THE SYNTHESIS OF A COMPOUND SUITABLE FOR THE ELABORATION TO THE C-RING OF NITIOL

by

JACQUELINE C. S. WOO
B.Sc., Simon Fraser University, 2002

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE in

THE FACULTY OF GRADUATE STUDIES
(Department of Chemistry)

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
September 2004

© Jacqueline C. S. Woo, 2004
Library Authorization

In presenting this thesis in partial fulfillment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

JACQUELINE C.S. WOO

04/10/2004

Name of Author (please print)

Date (dd/mm/yyyy)

Signature

Title of Thesis: THE SYNTHESIS OF A COMPOUND SUITABLE FOR THE ELABORATION TO THE C-RING OF NITIOL

Degree: H.Sc. Year: 2004

Department of CHEMISTRY

The University of British Columbia
Vancouver, BC Canada
Abstract

Compound 34 was a synthetic target suitable for the elaboration to the C-ring of nitiol (1), and was synthesized over six steps from the known alcohol 39. A convenient method for the synthesis of N-methoxy-N-methyl amides was also developed.

Ester 38 was synthesized from alcohol 39, and was subjected to an Ireland-Claisen rearrangement to give acid 37. This step established the stereochemical relationship of the substituents of 34. Carboxylic acid 37 was converted to amide 51 by the use of triethylamine, methanesulfonyl chloride, and N,O-dimethylhydroxylamine. This method was also used in the synthesis of seven other examples of N-methoxy-N-methyl amides with good to excellent yields (61-84 %). Amide 51 was converted to vinyl ketone 36, and subsequent ring-closing metathesis afforded cyclopentenone 35 with a cis/trans ratio of 12:1. A 1,4-hydride reduction of cyclopentenone 35 and the subsequent trapping of the enolate as a trifluoromethanesulfonate gave 34 with a cis/trans ratio of 9:1.
# Table of Contents

Title Page i  
Abstract ii  
Table of Contents iii  
List of Tables vi  
List of Figures vii  
List of Schemes viii  
List of Abbreviations and Symbols ix  
Acknowledgements xii  

1. Introductions  
   1.1 Isolation and biological activity 1  
   1.2 Biosynthesis 1  
   1.3 Retrosynthetic analysis 3  
   1.4 Synthetic challenges of the contiguous stereocentres of the C-ring 3  
   1.5 Examples from the literature 4  
   1.6 Retrosynthetic analysis of trifluoromethanesulfonate 34 9  

2. Discussion  
   2.1 Synthesis of ester 38 10  
   2.2 Synthesis of acid 37 12  
   2.3 Synthesis of vinyl ketone 36 15  
   2.4 Synthesis of enone 35 24  
   2.5 Trifluoromethanesulfonate 34 26  
   2.6 Concluding remarks 29  

3. Experimental  
   General 30  
   (+)-(3E)-pent-3-en-2-ol 31  
   (2R,3E)-pent-3-en-2-ol (39) 32  
   (1R,2E)-1-methylbut-2-enyl (2R)-methoxy(phenyl)acetate (41) 32
pent-3-yn-2-one

(±)-pent-3-yn-2-ol (48)

(1R,2E)-1-methylbut-2-enyl 5-[(4-methoxybenzyl)oxy]pentanoate (38)

2,2,2-trifluoroethyl 5-(benzoxo)pentanoate (46)

(±)-1-methylbut-2-ynyl 5-[(4-methoxybenzyl)oxy]pentanoate (49)

(±)-(2Z)-1-methylbut-2-enyl 5-[(4-methoxybenzyl)oxy]pentanoate (50)

(2S,3S,4E)-2-[(4-methoxybenzyl)oxy]propyl]-3-methylhex-4-enoic acid (37)

(±)-(2R,3S,4E)-2-{3-[(4-ethylbenzyl)oxy]propyl}-3-methylhex-4-enoate (52)

(±)-methyl (2S,3S,4E)-2-{3-[(4-methoxybenzyl)oxy]propyl]-3-methylhex-4-enoate (53)

(2S,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethylhex-4-enamide (51)

(±)-(2R,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethyl hex-4-enamide (67)

(±)-(3S)-3-[(1S,2E)-1-methylbut-2-ynyl]tetrahydro-2H-pyran-2-one (52)

N-methoxy-N-methylbenzamide (61)

N-methoxy-N-methyl-1-phenylcyclohexanecarboxamide (62)

N-methoxy-N-methyl-2-phenylcyclopropanecarboxamide (63)

N-methoxy-N-methyl-1,1′-biphenyl-2-carboxamide (64)

N-methoxy-N-methyl-2,2-diphenylacetamide (65)

(2S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (60)

tert-butyl (2S)-2-[[methoxy(methyl)amino]carbonyl]pyrrolidine-1-carboxylate (66)

(4S,5S,6E)-4-[(4-methoxybenzyl)oxy]propyl]-5-methyl octa-1,6-dien-3-one (36)

(±)-(4R,5S,6E)-4-[(4-methoxybenzyl)oxy]propyl]-5-methyl octa-1,6-dien-3-one (68)
(4S,5S)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methyl cyclopent-2-en-1-one (35) 49
(±)-(4S,5R)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methylcyclopent-2-en-1-one (69) 49
(±)-(2S,3S)-2-{3-[(4-methoxybenzyl)oxy]propyl}-3-methyl cyclopentanone (70) 50
(4S,5S)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methylcyclopent-1-en-1-yl trifluoromethanesulfonate (34) 51
(±)-(4S,5R)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methylcyclopent-1-en-1-yl trifluoromethanesulfonate (71) 51
Triflate 34 from cyclopentanone 70 52

4. References 53

Appendix: Selected Spectra 56
List of Tables

**Table 1:** Construction of amide 51 using peptide coupling reagents. 16

**Table 2:** Construction of amide 44 by the formation of an acyl halide *in situ.* 17

**Table 3:** Attempted conversion of ester 53 to amide 51. 18

**Table 4:** Attempted direct conversion from acid 37 to ketone 36. 19

**Table 5:** Examples of Weinreb amides. 23

**Table 6:** Chemical shift assignment for enone 35 and epimeric enone 69. 26
List of Figures

Figure 1: Structures of nitiol (1) and fusaproliferin (2). 1
Figure 2: Geranylfarnesyl pyrophosphate (3) may be constructed from five isoprene units. 2
Figure 3: Structure of ikarugamycin. 5
Figure 4: Proposed mechanism of the Ni-mediated carbozincation reaction. 8
Figure 5: Structures of peptide-coupling reagents and additives. 15
Figure 6: Structure of byproduct 54. 21
Figure 7: Selected regions on the $^1$H NMR spectra of enone 35 and epimeric enone 69. 25
Figure 8: Structures of triflating reagents. 27
Figure 9: (a) GC analysis of a 1:1 mixture of 41 and 42. (b) GC analysis of 41 as the major diastereomer. 33
List of Schemes

Scheme 1: Previously proposed biosynthesis of 2.  
Scheme 2: Possible biosynthesis of 1.  
Scheme 3: Retrosynthetic analysis of 1.  
Scheme 4: The vinyl pseudohalide within fragment C could be derived from a ketone (cyclopentanone or cyclopentenone).  
Scheme 5: Epimerization and alkene isomerization of methyl 12-oxo-cis-10,15-phytodienoate (5).  
Scheme 6: The synthesis of vinyl stannane 11.  
Scheme 7: The synthesis of dialdehyde 18.  
Scheme 8: Remaining steps to the western five membered ring portion of ikarugamycin by Whitesell and Minton.  
Scheme 9: Synthesis of 12-oxophytodienoic acid (26).  
Scheme 10: Construction of iodide 31.  
Scheme 11: Remaining sequence to (+)-methyl epijasmonate (27).  
Scheme 12: Retrosynthetic analysis of triflate 34  
Scheme 13: Synthesis of ester 38.  
Scheme 14: The Ireland-Claisen rearrangement of ester 31.  
Scheme 15: Pericyclic transition state of the Ireland-Claisen rearrangement.  
Scheme 16: Attempted synthesis of epimeric acid via a Z silyl ketene acetal.  
Scheme 17: Construction of ester 50.  
Scheme 18: Construction of epimeric acid 47.  
Scheme 19: Possible mechanism of the formation of lactone 52.  
Scheme 20: Direct conversion of sterically hindered carboxylic acids into diazoketones by in situ formation of an acyl mesylate.  
Scheme 21: Conversion of less sterically hindered carboxylic acids by in situ formation of a mixed anhydride with methanesulfonic acid.  
Scheme 22: Synthesis of epimeric enone 69.  
Scheme 23: Construction of triflate 34.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetate</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectra)</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celcius</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wavenumbers</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyltartrate</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>E</td>
<td>entgegen (opposite side in E, Z nomenclature)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramid e</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
</tbody>
</table>
\textsuperscript{1}Pr \quad \text{isopropyl}

J \quad \text{coupling constant}

LDA \quad \text{lithium diisopropylamide}

LHMDS \quad \text{lithium 1,1,1,3,3,3-hexamethyldisilazide}

m \quad \text{multiplet}

Me \quad \text{methyl}

mg \quad \text{milligram(s)}

min \quad \text{minute(s)}

mL \quad \text{milliliter(s)}

\mu L \quad \text{microliter(s)}

mmol \quad \text{millimole(s)}

m.p. \quad \text{melting point}

MS \quad \text{mass spectrometry}

Ms \quad \text{methanesulfonyl}

NMR \quad \text{nuclear magnetic resonance}

OTf \quad \text{triflate}

p \quad \text{para}

Ph \quad \text{phenyl}

PhNTf\textsubscript{2} \quad \text{N-phenyltrifluoromethanesulfonimide}

OPiv \quad \text{pivalate}

PMB \quad \text{para methoxybenzyl}

PP \quad \text{pyrophosphate}

ppm \quad \text{parts per million}

R \quad \text{rectus (right) (configuration } R, S \text{ about a stereogenic center)}

rt \quad \text{room temperature}

rxn \quad \text{reaction}

s \quad \text{singlet}

S \quad \text{sinister (left) (configuration } R, S \text{ about a stereogenic center)}

sm \quad \text{starting material}

S\text{N}2 \quad \text{nucleophillic biomolecular substitution}
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>t</td>
<td>time</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>wt/v</td>
<td>weight-to-volume ratio</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen (same side in $E, Z$ nomenclature)</td>
</tr>
<tr>
<td>±</td>
<td>racemic</td>
</tr>
</tbody>
</table>
Acknowledgements

I would like to thank my research supervisor, Dr. Gregory Dake, for his support and guidance throughout my studies and during the preparation of this manuscript. He has taught me to think critically, and to become a better chemist. I am very grateful to have the opportunity to carry out my graduate research in his group.

I would like to thank past and present members of the Dake group: Michaël Fenster, Michael Wilson, Erik Fenster, Paul Hurley, Leah Easton, Melissa Fleury, and Tyler Harrison. They have pushed me to limits that I didn't think I was capable of reaching, both in chemistry and in having fun. I am especially thankful to Michael Wilson for his help with the nitiol project.

I would like to thank members of the Scheffer group for their help with the chiral HPLC and GC-MS, and also Alison Lee and Erin MacLachlan for their help with inorganic chemistry. I would also like to thank the NMR and analytical staff at the University of British Columbia. None of the research would have been possible without their help and expertise.

I would like to thank Matthew Ring, my companion. He has shown an incredible amount of love, patience, and belief in me. I am blessed to have him share the good times and tough times.

