 (d, J=12.4 Hz, 1H, OCH\(_2\)Ph), 4.02 (d, J=6.3 Hz, 1H, O=CCHOBn), 2.88-2.85 (m, 1H, CHCH(CH\(_3\))\(_2\)), 2.07 (s, 3H, CH\(_3\)C=CH), 1.03 (dd, J=1.1, 7.1 Hz, 3H, CH(CH\(_3\))\(_2\)), 0.83 (dd, J=1.1, 7.1 Hz, 3H, CH(CH\(_3\))\(_2\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \[\text{207.3, 175.4, 138.3, 129.5, 128.5, 128.6, 129.8, 81.2, 73.3, 53.8, 28.1, 21.2, 20.6, 19.3; HRMS (Cl) exact mass calculated for (C\(_{16}\)H\(_{21}\)O\(_2\)) requires m/z 245.1542, found m/z 245.1535.}

nOe analysis to determine relative stereochemistry of the two isomers:

Synthesis of Alkyl Iodide 31.

Vinyl Iodide 39. To a solution of NaI (79.2 g, 0.53 mole) in 500 mL was added freshly distilled chlorotrimethylsilane (41 mL, 0.53 mole) followed by H\(_2\)O (4.8 mL, 0.26 mole) upon which the solution turned yellow. The mixture was stirred for 10 minutes to allow for the in situ formation of HI, then 20 mL (0.26 mole) of 3-butynol was added. The orange solution was stirred at room temperature in the dark for 5 hours. Water was then added (300 mL), and the mixture was washed with 3 x 300 mL Et\(_2\)O. The combined
organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed \textit{in vacuo} and the resultant crude oil was purified by silica gel chromatography (30\% EtOAc/Hexanes) to afford the title compound as an orange-red oil in 75\% yield (39 grams): IR (film) 3321, 2881, 1413, 1197, 1128 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 6.18 (m, 1H, IC=CHH), 5.85 (m, 1H, IC=CHH), 3.76 (t, \(J=5.8\) Hz, 2H, CH₂OH), 2.62 (dt, \(J=1.1, 5.8\) Hz, 2H, HOCH₂CH₂Cl); \(^13\)C NMR (75 MHz, CDCl₃) \(\delta\) 128.1, 107.8, 60.8, 48.0; HRMS (CI) exact mass calculated for (C₄H₇OI) requires \(m/z\) 197.9542, found \(m/z\) 197.9544.

**Alkyne 40.** To a solution of propargyl alcohol (4.5 mL, 77.3 mmol) in 16 mL DMF was added imidazole (6.7 g, 99.4 mmol), followed by \textit{tert}-butyl- chlorodiphenylsilane (15 mL, 57.3 mmol). The solution was stirred for 3 hours, then quenched with 1M NaHSO₄ (70 mL). The mixture was partitioned and the aqueous extracts were washed with 3 x 50 mL EtOAc. The combined organic extracts were washed with 2 x 30 mL 1M NaHSO₄, 2 x 40 mL H₂O, brine, dried over Na₂SO₄, and filtered. Volatiles were removed \textit{in vacuo} and the resultant crude oil (16.2 g, 96\% yield) was immediately carried onto the next step without further purification.

**Enyne 41.** To a solution of vinyl iodide 39 (100 mg, 0.51 mmol) in 1 mL THF was sequentially added alkyne 40 (193.3 mg, 0.66 mmol), triethylamine (0.21 mL, 1.5 mmol), Pd(PPh₃)₂Cl₂ (17.7 mg, 0.025 mmol), and Copper(I) iodide (4.8 mg, 0.025 mmol). The orange mixture was stirred at room temperature for 8 hours, then quenched with saturated NH₄Cl solution. Volatiles were removed \textit{in vacuo} and the resultant residue was taken up in EtOAc (10 mL) and partitioned. The aqueous phase was extracted with 2
x 10 mL EtOAc, and the combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (10-25% EtOAc/Hexanes gradient) to afford the title compound as an orange oil in 70% yield (131 mgs): IR (film) 3383, 2935, 2858, 1468, 1429, 1367, 1097 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.70 (m, 4H, ArH), 7.43-7.25 (m, 6H, ArH), 5.35 (s, 1H, C=C=C=CHH), 5.30 (m, 1H, C=C=C=CHH), 4.50 (s, 2H, CH₂OTBDPS), 3.76 (t, J=5.7 Hz, 2H, CH₂OH), 2.39 (t, J=5.9 Hz, 2H, HOCH₂CH₂C=CHH), 1.05 (s, 9H, OSi(CH₃)₃Ph₂); ¹³C NMR (75 MHz, CDCl₃) δ 135.1, 134.9, 132.6, 132.5, 129.2, 129.0, 127.1, 124.2, 63.3, 52.5, 39.7, 26.1, 18.8; HRMS (FAB+) exact mass calculated for (C₂₃H₂₇O₂Si) requires m/z 363.1780, found m/z 363.1768.

