NEW ASPECTS IN RING CLOSING METATHESIS REACTIONS
STUDIES TOWARD THE SYNTHESIS OF MANGICOL A

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

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*****

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2004

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ABSTRACT

Initially, we explore the possible trends in regioselectivity as a function of ring size in ring closing metathesis reactions in the compound series defined by 1.16 on exposure to ruthenium complexes 1.1 and 1.2b. In each case, the levels of cyclic alkene and conjugated diene were determined. Double bond geometric assignments were made on the basis of vinyl proton $^1$H-NMR chemical shifts and coupling constants.

The second stage of this work described a comparative investigation of kinetic consequences associated with long-range electronic effects in ring closing metathesis reactions. When exposed to the Grubbs ruthenium catalyst 2.1, trienyl substrates of type 2.10 undergo highly regioselective ring closure to give the common product 2.11. These reactions proceeded invariably under pseudo-first-order kinetics.

Inspired by the previous works, another kinetic study was performed on compounds of type 3.1 in presence of second generation Grubbs catalyst 3.2b. The experimental observations have been subjected to Hammett analysis. The $\rho$ value for the composite aromatic derivatives differs from that of the aliphatic series, although both are negative because electron-donating groups accelerate the reaction.

A synthetic approach towards the formation of tetracyclic core of mangicol A is described. All of the mangicols (A-G) are sesterterpenoids that share unprecedented
spirotricyclic structural features. In the first generation approach, the successful synthesis of carboxylic acid 4.20 and primary alcohol 4.21 were achieved. A ring opening reaction of cycloalkene to the dicarbonyl compound by ozonolysis followed by acid-catalyzed ring closure was a key reaction sequence in the synthesis of both fragments. Compounds 4.20 and 4.21 were coupled together efficiently in presence of EDC. However, all efforts towards the formation of diene moiety proved to be fruitless. At this point, a second generation approach was planned and the successful synthesis of keto phosphonate 5.4 and aldehyde 5.5 were achieved. However, the deoxygenation of carbonyl functional group proved to be troublesome and the choice of the protecting groups were found to be not compatible during the reactions attempted in the later part of the synthesis.
Dedicated to my parents
ACKNOWLEDGMENTS

I wish to express my sincere gratitude and respect to my advisor, Dr. Leo A. Paquette, for his guidance and encouragement during my stay at The Ohio State University. Without his dedication much of the research discussed in the dissertation would not have possible.

I wish to thank Dr. Hadad and Dr. Parquette for serving on my dissertation committee. I also thank Rebecca Martin and Donna Rothe, whose assistance have been invaluable to our research group.

Special thanks goes to two of my best friends in Columbus, Chris and Doug. I am extremely grateful for their friendship and the time we spent together. I would like to thank all the Paquette group members, particularly Serge, Fabrice, Bob, Pat, Graham, and Stephane for their help. I should definitely say life in laboratory would not have been so much fun and eventful without the presence of Matt and Ryan. Special thanks goes to both of them for proof reading my thesis as well as all the proposals that I have written in past.

I would specially like to acknowledge Partha and Jen who always made me feel at home and were always next to me when I needed them the most. I would like to thank all my Bengali friends, particularly Shubhayu. I always enjoyed playing cricket under his
captaincy. Finally, I would like to thank Antara for being my true friend and a part of my life for last couple of years. Life would not have been so great without her love and understanding.

This section would not be complete without thanking my parents and family. From the bottom of my heart, I know that whatever I am today is all because of your love and sacrifices. Thank you for giving me this opportunity.
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Research Publications


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Major Field: Chemistry
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LIST OF ABBREVIATIONS

α alpha

[α] specific rotation

Ac acetyl

br broad (IR and NMR)

β beta

n-Bu normal-butyl

t-Bu tert-butyl

Bz benzoyl

°C degrees Celsius

calcd calculated

CSA (1S)-(+) -10-camphorsulfonic acid

δ chemical shift in parts per million downfield from tetramethylsilane

d doublet (spectra); day(s)

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAP 4-(N,N-dimethylamino)pyridine

DMF N,N-dimethylformamide
<table>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>γ</td>
<td>gamma</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz (NMR)</td>
</tr>
<tr>
<td>k</td>
<td>kilo</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>milli; multiplet (NMR)</td>
</tr>
<tr>
<td>µ</td>
<td>micro</td>
</tr>
<tr>
<td>M</td>
<td>moles per liter</td>
</tr>
<tr>
<td>Mc</td>
<td>chloromethylsulfonyl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
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<td>MHz</td>
<td>megahertz</td>
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<td>mol</td>
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<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry; molecular sieves</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (MS)</td>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic reasonance</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
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<td>q</td>
<td>quartet (NMR)</td>
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<tr>
<td>rt</td>
<td>room temperature</td>
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<tr>
<td>s</td>
<td>singlet (NMR); second(s)</td>
</tr>
<tr>
<td>t</td>
<td>tertiary (tert)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<td>TMS</td>
<td>trimethylsilyl</td>
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CHAPTER 1

A SYSTEMATIC ANALYSIS OF INTRAMOLECULAR COMPETITION OF ENE-DIENE SYSTEMS IN RING CLOSING METATHESIS

1.1 BACKGROUND

Intramolecular cyclization reactions have played a pivotal role in the determination of important factors associated with the assembly of medium to large rings.\(^1\) The breadth of reaction types has been subjected to impressive variation, ranging from C-C bond formation (\(e.g.,\) the generation of carbocyclic malonates)\(^2\) to the formation of C-O (\(e.g.,\) the elaboration of cyclic ethers and lactones)\(^1,3,4\) and C-N bonds (\(e.g.,\) closure to produce \(N\)-tosylated amines)\(^5\). On the strength of the seminal investigations performed by Ziegler\(^6\) and Stoll\(^7\) among others, it was soon recognized that the probability for chain ends to meet in a bifunctional linear precursor decreases as the chain is made increasingly longer. In 1935, Ruzicka advanced the hypothesis that this probability factor contributes independently of ring strain effects to the global disincentive toward cyclization.\(^8\) The ensuing experimental determination of activation parameters for a number of cases suggested that simple relationships between \(\Delta H^\ddagger\) and the strain energy likely do not exist for this generic class of reactions.\(^9\)
During the past two decades, several effective methods for intramolecular macrolactonization have stimulated interest at many levels. Among these methods, the area of ring-closing metathesis (RCM) involving air-stable ruthenium catalysts has experienced tremendous growth and commanded a major share of the attention. According to the review by Armstrong examples of 8-membered to 21-membered ring closures were indeed quite uncommon. Success or failure was attributed more to the substrate conformation than to the properties of the catalyst. However, the discovery of new and more reactive catalysts has shown that this viewpoint is no longer correct. While 1.1 has become recognized to offer good functional group tolerance and reliable performance levels with many substrates, 1.2a and 1.2b exhibit higher reactivity, increased efficiency, and improved sensitivity toward functional groups as a direct result of their more favorable steric and electronic properties (Figure 1).

![RCM catalysts](image)

Wagner and co-workers examined the conversion of 1.3 and 1.4 into macrolides under catalysis by two of the above ruthenium catalysts (Scheme 1.1). Quite unexpectedly for them, distinctively different pathways were followed in the RCM reaction. With catalyst 1.1, the (E,E)-dienes 1.5 and 1.6 were produced in high yield (57-62%). Less than 5% of the (E,Z)-isomer was formed, and no other end products were
observed. In contrast, the heterocyclic carbene complex 1.2a showed the opposite selectivity, and produced the trans-cycloalkenes 1.7 and 1.8 (40-45%) as sole products. Therefore, while 1.1 reacts regioselectively with the less sterically hindered terminal double bond, 1.2a opts instead to engage the more substituted, electron-rich internal double bond in metathesis. The consequences are quite dramatic. Although solvent, temperature, and concentration effects were examined by these authors, no control experiments were reported.

Scheme 1.1  Wagner’s study on macrocycle formation with 1.1 and 1.2a

In a recent study targeting the asymmetric synthesis of radicol and monocillin I, the Danishefsky group examined the RCM of dithianes 1.9 and 1.11 (Scheme 1.2).15 Whereas the use of commercial 1.1 resulted in essentially no reaction of 1.9, application
of **1.2b** gave diene **1.10** (55% yield) as the only monomeric product. This scenario was repeated with **1.11**, which cyclized to the 14-membered **1.12** (60%) notwithstanding the presence of dithiane and epoxide functionality. It is important to note that in both cases a 14-membered diene is produced instead of the 12-membered monoene.

Scheme 1.2  
Danishefsky’s study on macrocycle formation

In a third report, Mioskowski and co-workers demonstrated that when C- versus O-centered ring cyclizations are both possible, exclusive formation of the heterocycle is favored.\(^{16}\) The example given in Scheme 1.3 is illustrative.
To explore possible trends in regioselectivity as a function of ring size, we have carried out a systematic analysis of RCM behavior in the compound series defined by 1.16. Throughout this study, the conjugated dienyl unit bonded to the nitrogen atom has been kept constant while the \( \omega \)-alkenyl chain linked to oxygen has been progressively lengthened. To achieve a semblance of electronic equivalence, the degree of alkyl substitution about both double bonds in the conjugated diene segment has been equalized. The commercially available catalysts 1.1 and 1.2b were independently evaluated while varying the ring size in each instance.

1.2 SYNTHESIS OF ENE-DIENE SUBSTRATES

The synthesis of 1.16 started with the synthesis of azido carbinol 1.18, readily available from the reaction of sodium azide with cyclohexene oxide 1.17 in refluxing aqueous ethanol (Scheme 1.4). The generic intermediate 1.19 was prepared by sequential O-pivaloylation, chemoselective reduction of azide over 10% palladium on charcoal, and N-tosylation. Addition of \((E,E)\)-1-bromo-2,4-hexadiene to the sodium
salt of 1.19 in DMF solution\(^\text{21}\) led to the desired 1.20, reduction of which with Dibal-H\(^\text{22}\) made available the functionalized cyclohexanol 1.21. Treatment of the sodium salt of 1.21 with the appropriate ω-alkenyl bromide via a protocol previously defined by others\(^\text{23}\) resulted in the formation of the desired products 1.16a-h. A progressive dropoff in coupling efficiency from 75% to 50% was noted as \(n\) was increased from 1 to 5. Greater extension of the methylene chain beyond this level was not accompanied by further erosion in reaction efficiency. The example involving \(n = 2\) was met with exclusive E\(_2\) elimination, thus causing us to dispense with further consideration of this substrate.

![Scheme 1.4 Synthesis of 1.16](image)

1.3 RESULTS AND DISCUSSION

Under the standardized reaction conditions, 1.16a (entries 1 and 2 in Table 1.1) produced the (Z)-monoene 1.22 efficiently in 71-75% yield with complete conversion of the starting ene-diene in the presence of either catalyst (Scheme 1.5). Noteworthily, in this case both ruthenium catalysts are notably effective in generating the 8-membered...
ring monoene without the formation of any geometric isomer of the conjugated cyclodecadiene. However, the insertion of two methylene groups in **1.16b** retards the cyclization process to a significant extent, as 15-20% of the starting material (entries 3 and 4) was recovered in this reaction with either catalyst. In principle, **1.16b** is amenable to the formation of a 10-membered cycloalkene or a 12-membered cyclic diene such as **1.23**. Interestingly, (**E,Z**)-diene **1.23** was formed as a single product (exclusive of oligomers) in 27-33% isolated yield to the exclusion of any (**E**)- or (**Z**)-monoene corresponding to **1.22**.

![Scheme 1.5 RCM on **1.16a** and **1.16b**](image)

The identical processing of **1.16c** resulted in notably inefficient ring closure with either catalyst (67-70% oligomerization, entries 5 and 6). An inseparable *ca* 1:1 mixture (from $^{13}$C-NMR analysis) of the (**Z**)-isomer **1.24** and the (**E**)-isomer **1.25** were produced (Scheme 1.6). It is important to note that **1.16c** cyclizes only in the direction of 11-membered macrocycles, which means that the transition states associated with the possible generation of a 13-membered diene are too energetically inaccessible. In
contrast, the ring closing on **1.16d** (entries 7 and 8) resulted in the formation of (E)-monoene **1.26** and (E,Z)-diene **1.27** as a separable mixture. It is important to note that catalyst **1.2b** exhibits a greater preference for the generation of smaller 12-membered monoene **1.26** than does **1.1**.

![Scheme 1.6 RCM on 1.16c and 1.16d](image)

Scheme 1.6   RCM on **1.16c** and **1.16d**

Scheme 1.7 shows that the incremental intercalation of yet more methylene groups as in **1.16e** and **1.16f**, was met with the exclusive generation of the (E)-monoenes **1.28** and **1.29**, where the ring sizes are constituted of 13 and 14 atoms, respectively (entries 9-12). Neither **1.16e** nor **1.16f** show evidence of proceeding to generate the larger-ring diene products (now 15- and 16-membered).
Scheme 1.7  RCM on \textbf{1.16e} and \textbf{1.16f}

The introduction of eight- and nine-membered methylene chains as in \textbf{1.16g} and \textbf{1.16h} resulted in the formation of (Z)-monoenes defined by \textbf{1.30} and \textbf{1.32}, respectively, and (\textit{E,}\textit{E})-dienes characterized as \textbf{1.31} and \textbf{1.33} (entries 13-16). With either catalyst, the production of (\textit{E,}\textit{E})-dienes is heightened (Scheme 1.8). This may be a reflection of recognition within the associated transition states of the stabilizing effects of more extended conjugation and/or the energetic advantage of minimizing nonbonded transannular interactions by increasing the number of double bonds within the loop.
Scheme 1.8  RCM on 1.16g and 1.16h

The geometrical assignment of the (Z)-monoene was readily ascertained on the basis of its two widely spaced multiplets positioned upfield and downfield of 5.5 ppm. The (E)-counterpart is characterized by a narrow multiplet of area 2 in this region.\textsuperscript{24,25} The geometrical assignment of (E,E) and (Z,Z)-dienes were ascertained by decoupling experiments. For example, the 500 MHz NMR spectrum of 1.33 consists of four distinctively separated downfield multiplets. The trans,trans nature of its double bonds was elucidated by irradiation of the multiplets at $\delta = 6.06$ and 5.91 ppm. In the first instance, the $\delta = 5.91$ ppm signal was simplified to a doublet with $J = 15.0$ Hz. The
complementary experiment caused the $\delta = 6.06$ ppm signal to collapse as well to a doublet with $J = 14.2$ Hz. On the other hand, the $^1$H NMR of the (E,Z)-diene, for example 1.23, features three relevant multiplets. Two of these, where each multiplet corresponds to one proton, are positioned at $\delta = 7.12-6.98$ and 6.24-6.17 ppm, and are attributed to the central olefinic protons of the diene. Twice as intense is the third multiplet positioned at $\delta = 5.51-5.36$ ppm, which originates from the remaining vinylic protons. Irradiation at $\delta = 6.2$ ppm caused the downfield signal to collapse to a doublet ($J = 15.5$ Hz) and the reciprocal experiment at $\delta = 7.0$ ppm left a doublet ($J = 9.9$ Hz) at $\delta = 6.24$ ppm. These features unequivocally define the (E,Z)-geometry. 26

<table>
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<tr>
<th>entry</th>
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Table 1.1  Outcome of RCM involving 1.16
1.4 CONTROL EXPERIMENT

The analysis for the formation of products in the ring closing metathesis reactions of 1.16a-h is based on the expectation that kinetic control is operative under these conditions. If reversibility is inherent to these processes, more so for the more reactive catalyst 1.2b than 1.1, the door is open for possible ring contraction of the dienes to monoenes under the proper conditions. Selected as the test case was 1.16d in light of its unique capability to produce both types of cyclization products. It was observed that 1.16d results in approximately equal amounts of (E)-monoene 1.26 and the (E,Z)-diene 1.27 in presence of catalyst 1.1. With 1.2b as the catalyst, (E,Z)-diene 1.27 is significantly more predominant (ratio 4:1). (E,Z)-Diene 1.27 was resubjected to the original RCM conditions (Scheme 1.9). In the presence of 1.1, no reaction was observed, and the diene was recovered quantitatively. In contrast, the use of 1.2b resulted in the complete disappearance of 1.27 and isolation of 1.26 in 73% yield.