Finally, I am forever thankful to Yuk-King Tam and Shing-Chi Woo, my mom and dad; Nelson Woo, my brother; and Melissa Woo, my sister. I could not have done it without their love and encouragement.
1. Introduction

1.1 Isolation and biological activity

Nitiol (1) is a novel sesterterpenoid isolated from the plant *Gentianella nitida* (Figure 1). This biennial medicinal plant is found in the Andes region and used in traditional Peruvian folk medicine as a remedy for hepatitis and obesity. A methanol extract of the plant was partitioned between dichloromethane and water, and nitiol was isolated from the dichloromethane fraction by chromatographic methods. Preliminary investigations have found that 1 acts as a potent enhancer of interleukin-2 in human T cell lines; The IL-2 mRNA level in the cells treated with 1 was about three times higher than that in the vehicle (ethanol) treated cells. Since nitiol has a distinctly different structure from the known modulators of the IL-2 gene expression, it is a possible tool in the discovery of the novel signal transduction pathways guiding the transcription of the IL-2 gene.

![Structure of nitiol (1) and fusaproliferin (2).](image)

**Figure 1:** Structure of nitiol (1) and fusaproliferin (2).

1.2 Biosynthesis

The sesterterpenes are the least studied amongst all other groups of natural terpenoids. The biogenetic precursor for the C₂₅ sesterterpenes is thought to be geranylgeranyl pyrophosphate (3), and it may be constructed from five isoprene units linked head-to-tail in a linear fashion (Figure 2).
Figure 2: Geranyl farnesyl pyrophosphate (3) may be constructed from five isoprene units.

The carbon skeleton of 1 has a similar structure to that of fusaproliferin (2), a toxic sesterterpene (Figure 1). The biosynthesis of 2 has been proposed to involve a series of cyclizations and hydride shifts starting from 3 (Scheme 1). The similarity in structures between 1 and 2 led to a closely related proposed biosynthesis of 1 (Scheme 2). This pathway involves an initial cyclization of 3. A 1,5-hydride shift accompanied by cyclization, the loss of a proton, and alkene isomerization would account for the final ring structure of 1.

Scheme 1: Previously proposed biosynthesis of 2.

Scheme 2: Possible biosynthesis of 1.
1.3 Retrosynthetic analysis

Disconnection at the C1-C2 bond results in an uncyclized precursor 4 (Scheme 3). It was envisioned that a metalmethylation of the terminal alkyne of 4, followed by a carbonyl addition or a tandem carbometalation–SN2 displacement would provide this ring-forming bond. Subsequent disconnection at the C10-C11 bond divides nitol into fragments A and C. The functional group, Y, on the A-ring fragment was planned to be an organometallic species, and the Z group on the C-ring fragment a pseudohalide. This requirement allows the connection of the two fragments via a metal-mediated coupling reaction.

![Scheme 3: Retrosynthetic analysis of 1.](image)

1.4 Synthetic challenges of the contiguous stereocentres of the C-ring

The vinyl pseudohalide within fragment C could be derived from a cyclopentanone or cyclopentenone (Scheme 4). The key synthetic challenge to these compounds is to establish the cis relationship of the two contiguous stereogenic centers. Methyl 12-oxo-cis-10,15-phytodienoate (5) is a known compound having such a structural motif (Scheme 5). Conversion of 5 to its epimer 6 occurred when heated in a sealed tube under nitrogen at 190 °C for 15 minutes, and when treated with 0.1 N potassium hydroxide or 0.1 N hydrochloric acid at rt for 30 minutes. By heating 5 in a sealed tube for 2 h, about 50 % was converted to 7, its isomer with a more highly substituted alkene. These results indicate this type of substituted cyclopentenones could easily undergo epimerization and alkene isomerization. Their synthesis as well as the subsequent reaction must avoid conditions that involve heat, mild aqueous bases or acids.
Scheme 4: The vinyl pseudohalide within fragment C could be derived from a ketone (cyclopentanone or cyclopentenone).

Scheme 5: Epimerization and alkene isomerization of methyl 12-oxo-cis-10,15-phytodienoate (5).

1.5 Examples from the literature

There are various methods for synthesizing cis 2,3 disubstituted cyclopentanones and cyclopentenones. Towards the total synthesis of ikarugamycin (8) (Figure 3), Paquette and Barth utilized a hydrogenation strategy on cyclopentenone 9 to give a racemic mixture of cyclopentanone 10 (Scheme 6).\textsuperscript{10} Shapiro reaction of 10 afforded vinylstannane 11 with a noticeable decrease in the cis/trans ratio from 18:1 to 4:1. This example illustrates the challenge in safeguarding the thermodynamically less stable configuration of the cis substitution pattern on the five membered ring.
A different approach towards the total synthesis of ikarugamycin was demonstrated by Whitesell and Minton.\textsuperscript{11} Diene ester 13, available in 5 steps from ethylidene norbornene (12),\textsuperscript{12,13} was converted to a mixture of acetates (14a, 14b, 15a and 15b) with an exo/endo selectivity of 1.2:1 by the Woodward oxidation (Scheme 7). This mixture was treated with methanol and $p$-toluenesulfonic acid to give a mixture of diols (16 and 17). This mixture was cleaved to the dialdehyde 18, and subsequent reduction gave diol 19 (Scheme 8). Diol 19 was converted to dimesylate 20, and zinc reduction gave 21.

Scheme 6: The synthesis of vinylstannane 11.

![Scheme 6: The synthesis of vinylstannane 11.](image)

Scheme 7: The synthesis of dialdehyde 18.

![Scheme 7: The synthesis of dialdehyde 18.](image)
Scheme 8: Remaining steps to the western five-membered ring portion of ikarugamycin by Whitesell and Minton.

A different strategy in preparing cis-2,3-disubstituted cyclopentanones was demonstrated in the synthesis of 12-oxophytodienoic acid (26) by a Lewis acid catalyzed retro Diels-Alder reaction. Dienone 22 was made in five steps from benzoquinone and cyclopentadiene. The tricyclic structure of dienone 22 enforces chemical transformations of the enone on the less sterically hindered face. Dienone 22 underwent a three-component coupling by the sequential addition of cuprate 23, tributyltin chloride, and (Z)-pent-2-enyl iodide to give norbornene 24 (Scheme 9). The THP ether of 24 was cleaved by pyridinium p-toluenesulfonate (PPTS) and the resultant primary hydroxyl group was oxidized to give acid 25. Acid 25 underwent a retro Diels-Alder reaction to afford the natural product 26.

Scheme 9: Synthesis of 12-oxophytodienoic acid (26).
Another class of natural products that contain a cis 2,3 substitution motif on a cyclopentanone is the jasmonoids. One particular member of the jasmonoid family, methyl epijasmonate, has been a target of interest in the perfume industry because it is a component of jasmine oil.\textsuperscript{18} In an enantioselective synthesis of (\textit{+})-methyl epijasmonate (27) by Knochel and co-workers, a radical nickel-catalyzed carbozincation strategy was used to establish the \textit{cis} 2,3 substitution of the cyclopentanone.\textsuperscript{19}

\begin{center}
\begin{align*}
\text{OHC} & \text{SiMe}_3 \\
\text{N(H)Tf} & \text{N(H)Tf} \\
\text{6 mol %} & \text{Tl(OiPr)}_4, \text{Toluene} \\
\text{81 \% yield, 91 \% ee} & \text{81 \% yield, 91 \% ee} \\
\end{align*}
\end{center}

\textbf{Scheme 10:} Construction of iodide 31.

Chiral allylic alcohol 30 was obtained by the catalytic asymmetric addition of the dialkyzine reagent 28 to 3-trimethylsilylacrolein with chiral additive 29 (Scheme 10). Alcohol 30 was converted into iodide 31, the cyclization precursor, in six steps. Under the Ni-catalyzed reaction conditions, the cyclopentymethyl zinc compound 32 was obtained (Scheme 11). The proposed mechanism of the nickel catalyzed cyclization involved a nickel species (33) with a significant amount of radical character (Figure 4). Subsequent cyclization and transmetallation gave 32. The \textit{cis}/\textit{trans} ratio was found to be 95:5 between C2 and C3 after the subsequent cross-coupling with 1-bromo-1-butyn. The preference for the \textit{cis} compound as the major product was the result of the reaction occurring via a proposed chair-like transition state. Further elaboration of this alkyne gave the target product with an 8 \% overall yield.
Figure 4: Proposed mechanism of the Ni-mediated carbozincation reaction.

Scheme 11: Remaining sequence to (+)-methyl epijasmonate (27).

The above four examples serve as a brief survey in the different approaches in dealing with the challenging, thermodynamically less stable *cis* 2,3 substitution motif. More methods can be found in other published enantioselective syntheses of 27. Some of the reactions in these syntheses are specific for the carbonyl sidechain of 27 and are
not applicable for the C-ring fragment of 1. It would be desirable to have a method in the synthesis of cis 2,3 disubstituted cyclopentenones that is general, short and can avoid epimerization.

1.6 Retrosynthetic analysis of trifluoromethanesulfonate 34

Trifluoromethanesulfonate (triflate) 34 could be obtained from cyclopentenone 35 (Scheme 12). Since cyclopentenones with a similar structure, such as 26, can easily undergo epimerization or alkene isomerization, cyclopentenone 35 was expected to easily undergo chemical transformation in a similar fashion. Heat, aqueous acid and base must be avoided in the synthesis of cyclopentenone 35 and its subsequent reaction. Cyclopentenone 35 could be derived from vinyl ketone 36 by a metathesis reaction. Vinyl ketone 36 could be synthesized by the elaboration of acid 37, the product of the Ireland-Claisen rearrangement of ester 38. The stereochemistry of chiral ester 38 would be transferred to both stereocenters of acid 37 by the Ireland-Claisen rearrangement.

![Scheme 12: Retrosynthetic analysis of triflate 34.](image-url)
2. Discussion

2.1 Synthesis of ester 38

A Grignard reaction with crotonaldehyde and methyl magnesium iodide afforded racemic (3E)-pent-3-en-2-ol (Scheme 13). A kinetic resolution of this racemic alcohol by the Sharpless epoxidation was first attempted using the protocol of Berson and Wessel. This protocol involved aging the catalyst components ((+)-diisopropyltartrate and titanium (IV) isopropoxide) with racemic (3E)-pent-3-en-2-ol at -40 °C for 1 h, and adding tert-butyl hydroperoxide dropwise over 2 h. The reaction was stirred at -40 °C for 30 h. The resulting alcohol 39 was converted to ester 38, and the optical rotation was obtained ([α]D22.4 = + 8.6 ± 0.009 (c 1.00, CHCl₃)). The synthesis of alcohol 39 was repeated several times, and at one occasion, the cooling bath temperature was raised to approximately -20 °C due to a malfunction of the cooling machine. The resulting alcohol 39 was converted to ester 38, and the optical rotation obtained was significantly different than the previous values ([α]D23.5 = + 24.3 ± 0.02 (c 1.00, CHCl₃)). The ee of alcohol 39 synthesized according to the exact protocol of Berson and Wessel was estimated to be approximately 30 % by comparing the optical rotation of the corresponding ester 38 with one synthesized later on using a modified procedure.

Alarmed by this result, the reaction conditions were modified by aging the catalyst components ((+)-diisopropyltartrate and titanium (IV) isopropoxide) with
tert-butyl hydroperoxide at -20 °C for 30 minutes. Alcohol 39 in dichloromethane was added over 1 hour at -40 °C and the reaction was stirred at -30 °C for 30 h. The chemical shifts of alcohol 39 on the 1H NMR spectrum were in good agreement with the published data. The methoxyphenylacetate derivatives 41 and 42 were synthesized and analyzed by gas chromatography (GC). The ee of alcohol 39 synthesized by using our modified protocol was 92 %.

![Reaction Equation 1](image)

The DCC-promoted coupling of alcohol 39 with 5-[(4-methoxybenzyl)oxy]pentanoic acid 40 afforded ester 38 in 90% yield. Acid 33 was synthesized from 1,5-pentanediol over three steps.