**Diene 32.** 317 mg (1.4 mmol) of anhydrous Zinc(II) Bromide was weighed out in the glovebox, equipped with a stir bar, and transferred to an argon line. The solid was then by heated to liquidity under vacuum with a bunson burner. Upon cooling to room temperature, the flask was back-filled with argon, and charged with 1.5 mL THF. 107 mg (2.7 mmol) of potassium metal (washed with hexanes to remove the mineral oil) was then added to the flask, and the mixture was heated to reflux for 3 hours, during which the solution turned black. Enyne 41 was then added in 1 mL of THF, 1.75 mL of methanol, and 0.36 mL of H₂O (slowly and very carefully). The solution was refluxed for 12 hours, during which it turned grey, and then cooled back to room temperature. 30 mL of saturated NH₄Cl solution was added, and the mixture was partitioned. The aqueous layer was washed with 2 x 15 mL Et₂O, and the combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (25% EtOAc/Hexanes, product cospots with enyne starting material) to afford the title compound as an orange
oil in 72% yield (230 mgs); IR (film) 3833, 3704, 2935, 2858, 1622, 1468, 1429, 1112, 826 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[7.78-7.67 (m, 4H, ArH), 7.52-7.43 (m, 6H, ArH), 5.92-5.80 (m, 2H, TBDPSOCH\(_2\)CH=CH and TBDPSOCH\(_2\)CH=CHC), 5.04 (s, 1H, C=CHH), 4.74 (m, 1H, C=CHH), 4.45 (d, \(J=5.1\) Hz, 2H, CH\(_2\)OTBDPS), 3.65 (t, \(J=6.3\) Hz, 2H, CH\(_2\)OH), 2.39 (t, \(J=6.3\) Hz, 2H, HOCH\(_2\)CH\(_2\)C=CHH), 1.09 (s, 9H, OSi(CH\(_3\))\(_3\)Ph); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \[141.3, 135.6, 133.7, 132.8, 129.9, 129.7, 127.7, 126.8, 116.9, 61.0, 60.9, 40.1, 19.2; HRMS (FAB) exact mass calculated for (C\(_{23}\)H\(_{29}\)O\(_2\)Si) requires \(m/z\) 365.1937, found \(m/z\) 365.1937.

**Diene 42.** To a solution of diene 32 (5.0 g, 13.6 mmol) in 135 mL of acetone was added 360 mg (1.3 mmol) of (naphthalene)Cr(CO)\(_3\). The solution was deoxygenated though 3 freeze-pump-thaw cycles, then stirred under argon for 8 hours. The reaction mixture was concentrated \textit{in vacuo} then loaded onto a silica gel column and eluted with 2-4% EtOAc/hexanes to afford the title compound as a yellow oil in 92% yield (4.6 g): IR (film) 3360, 2935, 2896, 1614, 1468, 1166, 1112, 1059, 702.9 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \[7.68-7.66 (m, 4H, ArH), 7.44-7.25 (m, 6H, ArH), 6.51 (d, \(J=12.3\) Hz, 1H, Ph\(_2\)(CH\(_3\))\(_3\)CSiOCH=CHC=CHC), 6.01 (dd, \(J=12.3, 12.3\) Hz, 1H, R\(_3\)SiOCH=CHC=CHC), 5.68 (d, \(J=12.3\) Hz, 1H, R\(_3\)SiOCH=CHC), 3.55 (t, \(J=5.6\) Hz, 2H, CH\(_2\)OH), 2.24 (t, \(J=5.6\) Hz, 2H, HOCH\(_2\)CH\(_2\)C=CH), 1.68 (s, 3H, Ph\(_2\)(CH\(_3\))\(_3\)CSiOCH=CHC=CHC), 1.08 (s, 9H, OSi(CH\(_3\))\(_3\)Ph); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \[144.5, 135.7, 135.1, 132.7, 130.3, 128.1, 123.3, 110.3, 60.5, 43.0, 26.8, 19.5, 16.5; HRMS (FAB) exact mass calculated for (C\(_{23}\)H\(_{29}\)O\(_2\)Si) requires \(m/z\) 365.1937, found \(m/z\) 365.1928.
nOe analysis used to confirm olefin geometry:

Alkyl iodide 31. To a cooled (0 °C) solution of triphenylphosphine (0.59 g, 2.25 mmol) and imidazole (153 mg, 2.25 mmol) in 10 mL of CH₂Cl₂ was added iodine (545 mg, 2.15 mmol). The solution was stirred until the solid iodine disappeared. Diene 42 (750 mg, 2.05 mmol) was then added in 4.0 mL of CH₂Cl₂ and stirred for 3 hours in the dark at 4 °C. The reaction was quenched with 10% NaS₂O₃, and then transferred to a sepratory funnel. The aqueous layer was washed with 3 x 15 mL Et₂O, and then the combined organic extracts were washed with 10% NaS₂O₃, brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was quickly purified by silica gel chromatography in the dark (1% EtOAc/Hexanes). Note: product decomposes on silica) to afford the title compound as clear, colorless oil in 69% yield (703 mg). Due to its instability, the compound was immediately carried onto the next step without full characterization. ¹H NMR (300 MHz, CDCl₃)  7.70-7.26 (m, 10H, ArH), 6.53 (d, J=11.5 Hz, 1H, Ph₂(CH₃)₃CSiOCH=CHHC=C(CH₃)CH₂), 5.98 (dd, J=11.5, 11.7 Hz, 1H, R₃SiOCH=CHHC=C(CH₃)CH₂), 5.64 (d, J=11.7 Hz, 1H, R₃SiOCH=CHCH), 3.17 (t, J=7.8 Hz, 2H, CH₃I), 2.53 (t, J=7.8 Hz, 2H, ICH₂CH₂C=C), 1.67 (s, 3H, Ph₂(CH₃)₃CSiOCH=CHHC=C(CH₃)CH₂), 1.11 (s, 9H, OSiC(CH₃)₃Ph₂); ¹³C NMR (75 MHz, CDCl₃)  144.64, 135.6, 132.6, 131.7, 130.2, 128.0, 122.8, 110.3, 44.5, 26.9, 19.6, 16.2, 5.0.
Synthesis of IMDA precursors.

Cyclopentanone 44. Iodide 31 (224.4 mg, 0.47 mmol) was weighed into and degassed under vacuum. The vessel was charged with 2.0 mL of Et₂O and cooled to −78°C. tert-Butyllithium (1.75M in pentane, 0.51 mL, 0.90 mmol) was added dropwise to the flask, turning the solution bright yellow towards the end of the addition. The solution was stirred for 20 min at this temperature, then cannulated into a cooled (−78°C) flask containing copper(I) cyanide (20.2 mg, 0.225 mmol), and washed with 1 mL Et₂O. The bright yellow mixture was slowly warmed to 0 °C, during with the yellow heterogenous mixture gradually turned to a tan, clear, homogenous solution. After 5 minutes, the solution was cooled back to −78 °C and cyclopentenone 4 (50 mg, 0.205 mmol) was added in 2 x 0.6 mL of Et₂O; the solution immediately turned red once the first drop of the cyclopentenone was added, and upon completion of the addition, the solution was completely red-orange in color. The solution was stirred at this temperature for 10 minutes and then transferred to a −20 °C bath and stirred for another 8 hours. The reaction was quenched with the addition of saturated NH₄Cl/10%NH₃OH solution. The mixture was partitioned and the aqueous layer was washed with 3 x 20 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (1-3% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 88% yield (104.2 mg). Note: product decomposes over prolonged exposure to silica gel. Chromatography should be done relatively rapidly, IR (film) 2935, 2866, 1738, 1460, 1383, 1267, 1112, 818 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) □ 7.97-7.25 (m, 15H, (C₆H₅)₂(CH₃)₃CSiO and (C₆H₅)CH₂O), 6.49 (d, J=11.5 Hz, 1H, SiOC14H=CHHC=C(CH₃)CH₂), 6.00 (dd, J=11.5, 11.5 Hz, 1H, SiOCH=C13HHC=C), 5.59 (d, J=11.5 Hz, 1H, SiOCH=CHC12H), 4.89 (d, J=11.4, 1H, PhC6H₂), 4.42 (d, J=11.4, 1H, PhC6H₂), 3.61 (d, J=6.9 Hz, 1H, C2HOBn), 2.24 (d, J=6.9 Hz, 2H,
O=CC5H2C), 2.21-2.13 (m, 1H, C7H(CH3)2), 2.05-1.87 (m, 2H, C10H2C(Me)=C), 1.77-1.40 (m, 2H, C9H5CH2C(Me)=C), 1.66 (s, 3H, C=C(C15H3)CH2), 1.52-1.39 (m, 1H, C3HCH(CH3)2), 1.19 (s, 3H, C16H3), 1.08 (s, 9H, OSiC(CH3)3Ph2), 1.04 (d, J=6.9 Hz, 3H, CH(C8H3)2), 0.92 (d, J=6.9 Hz, 3H, CH(C8H3)2); 13C NMR (75 MHz, CDCl3) Δ216.3, 143.6, 138.3, 135.6, 133.7, 132.8, 130.2, 128.4, 128.0, 127.7, 120.1, 110.6, 81.5, 72.5, 56.6, 51.9, 41.9, 41.7, 35.6, 26.9, 25.4, 23.4, 23.0, 19.6, 17.1; HRMS (FAB+) exact mass calculated for (C39H50O3Si) requires m/z 594.3529, found m/z 594.3529.