Scheme 1.9 Control experiment
1.5 CONCLUSION

Ene-dienes 1.16 are shown to be useful probes for the study of the effect of chain length on the mode of ring-closing metathesis. The key control experiment demonstrates the striking differences between 1.1 and 1.2b. Reversible ruthenacyclobutane formation always remains a distinct mechanistic possibility. The further chemical evolution of these intermediates is dependent on prevailing kinetic and thermodynamic factors.
CHAPTER 2

KINETIC STUDY OF ENE-DIENE SYSTEMS IN RING CLOSING METATHESIS

2.1 BACKGROUND

Ring closing metathesis has become very popular in organic synthesis\textsuperscript{13a,13b,27} because of the stability of ruthenium-based catalysts\textsuperscript{28} (Figure 2.1) and the excellent tolerance of the catalysts towards many polar functional groups.\textsuperscript{11,13}

![Figure 2.1 Ring closing metathesis catalysts](image)

In 1970 Chauvin\textsuperscript{29} proposed the general mechanistic pathway of ring closing metathesis where the diene 2.3 undergoes reaction with metal carbenoid 2.4 producing metal carbenoid 2.5, which in turn undergoes intramolecular [2+2] cycloaddition with the olefin to give the cyclobutane intermediate 2.6 (Scheme 2.1). Subsequently a [2+2] cycloreversion liberates the cyclic olefin 2.7 and regenerates metal alkylidene 2.4. This
newly generated metal carbenoid reacts with the starting diene in a second cycloaddition reaction

Scheme 2.1  Mechanism of RCM reaction proposed by Chauvin

Mechanistic studies by both Grubbs\textsuperscript{30} and Chen\textsuperscript{31} showed that phosphine dissociation is a critical step in the ring closing metathesis reaction. In another study, Grubbs examined the response of 2.8 to the action of 2.1 as a function of substituent R (Scheme 2.2).\textsuperscript{32} When 2.8 (R = Et) was treated with 2.1 in CH\textsubscript{2}Cl\textsubscript{2} at rt, 2.9 was formed in 93\% yield over 24 h. Under comparable conditions, enol ethers (R = OMe) remained unreactive.\textsuperscript{33} High yields were observed for 2.8 having R = CH\textsubscript{2}OH and CH\textsubscript{2}OAc while electron-withdrawing groups (R = Ph, COOMe) resulted in poor yields.
2.2 GOAL OF PROJECT

In the present study, we have chosen ene-diene systems of type 2.10 where group X would be attached directly to the diene moiety. The reason for attaching group X at the end of diene moiety is to achieve maximum electronic impact, while simultaneously arranging for a neighboring conjugated double bond to serve as a reaction center in order to normalize possible steric contributions (Scheme 2.3).

The substrates were designed to generate 2.11 as the only product in ring closing reaction as a consequence of the more favored rate of 6-membered ring formation. The goal was to determine how the electronic character in the C3-C4 double bond would affect the rate at which 2.11 was generated.
2.3 SYNTHESIS OF SUBSTRATES OF TYPE 2.10

The synthesis of 2.10 started with the known (Z)-4-[(tert)-butyldimethylsilyl]oxy-2-buten-1-ol (2.12) prepared following the procedure of Marshall (Scheme 2.4).\textsuperscript{35} Compound 2.12 was converted to the allylic bromide in two steps. This intermediate was subsequently treated with the lithium enolate of tert-butyl acetate resulting in the ester 2.13 in 60% overall yield. Treatment of 2.13 with 1.1 equivalent of diisobutylaluminum hydride at –78 °C produced the aldehyde, which on treatment with allylmagnesium bromide afforded homoallylic alcohol 2.14 in 78% yield over two steps. The secondary alcohol group in 2.14 was protected as the benzyl ether in 86% yield followed by the removal of TBS group with TBAF in almost quantitative yield to afford (Z)-allylic alcohol 2.15. Oxidation of 2.15 with pyridinium chlorochromate (PCC) in the presence of sodium acetate resulted in oxidation with concomitant isomerization of the double bond to achieve aldehyde 2.16 as a common intermediate.\textsuperscript{36} Reaction of aldehyde 2.16 under Wittig or Horner-Wadsworth-Emmons conditions produced ring-closing precursors 2.10a-h in good to excellent yield (see Experimental Section).\textsuperscript{37}
Scheme 2.4  Synthesis of 2.10

2.4  RESULTS AND DISCUSSION

2.4.1  RESULTS OF THE RING-CLOSING METATHESIS REACTION

Most of the substrates (e.g. 2.10a to 2.10f) underwent ring closure smoothly at rt in good to excellent yields (Table 2.1). Nitrile 2.10h did not undergo the cyclization process, demonstrating the well-known unreactivity of acrylonitrile towards olefin metathesis.\(^{38}\) In case of sulfide 2.10g, rapid catalyst deactivation was encountered. All of the reactions were carried out with 5 mol% of 2.1 in CH\(_2\)Cl\(_2\) at a concentration of 0.03 M. All the reactions were monitored by TLC where 2.11 was isolated as the only product in all cases. After the reaction was done, the product was isolated by column chromatography and the yields are reported in Table 2.1.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Isolated yield of 2.11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.10a</td>
<td>85</td>
</tr>
<tr>
<td>2.10b</td>
<td>83</td>
</tr>
<tr>
<td>2.10c</td>
<td>86</td>
</tr>
<tr>
<td>2.10d</td>
<td>77</td>
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<tr>
<td>2.10e</td>
<td>65</td>
</tr>
<tr>
<td>2.10f</td>
<td>80</td>
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</table>

Table 2.1 Results of RCM reactions

2.4.2 KINETIC STUDY

All the reactions were performed in an NMR tube at 300 K in the probe of a Bruker 300 MHz spectrometer under N₂ in the presence of 5 mol% of 2.1 at a substrate concentration of 0.03 M. The transformations of 2.10 were followed by monitoring the disappearance of the carbinol proton present in 2.10 and the appearance of the carbinol proton resident in 2.11. The concentration of 2.10 was derived from integration of ¹H NMR resonances as a function of time (Figure 2.2).

The fraction of 2.10 was established as CH₆/(CH₆+CH₆), where CH₆ is the integration of the methine proton in 2.11. This method assumes that all CH₆ is converted to CH₆, in line with the spectral observations and isolated yields. In the case of methoxy derivative 2.10a, the integration of CH₆ was not possible due to the coincidence of the chemical shift resonances for CH₆ and OCH₃. In this case, the fraction of starting material was established by referencing the integration of CH₆ to that of the C₆H₅ signal. Each fraction of CH₆ was then multiplied by the starting concentration 0.03 M to yield the concentration of CH₆ as a function of time.
Figure 2.2  A stacked $^1$H NMR plot for RCM on 2.10e

The resulting concentration of CH$_x$ at time $t$ for each run was then plotted as a function of $t$ in min according to first-order (Eq. (1)) and second order rate equations (Eq.
(2)), where \([\text{CH}_s]_t\) is the concentration of the carbinol proton at time \(t\) and \([\text{CH}_s]_0\) at the initial time.

\[
\ln[\text{CH}_s]_t = -k \times t + \ln[\text{CH}_s]_0 \text{ where } t_{1/2} = \frac{\ln 2}{k} \quad (1)
\]

\[
\frac{1}{[\text{CH}_s]_t} = +k \times t + \frac{1}{[\text{CH}_s]_0} \text{ where } t_{1/2} = \frac{1}{k \times [\text{CH}_s]_0} \quad (2)
\]

A linear correlation obtained from these plots indicates the order of the reaction and provides the apparent rate constant, \(k\), for the reaction. Second-order rate analysis yielded linear regression correlation values of less than 0.94. Instead, all of the kinetic data recorded were found to obey the first-order linear regression analysis (Eq. (1)). The relevant data are shown in Table 2.2 and a sample first-order kinetic plot is given in Figure 2.3.

![First-order kinetic plot for 2.10a](image)

Figure 2.3  First-order kinetic plot for 2.10a
2.4.3 DISCUSSION

Of the four examples bearing electron-withdrawing substituents, ethyl ester 2.10e was the most reactive, followed in turn by phenyl sulfone 2.10c and methyl ketone 2.10b. The least reactive nature of enol ether 2.10a and the overall kinetic profile reflected in Table 2.2 reveal that electronic modulation is an important contributing factor in ring-closing metathesis even when the substituent is not directly connected to the double bond that is undergoing cleavage. These phenomena are consistent with the concept that polarization within the ruthenium alkylidene is central to its reactivity.39

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<th>substrate</th>
<th>$k$/min (first order)</th>
<th>$t_{1/2}$ (min)</th>
<th>regression analysis, $r$</th>
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<td>2.10b</td>
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<tr>
<td>2.10c</td>
<td>0.0178</td>
<td>38.8±0.3</td>
<td>0.9866</td>
</tr>
<tr>
<td>2.10d-</td>
<td>0.0215</td>
<td>32.2±1.1</td>
<td>0.9712</td>
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<td>2.10e</td>
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<td>26.5±0.4</td>
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<tr>
<td>2.10f</td>
<td>0.0762</td>
<td>9.1±0.4</td>
<td>0.9695</td>
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</table>

Table 2.2 Summary of kinetic data

The PhSO$_2$ substituent is the most electron-withdrawing of those examined, yet 2.10c does not reflect this rate profile. The size of phenylsulfonyl group may be responsible for some of the modest kinetic retardation. On the other hand, allylic hydroxyls$^{40}$ and ester carbonyls$^{11a,41}$ have been implicated as good coordinators to the ruthenium atom in these metal carbenoids. If operational here, approach of the two ends of the reactant would be facilitated somewhat with associated kinetic consequences.
The present investigation raises many interesting issues. For example, is the terminal alkene invariably the site of initiation in electronically strongly biased substrates of the type \textbf{2.10a-f}? If so, is the presence of a remote electron-withdrawing substituent capable of negative charge stabilization conductive to a Michael-type intramolecular addition involving the Ru$^+\text{-CHR}$ species as nucleophile? Also a potential relevance of the fact that the propagating ruthenium carbenoids \textbf{2.18} formed from the retro \([2+2]\) fragmentation of \textbf{2.17} (Scheme 2.5) are structurally and electronically different, and constitute potential sources of mechanistic changeovers.

![Scheme 2.5 Generation of \textbf{2.18} from \textbf{2.17}](image)

\textbf{2.5 CONCLUSION}

In conclusion, we have demonstrated that the conversion of \textbf{2.10a-g} to the common product \textbf{2.11} proceeds efficiently, albeit at rates that reflect their electronic makeup. The observation that electron-donating substituents attached to the double bond decelerate the metathesis does not impact on reaction efficiency, which remains high throughout the series.
CHAPTER 3

KINETIC STUDY OF 1-SUBSTITUTED 1,7-OCTADIENES IN RING CLOSING METATHESIS

3.1 BACKGROUND

After finding interesting results in a kinetic study of ene-diene systems with different substituents at the end of diene moiety in ring closing metathesis (Chapter 2), we decided to continue a similar study on 1-substituted 1,7-octadienes.

3.2 GOAL OF THE PROJECT

In our view, a systematic investigation of the relative rates of RCM on a series of dienes of type 3.1 was warranted (Scheme 3.1). In this case, the highly active second generation Grubbs catalyst 3.2b was used. Our guidelines provided not only for the attachment of an R- or p-XC₆H₄-group directly to a reacting double bond, but also for generation of the identical product 3.3 in every instance. The presence of the benzyl ether in 3.1 is important, as it reduces the volatility of the reactant and particularly the product and hence facilitates quantitation of the process.
Scheme 3.1  Ring closing metathesis of 3.1

3.3  SYNTHESIS OF SUBSTRATES OF TYPE 3.1

Synthesis of 3.1 started with known compound 3.4 prepared by the ring opening of γ-butyrolactone under acidic conditions (Scheme 3.2). The hydroxyl group in 3.4 was protected as a TBS ether to provide compound 3.5 in 85% yield. Treatment of 3.5 with 1.1 eq of diisobutylaluminum hydride at –78 °C produced the aldehyde (76% yield), which on treatment with allylmagnesium bromide afforded the homoallylic alcohol 3.6 in 75% yield. The latter was protected as a benzyl ether in 80% yield followed by the removal of the TBS group with TBAF in 99% yield to afford the primary alcohol 3.7. Oxidation of 3.7 under Swern conditions followed by a Wittig reaction on the aldehyde resulted in the formation of 3.1 and its derivatives as RCM precursors (see experimental section).
Scheme 3.2 Synthesis of 3.1

3.4 RESULTS OF RCM REACTIONS

All the substrates underwent RCM reaction smoothly at rt in good to excellent yields (Table 3.1). All the reactions were carried out with 5 mol% catalyst 3.2b in CH₂Cl₂ at a concentration of 0.03 M. All the reactions were monitored by TLC where 3.3 was isolated as the only product in all cases. After the reaction was complete, the product was isolated by column chromatography and the yields are reported in Table 3.1. Electron-withdrawing as well as electron-donating groups responded well upon exposure to catalyst 3.2b. Initially reactions were carried out on 3.1e and 3.1f with 3.2a as catalyst. However, these reactions did not proceed at all with 3.2a even under forced conditions. As a result we decided to use more reactive 3.2b as the catalyst in our study.
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<td>3.1c</td>
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<td>3.1i</td>
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Table 3.1 Results of RCM reactions

3.5 KINETIC STUDY

All the cyclization reactions were performed with freshly prepared CD$_2$Cl$_2$ solutions of both the substrate and catalyst at 300 K in the probe of a Bruker 400 MHz spectrometer under N$_2$. When kinetic studies of 3.1a-b, and 3.1f-i were carried out with 5 mol% of 3.2b, reactions were too fast to obtain the initial points. Therefore, 3.1b was chosen as a model compound, which was subjected to kinetic study under both 1 mol% and 5 mol% catalyst loading. Similar results were obtained by extrapolation of the 1 mol% rates to the 5 mol% level. This allowed us to obtain the rate constant of cyclization of 3.1a-b and 3.1f-i with 1 mol% catalyst, which was extrapolated to the rate constant at the 5 mol% level.

The transformation of 3.1 to 3.3 was followed by monitoring the disappearance of the methine proton (-CH-OBn) in 3.1 and the appearance of methine proton (-CH-OBn) in 3.3. The concentrations of 3.1 were derived from integration of $^1$H NMR resonances as
a function of time. All of the kinetic data recorded was found to obey first-order linear regression analysis.

### 3.6 DISCUSSION

The kinetic study clearly indicates that the aromatic series (3.1f-i) reacts considerably faster than the aliphatic series (3.1a-e) as shown by the value $k_{(C_6H_5)} / k_{(H)} = 20.4$ (Table 3.2). Moreover, the kinetic data reveals that the electron-donating groups enhance the overall reaction rates. The effect is only moderate for the para substituents where faster rates are manifested in the aromatic series. For example, the $k_R / k_H$ ratio for $p$-CH$_3$OC$_6$H$_4$ is 20.9 and changes to 16.4 for $p$-O$_2$NC$_6$H$_4$, a factor of 1.3. The electronic effects are more pronounced for the substituents in the aliphatic series. The $k_R / k_H$ ratio for $R = CH_3$ is 4.5, while it is 0.68 for the methyl ketone (3.1d), a factor of 6.7.