It is of interest to note that alcohol 43, the enantiomer of alcohol 39, has been synthesized previously with high ee (> 95 %) by an enzyme kinetic resolution using porcine pancreatic lipase (PPL), a readily available enzyme. (Equation 2). The PPL kinetic resolution using 2,2,2-trifluoroethyllaurate (44) provided alcohol 43 with the best ee comparing to the use of ethylesters or trifluoroesters with shorter aliphatic chains. The use of 44 was also advantageous in product isolation because the boiling points of the reaction products differ substantially and can be separated easily by vacuum distillation.

![Reaction Equation 2](image)

In theory, our required starting material, alcohol 39, can be obtained by a two-step
method: kinetic resolution with PPL and hydrolysis of the resulting ester 45. In the hopes for a one-step enzyme kinetic resolution, trifluoroester 46 was synthesized by a DCC-promoted coupling of 2,2,2-trifluoroethanol and acid 40 (Equation 3). Treatment of racemic (3E)-pent-3-en-2-ol with trifluoroester 46 and PPL afforded ester 38 with approximately 79 % ee by optical rotation ([α]D240 = +22.3 ± 0.02 (c 0.28, CHCl3)) (Equation 4).

\[
\begin{align*}
\text{F} & \text{F} \text{OH} \quad \text{DCC, DMAP,CH}_2\text{Cl}_2 \quad \text{OPMB} \\
\text{HO} & \text{O} \quad \text{F} \text{F} \\
46 & \quad \text{40} \\
\text{(73 %)} & \\
\end{align*}
\]

2.2 Synthesis of acid 37

In the Ireland-Claisen rearrangement, predictable chirality transfer is dependent on the geometry of the alkene of the starting material and also the geometric integrity of the silyl ketene acetal that is formed.30 The geometry of the silyl ketene acetal is controlled by the selective formation of the E or Z ester enolate. The use of LDA as a base and THF as a solvent without any additives is known to favor the formation of the E silyl ketene acetal.24

Ester 38 was subjected to the Ireland-Claisen rearrangement to afford acid 37 in 80 % yield (Scheme 14).31,32 Two new multiplets in the 1H NMR spectrum were observed from δ 2.26 to δ 2.38, and from δ 2.07 to δ 2.22. They correspond to the two vicinal protons, Hₐ and Hₐ', of acid 37. The carbon chemical shift of the ester carbonyl at δ 172.7 was changed to δ 181.5 in the product.
Scheme 14: The Ireland-Claisen rearrangement of ester 31.

The stereochemistry of acid 37 is the result of the rearrangement having occurred in a pericyclic transition state (Scheme 15). The minor diastereomer in this Ireland-Claisen rearrangement, acid 47 (Scheme 18), is not observed in the NMR spectra.

Scheme 15: Pericyclic transition state of the Ireland-Claisen rearrangement.

Since one of our planned advanced intermediates, enone 35, is prone to epimerization, it was necessary to prepare its epimer in parallel. Spectroscopic data of the epimer would allow easy identification should epimerization occur with enone 35. Synthesis of epimer 40 could be achieved in one of two ways via the Ireland-Claisen rearrangement: by changing the alkene geometry of ester 38 from E to Z, or by forming the Z silyl ketene acetal from ester 38 instead of the E silyl ketene acetal.

Formation of the Z silyl ketene acetal from ester 38 followed by the Ireland-Claisen rearrangement would provide epimeric acid 47. Using DMPU as an additive has been shown previously by Ireland and coworkers to favor the formation of Z silyl ketene acetals. Our attempt using DMPU as an additive only led to the recovery of the starting material, ester 38 (Scheme 16).
Scheme 16: Attempted synthesis of epimeric acid via a Z ketene silyl acetal.

A change in the alkene geometry of ester 38 from E to Z could also provide the epimeric acid by the Ireland-Claisen rearrangement. Reduction of pent-3-yn-2-one using diisobutylaluminum hydride (DIBAL-H) afforded alkynol 48 (Scheme 17). A DCC-promoted coupling with acid 40 gave ester 49 and reduction of 49 using Lindlar’s catalyst afforded ester 50. On the $^1$H NMR spectrum, two new sets of chemical shifts appeared after the Lindlar reduction of ester 49: a multiplet from $\delta$ 5.56 to $\delta$ 5.66, and another multiplet from $\delta$ 5.46 to $\delta$ 5.54. Each set of chemical shifts has an integration of one proton, and together they correspond to the two protons of the newly formed alkene in 50.

Scheme 17: Construction of ester 50.

An Ireland-Claisen rearrangement of the ester 50 via the formation of the E silyl ketene acetal gave epimeric acid 47 (Scheme 18). The chemical shift of the two vicinal protons of acid 47 was observed from $\delta$ 2.19 to $\delta$ 2.42 as a multiplet.
Scheme 18: Construction of epimeric acid 47.

2.3 Synthesis of vinyl ketone 36

It was envisioned that acid 37 could be easily converted to its corresponding Weinreb amide 51. Weinreb amides are effective acylating reagents and can be transformed into ketones readily. Carboxylic acids can be converted to Weinreb amides directly by the use of peptide coupling reagents such as \(N,N'\)-dicyclohexylcarbodiimide (DCC), benzotriazol-1-yl-N-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), \(1\)-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), and benzotriazolyoxy-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP) (Figure 5). The use of these reagents along with additives such as 1-hydroxybenzotriazole (HOBBt) is known to result in little epimerization in peptide synthesis.

Figure 5: Structure of peptide-coupling reagents and additives.

Acid 37 was treated with various combinations of peptide coupling reagents and additives, bases, and \(N,O\)-dimethylhydroxylamine as a hydrochloride salt or free amine in dichloromethane (Table 1). Amide 51 was obtained in low yield consistently with recovered starting material. Little epimerization was detected on the \(^1\)H NMR spectrum with or without the use of peptide coupling additives.
peptide coupling conditions

DCC (1.0 equiv.),
Et$_3$N (1.0 equiv.),
(MeO)MeNH*HCl (1.5 equiv.)

0 °C → rt 15 h 21 % + sm

EDC (1.5 equiv.),
HOBT (1.0 equiv.),
Et$_3$N (1.0 equiv.),
(MeO)MeNH (3.0 equiv.)

0 °C → rt 15 h 38 % + sm

PyBOP (1.0 equiv.),
DIEA (2.75 equiv.),
(MeO)MeNH*HCl (1.1 equiv.)

rt 15 h 21 % + sm

Table 1: Construction of amide 51 using peptide coupling reagents.

$N,O$-dimethylhydroxylamine hydrochloride is commercially available.

$N,O$-dimethylhydroxylamine can be prepared by distilling a mixture of the hydrochloride salt with triethanolamine in ethylene glycol.$^{40}$

The formation of amide 51 was evident by the characteristic chemical shifts of two singlets on the $^1$H NMR spectrum, at δ 3.60 and δ 3.75, corresponding to the two methyl groups of the $N$-methoxy-$N$-methyl amide functional group.

Another well-known method in the direct conversion from carboxylic acids to Weinreb amides involves the generation of acyl halides in situ by using $N,O$-dimethylhydroxylamine as the hydrochloride salt or free amine, along with reagents such as carbon tetrabromide and triphenylphosphine,$^{41}$ thionyl chloride, and pivaloyl
chloride. Using these methods, acid 37 was converted to amide 51 in moderate yield (Table 2).

\[
\begin{align*}
\text{37} & \quad \rightarrow \quad \text{51}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CBr₄ (1.1 equiv.), PPh₃ (1.1 equiv.), pyridine (1.1 equiv.), (MeO)MeNH•HCl (1.1 equiv.), CH₂Cl₂</td>
<td>rt</td>
<td>30 min</td>
<td>39% + lactone 52</td>
</tr>
<tr>
<td>2</td>
<td>SOCl₂ (1.25 equiv.), (MeO)MeNH (10 equiv.), pyridine</td>
<td>0 °C → rt</td>
<td>15 h</td>
<td>54%</td>
</tr>
<tr>
<td>3</td>
<td>C(CH₃)₃CO₂Cl (1.0 equiv.), Et₃N (3.0 equiv.), (MeO)MeNH•HCl (1.0 equiv.), CH₂Cl₂</td>
<td>0 °C → rt</td>
<td>15 h</td>
<td>55%</td>
</tr>
</tbody>
</table>

Table 2: Construction of amide 44 by the formation of an acyl halide in situ.

When acid 37 was treated with carbon tetrabromide and triphenylphosphine (entry 1), a significant amount of a byproduct was observed. The $^1$H NMR spectrum of this byproduct was similar to that of acid 37, except that it lacked the chemical shifts of the aromatic protons (δ 7.21 to δ 7.24 and δ 6.80 to δ 6.89) as well as the benzylic protons (δ 4.40) of the p-methoxybenzyl ether protecting group. The structure of this byproduct is assumed to be lactone 52, the result of the deprotection of the p-methoxybenzyl ether protecting group. Removal of this protecting group under these reaction conditions has not been reported in the literature. In our case, it could be facilitated by the formation of a six-membered ring lactone (Scheme 19).
Weinreb amides have been synthesized from methyl esters by using N,O-dimethylhydroxylamine hydrochloride and reagents such as trimethylaluminum and isopropyl magnesium chloride. Acid 37 was converted to ester 53 (Equation 7), and attempts to convert ester 53 to amide 51 were unsuccessful (Table 3).

Scheme 19: Possible mechanism of the formation of lactone 52.

Table 3: Attempted conversion of ester 53 to amide 51.
There have been examples in the literature where carboxylic acids were converted to vinyl ketones by using vinylolithium or the combination of vinylmagnesium bromide and dibromotriphenylphosphorane. Attempts to convert acid 37 directly to vinyl ketone 36 under these conditions were not successful (Table 4).

![Chemical structure](image)

\[ \text{37} \xrightarrow{X} \text{36} \]  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Temperature</th>
<th>Time (h)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Li (2.2 equiv.), DME]</td>
<td>55 °C</td>
<td>15</td>
<td>no rxn</td>
</tr>
<tr>
<td>2</td>
<td>[MgBr (2.5 equiv.), Ph₃PBr₂ (1.2 equiv.), Et₃N (1.2 equiv.), THF]</td>
<td>-30 °C</td>
<td>3</td>
<td>no rxn</td>
</tr>
<tr>
<td>3ᵃ</td>
<td>[MgBr (1.5 equiv.), Ph₃PBr₂ (1.2 equiv.), THF]</td>
<td>-30 °C</td>
<td>1</td>
<td>no rxn</td>
</tr>
</tbody>
</table>

ᵃ The lithium carboxylate of acid 37 was used.

Table 4: Attempted direct conversion from acid 37 to ketone 36.

The low conversion of acid 37 to amide 51 prompted us to search for other ways to activate carboxylic acids. Sterically hindered carboxylic acids have been converted to diazoketones successfully by the formation of a reactive acyl mesylate in situ (Scheme 20). When less sterically hindered carboxylic acids such as benzoic acid and trans cinnamic acid were treated under the same reaction conditions, the corresponding symmetrical anhydride was formed (Scheme 21). The anhydride reacted slowly, or not at all, with diazomethane. Aqueous workup of the reaction hydrolyzed the anhydride, and the resulting carboxylic acid was trapped with diazomethane to give the methyl ester.
Scheme 20: Direct conversion of sterically hindered carboxylic acids to diazoketones by \textit{in situ} formation of an acyl mesylate.

Scheme 21: Conversion of less sterically hindered carboxylic acids by \textit{in situ} formation of a mixed anhydride with methanesulfonic acid.

On a fifty-milligram scale, acid 37 was treated with five equivalents of methanesulfonyl chloride, ten equivalents of triethylamine, and ten equivalents of \textit{N},\textit{O}-dimethylhydroxylamine. After stirring at 0 °C for 1 h, the reaction was complete by TLC and amide 51 was obtained in 80 % yield (equation 9). When the hydrochloride salt of \textit{N},\textit{O}-dimethylhydroxylamine was used, only a trace amount of product was observed by TLC.