Acetal 43. Cyclopentanone 44 was thoroughly dried prior to use (azeotroped with benzene, and dried though a Na2SO4 plug). To a -78 °C solution of diisopropyl amine (24 mL, 0.17 mmol) in 0.2 mL THF was added 55 mL (0.13 mmol) of nBuLi (2.42M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to -78 °C, and 39.9 mg (0.067 mmol) of cyclopentanone # was added in 0.2 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 42 mg (0.27 mmol) of 4,4-diethoxy-2-butyn-1-ol was added in 0.1 mL THF. After stirring for 20 minutes, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH4Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL EtOAc. The combined organic extracts were washed with brine, dried over Na2SO4, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (1:5 EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 56% yield (28.2 mg). Note: product decomposes over prolonged exposure to silica gel. Chromatography should be done relatively rapidly. IR (film) 3468, 3422, 2966, 2896, 1730, 1614, 1460, 1112, 1020 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.97-7.25 (m, 15H, (C6H5)2(CH3)3CSiO and (C6H5)CH2O),
6.49 (d, J=11.7 Hz, 1H, SiOC14H=CHHC=C(CH₃)CH₂), 6.00 (dd, J=11.7, 11.7 Hz, 1H, SiOCH=CHC12H), 5.20 (s, 1H, C20H(OEt)₂), 4.97 (d, J=11.7, 1H, PhC6H₂), 4.56-4.52 (m, 1H, (HO)C17H), 4.49 (d, J=11.4 Hz, 1H, PhC6H₂), 3.81 (d, J=6.3 Hz, 1H, C20H(OEt)₂), 3.76-3.45 (m, 4H, CH(OC₂H₂CH₃)₂), 3.36 (br d, J=10.5 Hz, 1H, HC17O), 2.17-1.68 (m, 6H, C₉H₂CH₂C(Me)=C and C₁₀H₂C(Me)=C and C₇H(CH₃)₂ and C₃HCH(CH₃)₂), 1.65 (s, 3H, C=C(C₁₅H₃)CH₂), 1.56 (s, 3H, C₁₆H₃), 1.19 (m, 6H, C(OCH₂C₂H₃)₂), 1.08 (s, 9H, OSi(CH₃)₂Ph₂), 1.01 (d, J=6.0 Hz, 3H, CH(C₈H₃)₂), 0.92 (d, J=6.0 Hz, 3H, CH(C₈H₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ 218.3, 143.8, 138.0, 135.7, 135.0, 133.7, 132.9, 130.2, 129.9, 128.5, 128.0, 127.9, 120.4, 110.7, 91.5, 84.3, 73.0, 64.1, 61.1, 60.6, 53.6, 45.0, 37.3, 35.3, 29.9, 25.6, 23.5, 23.2, 21.3, 19.5, 17.0, 15.3; HRMS (FAB+) exact mass calculated for (C₄₇H₆₂O₆Si) requires m/z 750.4316, found m/z 750.4315.

nOe analysis used to determine relative stereochemistry around the cyclopentanone ring:

Benzoate ester 50. Cyclopentanone 4 was thoroughly dried prior to use (azeotroped with benzene, and dried though a Na₂SO₄ plug). To a −78 °C solution of
diisopropyl amine (29 mL, 0.21 mmol) in 0.25 mL THF was added 70 mL (0.17 mmol) of nBuLi (2.41M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 50.0 mg (0.084 mmol) of cyclopentanone # was added in 0.15 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 63 mg (0.34 mmol) of benzoic acid 4-oxo-but-2-ynyl ester was added in 0.15 mL THF. After stirring for 20 minutes, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH₄Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (1:5 EtOAc/Hexamnes) to afford the title compound as a clear colorless oil in 50% yield (32.9 mg): ¹H NMR (300 MHz, CDCl₃) [8.05-7.25 (m, 20H, (C₆H₅)₂(C₂H₅)₂CSiO and (C₆H₅)CH₂O and O=C(C₆H₅)), 6.47 (d, J=11.4 Hz, 1H, SiOC14H=CHHC=C(CH₂)CH₂), 5.95 (dd, J=11.4, 11.4 Hz, 1H, SiOCH=C13HHHC=C), 5.63 (d, J=11.4 Hz, 1H, SiOCH=CHC12H), 5.04 (d, J=11.7 Hz, 1H, PhC6H₅), 4.86 (s, 2H, C20H₂), 4.67 (m, 1H, (HO)C17H), 4.46 (d, J=11.7 Hz, 1H, PhC6H₅), 4.15 (d, J=3.9 Hz, 1H, C2HOBn), 3.69 (br d, J=6.9 Hz, 1H, HC17OH), 2.57 (d, J=7.2 Hz, 1H, O=CC5HC), 2.23-1.70 (m, 6H, C9H₃CH₂C(Me)=C and C10H₅C(Me)=C and C7H(CH₃)₂ and C3H(CH₃)₂ and C3H(CH₃)₂, 1.65 (s, 3H, C=C(C15H₅)CH₂), 1.57 (s, 3H, C16H₃), 1.06 (s, 9H, OSiC(CH₃)₃Ph₂), 1.04 (d, J=6.3 Hz, 3H, CH(C8H₅)₂), 0.92 (d, J=6.3 Hz, 3H, CH(C8H₅)₂).