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<th>$t_{1/2}$, min</th>
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<th>$k_R / k_H$</th>
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<td>-$SO_2$C$_6$H$_5$</td>
<td>0.0280</td>
<td>24.7553</td>
<td>0.996</td>
<td>0.44</td>
<td>0.686</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.2 Summary of kinetic data
The Hammett plot of both aliphatic and aromatic series referenced against H is shown in Figure 3.1. It is evident from the plot that the reaction rates relative to \( R = H \) is divided into two parts. The upper line is defined by the aromatic series and the lower by the aliphatic congeners of 3.1. The \( \rho \) values in both segments are negative, suggesting that electron-donating substituents accelerate the reaction. The conclusion is consistent, for example, with the faster reaction rates for p-CH\(_3\)OC\(_6\)H\(_4\)- and CH\(_3\)- in the aromatic and aliphatic series, respectively. It is also clear from the plot that the \( \rho \) value is smaller for aromatic substituents (\( \rho = 0.0970, r = 0.924 \)) than that for aliphatic substituents (\( \rho = 0.8801, r = 0.695 \)). The two different \( \rho \) values need not indicate that the presence of an aromatic ring effects a change in the reaction sequence. The problem may lie in the unavailability of a consistent set of \( \sigma \) values for all of the compounds in the study.\(^{45} \)

Figure 3.1  Hammett plot with both series referenced against H
Chen has observed that electron-withdrawing substituents on the carbene moiety accelerates ring-opening metathesis.\textsuperscript{31b} The present study does not conform to this trend. Bulky R substituents on aliphatics have been shown to severely hinder cyclization with ruthenium alkylidenes.

### 3.7 CONCLUSION

In conclusion, the reactivity of a series of structurally related dienes has been studied in detail. The aromatic and aliphatic series are defined by different $\rho$ values, and the electron-donating groups accelerate the process.
CHAPTER 4

FIRST GENERATION APPROACH TOWARD THE SYNTHESIS OF MANGICOL A

4.1 INTRODUCTION AND BACKGROUND

Marine microorganisms, particularly marine fungi, represent an underdeveloped and potentially prolific source of structurally diverse secondary metabolites. In 2000, Fenical and co-workers disclosed the isolation and characterization of a new class of fungal metabolites, which they named the mangicols. The producing species, *Fusarium heterosporum*, is a marine organism that was discovered in the Bahamas. All of the mangicols (A-G) are sesterterpenoids that share unprecedented spirotricyclic structural features (Scheme 4.1). All the mangicols have a common architecture possessing five methyl, seven methylene, eight methine, and five quaternary carbons.

![Figure 4.1 Structure of the Mangicols](image)

**Figure 4.1** Structure of the Mangicols

4.1: Mangicol A, \( R_1 = \text{OH}, \ R_2 = \text{H} \)
4.2: Mangicol B, \( R_1 = \text{H}, \ R_2 = \text{OH} \)
4.3: Mangicol C, \( R_1 = \text{H}, \ R_2 = \text{H} \)
4.4: Mangicol D, \( R_1 = \text{OH}, \ R_2 = \text{H} \)
4.5: Mangicol E, \( R_1 = \text{H}, \ R_2 = \text{OH} \)
4.6: Mangicol F, \( R_1 = \text{H}, \ R_2 = \text{H} \)
4.7: Mangicol G
Mangicol A (4.1) and mangicol B (4.2) display modest cytotoxicity against human tumor cell lines, but show significant antiinflammatory activity in the phorbol myristate acetate induced edema mouse ear assay. At 81% and 57% reduction in edema levels, this pair of mangicols compare well with the existing, widely distributed antiinflammatory agent indomethacin (71% reduction). The significant clinical potential and unique structural features make the mangicols interesting synthetic targets.

To our knowledge, Uemura and coworkers were the first to report a successful synthesis of the spirotetracyclic core of Mangicol A.48 In their route, Stille coupling49 between vinyl stannane 4.8 and vinyl chloride 4.9 installed the diene moiety in 4.10 in excellent yield (Scheme 4.1). Intramolecular Nozaki-Hiyama-Kishi condensation50 involving 4.11 proceeded nicely to afford two diastereomers of the desired trienones 4.12a and 4.12b. When 4.12a was subjected to transannular Diels-Alder (TADA) reaction, 4.13 was produced as a sole product with the required stereochemistry of the spirotetracyclic core. On the other hand, 4.12b gave both desired isomer 4.13 and undesired isomer 4.14 in a ratio of 1:1.
Scheme 4.1 Uemura’s route for tetracyclic core of mangicol A

4.2 RETROSYNTHETIC ANALYSIS

Any retrosynthetic plan considered for arrival at 4.1 must take into account its unusual framework and the presence of ten stereogenic centers, four of which are quaternary in nature. The biosynthetic pathway that has been proposed is of little value in suggesting an avenue to attack on this problem.47

In planning our synthetic approach, we envisioned that the final distereoselective addition of the anion generated from primary iodide 4.15 to aldehyde 4.1651 would result
in completion of the target molecule (Scheme 4.2). The required tetracyclic core of 4.15 would be prepared by SmI$_2$ promoted ring opening$^{42}$ of the strained cyclobutane ring in 4.17 followed by a Shapiro reaction.$^{53}$ It is important to note that the ring opening would result in formation of the required methyl group on C$_5$ with the desired stereochemistry. Compound 4.17 would be prepared by an intramolecular [2+2] cycloaddition$^{54,55}$ between the terminal alkene and unsaturated ketone in 4.18. The tricyclic core in 4.18 can be generated by a transannular Diels-Alder reaction$^{56,57}$ on 4.19 followed by functional group manipulation. Ester 4.19 can be prepared by the coupling between carboxylic acid 4.20 and primary alcohol 4.21 followed by further manipulation.

Scheme 4.2  Retrosynthetic analysis
4.3 SYNTHESIS OF CARBOXYLIC ACID 4.20

The generation of enantiopure carboxylic acid 4.20, started with racemic keto ester 4.22 by means of a PLE-mediated kinetic resolution to obtain optically active keto ester 4.23 in 91% ee as determined by chiral HPLC (Scheme 4.3). The ketone was reduced with NaBH₄ to give two diastereomeric alcohols in 96% yield. Conversion of the alcohol to the corresponding mesylate (77% yield), followed by elimination, and concomitant saponification of the ester group using KOH/H₂O in MeOH (69% yield) gave carboxylic acid 4.24. Further reduction of the carboxylic acid to an alcohol using LiAlH₄ (89% yield) followed by protection as a TBDPS ether (91% yield) gave compound 4.25. When the protection was carried out at rt with TBDPSCI and imidazole in CH₂Cl₂, the reaction took almost 3 days to complete. However, when the same reaction was performed in DMF at 50 °C, completion was realized within 2 h and in 91% yield. At this point, the stage was set for a ring cleavage-reclosure sequence involving ozonolysis to give a dialdehyde, whose subsequent exposure to p-TsOH-promoted intramolecular aldolization furnished 4.26 in 81% overall yield over two steps. Oxidation of the aldehyde to the desired carboxylic acid 4.20 was accomplished in 94% yield using NaClO₂.
Scheme 4.3  Synthesis of carboxylic acid 4.20

4.4  SYNTHESIS OF ALCOHOL 4.21

The synthesis of alcohol 4.21 started with enantioselective alkylation of the enolate derived from oxazolidinone 4.27 with allyl iodide 4.28 (Scheme 4.4). The alkylation reaction worked extremely well when three equivalents of 4.27 was used with respect to one equivalent of 4.28. Removal of the chiral auxiliary with NaBH₄ in MeOH gave primary alcohol 4.29 in 60% yield over two steps. Esterification of the primary alcohol with PivCl yielded compound 4.30 in 93% yield. Diene 4.30 was subjected to ozonolysis to afford a ketoaldehyde, which upon treatment with p-TsOH in refluxing benzene gave cyclohexenone 4.31 in 65% yield over two steps.
Scheme 4.4  Synthesis of cyclohexenone 4.31

Reduction of ketone 4.31 under Luche conditions\textsuperscript{63} gave the equatorial alcohol\textsuperscript{64} (91% yield) as the only product (de >95% from 300 MHz \textsuperscript{1}H NMR), which was subsequently protected as a PMB ether (80% yield) using PMBImid and TfOH to afford 4.32 (Scheme 4.5). Aldehyde 4.33 was produced by careful ozonolysis followed by an aldol ring closure in the presence of piperidine and HOAc in 80% yield over two steps.\textsuperscript{60} Reduction of aldehyde 4.33 to the alcohol with NaBH\textsubscript{4} followed by protection of the primary alcohol as a TBS ether produced compound 4.34 in 80% yield over two steps. Selective removal of the benzoate group (93% yield) using K\textsubscript{2}CO\textsubscript{3} in MeOH released the primary alcohol which was subsequently protected as a MEM ether (93% yield) to yield 4.35. Removal of the pivaloyl ester with Dibal-H resulted in the formation of desired primary alcohol 4.21 in 87% yield.
Scheme 4.5  Completion of synthesis of 4.21

4.5  SYNTHESIS OF IODIDE 4.28

Synthesis of iodide 4.28 started with commercially available 1,8-octanediol (4.36), which upon monobenzoxylation resulted in the formation of 4.37 (Scheme 4.6). Swern oxidation of the primary alcohol afforded an intermediate aldehyde (90% yield), which subsequently underwent a Mannich reaction\(^6\) to produce the \(\alpha,\beta\)-unsaturated aldehyde 4.38 in 68% yield. Reduction of aldehyde 4.38 under Luche conditions resulted in allylic alcohol 4.39 in 97% yield, which was sequentially converted to a mesylate and transformed to allyl bromide 4.40 in 81% yield.\(^\) The bromide was then converted to iodide 4.28 immediately prior to use under Finkelstein reaction conditions.\(^\)
4.6 COUPLING BETWEEN 4.20 AND 4.21

Coupling of carboxylic acid 4.20 with alcohol 4.21 was accomplished through an esterification reaction to afford 4.41 using EDC as the coupling reagent in 70% yield (Scheme 4.7). The selective removal of the TBS group using CSA at 0 °C resulted in the formation of allylic alcohol 4.42 in 92% yield. The primary alcohol in 4.42 was converted to an allylic bromide in a two-step sequence as described before to afford 4.43 in 86% yield.

Scheme 4.6  Synthesis of iodide 4.28

Scheme 4.7  Coupling between 4.20 and 4.21
4.7 ATTEMPTS FOR THE PREPARATION OF DIENE 4.19

After the successful synthesis of allyl bromide 4.43, the next task was to synthesize conjugated diene 4.19 (Scheme 4.8). As shown in Table 4.1, all attempts to prepare the diene resulted in either decomposition or recovery of starting material.69

Scheme 4.8 Attemps to prepare 4.19 from allyl bromide 4.43

<table>
<thead>
<tr>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBU, PhMe, 80 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>KO-t-Bu, THF, 0 °C</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>KO-t-Bu, PhH, rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>KO-t-Bu, THF, 50 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>LiBr, LiCO₃, HMPA, 50 °C</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>LiBr, LiCO₃, HMPA, 100 °C</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 4.1 Conditions tried for synthesizing 4.19 from 4.43

At this point, it was decided to synthesize 4.19 directly from allylic alcohol 4.42 (Scheme 4.9). Compound 4.42 was treated with 2,4-dinitrobenzenesulfenyl chloride with the expectation that the intermediate would undergo a [1,3]-sigmatropic shift followed by elimination.70 However, the reaction stopped after the formation of intermediate 4.44, which did not undergo further [1,3]-sigmatropic shift.
Scheme 4.9  Reaction of 4.42 with 2,4-dinitrobenzenesulfenyl chloride

After these attempts, it was decided to generate the diene moiety in a stepwise fashion as shown in Scheme 4.10. The allylic alcohol was subjected to Sharpless asymmetric epoxidation conditions to obtain the epoxy alcohol as a 1:1 diastereomeric mixture.\(^7^1\) This crude epoxy alcohol was treated with PPh\(_3\), Im, and I\(_2\) followed by H\(_2\)O to form the rearranged alcohol 4.45.\(^7^2\) When 4.45 was subjected to xanthate formation, starting material was isolated in every case.

Scheme 4.10  Attempts to prepare xanthate

4.8 CONCLUSION

Carboxylic acid 4.20 and primary alcohol 4.21 were successfully synthesized and coupled together. However, all efforts towards the formation of the diene moiety proved
to be fruitless. An alternate strategy to build the tricyclic core of Mangicol A was then needed.
CHAPTER 5

SECOND GENERATION APPROACH TOWARD THE SYNTHESIS OF MANGICOL

5.1 RETROSYNTHETIC ANALYSIS

In this approach we envisioned compound 5.3 undergoing an intramolecular Diels-Alder\textsuperscript{73} reaction to create the tricyclic compound 5.2, which was to be converted to the desired compound 5.1 by functional group manipulations (Scheme 5.1). Compound 5.3 was to be synthesized by the coupling of keto phosphonate 5.4 and aldehyde 5.5 under Horner-Wadsworth-Emmons reaction conditions followed by deoxygenation.
Scheme 5.1  Retrosynthetic analysis for second-generation synthesis

5.2  SYNTHESIS OF KETO PHOSPHONATE 5.4

The synthesis of keto phosphonate 5.4 started with the known optically active hydroxy ester 5.6, prepared via Brown’s protocol (Scheme 5.2). Compound 5.6 was sequentially converted to the mesylate, subjected to reduction with Dibal-H to give a primary alcohol, and the primary alcohol was protected as a TBDPS ether to afford compound 5.7. Compound 5.7 was subjected to elimination conditions using DBU in DMF at 100 °C to yield cyclopentene 5.8. This reaction required high temperature; otherwise, the elimination reaction was too slow. Compound 5.8 was converted to diol 5.9 by exposure to ozone followed by reduction of the intermediate dialdehyde with sodium borohydride.
Diol 5.9 was converted to compound 5.10 by chemoselective pivaloylation\(^7^5\) of the more accessible alcohol, followed by protection of the remaining alcohol as a TBS ether and removal of the pivaloyl group using Dibal-H (Scheme 5.3).\(^7^6\) The overall yield was 71\% over three steps. The next goal was to perform a dehydration to form olefin 5.13. Compound 5.10 was converted to tosylate 5.11, which was further converted to iodide 5.12. When both 5.10 and 5.11 were subjected to elimination conditions, decomposition was observed in both cases. However, alcohol 5.10 was successfully converted to olefin 5.13 by sequential conversion of the primary hydroxy group to the phenyl selenide, followed by oxidation, and elimination under thermal conditions.\(^7^7\) Unfortunately, the overall yield was very low and decomposition was observed during the thermal elimination step. We thought that the reason of decomposition could be due to the instability of the TBS ether under thermal conditions during which the solution became acidic in nature. However, similar results were obtained even when elimination of the selenoxide was carried out in presence of bases such as triethylamine and pyridine.
Scheme 5.3  Attempts to synthesize olefin 5.13

At this point, we decided to carry out the elimination process with the pivaloyl group, which would be replaced by a TBS group after formation of the double bond. Again, the synthesis started with diol 5.9, which underwent chemoselective tosylation with the more accessible primary hydroxy group followed by pivaloylation of the remaining primary hydroxy group to furnish compound 5.15 in 72% yield over two steps (Scheme 5.4). Substitution of the tosylate group in 5.15 by phenylseleno, followed by oxidation and subsequent elimination resulted in the formation of olefin 5.16 in 70% yield over three steps. At this point, it was time to replace the pivaloyl group with a TBS ether, which was easily accomplished by sequential reduction with Dibal-H followed by the formation of a TBS ether using TBSOTf and 2,6-lutidine to afford the desired compound 5.13 in 96% overall yield. Olefin 5.13, upon ozonolysis, resulted in the
formation of an aldehyde, which was further oxidized to a carboxylic acid followed by esterification with K$_2$CO$_3$ and MeI to afford ester 5.17 in 78% yield over three steps.$^{79,80}$

When compound 5.17 was treated with the lithium salt of diethyl ethylphosphonate, keto phosphonate 5.4 was produced in 92% yield.$^{81}$