When this reaction was performed on a one-gram scale, a significantly lower yield
of 65 % was observed, and two byproducts were detected. Lactone 52 was isolated in 9 % yield and N-methoxy-N-methylmethanesulfonamide (54) was observed in the \(^1\)H NMR spectrum of the crude product (Figure 6).

\[
\text{MeO} - \text{O} - \text{Me}
\]

\[
\text{N} - \text{SO}_2\text{Me}
\]

54

**Figure 6:** Structure of byproduct 54.

Sulfonamide 54 is a known compound and was synthesized by reacting methanesulfonyl chloride, triethylamine, and \(N, O\)-dimethylhydroxylamine hydrochloride.\(^{48}\) On the \(^1\)H NMR spectrum of the crude product, three singlets were observed for the three methyl groups of 54 in addition to the signals of amide 51 and lactone 52. Their chemical shifts were at \(\delta 2.86, \delta 2.98\) and \(\delta 3.78\) in deuterochloroform. Sulfonamide 54 was successfully removed by column chromatography.

Clearly the formation of sulfonamide 54 was due to the large excess of the reagents used. The formation of sulfonamide 54 generated a large amount of chloride ions, and possibly facilitated the formation of lactone 52 according to our proposed mechanism. The reaction conditions were then optimized and on a one-gram scale a yield of 80 % was obtained (Equation 10).

\[
\text{HO} - \text{OPMB} \xrightarrow{1) \text{MsCl (1.1 equiv)}} \text{Et}_3\text{N (3.0 equiv)}} \text{0°C, THF} \xrightarrow{2) \text{N,O-dimethylhydroxylamine (80%)}} \text{O,N} - \text{OPMB} \quad (10)
\]

The direct conversion from acid 37 to vinyl ketone 36 was attempted by using vinyl lithium instead of \(N, O\)-dimethylhydroxylamine. After stirring at 0 °C for 2 h, and at rt for 2 h, no product was observed by TLC.
Using our newly developed method, several examples of Weinreb amides were synthesized from readily available carboxylic acids in good yield (Table 5). Amide 66 was synthesized without epimerization. Its optical rotation ($[\alpha]_D^{26.1} = -37.1 \pm 0.02$ (c 1.03, MeOH)) was comparable to the reported value in the literature ($[\alpha]_D^{25} = -36.6$ (MeOH)). Epimeric amide 67 was also synthesized.

Amide 51 was converted to vinyl ketone 36 by treating with vinyl magnesium bromide (Equation 11). Vinyl ketone 36 has three newly introduced signals in the alkenyl region on the $^1$H NMR spectrum, at $\delta$ 5.70, 6.19, and 6.41, corresponding to the three alkene protons of the vinyl ketone functional group.
Table 5: Examples of Weinreb amides.
2.4 Synthesis of enone 35

Vinyl ketone 36 was treated with benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (2nd generation Grubbs catalyst)\(^{51,52}\) to give the ring-closing metathesis product enone 35 (Equation 13). The two alkenyl protons of enone 35 have chemical shifts at \(\delta 6.05\) and \(\delta 7.56\) on the \(^1\)H NMR spectrum (Table 6). A minor product was also observed on the \(^1\)H NMR spectrum (Figure 7).

\[
\text{\[
\begin{array}{c}
\text{CH}_2\text{Cl}_2, \Delta \\
(71\%)
\end{array}
\right]
\]

Epimeric enone 69 was synthesized (Scheme 22) and by comparison of spectroscopic data, it was the minor product observed in the synthesis of enone 35. The alkenyl protons of epimeric enone 69 have chemical shifts at \(\delta 7.48\) and \(\delta 6.06\). The chemical signals of these two alkenyl protons were well separated on the \(^1\)H NMR spectrum, and their integration revealed that the product ratio between enone 35 and epimeric enone 69 was 12:1.

\[
\text{Scheme 22: Synthesis of epimeric enone 69.}
\]
Figure 7: Selected regions on the $^1$H NMR spectra of enone 35 (top) and epimeric enone 69 (bottom).

Enone 35 was purified by column chromatography without significant epimerization. It is interesting to note when the silica gel was prewashed with a solution of 5% triethylamine in petroleum ether, epimerization occurred to give a cis/trans ratio of 2:3.
<table>
<thead>
<tr>
<th>'H Assignment</th>
<th>δ, Multiplicity, J (Hz)</th>
<th>δ, Multiplicity, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-2</td>
<td>6.05, dd, J = 5.8, 1.5</td>
<td>6.06, dd, J = 5.8, 1.9</td>
</tr>
<tr>
<td>H-3</td>
<td>7.56, dd, J = 5.4, 2.7</td>
<td>7.48, dd, J = 5.8, 2.3</td>
</tr>
<tr>
<td>H-4</td>
<td>2.32-2.25, m</td>
<td>part of 1.87-1.63, m</td>
</tr>
<tr>
<td>H-5</td>
<td>1.01, d, J = 7.3</td>
<td>1.18, d, J = 7.3</td>
</tr>
<tr>
<td>H-6</td>
<td>3.10-2.99, m</td>
<td>2.67-2.59, m</td>
</tr>
<tr>
<td>H-7'</td>
<td>1.46-1.39, m</td>
<td>1.53-1.41, m</td>
</tr>
<tr>
<td>H-7'' and H-8</td>
<td>1.84-1.64, m</td>
<td>part of 1.87-1.63, m</td>
</tr>
<tr>
<td>H-9</td>
<td>3.52-3.38, m</td>
<td>3.49-3.42, m</td>
</tr>
<tr>
<td>H-10</td>
<td>4.39, s</td>
<td>4.43, s</td>
</tr>
<tr>
<td>H-12 and H-16</td>
<td>7.22, d, J = 8.5</td>
<td>7.23, d, J = 8.5</td>
</tr>
<tr>
<td>H-13 and H-15</td>
<td>6.84, d, J = 8.5</td>
<td>6.85, d, J = 8.5</td>
</tr>
<tr>
<td>H-17</td>
<td>3.75, s</td>
<td>3.77, s</td>
</tr>
</tbody>
</table>

Table 6: Chemical shift assignment for enone 35 and epimeric enone 69.

2.5 Trifluoromethanesulfonate 34

Enone 35 was reduced to ketone 70 using palladium on carbon (Scheme 23). Kinetic enolization\textsuperscript{53} of ketone 70 using lithium 1,1,1,3,3,3-hexamethyldisilazide (LHMDS) and the addition of N-phenyltrifluoromethanesulfonimide gave trifluoromethanesulfonate (triflate) 34 in 48 % yield and 9 % of unepimerized starting
material ketone 70 was recovered. The chemical shift at δ 5.59 on the $^1$H NMR spectrum corresponded to the alkenyl proton of triflate 34. The minor diastereomer, triflate 71 was observed, and its alkenyl proton had a chemical shift at δ 5.53. The ratio of the integration of these two signals was 9:1.

Scheme 23: Construction of triflate 34.

Enone 35 could be directly converted into triflate 34 by a 1,4 reduction and trapping of the resulting enolate as the triflate. This method was attempted by using Stryker's reagent$^{54,55}$ and N-phenyltrifluoromethanesulfonimide, but the product obtained was ketone 70 (Equation 14). The use of other triflating reagents such as N-(5-chloro-2-pyridyl)triflimide (Comins’ reagent)$^{56}$ and trifluromethanesulfonic anhydride (Figure 8) also gave ketone 70 and no reaction, respectively.

Figure 8: Structures of triflating reagents.
The use of chlorotrimethylsilane resulted in a mixture of ketone 70 and the corresponding silyl enol ether 72 (equation 15). Silyl enol ether 72 had a chemical shift at δ 6.08 for its alkenyl proton, and also at δ 0.18 for its methyl protons of the trimethylsilyl enol ether functional group. Attempted separation of this mixture by column chromatography on silica gel resulted in decomposition.

\[
\text{OPMB} \quad \stackrel{[\text{PPh}_3\text{CuH}]_6, \text{TMSCI}}{\text{[Toluen]}} \rightarrow \text{OPMB + 70} \quad (15)
\]

Alkenones had been converted into their corresponding triflates by the use of lithium tri-sec-butylborohydride (L-Selectride) and N-phenyltrifluoromethanesulfonimide by Scott and Crisp.\(^{57}\) Enone 35 was treated with L-Selectride and N-phenyltrifluoromethanesulfonimide, and triflate 34 was afforded in 41 % yield (Equation 16). The minor diastereomer, triflate 71, was observed on the \(^1\)H NMR spectrum and the product ratio was found to be 9:1 by proton integration.

\[
\text{OPMB} \quad \stackrel{\text{L-Selectride, PhNTf}_2}{\text{THF, -78°C to rt}} \rightarrow \text{OPMB + 34} \quad (41 \%)
\]

The epimeric triflate 71 was synthesized and spectroscopic data confirmed that it was the minor diastereomer that was observed (Equation 17).

\[
\text{OPMB} \quad \stackrel{\text{L-Selectride, PhNTf}_2}{\text{THF, -78°C to rt}} \rightarrow \text{OPMB + 34} \quad (40 \%)
\]

\[
(\pm) \text{69} \quad (\pm) \text{71}
\]
2.6 Concluding remarks

Trifluoromethanesulfonate 34 was prepared over six steps from the known alcohol 39. The Ireland-Claisen rearrangement and ring-closing metathesis established the stereochemical relationship of the substituents and constructed cyclopentenone 35, respectively. The 1,4-reduction of cyclopentenone 35 and formation of the corresponding trifluoromethanesulfonate led to the construction of compound 34 while preserving the cis/trans ratio of 9:1. A convenient method in the synthesis of Weinreb amides was also developed.
3. Experimental

General

All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium benzophenone ketyl. Dichloromethane, pyridine and toluene were distilled from calcium hydride. Acetone and ethyl acetate were distilled from anhydrous magnesium sulfate. Quinoline was distilled from anhydrous sodium sulfate and zinc dust under vacuum. Degassed dichloromethane was prepared by sparging with argon for 45 min.

Triethylamine, methanesulfonyl chloride, chlorotrimethylsilane, and diisopropylamine were distilled from calcium hydride. Solutions of diisobutylaluminum hydride (DIBAL-H, 1 M in hexanes), butyllithium (2.5 M in hexanes), vinyl magnesium bromide (1 M in THF), and L-Selectride (1 M in THF), as well as titanium (IV) isopropoxide and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine) ruthenium (2nd generation Grubbs catalyst) were purchased from Aldrich. Solutions of butyllithium (1.6 M in hexanes) were purchased from Acros. tert-Butyl hydroperoxide (5.5 M solution in decane) was purchased from Fluka.

Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV₂₅₄ pre-coated TLC plates. Melting points were performed using a Fisher-Johns melting point apparatus and are uncorrected. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard model 5890 capillary gas chromatograph equipped with a flame ionization detector and a 25 m x 0.20 mm fused silica column. Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded in deuterochloroform using either a Bruker WH-400 or a Bruker AV-300 spectrometer. Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded in deuterochloroform using a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ¹H NMR; δ 77.0 ¹³C NMR). Low
resolution mass spectra were recorded on a Kratos Concept II HQ or on a Kratos MS 80 mass spectrometer by the UBC MS laboratory. Microanalyses were performed by the Microanalytical laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108. Optical rotation measurements were recorded on a Jasco model P1010 polarimeter at 589 nm (sodium ‘D’ line).