Amide 48. Cyclopentanone 4 and 4-oxo-but-2-ynoic acid dimethylamide were thoroughly dried prior to use (azeotroped with benzene, and dried though a Na₂SO₄ plug).
To a −78 °C solution of diisopropyl amine (17 mL, 0.12 mmol) in 0.2 mL THF was added 41 mL (0.098 mmol) of nBuLi (2.41M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 29.4 mg (0.049 mmol) of cyclopentanone # was added in 0.1 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 25 mg (0.20 mmol) of 4-oxo-but-2-ynoic acid dimethylamide was added in 0.2 mL THF. After stirring for 20 minutes, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH₄Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (10-40-50% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 32% yield (11.0 mg): IR (film) 3414, 3360, 2935, 2866, 2248, 1746, 1622, 1460, 1398, 1174 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70-7.28 (m, 15H, (C₆H₅)₂(CH₃)₃CSiO and (C₆H₅)CH₂O), 6.52 (d, J=12.0 Hz, 1H, SiOC14H=CHHC=C(CH₃)CH₂), 6.01 (dd, J=12.0, 12.0 Hz, 1H, SiOCH=C13HHC=C), 5.60 (d, J=12.0 Hz, 1H, SiOCH=CHC12H), 4.93 (d, J=11.5, 1H, PhC6H₂), 4.67-4.65 (m, 1H, (HO)C17H), 4.52 (d, J=11.5 Hz, 1H, PhC6H₂), 3.89 (d, J=7.0 Hz, 1H, C2HOBn), 3.53 (br d, J=8.5 Hz, 1H, HC17OH), 3.11 (s, 3H, N(CH₃)(CH₃)), 2.94 (s, 3H, N(CH₃)(CH₃)), 2.62 (d, J=4.0 Hz, 1H, O=CC5HC), 2.19-2.09 (m, 6H, C9H₂CH₂C(Me)=C and C10H₃C(Me)=C and C7H(CH₃)₂ and C3HCH(CH₃)₂), 1.66 (s, 3H, C=C(C15H₅)CH₂), 1.24 (s, 3H, C16H₃), 1.08 (s, 9H, OSi(C(CH₃)₂)Ph₂), 1.09 (d, J=6.0 Hz, 3H, CH(C8H₃)₂), 0.92 (d, J=6.0 Hz, 3H, CH(C8H₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ 219.1, 154.1, 153.6, 143.9, 138.0, 135.7, 134.4, 133.1, 132.9, 130.2, 128.6, 128.0, 127.9, 120.4, 119.3, 110.6, 90.1, 81.1, 73.1, 63.5, 61.1, 53.0, 43.3, 38.3, 35.6, 35.2, 34.2, 26.8, 25.8, 23.5, 22.5, 19.5, 16.8; HRMS (FAB+) exact mass calculated for (C₄₃H₅₇NO₃Si) requires m/z 720.4084, found m/z 720.4085.
**Ester 49.** Cyclopentanone 4 and 4-oxo-but-2-enoic acid methyl ester were thoroughly dried prior to use (azeotroped with benzene, and dried though a Na$_2$SO$_4$ plug). To a −78 °C solution of diisopropyl amine (20 mL, 0.14 mmol) in 0.2 mL THF was added 49 mL (0.11 mmol) of nBuLi (2.32M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 33.8 mg (0.057 mmol) of cyclopentanone # was added in 0.1 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 50 mg (0.44 mmol) of 4-oxo-but-2-enoic acid methyl ester was added in 0.2 mL THF. After stirring for 20 minutes, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH$_4$Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL EtOAc. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (5-10-20% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 53% yield (21.3 mg): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74-7.25 (m, 15H, (C$_6$H$_3$)$_2$(CH$_3$)$_3$CSiO and (C$_6$H$_3$)CH$_2$O), 7.01 (dd, $J=6.3$, 16.2, 1H, C18H), 6.48 (d, $J=11.4$ Hz, 1H, SiOC14H=CHHC=C(CH$_3$)CH$_2$), 6.10 (d, $J=16.0$, 1H, C19H), 5.98 (dd, $J=11.4$, 11.4 Hz, 1H, SiOCH=C13HHC=C), 5.60 (d, J=11.4 Hz, 1H, SiOCH=CHC12H), 5.03 (d, J=11.5, 1H, PhC6H$_2$), 4.55-4.50 (m, 1H, (HO)C17H), 4.52 (d, J=11.5 Hz, 1H, PhC6H$_2$), 3.83 (d, J=7.8 Hz, 1H, C2HOBn), 3.81 (br d, J=7.0 Hz, 1H, HC17OH), 3.65 (s, 3H, CO$_2$Me), 2.42 (d, J=4.0 Hz, 1H, O=CC5HC), 2.21-1.45 (m, 6H, C9H$_2$CH$_2$C(Me)=C and C10H$_2$C(Me)=C and C7H(CH$_3$)$_2$) and C3HCH(CH$_3$)$_2$), 1.64 (s, 3H, C=C(C15H$_3$)CH$_2$), 1.18 (s, 3H, C16H$_3$), 1.08 (s, 9H, OSiC(CH$_3$)$_3$Ph$_2$), 1.08 (m, 3H, CH(C8H$_3$)$_2$), 0.92 (d, J=6.0 Hz, 3H, CH(C8H$_3$)$_2$); HRMS (FAB+) exact mass calculated for (C$_{44}$H$_{55}$O$_6$Si) requires m/z 707.3768, found m/z 707.3773.
Tetraene 56. Cyclopentanone 4 and 4-oxo-but-2-enoic acid methyl ester were thoroughly dried prior to use (azeotroped with benzene, and dried though a Na₂SO₄ plug). To a −78 °C solution of diisopropyl amine (25 μL, 0.16 mmol) in 0.2 mL THF was added 57 μL (0.13 mmol) of nBuLi (2.24M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 38.0 mg (0.064 mmol) of cyclopentanone # was added in 0.1 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 51 mg (0.45 mmol) of 4-oxo-but-2-enoic acid methyl ester was added in 0.2 mL THF. After stirring for 2 hours, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH₄Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (5-10-20% EtOAc/Hexanes) to afford the title compound as a bright yellow oil in 20% yield (8.8 mg). Owing to the somewhat unstable nature of the compound, it was immediately taken onto the next step without full characterization: ¹H NMR (300 MHz, CDCl₃) δ 8.58 (d, J=13.0, 19.8 Hz, 1H, C18H), 7.72-7.20 (m, 15H, (C₉H₈)₂(CH₃)₃SiO and (C₅H₃)CH₂O), 6.54 (d, J=11.7 Hz, 1H, SiOC14H=CHHC=C(CH₃)CH₂), 6.18 (d, J=13.0 Hz, 1H, C17H), 6.09 (d, 19.9 Hz, 1H, C19H), 6.00 (dd, J=11.7, 11.7 Hz, 1H, SiOCH=C13HHC=C), 5.57 (d, J=11.7 Hz, 1H, SiOCH=CHC12H), 5.85 (s, 1H, C19H), 4.80 (d, J=11.5, 1H, PhC6H₂), 4.46 (d, J=11.5 Hz, 1H, PhC6H₂), 3.78 (s, 3H, CO₂Me), 3.76 (m, 1H, C2HOBN), 2.06-1.52 (m, 6H, C₉H₈CH₂C(Me)=C and C10H₆C(Me)=C and C7H(CH₃)₂) and C3HCH(CH₃)₂), 1.58 (s, 3H, C=C(C15H₃)CH₂), 1.23 (s, 3H, C16H₃), 1.08 (s, 9H, OSiC(CH₃)₃Ph₂), 0.98 (d, J=6.6 Hz, 3H, CH(C8H₃)₂), 0.89 (d, J=6.6 Hz, 3H, CH(C8H₃)₂); HRMS (FAB+) exact mass calculated for (C₄₄H₇₈O₅Si) requires m/z 690.3741, found m/z 690.3739.
**Tricycle 57.** A solution of tetraene 56 (4.1 mg, 0.0059 mmol) in CDCl₃ (0.5 mL) was heated to 60 °C for 24 hours. As the reaction progressed, the solution turned from its initial almost fluorescent yellow color to a light, pale yellow color. The reaction was worked up by removing volatiles *in vacuo*. Purification by silica gel chromatography (5% EtOAc/Hexanes) afforded the title compound as a pale yellow oil in 51% yield (2.1 mg): IR (film) 2926, 2850, 2358, 1723, 1649, 1459, 1273, 1159, 1115 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.73-7.11 (m, 15H, (C₆H₅)₂(CH₃)₃CSiO and (C₆H₅)CH₂O), 7.13 (dd, J=7.0, 15.5 Hz, 1H, C₁₈H), 6.27 (d, J=12.0 Hz, 1H, C₁₄H), 5.66 (dd, J=1.0, 15.5 Hz, 1H, C₁₉H), 4.96 (dd, J=9.5, 12.5 Hz, 1H, C₁₃H), 4.85 (d, J=12.0 Hz, 1H, PhC₆H₂), 4.36 (d, J=12.0 Hz, 1H, PhC₆H₂), 3.68 (s, 3H, CO₂(CH₃)), 3.51 (d, J=5.5 Hz, 1H, C₂HOBn), 2.60 (dt, J=1.5, 9.5 Hz, C₁₇H), 2.51 (dd, J=9.0, 9.0, 1H, C₁₂H), 2.15-2.13 (m, 1H, C₉H), 2.08-2.03 (m, 1H, C₁₀H), 1.90-1.86 (m, 1H, C₃H), 1.64 -1.52 (m, 2H, C₉H, C₁₀H), 1.48-1.41 (m, 1H, C₇H), 1.12 (s, 3H, C₁₅H₃), 1.08 (s, 9H, OSi(CH₃)₃Ph₂), 1.03 (d, J=7.0 Hz, 3H, CH(C₈H₃)₂), 0.93 (s, 3H, C₁₆H₃), 0.89 (d, J=7.0 Hz, 3H, CH(C₈H₃)₂); connectivity of C₁₉-C₁₈-C₁₇-C₁₂-C₁₃-C₁₄ determined by 2D COSY analysis; ¹³C NMR (125 MHz, CDCl₃) δ 215.2, 166.9, 148.3, 142.8, 135.7, 130.2, 128.4, 128.0, 127.9, 127.6, 120.9, 110.2, 81.9, 72.0, 55.4, 54.3, 54.2, 51.5, 44.1, 42.1, 41.1, 33.8, 29.9, 25.1, 24.8, 22.7, 22.4, 19.5, 18.1; LRMS (MALDI) exact mass calculated for (NaC₄₆H₄₄O₅Si) requires m/z 713.36, found m/z 713.64.
Diketoester 58. Cyclopentanone 4 was thoroughly dried prior to use (azeotroped with benzene, and dried though a Na₂SO₄ plug). To a −78 °C solution of diisopropyl amine (20 mL, 0.14 mmol) in 0.2 mL THF was added 49 mL (0.11 mmol) of nBuLi (2.27M in hexanes, freshly titrated). The solution was warmed to 0 °C and stirred for 20 minutes. The reaction was then cooled back to −78 °C, and 33.1 mg (0.055 mmol) of cyclopentanone # was added in 0.1 mL THF + 0.1 mL THF (washing vessel). The solution was stirred at that temperature for 40 minutes, at which time 75 mL of 3-chlorocarbonyl-acrylic acid methyl ester was added. After stirring for 20 minutes, the reaction was quenched by pouring into a solution of cooled (0 °C) saturated NH₄Cl solution and stirring rapidly for 3 minutes. The mixture was partitioned and the aqueous layer was washed with 3 x 15 mL Et₂O. The combined organic extracts were washed with brine, dried over Na₂SO₄, and filtered. Volatiles were removed in vacuo and the resultant crude oil was purified by silica gel chromatography (5% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 54% yield (20.0 mg): IR (film) 3460, 3074, 2958, 2866, 1730, 1468, 1429, 1259, 1112 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78-7.09 (m, 15H, (C₆H₅)₂CH₂CSiO and (C₅H₃)CH₂O), 6.82 (s, 1H, C18H), 6.66 (d, J=11.7 Hz, 1H, SiOC14H=CHHC=C(CH₃)CH₃), 6.35 (dd, J=11.7, 11.7 Hz, 1H, SiOCH=C13HHC=C), 5.60 (d, J=11.7 Hz, 1H, SiOCH=CHC12H), 5.85 (s, 1H, C19H), 4.65 (d, J=11.7, 1H, PhC6H₂), 4.31 (d, J=11.7 Hz, 1H, PhC6H₂), 4.17 (d, J=6.0 Hz, 1H, C2HOBn), 3.53 (br d, J=8.5 Hz, 1H, HC17OH), 3.19 (s, 3H, CO₂Me), 2.10-1.42 (m, 6H, C9H₂CH₂C(Me)=C and C10H₂C(Me)=C and C7H(CH₃)₂) and C3HCH(CH₃)₂), 1.55 (s, 3H, C=C(C15H₅)CH₂), 1.19 (s, 3H, C16H₃), 1.07 (s, 9H, OSiC(CH₃)₃Ph₂), 0.91 (d, J=6.6 Hz, 3H, CH(C8H₃)₂), 0.85 (d, J=6.6 Hz, 3H, CH(C8H₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ 198.6, 165.3, 162.5, 149.4, 143.3, 139.3, 135.6, 135.3, 134.9, 134.4, 133.2, 132.8, 129.8, 129.0, 128.4, 127.9, 127.1, 119.8, 110.7, 83.3, 73.1, 54.8, 52.8, 47.4, 39.3, 35.6, 30.1, 26.9, 25.5, 23.9, 22.6, 19.6, 17.0.
Synthesis of Intermediates towards the Intermolecular Diels-Alder Strategy