Scheme 5.4  Synthesis of keto phosphonate 5.4

5.3  SYNTHESIS OF ALDEHYDE 5.5

Synthesis of aldehyde 5.5 started with the commercially available hydroxy ester 5.18, which was converted to known compound 5.19 following the procedure of Marshall (Scheme 5.5).$^{82}$ Allylic alcohol 5.19 was subjected to Sharpless asymmetric epoxidation conditions to obtain epoxy alcohol 5.20 in 86% yield with >95:5 diastereoselectivity
Alcohol 5.20 was converted to the primary iodide, which underwent epoxide opening in the presence of n-BuLi at –78 °C to afford the secondary allylic alcohol 5.21 in 94% yield.\(^\text{82}\) Protection of the secondary alcohol as a PMB ether followed by removal of the TBDPS ether with TBAF gave the primary alcohol. However, it was not possible to isolate this alcohol in pure form, and therefore, the alcohol was treated with PPh\(_3\), imidazole, and I\(_2\) to isolate iodide 5.22 in pure form in 81% overall yield.\(^\text{83}\) Primary iodide 5.22 was substituted with cyanide,\(^\text{84}\) which was subsequently reduced with Dibal-H to afford aldehyde 5.23 in 88% yield.\(^\text{85}\) Aldehyde 5.23 was subjected to the Mannich reaction using paraformaldehyde and dimethylamine hydrochloride in 1,2-dichloroethane at 75 °C, which resulted in a smooth conversion to conjugated aldehyde 5.24 in excellent yield (91%).\(^\text{86}\) Aldehyde 5.24 was subjected to Luche conditions to generate the corresponding allylic alcohol (89% yield), which upon treatment with second generation Grubbs catalyst 5.26 resulted in the formation of cyclic allylic alcohol 5.25 in 91% yield. When the oxidation of 5.25 was attempted under Swern oxidation\(^\text{87}\) as well as TPAP/NMO\(^\text{88}\) conditions, poor yields and loss of products were observed. However, clean conversion to the desired aldehyde 5.5 was observed with IBX in 89% yield.\(^\text{89}\)

It was found later that aldehyde 5.24 could undergo ring closure efficiently in the presence of second generation Grubbs catalyst 5.26 to deliver desired aldehyde 5.5 in a single step in 99% yield.
Scheme 5.5  Synthesis of aldehyde 5.5

5.4  COUPLING BETWEEN 5.4 AND 5.5

With ketophosphonate 5.4 and aldehyde 5.5 in hand, our focus was shifted towards their coupling (Scheme 5.6). When the sodium salt of 5.4 was treated with aldehyde 5.5 at 0 °C in THF, the coupled product was formed in excellent yield (86%). However, the reaction resulted in the formation of a 3:1 mixture of diastereomers in favor
of the desired \((E)\)-isomer. Fortunately, when \(5.4\) and \(5.5\) were treated with LiCl and DBU in acetonitrile at rt, compound \(5.27\) was formed as a single isomer in 89% yield.\(^{81}\)

Scheme 5.6  Coupling between \(5.4\) and \(5.5\)

5.5  ATTEMPTS FOR DEOXYGENATION AND DIELS-ALDER PRECURSOR FORMATION

After the successful synthesis of \(5.27\), our next goal was to do the deoxygenation. Our initial plan was to perform a Barton deoxygenation on the xanthate resulting from the allylic alcohol (Scheme 5.7). When \(5.27\) was reduced under Luche conditions, decomposition of the substrate along with a very low conversion to alcohol \(5.28\) was observed. However, upon treatment with Dibal-H \(-78\ ^\circ\text{C}\), clean conversion to \(5.28\) was observed. All attempts to prepare the corresponding xanthate using NaH, CS\(_2\), and MeI were fruitless.\(^9\) When the reactions were carried out at rt, no reaction with starting material was observed and higher temperatures resulted in the decomposition of starting material. Similar reactions were attempted with Im\(_2\)CS\(^{91}\) as well as \(p\)-tolyl-
chlorothionoformate\textsuperscript{92} at rt as well as elevated temperatures. All attempts resulted either in decomposition or recovery of starting materials. At this point, we were convinced regarding the steric crowding around the hydroxy group as well as the high sensitivity of allylic hydroxy group.

![Scheme 5.7 Attempts to prepare deoxygenation precursors](image)

**Conditions tried for preparing deoxygenation precursors**
1. KH, CS\textsubscript{2}, MeI, rt, and higher temperatures
2. \(p\)-Tolyl-chlorothionoformate, Py, rt and at 50 °C
3. Im\textsubscript{2}CS, DMAP, 70 °C

After all results failed, we decided to convert the hydroxy group to a formate and use Pd chemistry to perform the deoxygenation (Scheme 5.8). Inspired by Heathcock’s chemistry,\textsuperscript{93} the alcohol was converted to the corresponding formate, which was subsequently treated with Pd(PPh\textsubscript{3})\textsubscript{4} in presence of HCOONH\textsubscript{4} and Bu\textsubscript{3}P in cyclohexane at 60 °C. A new compound was isolated in 56% yield, which turned out to be compound 4.30 (assigned by 300 MHz NMR) formed by the \(\beta\)-elimination of the intermediate Pd species.
Scheme 5.8 Attempts for deoxygenation using Pd chemistry

At this point, we decided to do the deoxygenation directly on the allylic alcohol (Scheme 5.9). Allylic alcohols are known to undergo reductive deoxygenation in the presence of Et₃SiH/CF₃COOH\(^\text{94}\) and Et₃SiH/LiClO₄\(^\text{95}\). Unfortunately, all these conditions led to the decomposition of starting material. The substrate \(5.28\) found to be extremely unstable under acidic conditions as observed before.

Scheme 5.9 Attempts for reductive deoxygenation

After all the fruitless results, we decided to keep the ketone as a masked carbonyl group until the Diels-Alder reaction was performed. Initially, acetal formation was attempted using ethylene glycol in the presence of a catalytic amount of \(p\)-TsOH or PPTS (Scheme 5.10).\(^\text{96}\) Only decomposition was observed under those conditions. Even a mild Lewis acid like Sc(OTf)\(_3\) resulted in the decomposition of starting material.\(^\text{97}\)
point, we were sure that the unsaturated ketone and the corresponding alcohol were very sensitive to acid-catalyzed reactions.

Scheme 5.10 Attempts to prepare acetal

An alternative route to the formation of the precursor to the Diels-Alder reaction was taken at this point. We decided to keep the intermediate allylic alcohol in a protected form, while making the dienophile segment by removing the TBS group. With this goal in mind, compound 5.27 was reduced to compound 5.28 using Dibal-H and the alcohol was protected as a benzoate ester to afford compound 5.32 in 70% yield (Scheme 5.11). When compound 5.32 was treated with CSA in CH₂Cl₂:MeOH (1:1) at 0 °C, decomposition of the starting material was observed. Treatment of 5.32 with 1.1 equivalent of TBAF at 0 °C resulted in the partial removal of both TBS and TBDPS. Lowering the temperature to −10 or −20 °C resulted in an extremely slow reaction or no reaction. Treatment of HF in CH₃CN at −20 °C resulted only in decomposition. This reaction shows the sensitivity of the substrate under acidic conditions even at a lower temperature. Alternative attempts for the removal of the TBS ether with NBS in DMSO:H₂O (40:1) and Cu(NO₃)₂ in CH₃CN resulted only in decomposition.
5.6 CONCLUSION

It was clear at this point that the TBS and PMB groups are not the protecting groups of choice. The PMB ether was found to be very sensitive to acidic conditions, and should be replaced by a more stable benzyl (Bn). The TBS ether also acts as a secondary hydroxy ether rather than a primary hydroxy ether for steric reasons. Therefore, it was hard to remove selectively without affecting the rest of the molecule. It can be replaced by a free alcohol. Moreover, we need to design the synthesis in such a way that at any stage during the synthesis we do not have to deal with a step involving deoxygenation. In light of the problems encountered, we understand what changes should be made in order to prepare the Diels-Alder precursor towards the synthesis of Mangicol A.
All reactions were performed in the appropriate oven-dried glass apparatus under a static N₂ or Ar atmosphere. Solvents were reagent grade and in most cases properly dried before used. All reagents were obtained commercially as reagent grade and, unless otherwise noted, used without further purification. Thin-layer chromatography was performed on precoated silica gel 60 F₂₅₄ analytical plates. The organic extracts were dried over anhydrous MgSO₄. The column chromatographic purifications were performed on silica gel (230-400 mesh).

Optical rotations were measured using a Perkin-Elmer Model 241 polarimeter at 589 nm with a Na lamp and concentrations are reported in g/100 mL. A Perkin-Elmer 1600 Series FT-IR spectrometer was used to record infrared spectra and absorptions are reported in reciprocal centimeters (cm⁻¹). Proton (¹H) and carbon (¹³C) nuclear magnetic resonance spectra were recorded on Bruker DPX-250, AC-300, DPX-400 and 75 MHz respectively. Chemical shifts are reported in parts per million (ppm, δ) with the residual non-deuterated solvent as an internal standard; 7.26 ppm for chloroform and 7.16 for benzene. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded at The Ohio State
Preparation of compound 1.19

Alcohol 1.18 (44.4 g, 314.9 mmol) was dissolved in dry CH$_2$Cl$_2$ (400 mL), cooled to 0 °C, and treated with triethylamine (40.9 g, 629.7 mmol) and pivaloyl chloride (57.0 g, 472.4 mmol). The resulting mixture was stirred at rt for 36 h and quenched with 1 N HCl (200 mL) followed by H$_2$O (500 mL). The separated aqueous layer was extracted with CH$_2$Cl$_2$, and the combined organic phases were dried, concentrated, and purified by chromatography on silica gel (elution with 40:1 petroleum ether/ether) to furnish 68.1 g (96%) of pivaloyl protected alcohol as a colorless liquid; IR (neat, cm$^{-1}$): 1728, 1170; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.69-4.61 (m, 1 H), 3.46-3.36 (m, 1 H), 2.09-2.01 (m, 2 H), 1.78-1.68 (m, 2 H), 1.45-1.15 (m, 13 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.1, 75.0, 63.5, 38.8, 30.4, 30.3, 27.1 (2C), 23.8, 23.3; HRMS ES $m$/z (M + Na)$^+$ calcd 248.1369, obsd 248.1381.

To a stirred solution of pivaloate ester (80.7 g, 358 mmol) prepared above in methanol (300 mL) was added 10% palladium on charcoal (1.5 g). The solution was saturated with H$_2$ and stirred under H$_2$ overnight. The reaction mixture was filtered through Celite, rinsed with ether (200 mL), and concentrated to leave the amine as colorless oil that was used directly.
To a solution of the crude amine in dry CH$_2$Cl$_2$ (500 mL) were added dry Et$_3$N (46.5 g, 71.6 mmol) and $p$-toluenesulfonyl chloride (88.7 g, 465 mmol) at rt under N$_2$. The resulting solution was stirred overnight at rt and quenched with 1 N HCl (100 mL) and H$_2$O (300 mL). The separated aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic phases were dried, concentrated. The residue was purified by chromatography on silica gel (elution with 2:1 petroleum ether/ether) to furnish 82.7 g (65% over two steps) of 1.19 as a white solid, mp 93-95 °C; IR (neat, cm$^{-1}$) 3402, 3278, 1728, 1651; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 8.3$ Hz, 2 H), 7.25 (d, $J = 8.3$ Hz, 2 H), 5.96-5.89 (m, 1 H), 4.75-4.61 (m, 1 H), 3.88-3.75 (m, 1 H), 3.38-3.20 (m, 1 H), 2.39 (s, 3 H), 2.17-2.08 (m, 1 H), 1.97-1.15 (m, 15 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.9, 142.9, 138.9, 129.5 (2C), 126.7 (2C), 73.9, 56.5, 38.7, 32.1, 30.6, 27.1 (3C), 24.1, 23.4, 21.4; HRMS ES m/z (M + Na)$^+$ calcd 376.1553, obsd 376.1547.

Preparation of compound 1.20

A solution of 1.19 (24.4 g, 69.2 mmol) in dry DMF (100 mL) was treated portionwise with NaH (3.32 g of 60% mixture in oil, 83.1 mmol) at 0 °C, and stirred at this temperature for 30 min prior to the addition of (E,E)-1-bromo-2,4-hexadiene (13.2 g, 83.1 mmol). The resulting mixture was stirred at 0 °C for 1 h and at rt overnight, carefully quenched with H$_2$O (200 mL), and diluted with ether (300 mL). The separated aqueous layer was extracted with ether and the combined ethereal phases were washed with water, dried, and concentrated. The residue was purified chromatographically on silica gel (elution with 5:1 petroleum ether/ether) to furnish 25.4 g (70%) of pure 1.20 as a white
solid, mp 122-124 °C; IR (neat, cm⁻¹) 1728; ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.68 (m, 2 H), 7.35-7.20 (m, 2 H), 6.10-6.01 (m, 1 H), 5.95-5.86 (m, 1 H), 5.72-5.61 (m, 1 H), 5.37-5.27 (m, 1 H), 4.79-4.72 (m, 1 H), 3.97-3.88 (m, 1 H), 3.82-3.67 (m, 2 H), 2.41 (s, 3 H), 2.12-2.08 (m, 1 H), 1.76-1.58 (m, 8 H), 1.33-1.07 (m, 11 H); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 142.7, 139.1, 133.1, 130.5, 130.0, 129.5 (2C), 127.1, 126.9 (2C), 71.2, 60.4, 46.1, 38.7, 31.8, 30.7, 27.0 (3C), 25.2, 23.9, 21.4, 18.0; HRMS ES m/z (M + Na)+ calcd 456.2179, obsd 456.2165.


*Preparation of compound 1.21*

To a solution of 1.20 (25.4 g, 58.7 mmol) in dry CH₂Cl₂ (200 mL) was slowly added Dibal-H (146.8 mL of 1.0 M solution in hexane, 146.8 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 2 h, warmed to rt, carefully quenched with a saturated solution of K-Na-tartrate (150 mL), and stirred overnight. The separated aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 2:1 petroleum ether/ether) to furnish 16.4 g (80%) of 1.21 as a yellow oil; IR (neat, cm⁻¹) 3520, 1598, 1334; ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.69 (m, 2 H), 7.29-7.27 (m, 2 H), 6.18-6.09 (m, 1 H), 6.03-5.93 (m, 1 H), 5.73-5.63 (m, 1 H), 5.56-5.47 (m, 1 H), 4.06-3.95 (m, 1 H), 3.79-3.67 (m, 1 H), 3.51-3.44 (m, 2 H), 2.41 (s, 3 H), 2.12-2.07 (m, 1 H), 1.80-1.63 (m, 5 H), 1.43-1.12 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 143.0, 137.8, 133.2,
130.2, 130.07, 130.04, 129.4 (2C), 126.9 (2C), 69.7, 63.8, 45.6, 34.2, 28.9, 25.2, 23.8, 21.2, 17.8; HRMS ES \textit{m/z} (M + Na)^{+} \text{calcd} 372.1604, \text{obsd} 372.1595.

Anal. Calcd for C_{19}H_{27}NO_{3}S: C 65.30, H 7.79. Found: C 65.40, H 7.94.