(±)-(3E)-pent-3-en-2-ol

A 2-neck flask equipped with a condenser was charged with 4.75 g of magnesium (10.2 mmol, 1.0 equiv.) in 100 mL of Et₂O at 0 °C, and 12.5 mL of methyl iodide (10.2 mmol, 1.0 equiv.) was added intermittently to give a controlled reflux. The resulting grey suspension was stirred at rt for 30 min and cooled to 0 °C. 16.0 mL of crotonaldehyde (10.2 mmol, 1.0 equiv.) was added dropwise to maintain a controlled reflux. The reaction was further stirred at 0 °C for 30 min, then quenched slowly with a saturated solution of aqueous ammonium chloride and diluted with 100 mL of Et₂O and 100 mL of H₂O to dissolve salts. The separated aqueous layer was extracted with 2 x 100 mL of Et₂O. The combined organic layers were washed with a solution of saturated aqueous sodium bicarbonate, brine, and dried over anhydrous magnesium sulfate. Distillation at atmospheric pressure using an apparatus equipped with an 8-inch Vigreux column and a condenser gave ~ 11.3 g (~ 65 %) of a yellow oil containing a small amount of Et₂O. The yellow oil turned colorless upon storing in the refrigerator overnight.

IR (NaCl): 3365, 2972, 1672 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.67-5.60 (m, 1H), 5.54-5.48 (m, 1H), 4.23 (m, 1H), 1.67 (d, J=6.4 Hz, 3H), 1.23 (d, J=6.4 Hz, 3H).
(2R,3E)-pent-3-en-2-ol (39)

To a 1-L round bottom flask, charged with 6 g of 3Å molecular sieves and flame-dried, was added 600 mL of CH₂Cl₂ and cooled to -20 °C. To the suspension was added 5.5 mL of (+)-diisopropyltartrate (26.0 mmol, 0.15 equiv.), 5.2 mL of titanium (IV) isopropoxide (18.0 mmol, 0.1 equiv.) and 22.2 mL of a 5.5 M solution of tert-butyl hydroperoxide in decane (123.0 mmol, 0.7 equiv.) dropwise. The resulting mixture was allowed to age at -20 °C for 30 min. After aging, the mixture was cooled to -40 °C, and a prechilled (-40 °C) solution of 15 g of (±)-(3E)-pent-3-en-2-ol (176 mmol, 1.0 equiv.) in 100 mL of CH₂Cl₂ was added over 45 min. The reaction was warmed to -30 °C and stirred for 30 h. The reaction was warmed to 0 °C and quenched carefully with a prechilled (0 °C) solution made of 100 g of ferrous sulfate and 30 g of tartaric acid in 300 mL of H₂O. The resulting mixture was stirred vigorously for 15 min. The separated aqueous layer was extracted with 2 x 100 mL of Et₂O. The combined organic layers were cooled to 0 °C and treated with 30 mL of a prechilled (0 °C) solution of sodium hydroxide in brine (30% wt/v). The resulting mixture was stirred vigorously at 0 °C for 1 h. The separated aqueous layer was diluted with 100 mL of H₂O and extracted with Et₂O (3 x 200 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Distillation using an 8-inch vacuum-jacketed Vigreux column at atmospheric pressure afforded a pale yellow oil with a small amount of Et₂O (bp 116-118 °C).

(1R,2E)-1-methylbut-2-enyl (2R)-methoxy(phenyl)acetate (41)

To a solution of 50 mg of (±)-(3E)-pent-3-en-2-ol containing a small amount of Et₂O (~ 0.58 mmol, slightly less than 1 equiv.) in 2 mL of CH₂Cl₂ at 0 °C was added a solution of 170 mg of N,N’-dicyclohexylcarbodiimide (0.81 mmol, 1.4 equiv.) and 7 mg of
4-(dimethylamino)pyridine (0.06 mmol, 0.1 equiv.) in 2 mL of CH₂Cl₂ dropwise. The reaction was stirred overnight, warming to rt. The suspension was filtered through a pad of silica gel and concentrated in vacuo. Purification by column chromatography on silica gel (4/1 petroleum ether-ether) afforded a yellow oil. Capillary GC analysis [120 °C (7 min) to 150 °C at 3 °C / min] revealed 41 having a retention time at 31.26 min, and 42 at 31.93.

Following the exact procedure of the above synthesis, acetate 41 was synthesized from alcohol 39. Capillary GC analysis [120 °C (7 min) to 150 °C at 3 °C / min] revealed 41 at 31.29 min and 42 at 31.62 min.

**Figure 9:** GC analyses were performed on a Hewlett-Packard model 5890 capillary gas chromatograph equipped with a flame ionization detector and a 25 m x 0.20 mm fused silica column. (a) GC analysis of a 1:1 mixture of 41 and 42. (b) GC analysis of 41 as the major diastereomer.

IR (NaCl): 2982, 2936, 1747 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.41-7.24 (m, 5H), 5.71-5.62 (m, minor diastereomer), 5.54-5.42 (m, 1H), 5.36-5.27 (m, 2H), 4.70 (s, 1H), 3.37 (s, 3H), 1.64 (d, J=6.9 Hz, minor diastereomer), 1.54 (d, J=6.2 Hz, 3H), 1.25 (d, J=6.2 Hz, 3H), 1.13 (d, J=6.6 Hz, minor diastereomer). ¹³C NMR (75 MHz, CDCl₃): δ 169.8, 136.2, 129.9, 128.5, 128.4, 128.1, 127.1, 82.7, 71.8, 57.1, 20.1, 17.4.
pent-3-yn-2-one

Anhydrous zinc chloride was prepared by heating 25 g of hydrated zinc chloride, 2.5 g of zinc dust in 200 mL of 1,4-dioxane at reflux for 2 h. The hot mixture was filtered through a hot glass frit and rinsed with hot 1,4 dioxane. The filtrate was cooled to allow the precipitation of white solids, which were filtered and dried under vacuum prior to use.

To a solution of 6.05 g of 1-bromo-1-propene (5.0 mmol, 1.0 equiv.) in 40 mL of THF at -78 °C was added 58.0 mL of a solution of 1.6 M of nBuLi in hexanes (92.5 mmol, 1.85 equiv.) dropwise over 10 min. The resulting blue solution was stirred at -78 °C for 2 h, and then warmed to -20 °C. At this point the reaction exhibited a greenish white color. A solution of 5.79 g of anhydrous zinc chloride (42.5 mmol, 0.85 equiv.) in 20 mL of THF was added. The resulting mixture was warmed to 0 °C, and 3.63 mL of acetyl chloride (51.0 mmol, 1.02 equiv.) was added all at once. The reaction was warmed to rt and stirred for 1.5 h. The yellow mixture was poured into a solution of 12 g of ammonium chloride in 100 mL of H2O, followed by the addition of 10 mL of ammonium hydroxide. After vigorous shaking of the mixture, two layers were observed. The aqueous layer was separated and extracted with 3 x 75 mL of Et2O. The combined organic layers were washed with 5 x 20 mL of a solution of saturated aqueous ammonium chloride and dried over anhydrous magnesium sulfate. Purification by distillation afforded 2.62 g (64%) of a colorless oil (bp 72 °C at 100 mmHg).

IR (NaCl): 2963, 2219, 1675, 1245 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 2.05 (s, 3H), 1.77 (s, 3 H).
To a solution of 1.0 g of pent-3-yn-2-one (12.18 mmol, 1.0 equiv.) 120 mL of Et₂O at 0 °C was added 14.6 mL of a solution of 1 M DIBAL-H in hexanes (14.6 mmol, 1.2 equiv.) dropwise. The reaction was stirred at 0 °C for 30 min, and was slowly quenched with 3.65 mL of a solution of pH 8 ammonia/ammonium chloride buffer, prepared by treating 950 mL of a solution of saturated aqueous ammonium chloride with 50 mL of concentrated ammonia. The resulting mixture was stirred vigorously for 30 min to promote the formation of aluminum salts. Anhydrous magnesium sulfate was added and the resulting mixture was stirred for 1 h and filtered through a pad of Celite to give a yellow solution. Distillation afforded the product as a ~50 % solution in Et₂O which was used without further purification for the next step.

(1R,2E)-1-methylbut-2-enyl 5-[(4-methoxybenzyl)oxy]pentanoate (38)

Following the procedure of the synthesis of acetate 41, ester 38 was synthesized with the following quantities of reagents and solvents: 1.5 g of alcohol 37 (17.42 mmol, 1.0 equiv.), 4.56 g of acid 40 (19.16 mmol, 1.1 equiv.), 45 mL of CH₂Cl₂, 5.03 g of N,N'-dicyclohexylcarbodiimide (24.38 mmol, 1.4 equiv.), 0.21 g of 4-(dimethylamino)pyridine (1.74 mmol, 0.1 equiv.) and 25 mL of CH₂Cl₂. Workup and purification by column chromatography on silica gel (4/1 petroleum ether-ether) afforded 4.82 g (90 %) of a colorless oil.

[α]D₂₃³ = +26.1 ± 0.005 (c 1.70, CHCl₃). IR (NaCl): 2937, 2858, 1733, 1614 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ 7.22 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 5.73-5.62
(m, 1H), 5.48-5.41 (m, 1H), 5.32-5.24 (m, 1H), 4.38 (s, 2H), 3.75 (s, 3H), 3.44 (t, J=6.2 Hz, 2H), 2.28 (t, J=7.3 Hz, 2H), 1.73-1.55 (m, 7H), 1.25 (d, J=6.2 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 172.7, 159.0, 130.8, 130.5, 129.1, 127.8, 113.6, 72.4, 70.8, 69.4, 55.1, 34.2, 29.0, 21.7, 20.2, 17.5. Anal. Calcd for C$_{18}$H$_{26}$O$_4$: C, 70.56; H, 8.55. Found: C, 70.41; H, 8.35.

2,2,2-trifluoroethyl 5-(benzyloxy)pentanoate (46)

Following the procedure of the synthesis of acetate 41, ester 46 was synthesized with the following quantities of reagents and solvents: 900 mg of acid 40 (3.81 mmol 1.0 equiv.), 218 μL of 2,2,2-trifluoroethanol (3.81 mmol, 1.0 equiv.), 1.10 g of N,N'-dicyclohexylcarbodiimide (5.33, 1.4 equiv.), 46.5 mg of 4-(dimethylamino)pyridine (0.38 mmol, 0.1 equiv.), and 30 mL of CH$_2$Cl$_2$. Work up and purification by column chromatography on silica gel (5 / 1 petroleum ether-ether) afforded 727 mg (73 %) of a colorless oil.

IR (NaCl): 2941, 2863, 1758, 1613 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.23 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 4.47-4.39 (m, 4H), 3.75 (s, 3H), 3.43 (t, J=6.2 Hz, 2H), 2.41 (t, J=7.3 Hz, 2H), 1.78-1.57 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 171.7, 159.1, 130.5, 129.0, 124.8, 121.1, 113.6, 72.4, 69.1, 60.6, 60.1, 59.7, 59.2, 55.0, 33.1, 28.8, 21.4. Anal. Calcd for C$_{15}$H$_{19}$O$_4$F$_4$: C, 56.25; H, 5.98. Found: C, 56.31; H, 6.20.
Following the procedure of the synthesis of acetate 41, ester 49 was synthesized with the following quantities of reagents and solvents: ~ 0.3 g of eynol 48 (~ 3.6 mmol, 1.0 equiv.), 0.94 g of acid 40 (3.92 mmol, 1.1 equiv.), 1.03 g of N,N'-dicyclohexylcarbodiimide (4.99 mmol, 1.4 equiv.), 43.6 mg of 4-(dimethylamino)pyridine (0.36 mmol, 0.1 equiv.), and 15 mL of CH2Cl2. Work up and purification by column chromatography on silica gel (5 / 1 petroleum ether-ether) afforded 756 mg (70 %) of a colorless oil.