Diene 61. To a solution of diene 42 (317 mg, 0.87 mmol) in 3 mL of DMF was added imidazole (147 mg, 2.1 mmol) followed by TBSCl (156 mg, 1.04 mmol). The solution was stirred for 3 hours at room temperature. Saturated NH₄Cl solution was added to the reaction, and the mixture was then partitioned. The organic extracts were washed with 3 x 10 mL of Et₂O, brine, dried over Na₂SO₄, filtered, then concentrated in vacuo. The resultant crude oil was purified by silica gel chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 93% yield (380 mg): IR (film) 2935, 2858, 1614, 1468, 1429, 1251, 1104 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.70 (m, 4H, ArH), 7.49-7.38 (m, 6H, ArH), 6.53 (d, J=11.4 Hz, 1H, TBDPSOCH=CHHC=C(CH₃)CH₂), 6.05 (dd, J =11.4, 11.4 Hz, 1H, TBDPSOCH=CHHC=C(CH₃)CH₂), 5.64 (d, J=11.4 Hz, 1H, TBDPSOCH=CHCH), 3.67 (t, J=7.2 Hz, 2H, CH₂OTBS), 2.22 (t, J=7.2 Hz, 2H, TBSOCH₂CH₂C=C), 1.70 (s, 3H, Ph₂(CH₃)₃CSiOCH=CHHC=C(CH₃)CH₂), 1.11 (s, 9H, OSiC(CH₃)₃Ph₂), 0.89 (s, 9H, OSiC(CH₃)₃Ph₂), 0.05 (s, 6H, OSi[C(CH₃)₃](CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 135.6, 132.8, 130.6, 130.2, 128.1, 122.3, 110.7, 62.5, 43.6, 26.8, 26.4, 19.5, 18.5, 17.3, -4.8.
**Bicycle 63.** A solution of maleic anhydride (15 mg, 0.15 mmol) and diene 61 (25 mg, 0.52 mmol) in toluene (0.1 mL) was heated to 110 °C for 5 hours. The reaction was then concentrated in vacuo, and the resultant residue was purified by silica gel chromatography to afford the title compound as an oil in 57% yield (49.4 mg): IR (film) 1789, 1720, 1600, 1425, 1360, 1120 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) à 7.78-7.09 (m, 10H, ArH), 5.69 (d, J=9.9 Hz, 1H, C4H), 5.38 (dd, J=4.8, 9.9 Hz, 1H, C3H), 4.55 (dd, J=5.0, 5.9 Hz, 1H, C2H), 3.75 (t, J=6.6 Hz, 2H, C9H₂), 3.32 (dd, J=6.0, 9.3 Hz, 1H, C1H), 3.14 (d, J=9.3, 1H, C6H), 2.37 (ddd, J=6.9, 6.9, 13.5 Hz, 1H, C8H), 2.02 (ddd, J=6.8, 7.8 Hz, 1H, C8H), 1.08 (s, 3H, C7H), 1.01 (s, 9H, OSi[C(CH₃)₃](CH₃)₂) 0.84 (s, 9H, OSiC(CH₃)₃Ph₂), 0.04 (s, 6H, OSi[C(CH₃)₃](CH₃)₂); \(^{13}\)C NMR (125 MHz, CDCl₃) à 170.5, 169.8, 139.8, 136.5, 135.4, 130.3, 127.7, 125.9, 62.1, 60.0, 49.0, 46.9, 40.7, 31.8, 26.8, 26.2, 22.9, 19.2, 14.3, -5.2; HRMS (FAB+) exact mass calculated for (C₃₃H₄₆O₅Si₂) requires m/z 579.2962, found m/z 579.2967.