\textit{Preparation of compound} 1.16a

A solution of \textbf{1.21} (0.50 g, 1.3 mmol) in dry DMF (10 mL) was treated portionwise with NaH (0.1 g of 60\% mixture in oil, 2.6 mmol) at 0 °C, and stirred at this temperature for 30 min prior to the addition of allyl bromide (0.24 g, 2.0 mmol) along with a catalytic amount of \textit{n}-Bu_{4}NI. The resulting mixture was stirred at 0 °C for 1 h and at rt overnight, carefully quenched with water (30 mL), and diluted with ether (30 mL). The separated aqueous layer was extracted with ether, and the combined ethereal layers were washed with water, dried, and concentrated. The residue was purified chromatographically on silica gel (elution with 5:1 petroleum ether/ether) to furnish 0.38 g (75\%) of \textbf{1.16a} as a yellowish oil; IR (neat, cm^{-1}) 1450, 1334, 1152; \textit{\textit{1H NMR}} (300 MHz, CDCl\textsubscript{3}) \delta 7.75 (d, \textit{J} = 8.3 Hz, 2 H), 7.25 (d, \textit{J} = 8.3 Hz, 2 H), 6.09-5.91 (m, 2 H), 5.68-5.57 (m, 2 H), 5.53-5.45 (m, 1 H), 5.13-5.02 (m, 2 H), 4.02-3.96 (m, 1 H), 3.95-3.66 (m, 4 H), 3.33-3.29 (m, 1 H), 2.39 (s, 3 H), 2.19-2.15 (m, 1 H), 1.86-1.56 (m, 7 H), 1.29-1.12 (m, 3 H); \textit{\textit{13C NMR}} (75 MHz, CDCl\textsubscript{3}) \delta 142.2, 138.8, 135.1, 132.1, 130.5, 129.5, 128.9 (2C), 128.1, 127.5 (2C), 115.9, 77.4, 68.9, 62.2, 46.5, 31.9, 31.3, 25.4, 23.9, 21.3, 17.9; HRMS ES \textit{m/z} (M + Na)^{+} \text{calcd} 412.1917, \text{obsd} 412.1895.
Data for compound 1.16b

74% yield; yellowish oil; IR (neat, cm⁻¹) 1334, 1153; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 8.3 Hz, 2 H), 7.27-7.20 (m, 2 H), 6.09-5.92 (m, 2 H), 5.79-5.62 (m, 2 H), 5.54-5.44 (m, 1 H), 4.99-4.94 (m, 2 H), 3.94-3.62 (m, 3 H), 3.52-3.45 (m, 1 H), 3.23-3.16 (m, 1 H), 3.11-3.04 (m, 1 H), 2.39 (s, 3 H), 2.19-2.17 (m, 1 H), 1.95-1.85 (m, 3 H), 1.76-1.55 (m, 6 H), 1.41-1.07 (m, 5 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.2, 138.8, 138.2, 132.1, 130.5, 129.4, 128.9 (2C), 128.2, 127.4 (2C), 114.3, 77.3, 67.0, 62.3, 46.2, 32.4, 31.2, 30.1, 28.9, 25.4, 23.9, 21.4, 17.9; HRMS ES m/z (M + Na)+ calcd 440.2229, obsd 440.2205.


Data for compound 1.16c

61% yield; yellowish oil; IR (neat, cm⁻¹) 1450, 1335, 1153; ¹H NMR (300 MHz, CDCl₃) δ 7.76-7.72 (m, 2 H), 7.27-7.19 (m, 2 H), 6.09-5.91 (m, 2 H), 5.82-5.71 (m, 1 H), 5.68-5.61 (m, 1 H), 5.53-5.46 (m, 1 H), 5.03-4.93 (m, 2 H), 3.92-3.63 (m, 3 H), 3.49-3.44 (m, 1 H), 3.23-3.19 (m, 1 H), 3.08-3.03 (m, 1 H), 2.39 (s, 3 H), 2.19-2.18 (m, 1 H), 2.17-1.95 (m, 2 H), 1.89-1.84 (m, 1 H), 1.75-1.55 (m, 7 H), 1.33-1.07 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.2, 138.9, 138.7, 132.1, 130.6, 129.5, 128.9 (2C), 128.3, 127.5 (2C), 114.4, 77.4, 67.7, 62.4, 46.4, 33.5, 32.4, 31.3, 29.4, 25.43, 25.40, 24.1, 21.4, 18.0; HRMS ES m/z (M + Na)+ calcd 454.2386, obsd 454.2418.

Anal. Calcd for C₂₅H₃₇NO₃S: C 69.57, H 8.64. Found: C 69.51, H 8.68.
Data for compound 1.16d

51% yield; yellowish oil; IR (neat, cm⁻¹) 1451, 1334; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 8.3 Hz, 2 H), 7.22 (d, J = 8.3 Hz, 2 H), 6.09-5.91 (m, 2 H), 5.85-5.74 (m, 1 H), 5.68-5.61 (m, 1 H), 5.54-5.46 (m, 1 H), 5.03-4.93 (m, 2 H), 3.90-3.64 (m, 3 H), 3.49-3.44 (m, 1 H), 3.21-3.19 (m, 1 H), 3.09-3.01 (m, 1 H), 2.39 (s, 3 H), 2.19-2.17 (m, 1 H), 2.05-1.98 (m, 2 H), 1.89-1.85 (m, 1 H), 1.76-1.55 (m, 7 H), 1.35-1.07 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.1, 138.9, 138.8, 132.1, 130.6, 129.4, 128.9 (2C), 128.3, 127.5 (2C), 114.2, 77.4, 67.8, 62.3, 46.3, 33.6, 32.4, 31.2, 29.8, 28.7, 25.6, 25.4, 24.0, 21.4, 18.0; HRMS ES m/z (M + Na)+ calcd 468.2543, obsd 468.2549.

Anal. Calcd for C₂₆H₃₉NO₃S: C 70.07, H 8.82. Found: C 70.25, H 8.89.

Data for compound 1.16e

45% yield; yellowish oil; IR (neat, cm⁻¹) 1450, 1335; ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.72 (m, 2 H), 7.27-7.18 (m, 2 H), 6.08-5.90 (m, 2 H), 5.89-5.74 (m, 1 H), 5.67-5.59 (m, 1 H), 5.52-5.45 (m, 1 H), 5.03-4.91 (m, 2 H), 3.91-3.63 (m, 3 H), 3.47-3.42 (m, 1 H), 3.21-3.18 (m, 1 H), 3.05-2.99 (m, 1 H), 2.38 (s, 3 H), 2.18-2.16 (m, 1 H), 2.07-1.99 (m, 2 H), 1.87-1.83 (m, 1 H), 1.78-1.54 (m, 7 H), 1.37-1.06 (m, 10 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.1, 138.92, 138.90, 132.1, 130.6, 129.4, 128.9 (2C), 128.3, 127.5 (2C), 114.2, 77.4, 67.8, 62.3, 46.3, 33.7, 32.4, 31.2, 29.9, 28.9, 28.8, 25.9, 25.4, 24.0, 21.3, 18.0; HRMS ES m/z (M + Na)+ calcd 482.2699, obsd 482.2680.

Data for compound 1.16f

48% yield; yellowish oil; IR (neat, cm\(^{-1}\)) 1463, 1336; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.76-7.73 (m, 2 H), 7.27-7.20 (m, 2 H), 6.09-5.91 (m, 2 H), 5.86-5.75 (m, 1 H), 5.68-5.61 (m, 1 H), 5.53-5.46 (m, 1 H), 5.04-4.92 (m, 2 H), 3.92-3.63 (m, 3 H), 3.49-3.43 (m, 1 H), 3.20-3.19 (m, 1 H), 3.06-3.01 (m, 1 H), 2.39 (s, 3 H), 2.19-2.18 (m, 1 H), 2.09-2.01 (m, 2 H), 1.89-1.85 (m, 1 H), 1.75-1.55 (m, 7 H), 1.45-1.07 (m, 12 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.2, 139.0, 138.9, 132.1, 130.6, 129.5, 129.0 (2C), 128.4, 127.6 (2C), 114.2, 77.4, 67.9, 62.4, 46.4, 33.7, 32.5, 31.3, 30.0, 29.4, 29.1, 28.9, 26.1, 25.5, 24.1, 21.4, 18.0; HRMS ES \(m/z\) (M + Na)+ calcd 496.2856, obsd 496.2848.


Data for compound 1.16g

52% yield; yellowish oil; IR (neat, cm\(^{-1}\)) 1460, 1336; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.76-7.73 (m, 2 H), 7.27-7.19 (m, 2 H), 6.09-5.91 (m, 2 H), 5.89-5.75 (m, 1 H), 5.68-5.61 (m, 1 H), 5.54-5.47 (m, 1 H), 5.04-4.92 (m, 2 H), 3.91-3.67 (m, 3 H), 3.48-3.43 (m, 1 H), 3.21-3.19 (m, 1 H), 3.06-3.01 (m, 1 H), 2.39 (s, 3 H), 2.18-2.17 (m, 1 H), 2.09-2.02 (m, 2 H), 1.95-1.80 (m, 1 H), 1.74-1.56 (m, 7 H), 1.44-1.07 (m, 14 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.2, 139.1, 139.0, 132.1, 130.6, 129.5, 129.0 (2C), 128.4, 127.6 (2C), 114.1, 77.5, 67.9, 62.4, 46.4, 33.8, 32.5, 31.3, 30.0, 29.48, 29.45, 29.1, 28.9, 26.2, 25.5, 24.1, 21.4, 18.0; HRMS ES \(m/z\) (M + Na)+ calcd 510.3012, obsd 510.2999.

Data for compound 1.16h

54% yield; yellowish oil; IR (neat, cm⁻¹) 1463, 1335; ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.73 (m, 2 H), 7.27-7.20 (m, 2 H), 6.09-5.91 (m, 2 H), 5.87-5.76 (m, 1 H), 5.68-5.61 (m, 1 H), 5.54-5.47 (m, 1 H), 5.04-4.92 (m, 2 H), 3.91-3.64 (m, 3 H), 3.48-3.43 (m, 1 H), 3.21-3.19 (m, 1 H), 3.06-3.01 (m, 1 H), 2.39 (s, 3 H), 2.19-2.17 (m, 1 H), 2.08-2.01 (m, 2 H), 1.89-1.85 (m, 1 H), 1.76-1.55 (m, 7 H), 1.42-1.07 (m, 16 H); ¹³C NMR (75 MHz, CDCl₃) δ 142.1, 139.0, 138.9, 132.1, 130.6, 129.4, 128.9 (2C), 128.4, 127.5 (2C), 114.1, 77.6, 67.9, 62.4, 46.5, 33.8, 32.5, 31.3, 30.0, 29.53, 29.51, 29.50, 29.1, 28.9, 26.1, 25.5, 24.1, 21.4, 18.0; HRMS ES m/z (M + Na)+ calcd 524.3169, obsd 524.3123.

General Ring Closing Metathesis Procedure

All reactions were performed at a substrate concentration of 0.003 M. The ruthenium catalyst (20 mol%) was carefully weighed in a dry box and placed in a flame-dried flask inside the dry box. A 0.03 M stock solution of 1.16 in CH₂Cl₂ was previously prepared. The remainder of the required solvent volume was added to the catalyst and the proper volume of the substrate solution was introduced by syringe pump over 12 h, while stirring was maintained at 50 °C. The reaction mixture was agitated at this temperature for an additional 12 h, cooled to rt, quenched with lead tetraacetate (10 mg, 0.022 mmol), and stirred overnight under N₂. The solvent was evaporated under vacuum and the dark residue was purified by column chromatography. The results are compiled in Table 1. The spectroscopic characterizations follow.
**Cyclization of 1.16a: Data for 1.22.**

White solid, mp 91-93 °C; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, \(J = 8.3\) Hz, 2 H), 7.23 (d, \(J = 8.1\) Hz, 2 H), 5.59-5.53 (m, 1 H), 5.44-5.35 (m, 1 H), 4.41-4.33 (m, 2 H), 4.03-3.96 (m, 1 H), 3.81-3.65 (m, 2 H), 3.41-3.32 (m, 1 H), 2.38 (s, 3 H), 1.97-1.91 (m, 1 H), 1.71-1.56 (m, 3 H), 1.42-1.11 (m, 4 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.5, 138.9, 129.1 (2C), 128.5, 127.2 (2C), 126.2, 74.7, 64.7, 62.3, 42.8, 32.7, 28.8, 24.6, 24.3, 21.4; HRMS ES \(m/z\) (M + Na)\(^+\) calcd 344.1291, obsd 344.1308.

**Cyclization of 1.16b: Data for 1.23.**

Colorless gum; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.3\) Hz, 2 H), 7.26 (d, \(J = 8.6\) Hz, 2 H), 7.12-6.98 (m, 1 H), 6.24-6.17 (m, 1 H), 5.51-5.36 (m, 2 H), 4.46-4.39 (m, 1 H), 3.92-3.83 (m, 1 H), 3.61-3.56 (m, 2 H), 2.79-2.66 (m, 2 H), 2.40-2.28 (m, 5 H), 1.81-0.86 (m, 10 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.6, 139.1, 129.74, 129.71, 129.3 (2C), 128.3, 127.2, 123.5, 77.5, 63.6, 61.3, 44.1, 30.5, 29.3, 28.2, 25.1, 24.0, 22.4, 21.4; HRMS ES \(m/z\) (M + Na)\(^+\) calcd 398.1759, obsd 398.1766.

**Cyclization of 1.16c: Data for a mixture of 1.24 and 1.25.**

Colorless gum; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.77 (m, 2 H), 7.26-7.20 (m, 2 H), 5.69-5.62 (m, 1 H), 5.44-5.39 (m, 1 H), 3.95-3.55 (m, 2 H), 3.44-3.39 (m, 1 H), 2.40 (s, 3 H), 2.19-2.17 (m, 1 H), 1.98-1.96 (m, 1 H), 1.70-1.09 (m, 15 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.4, 136.2, 129.2 (2C), 128.8, 127.3 (2C), 124.1, 78.3, 68.6, 62.1, 39.7, 31.2, 31.1, 30.8, 27.9, 26.1, 25.1, 24.0, 21.5; HRMS ES \(m/z\) (M + Na)\(^+\) calcd 386.1760, obsd 386.1758.
Cyclization of 1.16d: Data for 1.26.

Colorless gum; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.78 (m, 2 H), 7.29-7.18 (m, 2 H), 5.48-5.30 (m, 2 H), 4.21-4.15 (m, 1 H), 3.75-3.73 (m, 1 H), 3.65-3.59 (m, 1 H), 3.45-3.38 (m, 1 H), 3.10-3.08 (m, 1 H), 2.98-2.92 (m, 1 H), 2.39 (s, 3 H), 2.28-2.26 (m, 1 H), 2.09-2.07 (m, 1 H), 1.77-1.05 (m, 14 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.3, 139.5, 131.7, 128.9 (2C), 128.5, 127.5 (2C), 78.2, 63.9, 61.9, 44.3, 31.1, 30.9, 30.4, 28.2, 25.1, 24.0, 23.2, 21.4, 19.6; HRMS ES \(m/\dot{z}\) (M + Na)\(^+\) calcd 400.1917, obsd 400.1923.

Data for 1.27: Colorless gum; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.83-7.78 (m, 2 H), 7.33-7.21 (m, 2 H), 6.65-6.56 (m, 1 H), 6.00-5.92 (m, 1 H), 5.44-5.33 (m, 2 H), 4.09-4.02 (m, 1 H), 3.81-3.74 (m, 1 H), 3.62-3.55 (m, 1 H), 3.20-3.18 (m, 1 H), 2.40 (s, 3 H), 2.28-2.02 (m, 1 H), 1.88-1.17 (m, 17 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.7, 139.2, 131.2, 129.2, 129.1 (2C), 128.5, 127.5 (2C), 125.8, 77.4, 67.2, 62.1, 46.8, 31.4, 29.5, 27.3, 25.8, 24.7, 24.0, 23.7, 23.6, 21.4; HRMS ES \(m/\dot{z}\) (M + Na)\(^+\) calcd 426.2073, obsd 426.2079.

Cyclization of 1.16e: Data for 1.28

Colorless gum; IR (neat, cm\(^{-1}\)) 1600; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.80-7.75 (m, 2 H), 7.27-7.19 (m, 2 H), 5.61-5.52 (m, 1 H), 5.48-5.39 (m, 1 H), 3.85-3.54 (m, 3 H), 3.46-3.37 (m, 2 H), 2.39 (s, 3 H), 2.27-2.19 (m, 1 H), 2.03-1.99 (m, 2 H), 1.69-1.06 (m, 16 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 142.3, 139.5, 132.2, 128.9 (2C), 127.4, 77.8, 65.8,
58.3, 46.9, 31.7, 30.4, 30.2, 29.8, 28.4, 25.5, 25.0, 24.0, 22.9, 21.4; HRMS ES m/z (M + Na)⁺ calcd 414.2073, obsd 414.2070.