IR (NaCl): 2937, 2858, 1736, 1613 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.19 (d, \(J=8.5\) Hz, 2H), 6.81 (d, \(J=8.5\) Hz, 2H), 5.40-5.33 (m, 1H), 4.36 (s, 2H), 3.72 (s, 2H), 3.40 (t, \(J=6.6\) Hz, 2H), 2.57 (t, \(J=6.6\) Hz, 2H), 1.76-1.53 (m, 7H), 1.38 (d, \(J=6.6\) Hz, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 172.1, 158.9, 130.4, 128.9, 113.5, 80.6, 77.7, 72.2, 69.2, 60.3, 54.9, 33.7, 28.8, 21.42, 21.41, 3.2. Anal. Calcd for C\(_{18}\)H\(_{24}\)O\(_4\): C, 71.03; H, 7.95. Found: C, 70.63; H, 8.01.

A 25 mL Schlenk flask was charged with 200 mg of ester 49 (0.66 mmol, 1.0 equiv.), 80 mg of Lindlar’s catalyst (40 % by wt) and 73 \(\mu\)L of quinoline (40 % by weight) in 5.5 mL of EtOAc. The reaction vessel was carefully evacuated using a water aspirator for 20 seconds, and then charged with hydrogen gas. The reaction was stirred vigorously under an atmosphere of hydrogen for 1 h, filtered through a pad of Celite and
concentration in vacuo to give a crude yellow oil. Purification by column chromatography on silica gel (4/1 petroleum ether-ether) afforded 178 mg (88%) of a colorless oil.

IR (NaCl): 2937, 2859, 1733, 1515 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.20 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H) 5.66-5.56 (m, 1H), 5.54-5.46 (m, 1H), 5.36-5.29 (m, 1H), 4.34 (s, 2H), 3.72 (s, 3H), 3.39 (t, J=6.6 Hz, 2H), 2.26 (t, J=6.9 Hz, 2H), 1.71-1.56 (m, 7H), 1.22 (d, J=6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 172.4, 158.9, 130.4, 130.2, 128.9, 126.8, 113.4, 72.2, 69.2, 66.3, 54.8, 34.0, 28.8, 21.5, 20.3, 13.0. Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.73; H, 8.62.

(2S,3S,4E)-2-{3-[(4-methoxybenzyl)oxy]propyl}-3-methylhex-4-enoic acid (37)

A stock solution of 1:1 chlorotrimethylsilane-triethylamine was prepared by mixing 3.0 mL of chlorotrimethylsilane and 3.0 mL of triethylamine. The resulting mixture had a smoky-white color.

A 0.5 M stock solution of lithium diisopropylamide (LDA) was prepared by stirring 1.13 mL of diisopropylamine (8.04 mmol), 3.1 mL of a solution of 2.43 M of nBuLi in hexanes (7.5 mmol) and 10.77 mL of THF at -78 °C for 30 min.

To a solution of 1.31 g of ester 38 (4.28 mmol, 1.0 equiv.) in 87 mL of THF at -78 °C was added 5.4 mL of a pre-mixed solution of 1:1 chlorotrimethylsilane-triethylamine and 11.9 mL of a 0.5 M solution of LDA (5.95 mmol, 1.4 equiv.). Upon completion of addition, the reaction was stirred at -78 °C for 90 min, at rt for 2 h, and was heated at reflux overnight. The reaction was cooled to rt, diluted with 100 mL of Et₂O and quenched with ~ 80 mL of 1 N hydrochloric acid. The separated organic layer was washed with 2 x 80 mL of 1 N HCl, and the combined aqueous layers were back-extracted with 2 x 150 mL of Et₂O. The combined organic layers were concentrated in vacuo to ~80 mL, and were stirred with 80 mL of 1 N hydrochloric acid at rt for 1 h. The
separated aqueous layer was extracted with 2 x 80 mL of Et₂O and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (4 / 1 petroleum ether-ether with 1 % acetic acid) afforded 1.05 g (80 %) of a colorless oil.

\[ \alpha \] D²⁶ = -27.9 ± 0.007 (c 1.19, CHCl₃). IR (NaCl): 2933, 2872, 1703, 1614 cm⁻¹.

\(^1\)H NMR (300 MHz, CDCl₃): δ 7.23 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.5 Hz, 2H), 5.50-5.34 (m, 1H), 5.24-5.14 (m, 1H), 4.40 (s, 2H), 3.77 (s, 3H), 3.47-3.38 (m, 2H), 2.38-2.26 (m, 1H), 2.22-2.07 (m, 1H), 1.72-1.45 (m, 7H), 1.04 (d, J=6.6 Hz, 3H). \(^13\)C NMR (75 MHz, CDCl₃): δ 181.5, 159.1, 133.8, 130.5, 129.2, 125.7, 113.7, 72.4, 69.6, 55.2, 51.3, 39.6, 27.6, 26.9, 19.1, 17.8. Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C, 70.16; H, 8.55.

(±)-(2R,3S,4E)-2-\{-3-[\{4-ethylbenzyl\}oxy]propyl\}-3-methylhex-4-enoic acid (47)

Following the procedure of the synthesis of acid 37, acid 47 was synthesized with the following quantities of reagents and solvents: 390 mg of ester 50 (1.27 mmol, 1.0 equiv.), 1.61 mL of a 1:1 premixed solution of chlorotrimethylsilane-triethylamine, 3.56 mL of a 0.5 M solution of LDA and 25 mL of THF. Work-up and column chromatography on silica gel (4 / 1 petroleum ether-ether with 1% acetic acid) afforded 247 mg (63 %) of a colorless oil (247 mg, 63 %).

IR (NaCl): 2936, 2872, 1703, 1614 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃): δ 7.23 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H) 5.50-5.29 (m, 2H), 4.39 (s, 2H), 3.81 (s, 3H), 3.47-3.34 (m, 2H), 2.42-2.19 (m, 2H), 1.65-1.50 (m, 7H), 1.02 (d, J=6.6 Hz, 3H). \(^13\)C NMR (75 MHz, CDCl₃): δ 181.1, 159.0, 133.6, 130.4, 129.1, 125.2, 113.6, 72.3, 69.5, 55.1, 51.1, 39.0, 27.6, 25.6, 17.8, 17.7. Anal. Calcd for C₁₈H₂₆O₄: C, 70.56; H, 8.55. Found: C,
(±)-methyl (2S,3S,4E)-2-{3-[(4-methoxybenzyl)oxy]propyl}-3-methylhex-4-enoate
(53)

To a suspension of 70 mg of acid 37 (0.228 mmol, 1.0 equiv.) and 47.4 mg of potassium carbonate (0.343 mmol, 1.5 equiv.) in 0.5 mL of acetone was added 71 µL of methyl iodide (1.14 mmol, 5.0 equiv.) and the reaction was stirred at rt overnight. The reaction was diluted with 5 mL of H₂O and 5 mL of Et₂O. The separated aqueous layer was extracted with 4 x 5 mL of Et₂O. The combined organic layers were washed with a solution of saturated aqueous sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (8 / 1 petroleum ether-ether) afforded 55.2 mg (75 %) of a colorless oil.

IR (NaCl): 2952, 2858, 1734, 1614 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.23 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.5 Hz, 2H), 5.35-5.49 (m, 1H), 5.24-5.13 (m, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 3.34-3.45 (m, 2H), 2.23-2.33 (m, 1H), 2.17-2.07 (m, 1H), 1.70-1.43 (m, 7H), 0.93 (d, J=6.7 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 175.7, 150.9, 134.1, 130.5, 129.1, 125.3, 113.6, 72.3, 69.5, 55.1, 51.4, 51.1, 39.8, 27.7, 27.0, 19.0, 17.7.
(2S,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethylhex-4-enamide (51)

N,O-dimethylhydroxylamine was prepared from the hydrochloride salt. A 250 mL round bottom flask was charged with 24.3 g of N,O-dimethylhydroxylamine hydrochloride (250 mmol) 100 mL of ethylene glycol and 41 mL of triethanolamine (310 mmol). A short-path distillation head was affixed to the flask, the thick slurring heated to reflux, and the free amine collected (bp 47-50 °C).

To a solution of 7.33 g of acid 37 (23.92 mmol, 1.0 equiv.) in 240 mL of THF at 0 °C was added 10.0 mL of triethylamine (71.77 mmol, 3.0 equiv.), then 2.04 mL of methanesulfonyl chloride (26.31 mmol, 1.1 equiv.) dropwise. The reaction was stirred at 0 °C for 10 min, and salt formation was observed. To the suspension was added 2.64 mL of N,O-dimethylhydroxylamine (35.88 mmol, 1.5 equiv.) and the reaction was stirred at 0 °C for 1 h. The reaction was quenched with 120 mL of H₂O and diluted with 120 mL of Et₂O. The separated aqueous layer was extracted with 3 x 120 mL of Et₂O. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (1 / 1 petroleum ether-ether) afforded 6.7 g (80 %) of a colorless oil.

[α]D^26.5 = -5.05 ± 0.007 (c 1.20, CHCl₃). IR (NaCl): 2937, 2857, 1661, 1614 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ 7.22 (d, J=8.5 Hz, 2H), 6.83 (d, J=8.5 Hz, 2H), 5.47-5.33 (m, 1H), 5.21 (ddd, J=15.4, 8.9, 1.5 Hz, 1H), 4.34 (s, 2H), 3.75 (s, 3H), 3.60 (s, 3H), 3.41-3.29 (m, 2H), 3.17 (s, 3H), 2.72-2.56 (m, 1H), 2.37-2.22 (m, 1H), 1.69-1.42 (m, 7H), 0.89 (d, J=6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 177.2, 159.0, 134.8, 130.7, 129.1, 125.2, 113.6, 72.4, 70.0, 61.2, 55.2, 45.9, 45.8, 40.2, 27.8, 27.6, 19.4, 17.9. Anal. Calcd for C₂₉H₃₁NO₄: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.89; H, 8.92, N, 4.03.
(+)-(2R,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethylhex-4-enamide (67)

Following the procedure of the synthesis of amide 51, amide 67 was synthesized with the following quantities of reagents and solvents: 247 mg of acid 47 (0.807 mmol, 1.0 equiv.), 337 μL of triethylamine (2.42 mmol, 3.0 equiv.), 69 μL of methanesulfonyl chloride (0.888 mmol, 1.1 equiv.), 178 μL of N,O-dimethylhydroxylamine (1.21 mmol, 1.5 equiv.), and 27 mL of THF. Work-up and column chromatography on silica gel (1/1 petroleum ether-ether) afforded 237 mg (84 %) of a colorless oil.

IR (NaCl): 2937, 2857, 1661, 1614 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.17 (d, J=8.5 Hz, 2H), 6.78 (d, J=8.5 Hz, 2H) 5.36-5.29 (m, 2H), 4.32 (s, 2H), 3.70 (s, 3H), 3.53 (s, 3H), 3.37-3.30 (m, 2H), 3.06 (s, 3H), 2.76-2.58 (m, 1H), 2.33-2.22 (m, 1), 1.60-1.40 (m, 7H), 0.93 (d, J=6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 176.5, 158.8, 134.6, 130.4, 128.9, 124.0, 113.4, 72.2, 69.7, 60.9, 54.9, 45.9, 45.8, 39.2, 27.7, 25.7, 17.6, 17.3. Anal. Calcd for C₂₀H₃₁NO₄: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.67; H, 9.00, N, 4.04.

(3S)-3-[(1S,2E)-1-methylbut-2-enyl]tetrahydro-2H-pyran-2-one (52)

¹H NMR (400 MHz, CDCl₃): δ 5.49-5.33 (m, 2H), 4.32-4.17 (s, 2H), 2.93-2.85 (m, 1H), 2.45-2.40 (m, 1H), 1.95-1.76 (m, 3H), 1.70-1.56 (m, 4H), 1.07 (d, J=7.09 Hz, 3H).
**N-methoxy-N-methylbenzamide (61)**

Following the procedure of the synthesis of amide 51, amide 61 was synthesized with the following quantities of reagents and solvents: 1.0 g of benzoic acid (55) (8.19 mmol, 1.0 equiv.), 3.42 mL of triethylamine (24.57 mmol, 3.0 equiv.), 697 µL of methanesulfonyl chloride (9.01 mmol, 1.1 equiv.), 82 mL of THF, and 904 µL of N,O-dimethylhydroxylamine (12.28 mmol, 1.5 equiv.). Work up and column chromatography on silica gel (1/1 petroleum ether-ether) afforded 828 mg (61%) of a pale yellow oil.