nOe analysis used to determine relative stereochemistry:
Diester 64. To a solution of cyclohexadiene 63 (7.6 mg) in 0.5 mL of methanol was added triethylamine (4 µL). The solution was stirred for 3 hours, then quenched with 1M NaHSO₄ solution (0.1 mL). The mixture was partitioned and the aqueous extracts were washed with EtOAc. The organic extracts were washed with 3 x 10 mL of EtOAc, brine, dried over Na₂SO₄, filtered, then concentrated in vacuo. The resultant crude oil was purified by silica gel chromatography (10% EtOAc/Hexanes) to afford the title compound as a clear colorless oil in 90% yield (7.3 mg): IR (film) 2950, 2858, 1746, 1429, 1197, 1104 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76-7.36 (m, 10H, ArH), 5.62 (d, J=10.5 Hz, 1H, C4H), 5.44 (dd, J=2.7, 10.3 Hz, 1H, C3H), 4.44 (m, 1H, C2H), 3.76 (m, 2H, C9H₂), 3.69 (s, 3H, CO₂CH₃), 3.66 (s, 3H, CO₂CH₃), 3.07 (dd, J=4.2, 5.0 Hz, 1H, C1H), 2.70 (d, J=4.2, 1H, C6H), 2.00-1.92 (m, 1H, C8H), 1.63-1.53 (m, 1H, C8H), 1.13 (s, 3H, C7H), 1.02 (s, 9H, OSi[C(CH₃)₃][CH₃]₂), 0.88 (s, 9H, OSi[C(CH₃)₃]Ph₂), 0.05 (s, 6H, OSi[C(CH₃)₃][CH₃]₂); ¹³C NMR (125 MHz, CDCl₃) δ 172.5, 171.9, 136.4, 135.7, 134.1, 129.9, 127.8, 126.2, 67.0, 59.9, 51.8, 51.7, 46.1, 40.0, 36.3, 28.7, 27.1, 26.2, 19.4, 18.5, -5.1; HRMS (FAB+) exact mass calculated for (C₃₅H₅₁O₆Si₂) requires m/z 623.3224, found m/z 623.3222.