**Cyclization of 1.16f: Data for 1.29.**

Colorless gum; IR (neat, cm⁻¹) 1600; ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.77 (m, 2 H), 7.28-7.21 (m, 2 H), 5.54-5.44 (m, 2 H), 3.91-3.86 (m, 1 H), 3.64-3.55 (m, 3 H), 3.28-3.18 (m, 2 H), 2.40 (s, 3 H), 2.24-2.22 (m, 1 H), 2.04-2.02 (m, 2 H), 1.71-1.08 (m, 17 H); ¹³C-NMR (75 MHz, CDCl₃) δ 142.3, 139.3, 133.3, 129.1 (2C), 127.7 (2C), 127.5, 77.7, 66.6, 62.8, 45.9, 31.8, 30.3, 29.8, 29.6, 28.3, 25.5, 25.4, 25.2, 24.8, 24.1, 21.4; HRMS ES m/z (M + Na)⁺ calcd 428.2229, obsd 428.2228.

**Cyclization of 1.16g: Data for 1.30.**

Colorless gum; IR (neat, cm⁻¹) 1600; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 8.3 Hz, 2 H), 7.21 (d, J = 8.1 Hz, 2 H), 5.53-5.46 (m, 1 H), 5.34-5.30 (m, 1 H), 3.78-3.73 (m, 2 H), 3.60-3.45 (m, 3 H), 3.23-3.18 (m, 1 H), 2.39 (s, 3 H), 2.29-2.26 (m, 1 H), 2.03-1.84 (m, 3 H), 1.73-1.62 (m, 3 H), 1.46-1.06 (m, 15 H); ¹³C-NMR (75 MHz, CDCl₃) δ 142.2, 139.7, 132.7, 129.0 (2C), 127.6 (2C), 126.0, 77.4, 66.3, 63.8, 47.5, 31.3, 30.2, 29.7, 29.6, 28.3, 26.2, 26.1, 25.5, 25.4, 25.0, 24.4, 24.0, 21.4; HRMS ES m/z (M + Na)⁺ calcd 442.2386, obsd 442.2372.

**Data for 1.31:** colorless gum; IR (neat, cm⁻¹) 1600; ¹H NMR (300 MHz, CDCl₃) δ 7.82-7.77 (m, 2 H), 7.29-7.21 (m, 2 H), 5.98-5.86 (m, 2 H), 5.56-5.45 (m, 2 H), 4.15-4.05 (m, 1 H), 3.67-3.57 (m, 1 H), 3.51-3.44 (m, 1 H), 3.28-3.23 (m, 1 H), 3.01-2.98 (m,
1 H), 2.41 (s, 3 H), 2.38-2.09 (m, 3 H), 1.75-1.09 (m, 20 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.3, 139.5, 132.8, 131.1, 131.0, 129.1 (2C), 127.7 (2C), 127.6, 77.6, 68.4, 62.5, 47.4, 31.9, 30.6, 30.2, 29.6, 27.7, 27.4, 26.3, 25.7, 25.5, 24.6, 24.0, 21.5; HRMS ES $m/z$ (M + Na)$^+$ calcd 468.2543, obsd 468.2549.

Cyclization of 1.16h: Data for 1.32.

Colorless gum; IR (neat, cm$^{-1}$) 1600; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.79-7.74 (m, 2 H), 7.24-7.19 (m, 2 H), 5.61-5.52 (m, 1 H), 5.25-5.16 (m, 1 H), 3.99-3.73 (m, 1 H), 3.73-3.56 (m, 2 H), 3.30-3.29 (m, 1 H), 3.08-3.02 (m, 1 H), 2.38 (s, 3 H), 2.27-2.21 (m, 1 H), 1.92-1.81 (m, 2 H), 1.73-1.55 (m, 3 H), 1.44-1.15 (m, 19 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.1, 139.8, 133.1, 128.9 (2C), 127.8, 126.2 (2C), 77.9, 67.2, 62.5, 45.9, 31.2, 30.2, 30.0, 28.4, 26.3, 26.1, 26.0, 25.3, 25.0, 24.8, 24.1, 23.3, 21.4; HRMS ES $m/z$ (M + Na)$^+$ calcd 456.2543, obsd 456.2547.

Data for 1.33: Colorless gum; IR (neat, cm$^{-1}$) 1600; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.79-7.75 (m, 2 H), 7.27-7.19 (m, 2 H), 6.06-5.98 (m, 1 H), 5.88-5.83 (m, 1 H), 5.57-5.47 (m, 1 H), 5.46-5.29 (m, 1 H), 4.26-4.18 (m, 1 H), 3.81-3.72 (m, 1 H), 3.61-3.46 (m, 2 H), 3.11-3.03 (m, 1 H), 2.99-2.92 (m, 1 H), 2.38 (s, 3 H), 2.21-2.09 (m, 3 H), 1.75-1.68 (m, 4 H), 1.59-1.08 (m, 17 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.2, 139.3, 133.6, 131.9, 130.6, 128.9 (2C), 128.3, 127.7 (2C), 77.9, 68.5, 61.8, 44.4, 31.3, 30.1, 29.9, 29.1, 27.2, 26.9, 26.3, 25.2, 25.1, 25.09, 24.0, 23.9, 21.4; HRMS ES $m/z$ (M + Na)$^+$ calcd 482.2699, obsd 482.2706.
**Control Experiments**

Catalyst **1.2b** (12.65 mg, 0.015 mmol) was weighed in a dry box, placed in a flame-dried flask, and diluted with CH$_2$Cl$_2$ (22.2 mL). A solution of **1.27** (30 mg, 0.074 mmol) in CH$_2$Cl$_2$ (2.47 mL to give 0.03 M solution) was introduced to the catalyst solution via a syringe pump over 3 h with stirring and heating of the reaction mixture at 50 °C. After an additional 21 h, the contents were cooled to rt, quenched with lead tetraacetate (10 mg, 0.022 mmol), and stirred overnight under N$_2$. Solvent was removed under vacuum and the dark residue was purified by column chromatography on silica gel to give **1.26** (20.4 mg, 73%) with no evidence of residual **1.27**.

Submission of **1.27** to the action of **1.1** under identical conditions led to the complete recovery of starting material.

**Preparation of 2.13**

To a solution of (Z)-4-[(tert)-butyldimethylsilyl]oxy-2-buten-1-ol (5 g, 25 mmol) in dry CH$_2$Cl$_2$ (100 mL) was added dry Et$_3$N (7 mL, 50 mmol) at rt under N$_2$. The mixture was cooled to -78 °C, stirred for 5 min at this temperature, and treated with MsCl (3.83 mL, 49.5 mmol) slowly over 10 min. After the addition was complete and formation of a white solid was observed, stirring was maintained at -78 °C for 30 min and was followed by the addition of 1N HCl (20 mL) and H$_2$O (100 mL), then warming to 20 °C. The separated aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 100 mL) and the combined organic phases were washed with saturated NaHCO$_3$ solution and brine, dried, and concentrated to give a yellow liquid.

This crude oil was dissolved in dry THF (100 mL), anhydrous LiBr (2.15 g, 24.8 mmol) was added, and the mixture was stirred at rt for 1.5 h. After filtration through a
pad of silica gel and rinsing with ether, the filtrate was concentrated and purified by column chromatography on silica gel (elution with 50:1 petroleum ether:ethyl acetate) to provide 5.5 g of bromide as a colorless oil.

Dry i-Pr₂NH (3.33 mL, 24.9 mmol) was added to 30 mL of dry THF under N₂. The solution was cooled to 0 °C, treated slowly with n-BuLi (14.8 mL of 1.54 M solution in hexane, 22.8 mmol), and stirred at 0 °C for 15 min prior to cooling to -78 °C. At this point, HMPA (4.04 mL, 22.8 mmol) was introduced and tert-butyl acetate (3.1 mL, 22.8 mmol) dissolved in 30 mL of dry THF was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 45 min, treated dropwise with a solution of the allylic bromide (5.5 g, 20.8 mmol) in THF (30 mL), stirred at -78 °C for another 30 min, and quenched with 1N HCl (50 mL). The separated THF layer was washed successively with saturated NaHCO₃ solution (2 x 50 mL), H₂O (2 x 50 mL) and brine (50 mL), dried, and concentrated to leave a yellow liquid. This residue was purified by column chromatography on silica gel (elution with 50:1 petroleum ether:ethyl acetate) to afford 4.46 g (60% over three steps) of the pure ester as a colorless liquid; IR (neat, cm⁻¹) 1730; ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.47 (m, 1 H), 5.39-5.31 (m, 1 H), 4.21-4.19 (d, J = 6.1 Hz, 2 H), 2.30-2.19 (m, 4 H), 1.39 (s, 9 H), 0.86 (s, 9 H), 0.03 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 172.6, 130.7, 128.5, 80.5, 59.2, 35.2, 28.0 (3C), 25.9 (3C), 23.2, 18.5, -5.2 (2C); HRMS EI m/z (M+ + H) calcd 301.2199, obsd 301.2195.

Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95; H, 10.73. Found: C, 64.16; H, 10.71.

**Preparation of 2.14**

To a solution of 2.13 (16.89 g, 56.1 mmol) in dry CH₂Cl₂ (150 mL) was slowly added Dibal-H (61.6 mL of 1.0 M solution in hexane, 61.6 mmol) at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h, quenched with a saturated aqueous solution of K-Na-tartrate (150 mL), allowed to come to rt, and stirred overnight. The separated aqueous
layer was extracted with CH₂Cl₂ (3 x 150 mL), and the combined organic phases were concentrated and purified by column chromatography on silica gel (elution with 20:1 petroleum ether:ether) to furnish 11.43 g of the aldehyde as a colorless liquid.

To a stirred solution of this aldehyde (11.43 g, 50.13 mmol) under N₂ in 150 mL of dry THF was added at -78 °C a solution of allylmagnesium bromide (80.03 mL of 1 M solution in THF, 80.03 mmol). The reaction mixture was stirred at -78 °C for 1 h and then raised to rt. The reaction mixture was stirred at rt for 30 min and carefully quenched with a saturated solution of NH₄Cl (150 mL). The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic phases were washed with saturated NaHCO₃ solution and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (elution with 8:1 petroleum ether:ether) to give 10.76 g (78% over two steps) of pure alcohol 2.14 as a colorless liquid; IR (neat, cm⁻¹) 3402; ¹H NMR (300 MHz, CDCl₃) δ 5.88-5.74 (m, 1 H), 5.60-5.41 (m, 2 H), 5.13-5.07 (m, 2 H), 4.29-4.13 (m, 2 H), 3.65-3.59 (m, 1 H), 2.29-2.09 (m, 4 H), 1.54-1.09 (m, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 134.9, 131.1, 129.5, 117.8, 69.5, 59.0, 42.0, 36.2, 25.9 (3C), 23.7, 18.3, -5.1 (2C); HRMS ES m/z (M + Na)+ calcd 269.1517, obsd 269.1505.


Preparation of 2.15

Alcohol 2.14 (1.67 g, 6.19 mmol) was dissolved in dry DMF (10 mL), treated portionwise with NaH (0.39 g of 60% mixture in oil, 9.62 mmol) at 0 °C, and stirred at this temperature for 20 min prior to the addition of BnBr (1 mL, 8.48 mmol). The resulting mixture was stirred at 0 °C for 1 h and overnight at rt, carefully quenched with H₂O (30 mL), and diluted with ether (50 mL). The separated aqueous layer was extracted with ether (3 x 30 mL). The combined ethereal layers were washed with H₂O (3 x 20
mL), dried, and concentrated. The residue was purified by column chromatography on silica gel (elution with 60:1 petroleum ether:ether) to furnish 1.93 g (86%) of the pure benzyl ether as a colorless liquid; IR (neat, cm⁻¹) 1462, 1253, 1089; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.26 (m, 5 H), 5.89-5.81 (m, 1 H), 5.55-5.40 (m, 2 H), 5.14-5.06 (m, 2 H), 4.59 (d, J = 11.5 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.24-4.22 (d, J = 6.0 Hz, 2 H), 3.49-3.45 (m, 1 H), 2.38-2.32 (m, 2 H), 2.19-2.09 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 134.6, 130.3, 129.8, 128.2 (2C), 127.6 (2C), 127.4, 117.0, 77.8, 70.8, 59.3, 38.1, 33.6, 25.9 (3C), 23.4, 18.3, -5.2 (2C); HRMS ES m/z (M + Na)+ calcd 383.2382, obsd 383.2366.

Anal. Calcd for C₂₂H₃₆O₂Si: C, 73.28; H, 10.06. Found: C, 73.16; H, 10.07.

To a solution of the above benzyl ether (1.41 g, 3.92 mmol) in dry THF (6 mL) was added slowly TBAF (4.5 mL of 1.0 M solution in THF, 4.5 mmol) at rt. The resulting mixture was stirred at rt for 45 min and quenched by the addition of water (5 mL). The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ether). There was obtained 1.00 g (99%) of the pure alcohol 2.15 as a colorless liquid; IR (neat, cm⁻¹) 3374, 1641, 1454; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.26 (m, 5 H), 5.92-5.78 (m, 1 H), 5.64-5.46 (m, 2 H), 5.13-5.06 (m, 2 H), 4.59 (d, J = 11.6 Hz, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 4.16-4.13 (d, J = 6.3 Hz, 2 H), 3.52-3.44 (m, 1 H), 2.43-2.29 (m, 2 H), 2.27-2.11 (m, 2 H), 1.68-1.54 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 134.6, 132.2, 128.9, 128.3 (2C), 127.6 (2C), 127.5, 117.0, 77.8, 70.7, 58.3, 38.1, 33.6, 23.3; HRMS ES m/z (M + Na)+ calcd 269.1517, obsd 269.1505.
Preparation of 2.16

To a stirred solution of allylic alcohol 2.15 (0.90 g, 3.66 mmol) in dry CH₂Cl₂ (20 mL), were added PCC (1.23 g, 5.49 mmol), NaOAc (0.9 g, 11 mmol), and 4 Å MS (0.4 g) under N₂ at 0 °C. The reaction mixture was stirred at rt for 18 h, diluted with 100 mL of dry ether, stirred under N₂ for another 5 h, and filtered through a pad of silica gel. The pad was rinsed with 500 mL of ether and the combined filtrates were evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 8:1 petroleum ether:ether). There was isolated 0.72 g (81%) of pure trans α,β-unsaturated aldehyde 2.16 as a colorless oil; IR (neat, cm⁻¹) 1692, 1639; ¹H NMR (300 MHz, CDCl₃) δ 9.47-9.44 (d, J = 7.9 Hz, 1 H), 7.38-7.26 (m, 5 H), 6.85-6.76 (m, 1 H), 6.12-6.03 (m, 1 H), 5.90-5.76 (m, 1 H), 5.16-5.08 (m, 2 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 3.52-3.45 (m, 1 H), 2.49-2.28 (m, 4 H), 1.76-1.68 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 193.9, 158.4, 138.4, 134.1, 132.9, 128.4 (2C), 127.8 (2C), 127.6, 117.5, 77.4, 71.0, 38.0, 32.0, 28.7; HRMS ES m/z (M⁺) calcd 244.1463, obsd 244.1488.