IR (NaCl): 2971, 2936, 1646, 979 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.66-7.64 (m, 2H), 7.46-7.35 (m, 3H), 3.55 (s, 3H), 3.34 (s, 3H). Anal. Calcd for C₉H₉N0₂: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.41; H, 6.84, N, 8.88.

**N-methoxy-N-methyl-1-phenylcyclohexanecarboxamide (62)**

Following the procedure of the synthesis of amide 51, amide 62 was synthesized with the following quantities of reagents and solvents: 1.0 g of 1-phenylcyclohexanecarboxylic acid (56) (5.29 mmol, 1.0 equiv.), 2.21 mL of triethylamine (15.56 mmol, 3.0 equiv.), 450 µL of methanesulfonyl chloride (5.82 mmol, 1.1 equiv.), 53 mL of THF, and 584 µL of N,O-dimethylhydroxylamine (7.93 mmol, 1.5 equiv.). Work up and column chromatography (2/1 petroleum ether-ether) gave 1.15 g (88%) of a yellow oil.
IR (NaCl): 2932, 2860, 1652, 996 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.33-7.25 (m, 4H), 7.22-7.12 (m, 1H), 3.06 (s, 3H), 2.48-2.36 (m, 2H), 1.82-1.53 (m, 7H), 1.38-1.22 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 175.7, 144.8, 127.9, 125.9, 125.7, 58.8, 50.4, 34.8, 33.1, 25.7, 23.0. Anal. Calcd for C₁₅H₂₁N⁰₂: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.73; H, 8.56; N, 5.66.

**N-methoxy-N-methyl-2-phenylcyclopropanecarboxamide (63)**

Following the procedure of the synthesis of amide 51, amide 63 was synthesized with the following quantities of reagents and solvents: 300 mg of *trans*-2-phenyl-1-cyclopropanecarboxylic acid (57) (1.76 mmol, 1.0 equiv.), 735 µL of triethylamine (5.27 mmol, 3.0 equiv.), 150 µL of methanesulfonyl chloride (1.94 mmol, 1.1 equiv.), 17 mL of THF, and 194 µL of N,O-dimethylhydroxylamine (2.64 mmol, 1.5 equiv.). Work up and column chromatography (1/1 petroleum ether-ether) gave 220 mg (61 %) of a pale yellow oil.

IR (NaCl): 2966, 2937, 1652, 995 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.29-7.10 (m, 5H), 3.67 (s, 3H), 3.22 (s, 3H), 2.39-2.52 (m, 2H), 1.64-1.58 (m, 1H), 1.32-1.26 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 172.7, 140.5, 128.2, 126.0, 125.9, 61.3, 32.3, 25.6, 21.3, 16.1. LRMS (EI+): 205 (M+).
**N-methoxy-N-methyl-1,1'-biphenyl-2-carboxamide (64)**

Following the procedure of the synthesis of amide 51, amide 64 was synthesized with the following quantities of reagents and solvents: 1.0 g of 1,1'-biphenyl-2-carboxylic acid (58) (5.04 mmol, 1.0 equiv.), 2.11 mL of triethylamine (15.13 mmol, 3.0 equiv.), 430 μL of methanesulfonyl chloride (5.55 mmol, 1.1 equiv.), 50 mL of THF, and 557 μL of N,O-dimethylhydroxylamine (7.57 mmol, 1.5 equiv.). Work up and recrystallization (hexanes) gave 833 mg (68%) of pale yellow solids (mp 78-80 °C).

IR (KBr): 2965, 2928, 1650, 995 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.84-7.32 (m, 9H), 3.57 (s, 3H), 3.56 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 169.2, 143.0, 140.0, 132.5, 130.1, 128.53, 128.50, 127.5, 126.8, 126.6, 126.3, 60.7, 33.4. Anal. Calcd for C₁₅H₁₅NO₂: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.73; H, 6.40; N, 6.20.

**N-methoxy-N-methyl-2,2-diphenylacetamide (65)**

Following the procedure of the synthesis of amide 51, amide 65 was synthesized with the following quantities of reagents and solvents: 1.0 g of diphenylacetic acid (59) (4.71 mmol, 1.0 equiv.), 1.97 mL of triethylamine (14.13 mmol, 3.0 equiv.), 401 μL of methanesulfonyl chloride (5.18 mmol, 1.1 equiv.), 47 mL of THF, and 520 μL of N,O-dimethylhydroxylamine (7.07 mmol, 1.5 equiv.). Work-up and recrystallization
(1 / 1 petroleum ether - ether) gave 770 mg (64 %) of white solids (mp 105-107 °C).

IR (KBr): 2969, 2936, 1656, 997 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.21 (m, 10H), 5.53 (s, 1H), 3.48 (s, 3H), 3.22 (s, 3H). Anal. Calcd for C₁₆H₁₇NO₂: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.26; H, 6.81; N, 5.62.

(2S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (60)

To a suspension of 2.0 g of L-proline (18.0 mmol, 1.0 equiv.) in 32 mL of CH₂Cl₂ at 0 °C was added 3.3 mL of triethylamine (23.7 mmol, 1.3 equiv.) and a solution of 5.44 g of di-tert-butyl dicarbonate (26.0 mmol, 1.4 equiv.) in 7 mL of CH₂Cl₂. The reaction was stirred at 0 °C for 2 h and became homogeneous. It was quenched with 10 mL of a solution of saturated citric acid. The separated organic layer was washed with 10 mL of H₂O, 2 x 10 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting cloudy residue was dissolved in 10 mL of CH₂Cl₂, filtered through a pad of Celite and concentrated in vacuo to give a yellow oil. Recrystallization in 10 mL of hot EtOAc, followed by the addition of 50 mL of hexanes afforded 2.45 g (89 %) of white crystals (mp 133-135 °C).

IR (KBr): 2977, 1740, 1640 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 9.55-9.33 (br s, 1H), 4.33-4.21 (m, 1H), 3.51-3.32 (m, 2H), 2.23-1.86 (m, 4H), 1.44 (s, 9/2 H), 1.39 (s, 9/2 H). Anal. Calcd for C₁₀H₁₇NO₄: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.40; H, 7.97; N, 6.49.
Following the procedure of the synthesis of amide 51, amide 66 was synthesized with the following quantities of reagents and solvents: 500 mg of acid 60 (2.32 mmol, 1.0 equiv.), 970 µL of triethylamine (6.96 mmol, 3.0 equiv.), 198 µL of methanesulfonyl chloride (2.55 mmol, 1.1 equiv.), 105 mL of THF, and 256 µL of \(N,O\)-dimethylhydroxylamine (3.48 mmol, 1.5 equiv.). Work-up and column chromatography (1/1 petroleum ether - ether) gave 454 mg (76 %) of a yellow oil.

\([\alpha]_D^{26.1} = -37.1 \pm 0.02\) (c 1.03, MeOH). \(\text{IR (NaCl): } 2933, 2859, 1661, 1614 \text{ cm}^{-1}\). \(^1\text{H NMR (300 MHz, CDCl}_3\): \(\delta 4.59\) (d, \(J = 7.7 \text{ Hz, } 1/2\text{H)
, 4.49\) (d, \(J = 7.7 \text{ Hz, } 1/2\text{H)
, 3.65\) (s, 3/2H), 3.60 (s, 3/2 H), 3.49-3.24 (m, 2H), 3.07 (s, 3H), 2.10-1.68 (m, 4H), 1.33 (s, 9/2H), 1.28 (s, 9/2H). Anal. Calcd for C\(_{12}\)H\(_{22}\)N\(_2\)O\(_4\): C, 55.80; H, 8.58; N, 10.84. Found: C, 56.20; H, 8.80; N, 11.21.

To a solution of 0.84 g of amide 51 (2.4 mmol, 1.0 equiv.) in 31 mL of THF at 0 °C was added 14.42 mL of a solution of 1.0 M vinyl magnesium bromide in THF (14.42 mmol, 6.0 equiv.). The reaction was stirred overnight, warming to rt, and was poured into 150 mL of a cold solution of 2:1 saturated aqueous ammonium chloride-THF. To the mixture were added 200 mL of H\(_2\)O and 100 mL of Et\(_2\)O. The separated aqueous layer was extracted with 2 x 250 mL of Et\(_2\)O. The combined organic layers were dried
over anhydrous magnesium sulfate and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (4/1 petroleum ether-ether) afforded 557 mg (74%) of a pale yellow oil.

\[ \alpha \] D \text{26.1} = -11.6 \pm 0.01 (c 0.67, CHCl₃). IR (NaCl): 2936, 2858, 1694, 1515 cm⁻¹.

\( ^1H \) NMR (300 MHz, CDCl₃): \( \delta 7.16 \) (d, \( J=8.5 \) Hz, 2H), 6.83 (d, \( J=8.5 \) Hz, 2H), 6.41 (dd, \( J=17.7, 10.4 \) Hz, 1H) 6.19 (dd, \( J=17.3, 1.2 \) Hz, 1H), 5.70 (dd, \( J=10.4, 1.2 \) Hz, 1H), 5.46-5.32 (m, 1H), 5.18 (ddd, \( J=15, 8.5, 1.2 \) Hz, 1H), 4.35 (s, 2H), 3.71 (s, 3H), 3.39-3.31 (m, 2H), 2.56 (ddd, \( J=8.5, 8.5, 5.8 \) Hz, 1H), 2.39-2.29 (m, 1H), 1.69-1.35 (m, 7H), 0.87 (d, \( J=6.6 \) Hz, 3H). \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta 203.9, 160.0, 136.5, 134.1, 130.5, 129.0, 127.8, 125.3, 113.6, 72.2, 69.6, 55.1, 54.3, 39.4, 27.5, 26.5, 19.1, 17.7. \)


(±)-(4R,5S,6E)-4-{3-[((4-methoxybenzyl)oxy]propyl}-5-methylocta-1,6-dien-3-one (68)

Following the procedure of the synthesis of ketone 36, ketone 68 was synthesized with the following quantities of reagents and solvents: 237 mg of amide 67 (0.679 mmol, 1.0 equiv.), 4.07 mL of a 1.0 M solution of vinyl magnesium bromide in THF (4.07 mmol, 6.0 equiv.), and 14 mL of THF. Work-up and column chromatography on silica gel (5/1 petroleum ether-ether) afforded 173 mg (80%) of a colorless oil.

IR (NaCl): 2936, 2858, 1694, 1515 cm⁻¹. \( ^1H \) NMR (300 MHz, CDCl₃): \( \delta 7.20 \) (d, \( J=8.5 \) Hz, 2H), 6.83 (d, \( J=8.5 \) Hz, 2H), 6.35 (dd, \( J=17.4, 10.4 \) Hz, 1H), 6.13 (dd, \( J=17.3, 1.5 \) Hz, 1H), 5.66 (d, \( J=10.4, 1.5 \) Hz, 1H), 5.40-5.22 (m, 2H), 4.35 (s, 2H), 3.74 (s, 3H), 3.38-3.29 (m, 2H), 2.69-2.64 (m, 1H), 2.42-2.28 (m, 1H), 1.73-1.34 (m, 7H), 0.91 (d, \( J=6.9 \) Hz, 3H). \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta 203.3, 159.0, 136.6, 134.1, 130.5, 129.1, 127.4, 113.6, 72.3, 69.7, 55.1, 54.2, 38.7, 27.7, 24.7, 17.7, 17.3. \)
(4S,5S)-5-{3-[4-methoxybenzyl]oxy}propyl]-4-methylcyclopent-2-en-1-one (35)

A 2-neck-flask was charged with 75.8 mg of benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (0.092 mmol, 0.05 equiv.) and 38 mL of degassed CH₂Cl₂, and a solution of 557 mg of vinyl ketone 36 (1.76 mmol, 1.0 equiv.) in 60 mL of degassed CH₂Cl₂ was added. The reaction flask was equipped with a condenser and the reaction was heated at reflux overnight, and stirred at rt for 8 h. The solvent was removed in vacuo, and the resulting brown oil was purified by column chromatography on silica gel (1/1 petroleum ether-ether) to afford 344 mg (71%) of a brown oil.