Preparation of 2.10a

Ph₃PCH₂OCH₃Cl (0.42 g, 1.23 mmol) was added to 5 mL of dry THF under N₂, cooled to 0 °C, and treated with KHMDS (3.3 mL of 0.37 M solution in toluene, 1.23 mmol) via syringe. The resulting orange solution was stirred at 0 °C for 30 min, 2.16 (0.20 g, 0.82 mmol) dissolved in dry THF (5 mL) was introduced, the ice bath was removed, and the reaction mixture was stirred at rt for 4 h before being quenched with saturated NH₄Cl solution (10 mL). The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 40:1 petroleum ether:ether containing 3% Et₃N) to give 0.52 g (52%) of pure 2.10a as a colorless liquid; IR (neat, cm⁻¹) 1641, 1454; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.25 (m, 5 H), 5.93-5.78
(m, 2 H), 5.59-5.42 (m, 2 H), 5.13-5.00 (m, 3 H), 4.60-4.46 (m, 2 H), 3.56 (s, 3 H), 3.51-
3.43 (m, 1 H), 2.37-2.32 (m, 2 H), 2.25-2.10 (m, 2 H), 1.69-1.56 (m, 2 H); 13C NMR (75
MHz, CDCl3) δ 145.7, 138.8, 134.8, 130.7, 128.3 (2C), 127.7 (2C), 127.4, 126.3, 116.9,
105.6, 77.8, 70.9, 56.3, 38.2, 33.6, 28.6; HRMS EI m/z (M+) calcd 272.1780, obsd
272.1771.

Preparation of 2.10b

To a stirred suspension of NaH (60 mg of 60% in oil, 1.48 mmol) in dry THF (5
mL) was added dropwise at 0 °C under N2 a solution of (EtO)2POCH2COCH3 (0.30 g,
1.54 mmol) in dry THF (5 mL). After 10 min, a solution of 2.16 (0.30 g, 1.23 mmol) in
THF (5 mL) was introduced slowly at 0 °C. After the addition was complete, the solution
was heated to reflux for 5 h, cooled, and quenched with 10 mL of saturated aqueous
NH4Cl solution. The separated aqueous layer was extracted with ether (2 x 10 mL). The
organic layers were combined, dried, and concentrated. The residue was purified by
column chromatography on silica gel (elution with 6:1 petroleum ether:ether) to give 0.23
g (66%) of pure 2.10b as a colorless liquid; IR (neat, cm⁻¹) 1667; 1H NMR (300 MHz,
CDCl3) δ 7.38-7.26 (m, 5 H), 7.10-7.02 (m, 1 H), 6.16-6.12 (m, 2 H), 6.07-6.01 (d, J =
15.5 Hz, 1 H), 5.88-5.79 (m, 1 H), 5.14-5.07 (m, 2 H), 4.61 (d, J = 11.6 Hz, 1 H), 4.45 (d,
J = 11.6 Hz, 1 H), 3.48-3.45 (m, 1 H), 2.39-2.19 (m, 7 H), 1.71-1.62 (m, 2 H); 13C NMR
(75 MHz, CDCl3) δ 198.6, 145.0, 143.7, 138.9, 134.5, 129.0, 128.9, 128.4 (2C), 127.8
(2C), 127.6, 117.3, 77.6, 71.0, 38.2, 32.9, 29.1, 27.1; HRMS ES m/z (2M + Na)+ calcd
569.3601, obsd 569.3625.
**Preparation of 2.10c**

To a stirred suspension of NaH (60 mg of 60% in oil, 1.48 mmol) in dry THF (5 mL) was added dropwise at 0 °C under N₂ a solution of (EtO)₂POCH₂SO₂Ph (0.47 g, 1.60 mmol) in dry THF (5 mL). After 10 min, a solution of 2.16 (0.30 g, 1.23 mmol) in THF (5 mL) was slowly introduced at 0 °C. After the addition was complete, the reaction mixture was heated to reflux for 45 min, cooled, and quenched with 10 mL of saturated NH₄Cl solution. The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 4:1 petroleum ether:ether) to afford 0.34 g (73%) of pure 2.10c as a colorless liquid; IR (neat, cm⁻¹) 1643, 1592, 1446, 1316; ¹H NMR (300 MHz, CDCl₃) δ 7.92-7.87 (m, 2 H), 7.63-7.50 (m, 3 H), 7.37-7.18 (m, 6 H), 6.27-6.16 (m, 2 H), 6.09-6.00 (m, 1 H), 5.90-5.76 (m, 1 H), 5.14-5.08 (m, 2 H), 4.60 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 3.50-3.41 (m, 1 H), 2.42-2.19 (m, 4 H), 1.69-1.61 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 147.09, 147.08, 142.6, 141.1, 138.5, 134.3, 133.1, 129.2 (2C), 128.3 (2C), 127.7 (2C), 127.5, 127.4 (2C), 126.2, 117.3, 77.4, 70.9, 38.1, 32.6, 28.9; HRMS ES m/z (M + Na)⁺ calcd 405.1495, obsd 405.1489.


**Preparation of 2.10d**

Dibal-H (1.12 mL of a 1.0 M solution in hexane, 1.12 mmol) was added slowly at -78 °C to a solution of 2.10e (0.16 g, 0.51 mmol) in dry CH₂Cl₂ (3 mL). The resulting mixture was stirred at -78 °C for 1.5 h, warmed to 0 °C, and agitated for another 30 min prior to quenching with a saturated aqueous solution of K-Na-tartrate (5 mL). After overnight stirring, the separated aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic layers were dried and concentrated to leave a residue that was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ether)
to afford 0.12 g (86%) of pure 2.10d as a colorless liquid; IR (neat, cm\(^{-1}\)) 3388, 1464; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.27 (m, 5 H), 6.25-6.17 (m, 1 H), 6.17-6.01 (m, 1 H), 5.94-5.80 (m, 1 H), 5.76-5.64 (m, 2 H), 5.16-5.09 (m, 2 H), 4.61 (d, \(J = 11.6\) Hz, 1 H), 4.49 (d, \(J = 11.5\) Hz, 1 H), 4.14-4.12 (d, \(J = 5.8\) Hz, 2 H), 3.53-3.45 (m, 1 H), 2.43-2.23 (m, 2 H), 1.73-1.58 (m, 2 H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 138.7, 134.6, 134.5, 131.4, 129.7, 129.6, 128.2 (2C), 127.7 (2C), 127.4, 117.0, 77.6, 70.8, 63.0, 38.0, 33.2, 28.3; HRMS ES \(m/z\) (M + Na\(^+\)) calcd 295.1674, obsd 295.1667.

**Preparation of 2.10e**

To a solution of 2.16 (0.10 g, 0.41 mmol) in dry THF (3 mL), was added Ph\(_3\)PCHCOOEt (0.22 g, 1.23 mmol) at rt. The resulting mixture was heated under reflux for 4 h, cooled, and quenched with water (5 mL). The separated aqueous layer was extracted with ether (2 x 5 mL) and the combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (elution with 10:1 petroleum ether:ether) to deliver 0.09 g (70%) of pure 2.10e as a colorless liquid; IR (neat, cm\(^{-1}\)) 1707, 1643; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.20 (m, 7 H), 6.18-6.08 (m, 1 H), 5.89-5.76 (m, 2 H), 5.15-5.07 (m, 2 H), 4.60 (d, \(J = 11.6\) Hz, 1 H), 4.45 (d, \(J = 11.6\) Hz, 1 H), 4.24-4.17 (q, \(J = 7.1\) Hz, 2 H), 3.49-3.42 (m, 1 H), 2.39-2.21 (m, 4 H), 1.69-1.61 (m, 2 H), 1.32-1.27 (t, \(J = 7.1\) Hz, 3 H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 167.1, 144.7, 143.9, 138.5, 134.4, 128.4, 128.2 (2C), 127.7 (2C), 127.5, 119.2, 117.2, 77.3, 70.8, 60.0, 38.0, 32.7, 28.8, 14.2; HRMS ES \(m/z\) (M + H) calcd 315.1955, obsd 315.1972.

Anal. Calcd for C\(_{20}\)H\(_{26}\)O\(_3\): C, 76.40; H, 8.33. Found: C, 76.53; H, 8.34.

**Preparation of 2.10f**

Ph\(_3\)PCH\(_3\)Br (0.54 g, 1.50 mmol) was added to 4 mL of dry THF under N\(_2\). The resulting mixture was cooled to -78 °C, n-BuLi (1.1 mL of 1.40 mL M solution in THF,
1.50 mmol) was introduced, and stirring was maintained at -78 °C for 30 min prior to addition of the aldehyde (0.28 g, 1.15 mmol) dissolved in dry THF (5 mL). The resulting mixture was stirred at -78 °C for 45 min, warmed to 0 °C, and quenched with saturated aqueous NH₄Cl solution (10 mL). The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried and concentrated to leave a residue that was purified by column chromatography on silica gel (elution with 40:1 petroleum ether:ether) to give 0.19 g (70%) of pure 2.10f as a colorless liquid; IR (neat, cm⁻¹) 1641, 1454, 1349; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.26 (m, 5 H), 6.38-6.25 (m, 1 H), 6.10-6.01 (m, 1 H), 5.94-5.80 (m, 1 H), 5.75-5.66 (m, 1 H), 5.15-5.07 (m, 3 H), 4.99-4.96 (d, J = 10.1 Hz, 1 H), 4.61 (d, J = 11.6 Hz, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 3.53-3.45 (m, 1 H), 2.39-2.13 (m, 4 H), 1.73-1.55 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.8, 137.2, 134.8, 134.7, 131.2, 128.3 (2C), 127.7 (2C), 127.5, 117.0, 114.8, 77.8, 70.9, 38.2, 33.3, 28.4; HRMS ES m/z (M + Na)+ calcd 265.1563, obsd 265.1568.


Preparation of 2.10g

Ph₃PCH₂SPhCl (3.00 g, 6.97 mmol) was added to 15 mL of dry THF under N₂, cooled to 0 °C, and treated with n-BuLi (4.0 mL of 1.54 M solution in hexane, 6.97 mmol) via syringe. The resulting orange solution was stirred at 0 °C for 30 min, treated with 2.16 (1.0 g, 4.1 mmol) dissolved in dry THF (15 mL), and stirred at rt for 4 h. The reaction mixture was quenched with saturated NH₄Cl solution (10 mL), the separated aqueous layer was extracted with ether (2 x 20 mL), and the combined organic layers were dried and concentrated to leave a residue that was purified by column chromatography on silica gel (elution with 40:1 petroleum ether:ether containing 3% Et₃N) to provide 1.0 g (70%) of pure 2.10g as a colorless liquid; IR (neat, cm⁻¹) 1640, 1583; ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.19 (m, 10 H), 6.51-6.03 (m, 3 H), 5.92-5.63
(m, 2 H), 5.15-5.08 (m, 2 H), 4.63-4.46 (m, 2 H), 3.54-3.45 (m, 1 H), 2.42-2.15 (m, 4 H), 1.72-1.59 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 136.8, 134.7, 134.4, 133.6, 131.0, 129.0, 128.8, 128.3 (2C), 127.8 (2C), 126.5 (2C), 126.3 (2C), 121.6, 117.1, 77.8, 70.9, 38.2, 33.3, 28.5.

**Preparation of 2.10h**

Ph₃PCH₂CNBr (2.11 g, 6.25 mmol) was added to 10 mL of dry THF under N₂, cooled to -78 °C, and treated with n-BuLi (3.61 mL of 1.6 M solution in THF, 5.77 mmol). The reaction mixture was stirred at -78 °C for 30 min, 2.16 (1.18 g, 4.81 mmol, 1.0 eq) dissolved in dry THF (10 mL) was introduced, and stirring was maintained at -78 °C for 45 min prior to warming to 0 °C and quenching with saturated NH₄Cl solution (20 mL). The separated aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 6:1 petroleum ether:ether) to deliver 1.0 g (78%) of pure 2.10h as a colorless liquid; IR (neat, cm⁻¹) 2214, 1642; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.26 (m, 5 H), 6.96-6.88 (m, 1 H), 6.17-6.05 (m, 2 H), 5.90-5.78 (m, 1 H), 5.23-5.07 (m, 3 H), 4.63-4.42 (m, 2 H), 3.74-3.43 (m, 1 H), 2.40-2.21 (m, 4 H), 1.72-1.61 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 149.5, 145.3, 138.5, 134.3, 128.3, 128.0 (2C), 127.7 (2C), 127.5, 126.8, 117.3, 94.8, 77.4, 70.8, 38.0, 32.6, 28.8; HRMS ES m/z (M + Na)+ calcd 290.1515, obsd 290.1486.

**General Procedure for Ring Closing Metathesis**

The Grubbs catalyst 1 (5 mol%) was carefully weighed in a dry box and placed into a flame-dried flask inside the dry box. A stock CH₂Cl₂ solution 0.03 M in the substrate was prepared earlier. The required volume of this solution was added to the catalyst in one portion at rt. The resulting pink solution was stirred at rt and the progress
of reaction was monitored by TLC. When the conversion to 5 was complete, isolation was accomplished in a well established manner.15

For **2.11**: IR (neat, cm⁻¹) 1453, 1360; ^1^H NMR (300 MHz, CDCl₃) δ 7.39-7.26 (m, 5 H), 5.70-5.59 (m, 2 H), 4.66-4.57 (dd, J = 12.0, 2.4 Hz, 2 H), 3.72-3.64 (m, 1 H), 2.45-2.39 (m, 1 H), 2.21-1.98 (m, 4 H), 1.71-1.65 (m, 1 H); ^1^C NMR (300 MHz, CDCl₃) δ 139.1, 128.4 (2C), 127.6 (2C), 127.4, 126.9, 124.3, 73.9, 69.9, 31.7, 27.9, 24.1; HRMS EI m/z (M⁺) calcd 188.1201, obsd 188.1207.

Anal. Calcd for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C, 82.78; H, 8.68.

**Preparation of 3.5.**

To a mixture of alcohol 3.4 (2 g, 15 mmol) and imidazole (3.12 g, 45.5 mmol) in dry CH₂Cl₂ (30 mL), TBSCl (2.9 g, 19.7 mmol) was added at rt under N₂. The mixture was stirred overnight at rt and quenched with water (50 mL). The CH₂Cl₂ layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (2 x 30 mL). The combined CH₂Cl₂ layers were washed with brine, dried and concentrated to give a yellow residue. This residue was purified by column chromatography on silica gel (elution with 20:1 petroleum ether:ether) to afford 3.7 g (85%) of pure 3.5 as a colorless liquid; IR (neat, cm⁻¹) 2930, 1738, 1255; ^1^H NMR (300 MHz, CDCl₃) δ 4.15-4.08 (q, J = 7.14, 7.13 Hz, 2 H), 3.64-3.61 (t, J = 6.13 Hz, 2 H), 2.38-2.33 (t, J = 7.41 Hz, 2 H), 1.84-1.79 (m, 2 H), 1.26-1.21 (t, J = 7.13 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^1^C NMR (75 MHz, CDCl₃) δ 173.6, 62.0, 60.1, 30.7, 28.0, 25.9 (3 C), 18.3, 14.2, -5.4 (2 C); HRMS EI m/z (M⁺) calcd 246.1651, obsd 246.1622.
**Preparation of compound 3.6.**

To a solution of ester 3.5 (2.2 g, 8.9 mmol) in dry CH₂Cl₂ (20 mL) was slowly added Dibal-H (9 mL of 1.0 M solution in hexane, 8.9 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1.5 h, quenched with a saturated solution of K-Na-tartrate (15 mL), allowed to come to rt, and stirred overnight. The separated aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL), and the combined organic phases were concentrated and purified by column chromatography on silica gel (elution with 15:1 petroleum ether: ether) to furnish 1.4 g (76 %) of the aldehyde as a colorless liquid.

To a stirred solution of this aldehyde (1.4 g, 6.4 mmol) under N₂ in 25 mL of dry THF was added at −78 °C a solution of allylmagnesium bromide (9.7 mL of 1.0 M solution in THF, 9.7 mmol). The reaction mixture was then stirred at −78 °C for 1 h and then raised to the rt. The reaction mixture was stirred at rt for 30 min and quenched with a saturated solution of NH₄Cl (30 mL). The aqueous layer was extracted with ether (3 x 30 mL) and the combined organic phases were washed with saturated NaHCO₃ solution and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether: ether) to give 1.2 g (75%) of the pure 3.6 as a colorless liquid; IR (neat, cm⁻¹) 3363, 2928, 2857, 1642; ¹H NMR (300 MHz, CDCl₃) δ 5.90-5.75 (m, 1 H), 5.14-5.08 (m, 2 H), 3.68-3.64 (m, 3 H), 2.27-2.19 (m, 2 H), 1.67-1.60 (m, 3 H), 1.58-1.48 (m, 1 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.1, 117.5, 70.6, 63.4, 41.9, 33.9, 29.1, 25.9 (3C), 18.3, -5.3 (2C).
Preparation of compound 3.7.