[α]D²⁴ = +92.8 ± 0.01 (c 0.91, CHCl₃). IR (NaCl): 2937, 2859, 1703, 1514 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.56 (dd, J=5.4, 2.7 Hz, 1H), 7.22 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 6.05 (dd, J=5.8, 1.5 Hz, 1H), 4.39 (s, 2H), 3.75 (s, 3H), 3.52-3.38 (m, 2H), 3.10-2.99 (m, 1H), 2.32-2.25 (m, 1H), 1.84-1.64 (m, 3H), 1.46-1.39 (m, 1H), 1.01 (d, J=7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 211.9, 168.2, 159.1, 132.4, 130.5, 129.2, 113.7, 72.5, 69.8, 55.2, 53.2, 42.7, 27.5, 27.2, 19.6. LRMS (EI+): 274 (M+).

(±)-(4S,5R)-5-{3-[4-methoxybenzyl]oxy}propyl]-4-methylcyclopent-2-en-1-one (69)

Following the procedure of the synthesis of enone 35, enone 69 was synthesized with the following quantities of reagents and solvents: 87.6 mg of ketone 61 (0.277 mmol, 1.0 equiv.), 16 mg of benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (0.019 mmol, 0.07
equiv.), and 16 mL of degassed CH₂Cl₂. Work-up and column chromatography on silica gel (4 / 1 petroleum ether-ether) afforded 53.2 mg (70%) of a brown oil.

IR (NaCl): 2937, 2859, 1703, 1514 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.48 (dd, J=5.8, 2.3 Hz, 1H), 7.23 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.5 Hz, 2H), 6.06 (dd, J=5.8, 1.9 Hz, 1H), 4.43 (s, 2H), 3.77 (s, 3H), 3.49-3.40 (m, 2H), 2.67-2.59 (m, 1H), 1.87-1.63 (m, 4H), 1.53-1.41 (m, 1H), 1.18 (d, J=7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 211.9, 168.2, 159.1, 132.4, 130.5, 129.2, 113.7, 72.6, 69.9, 55.2, 53.2, 42.7, 27.5, 27.2, 19.6.

(±)-(2S,3S)-2-[3-[(4-methoxybenzyl)oxy]propyl]-3-methylcyclopentanone (70)

To a solution of 52.3 mg of enone 35 (0.191 mmol, 1.0 equiv.) in 2 mL of EtOAc was added 9 mg of 10% Pd/C (15% by wt.). The reaction vessel was carefully evacuated by a water aspirator for 10 seconds and charged with hydrogen gas. The reaction was stirred under an atmosphere of hydrogen gas for 2 h, filtered through a pad of Celite and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (4 / 1 petroleum ether-ether) afforded 46.3 mg (88%) of a colorless oil.

IR (NaCl): 2953, 2861, 1739, 1614 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.23 (d, J=8.5 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 4.40 (s, 2H), 3.76 (s, 3H), 3.48-3.39 (m, 2H), 2.50-2.39 (m, 1H), 2.26-2.05 (m, 3H), 2.02-1.81 (m, 1H), 1.75-1.55 (m, 4H), 1.38-1.23 (m, 1H), 0.83 (d, J=7.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 220.2, 159.0, 130.6, 129.1, 113.7, 72.5, 70.0, 55.2, 53.7, 34.8, 32.9, 27.8, 27.7, 21.4, 14.4.
A 25 mL round bottom flask was charged with 1.29 mL of a 1.0 M solution of L-Selectride and 9 mL of THF at -78 °C. A solution of 343.6 mg of enone 35 (1.25 mmol, 1.0 equiv.) in 7 mL of THF was added over 30 min. The resulting solution was stirred at -78 °C for 20 min, and 470 mg of N-phenyltrifluoromethanesulfonylimide (1.31 mmol, 1.05 equiv.) was added. The reaction was allowed to warm to rt over 4 h. The reaction was washed with 2 x 85 mL of brine, and the combined aqueous layers were back-extracted with 2 x 150 mL of Et₂O. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo to give a brown oil. Purification by column chromatography on silica gel (30 / 1, petroleum ether-ether with 1 % triethylamine) afforded 212 mg (41 %) of a yellow oil.

\[ [\alpha]_{D}^{26.0} = -17.1 \pm 0.01 \text{ (c 0.92, CHCl}_3) \]. IR (NaCl): 2926, 2855, 1615, 1515 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.25 (d, \(J=8.5\) Hz, 2H), 6.87 (d, \(J=8.5\) Hz, 2H), 5.60 (dd, \(J=3.9, 1.5\) Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.44 (t, \(J=6.6\) Hz, 2H), 2.70 (dd, \(J=12.3, 6.6\) Hz, 1H), 2.60-2.40 (m, 2H), 2.00-1.91 (m, 1H), 1.73-1.49 (m, 4H), 1.00 (d, \(J=6.9\) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 159.1, 152.2, 130.6, 129.1, 116.3, 113.7, 72.5, 69.8, 55.2, 45.7, 35.1, 34.3, 27.6, 23.6, 15.4. LRMS (EI+): 408 (M+).

Following the procedure of the synthesis of triflate 34, triflate 71 was synthesized.
with the following quantities of reagents and solvents: 52 mg of enone 69 (0.190 mmol, 1.0 equiv.), 0.195 mL of a solution of 1.0 M of L-Selectride in THF (0.195 mmol, 1.03 equiv.), 2.4 mL of THF, and 71.1 mg of N-phenyltrifluoromethanesulfonimide (0.20 mol, 1.05 equiv.). Work-up and column chromatography on silica gel (30 / 1, petroleum ether-ether with 1 % triethylamine) afforded 31 mg (40 %) of a yellow oil.

IR (NaCl): 2926, 2855, 1615, 1515 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.24 (d, \(J=8.5\) Hz, 2H), 6.86 (d, \(J=8.5\) Hz, 2H), 5.54 (d, \(J=0.8\) Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.56-3.32 (m, 2H), 2.62-2.48 (m, 1H), 2.41-2.30 (m, 1H), 2.16-2.00 (m, 1H), 1.97-1.83 (m, 1H), 1.27-1.15 (m, 4H), 1.09 (d, \(J=6.9\) Hz, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 150.8, 130.6, 129.2, 115.7, 113.8, 72.6, 69.9, 55.3, 50.9, 35.9, 35.2, 29.7, 28.6, 26.8, 21.8. LRMS (EI+): 408 (M+).

Triflate 34 from cyclopentanone 70

To a solution of 21.3 mg of lithium 1,1,1,3,3,3-hexamethyldisilazide (LHMDS) (0.0123 mmol, 1.1 equiv.) in 0.23 mL of toluene was added a solution of 31 mg of cyclopentanone 70 (0.112 mmol, 1.0 equiv.) in 3.2 mL of THF dropwise at -78 °C. The reaction was stirred for 1 h, and a solution 48 mg of \(N\)-phenyltrifluoromethanesulfonimide (0.135 mmol, 1.2 equiv.) in 1.2 mL of THF was added. The resulting solution was stirred for 4 h, warming to rt. The reaction was quenched with 3 mL of a solution of saturated aqueous sodium bicarbonate and diluted with 5 mL of Et\(_2\)O. The separated aqueous layer was extracted with 3 x 5 mL of Et\(_2\)O. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo to give a brown oil. Purification by column chromatography on silica gel (30 / 1, petroleum ether-ether with 1 % triethylamine) afforded 19.5 mg (43%) of a yellow oil along with 2.9 mg (9 %) of recovered starting material.
4. References


4. For a review on the biosynthesis of sesterterpenes, see: Cordell, G. A. Phytochemistry 1974, 13, 2343-2364.


27. Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.;
28. For enzyme catalyzed esterification reactions in organic synthesis, see Cambou, B.;
32. For a review of the Ireland and related Claisen rearrangements, see Chai, Y.; Hong,
S-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. Tetrahedron 2002, 58, 2905.
44. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Doling, U-H.;
47. Nicolaou, K. C.; Baran, P. S.; Zhong, Y-L.; Choi, H-S.; Fong, K. C.; He, Y.; Yoon,
49. Carboxylic acid 60 was synthesized using a known protocol: Bartoli, G.; Bosco, M.;
   Dalpizzo, R.; Giuliani, A.; Marcantoni, E.; Mecozzi, T.; Sambri, L.; Torregiani, E.
53. For a discussion on the kinetic enolization using lithium bases, see: Xie, L.;
   1988, 29, 3749.
59. For published NMR data for compounds 61, 65, and 66, see: Banwell, M; Smith, J.
(±)-(3E)-pent-3-en-2-ol
(1R,2E)-1-methylbut-2-enyl (2R)-methoxy(phenyl)acetate (41)
pent-3-yn-2-one
(1R,2E)-1-methylbut-2-enyl 5-[(4-methoxybenzyl)oxy]pentanoate (38)
2,2,2-trifluoroethyl 5-(benzyloxy)pentanoate (46)
(±)-1-methylbut-2-ynyl 5-[(4-methoxybenzyl)oxy]pentanoate (49)
(±)-(2Z)-1-methylbut-2-enyl 5-[(4-methoxybenzyl)oxy]pentanoate (50)
(2S,3S,4E)-2-\{3-[(4-methoxybenzyl)oxy]propyl\}-3-methylhex-4-enoic acid (37)
(±)-(2R,3S,4E)-2-[(4-ethylbenzyl)oxy|propyl]-3-methylhex-4-enoic acid (47)
(±)-methyl (2S,3S,4E)-2-[(4-methoxybenzyl)oxy]propyl]-3-methylhex-4-enoate

(53)
(2S,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethylhex-4-enamide (51)
(±)-(2R,3S,4E)-N-methoxy-2-{3-[(4-methoxybenzyl)oxy]propyl}-N,3-dimethylhex-4-enamide (67)
(±)-(3S)-3-[(1S,2E)-1-methylbut-2-enyl]tetrahydro-2H-pyran-2-one (52)
N-methoxy-N-methylbenzamide (61)
$N$-methoxy-$N$-methyl-1-phenylecyclohexanecarboxamide (62)
N-methoxy-N-methyl-2-phenylcyclopropanecarboxamide (63)
N-methoxy-N-methyl-1,1'-biphenyl-2-carboxamide (64)
(2S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (60)
tert-butyl (2S)-2-\{(methoxy(methyl)amino)carbonyl\}pyrrolidine-1-carboxylate (66)
(4S,5S,6E)-4-[(4-methoxybenzyl)oxy]propyl]-5-methylocta-1,6-dien-3-one (36)
(±)-(4R,5S,6E)-4-{3-[(4-methoxybenzyl)oxy]propyl}-5-methylocta-1,6-dien-3-one (68)
(4S,5S)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methylcyclopent-2-en-1-one (35)
(±)-(4S,5R)-5-{3-[(4-methoxybenzyl)oxy]propyl}-4-methylcyclopent-2-en-1-one (69)
(±)-(2S,3S)-2-{3-[(4-methoxybenzyl)oxy]propyl}-3-methylcyclopentanone (70)
(4S,5S)-5-[(4-methoxybenzyl)oxy]propyl]-4-methylcyclopent-1-en-1-yl trifluoromethanesulfonate (34)
(±)-(4S,5R)-5-[(4-methoxybenzyl)oxy]propyl]-4-methylcyclopent-1-en-1-yl trifluoromethanesulfonate (71)