Alcohol 3.6 (0.7 g, 2.87 mmol) was dissolved in dry DMF (5 mL), treated portionwise with NaH (0.24 g of 60% mixture in oil, 5.74 mmol) at 0 °C, and stirred at this temperature for 20 min prior to the addition of benzyl bromide (0.42 mL, 3.6 mmol). The resulting mixture was stirred at 0 °C for 1 h and overnight at rt, carefully quenched with H2O (20 mL), and diluted with ether (50 mL). The separated aqueous layer was extracted with ether (3 x 40 mL). The combined ethereal layers were washed with H2O (2 x 20 mL), dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 60:1 petroleum ether: ether) to furnish 0.77 g (80%) of the pure ether as a colorless liquid; IR (neat, cm⁻¹) 3066, 3030, 2929, 2857, 1641; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.27 (m, 5 H), 5.91-5.75 (m, 1 H), 5.15-5.06 (m, 2 H), 4.61-4.49 (q, J = 11.6, 11.5 Hz, 2 H), 3.64-3.61 (m, 2 H), 3.51-3.49 (m, 1 H), 2.39-2.33 (m, 2 H), 1.66-1.56 (m, 4 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.8, 134.9, 128.3 (2C), 127.7 (2C), 127.4, 116.9, 78.3, 70.8, 63.1, 38.3, 29.9, 28.6, 25.9 (3C), 18.3, -5.3 (2C); HRMS ES m/z (M + Na)⁺ calcd 357.2220, obsd 357.2239.

To a solution of the above ether (1.0 g, 3.0 mmol) in dry THF (8 mL) was added slowly TBAF (3 mL of 1.0 M solution of THF, 3 mmol) at rt. The resulting mixture was stirred at rt for 45 min and quenched by the addition of water (10 mL). The separated aqueous layer was extracted with ether (2 x 15 mL) and the combined organic layers were dried, concentrated, and purified by column chromatography on silica gel (elution with 3:1 petroleum ether: ether) to obtain 0.5 g (99%) of pure alcohol 3.7 as a colorless liquid; IR (neat, cm⁻¹) 3382, 3068, 2921, 1641; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.27 (m, 5 H), 5.92-5.78 (m, 1 H), 5.16-5.06 (m, 2 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.50 (d, J =
11.5 Hz, 1 H), 3.63-3.59 (m, 2 H), 3.54-3.49 (m, 1 H), 2.44-2.31 (m, 2 H), 2.21 (s, 1 H), 1.71-1.59 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.4, 134.6, 128.3 (2C), 127.8 (2C), 127.6, 117.2, 78.3, 70.9, 62.8, 38.0, 30.2; HRMS ES $m/z$ (M + Na)$^+$ calcd 243.1356, obsd 243.1349.

Preparation of 3.1a.

Ph$_3$PCH$_2$CH$_3$I (1.14 g, 2.76 mmol) was added to 5 mL of dry THF under N$_2$. The resulting mixture was cooled to 0 °C, KHMDS (5.6 mL of 0.37 M solution in toluene, 2.1 mmol) was introduced, and stirring was maintained at 0 °C for 30 min prior to addition of the aldehyde (0.3 g, 1.4 mmol) dissolved in dry THF (5 mL). The resulting mixture was stirred at rt overnight, and quenched with saturated aqueous NH$_4$Cl solution (10 mL). The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried and concentrated to leave a residue that was purified by column chromatography on silica gel (elution with 40:1 petroleum ether: ether) to afford 0.17 g (55%) of pure 3.1a as a colorless liquid; IR (neat, cm$^{-1}$) 3012, 2928, 2858; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38-7.25 (m, 5 H), 5.92-5.80 (m, 1 H), 5.49-5.36 (m, 2 H), 5.14-5.06 (m, 2 H), 4.59 (d, $J$ = 11.5 Hz, 1 H), 4.49 (d, $J$ = 11.5 Hz, 1 H), 3.52-3.44 (m, 1 H), 2.38-2.29 (m, 2 H), 2.16-2.09 (m, 2 H), 1.70-1.51 (m, 5 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.8, 134.9, 130.2, 128.3 (2C), 127.7 (2C), 127.4, 124.1, 116.9, 78.0, 70.9, 38.2, 33.6, 22.7, 12.8; HRMS EI $m/z$ (M$^+$) calcd 230.1671, obsd 230.1728.
Preparation of 3.1b.

To a solution of the aldehyde (0.5 g, 2.3 mmol) in dry THF (5 mL), was added Ph₃PCHCOOEt (1.5 g, 4.6 mmol) at rt. The resulting mixture was heated under reflux for 3 h, cooled, and quenched with water (5 mL). The separated aqueous layer was extracted with ether (2 x 5 mL) and the combined organic layers were dried, concentrated and purified by column chromatography on silica gel (elution with 20:1 petroleum ether:ether) to deliver 0.55 g (84%) of pure ester 3.1b as a colorless liquid; IR (neat, cm⁻¹) 3066, 2979, 1722, 1651, 1166; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.26 (m, 5 H), 7.00-6.90 (m, 1 H), 5.90-5.77 (m, 2 H), 5.14-5.07 (m, 2 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 4.22-4.15 (q, J = 7.1 Hz, 2 H), 3.51-3.43 (m, 1H), 2.42-2.21 (m, 4 H), 1.72-1.65 (m, 2 H), 1.31-1.26 (t, J = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.6, 148.8, 138.6, 134.4, 128.3 (2C), 127.7 (2C), 127.6, 121.5, 117.3, 77.5, 71.0, 60.1, 38.1, 32.2, 28.1, 14.2; HRMS ES m/z (M + Na)^+ calcd 311.1617, obsd 311.1624.


Preparation of 3.1c.

Ph₃PCH₃Br (1.0 g, 2.76 mmol) was added to 4 mL of dry THF under N₂. The resulting mixture was cooled to −78 °C, KHMDS (5.6 mL of 0.37 M solution in toluene, 2.1 mmol) was introduced, and stirring was maintained at −78 °C for 30 min prior to addition of the aldehyde (0.3 g, 1.4 mmol) dissolved in dry THF (5 mL). The resulting mixture was stirred at −78 °C for 45 min, warmed to 0 °C, and quenched with saturated aqueous NH₄Cl solution (10 mL). The separated aqueous layer was extracted with ether (2 x 10 mL) and the combined organic layers were dried and concentrated to leave a
residue that was purified by column chromatography on silica gel (elution with 40:1 petroleum ether: ether) to afford 0.25 g (84%) of pure olefin 3.1c as a colorless liquid; IR (neat, cm\(^{-1}\)) 3075, 2935, 2860, 1641; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.27 (m, 5 H), 5.94-5.79 (m, 2 H), 5.17-5.06 (m, 3 H), 5.02-4.97 (m, 1 H), 4.62 (d, \(J = 11.6\) Hz, 1 H), 4.51 (d, \(J = 11.5\) Hz, 1 H), 3.55-3.47 (m, 1 H), 2.41-2.35 (m, 2 H), 2.24-2.13 (m, 2 H), 1.72-1.62 (m, 2 H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 138.7, 138.6, 134.8, 128.3 (2C), 127.7 (2C), 127.5, 117.0, 114.5, 77.8, 70.9, 38.2, 33.0, 29.6; HRMS EI \(m/z\) (M\(^+\)) calcd 216.1514, obsd 216.1502.


**Preparation of 3.1d.**

To a stirred suspension of NaH (90 mg of 60% in oil, 2.2 mmol) in dry THF (5mL) was added dropwise at 0 °C under N\(_2\) a solution of (EtO)\(_2\)POCH\(_2\)COCH\(_3\) (0.45 g, 2.30 mmol) in dry THF (5 mL). After 10 min, a solution of the aldehyde (0.4 g, 1.8 mmol) in dry THF (5 mL) was slowly introduced at 0 °C. After the addition was complete, the reaction mixture was stirred at rt overnight and quenched with 10 mL of saturated NH\(_4\)Cl solution. The separated aqueous layer was extracted with ether (2 x 15 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether: ether) to afford 0.39 g (82%) of ketone 3.1d as a colorless liquid; IR (neat, cm\(^{-1}\)) 3066, 3006, 2928, 1697, 1626; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.25 (m, 5 H), 6.82-6.72 (m, 1 H), 6.03 (d, \(J = 16.0\) Hz, 1 H), 5.90-5.76 (m, 1 H), 5.15-5.08 (m, 2 H), 4.61 (d, \(J = 11.6\) Hz, 1 H), 4.45 (d, \(J = 11.5\) Hz, 1 H), 3.51-3.43 (m, 1 H), 2.39-2.23 (m, 4 H), 2.19 (s, 3 H), 1.75-
1.66 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 198.4, 148.0, 138.5, 134.3, 131.3, 128.3 (2C), 127.7 (2C), 127.6, 117.4, 77.5, 71.0, 38.1, 32.3, 28.4, 26.8; HRMS ES m/z (M + Na)$^+$ calcd 281.1512, obsd 281.1513.

Preparation of 3.1e.

To a stirred suspension of NaH (68 mg of 60% in oil, 1.7 mmol) in dry THF (5mL) was added dropwise at 0 °C under N$_2$ a solution of (EtO)$_2$POCH$_2$SO$_2$Ph (0.5 g, 1.8 mmol) in dry THF (5 mL). After 10 min, a solution of the aldehyde (0.3 g, 1.4 mmol) in dry THF (5 mL) was slowly introduced at 0 °C. After the addition was complete, the reaction mixture was heated under reflux for 45 min, cooled, and quenched with 10 mL of saturated NH$_4$Cl solution. The separated aqueous layer was extracted with ether (2 x 15 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether: ether) to afford 0.48 g (98%) of pure sulfone 3.1e as a colorless liquid; IR (neat, cm$^{-1}$) 3065, 2926, 1641, 1626, 1446, 1317, 1147; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.87-7.84 (m, 2 H), 7.63-7.49 (m, 3 H), 7.35-7.25 (m, 5 H), 7.01-6.91 (m, 1 H), 6.28-6.21 (d, $J = 17.9$ Hz, 1 H), 5.86-5.72 (m, 1 H), 5.12-5.02 (m, 2 H), 4.58 (d, $J = 11.6$ Hz, 1 H), 4.39 (d, $J = 11.6$ Hz, 1 H), 3.47-3.39 (m, 1 H), 2.43-2.20 (m, 4 H), 1.70-1.63 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 146.6, 140.6, 138.2, 133.9, 133.0, 130.5, 129.0 (2C), 128.2 (2C), 127.6, 127.5 (2C), 127.4 (2C), 117.4 (1C), 77.3, 70.8, 37.8, 31.6, 27.3; HRMS ES m/z (M + Na)$^+$ calcd 379.1338, obsd 379.1354.

Anal. Calcd for C$_{21}$H$_{24}$O$_3$S: C, 70.75; H, 6.79. Found: C, 71.04; H, 6.62.
Preparation of 3.1f.

Ph₃PCH₂C₆H₅OMeBr (1.3 g, 2.8 mmol) was added to 8 mL of dry THF under N₂. The resulting mixture was cooled to 0 °C, n-BuLi (1.58 mL of 1.33 M solution in hexane, 2.1 mmol) was introduced, and stirring was maintained at 0 °C for 30 min prior to addition of the aldehyde (0.3 g, 1.4 mmol) dissolved in dry THF (5 mL). The resulting mixture was stirred at rt overnight, and quenched with saturated aqueous NH₄Cl solution (10 mL). The separated aqueous layer was extracted with ether (2 x 25 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 35:1 petroleum ether: ether) to afford 0.23 g (52%) of 3.1f as a colorless liquid; IR (neat, cm⁻¹) 3067, 3030, 2934, 2836, 1607, 1511, 1248; ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.27 (m, 7 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.34 (d, J = 15.8 Hz, 1 H), 6.13-6.03 (m, 1 H), 5.95-5.86 (m, 1 H), 5.18-5.11 (m, 2 H), 4.64 (d, J = 11.5 Hz, 1 H), 4.53 (d, J = 11.6 Hz, 1 H), 3.83 (s, 3 H), 3.57-3.53 (m, 1 H), 2.43-2.27 (m, 4 H), 1.78-1.64 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 158.6, 138.7, 134.8, 130.5, 129.3, 128.3 (3C), 127.8 (2C), 127.5, 126.9 (2C), 117.0, 114.0, 113.8, 77.7, 70.9, 55.2, 38.2, 33.6, 28.9; HRMS ES m/z (M + Na)⁺ calcd 345.1825, obsd 345.1818.

Preparation of 3.1g

Ph₃PCH₂C₆H₅Br (1.2 g, 2.8 mmol) was added to 8 mL of dry THF under N₂. The resulting mixture was cooled to 0 °C, n-BuLi (1.58 mL of 1.33 M solution in hexane, 2.1 mmol) was introduced, and stirring was maintained at 0 °C for 30 min prior to addition of the aldehyde (0.3 g, 1.4 mmol) dissolved in dry THF (5 mL). After the addition was complete, the reaction mixture was stirred at rt overnight and quenched with 10 mL of
saturated NH₄Cl solution. The separated aqueous layer was extracted with ether (2 x 25 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 40:1 petroleum ether: ether) to afford 0.25 g (61%) of 3.1g as a colorless liquid; IR (neat, cm⁻¹) 3066, 3031, 2936, 2832, 1605; ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.21 (m, 10 H), 6.42 (d, J = 15.9 Hz, 2 H), 6.29-6.19 (m, 1 H), 5.99-5.85 (m, 1 H), 5.20-5.12 (m, 2 H), 4.66 (d, J = 11.6 Hz, 1 H), 4.54 (d, J = 11.6 Hz, 1 H), 3.60-3.53 (m, 1 H), 2.48-2.29 (m, 4 H), 1.81-1.71 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 137.7, 134.7, 130.5, 130.0, 128.4 (2C), 128.3 (2C), 127.8 (2C), 127.5, 126.8, 125.9 (2C), 117.1, 77.7, 70.9, 38.2, 33.5, 28.9; HRMS ES m/z (M + Na)⁺ calcd 315.1719, obsd 315.1707.

Preparation of 3.1h

Ph₃PCH₂C₆H₄CF₃Br (0.46 g, 0.92 mmol) was added to 4 mL of dry THF under N₂. The resulting mixture was cooled to 0 °C, n-BuLi (0.52 mL of 1.33 M solution in hexane, 0.83 mmol) was introduced, and stirring was maintained at 0 °C for 30 min prior to addition of the aldehyde (0.1 g, 0.46 mmol) dissolved in dry THF (3 mL). After the addition was complete, the reaction mixture was stirred at rt overnight and quenched with 8 mL of saturated NH₄Cl solution. The separated aqueous layer was extracted with ether (2 x 15 mL) and the combined organic layers were dried and concentrated. The residue was purified by column chromatography on silica gel (elution with 25:1 petroleum ether: ether) to afford 95 mg (57%) of 3.1h as a colorless liquid; IR (neat, cm⁻¹) 2932, 2858, 1642, 1615, 1496, 1454, 1415; ¹H NMR (400 MHz, CDCl₃) δ 7.59-7.28 (m, 9 H), 6.49-6.29 (m, 1.5 H), 5.96-5.77 (m, 1.5 H), 5.19-5.10 (m, 2 H), 4.67 (d, J = 11.6 Hz, 0.54 H), 4.54 (d, J = 11.6 Hz, 1 H), 3.60-3.53 (m, 1 H), 2.48-2.29 (m, 4 H), 1.81-1.71 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 137.7, 134.7, 130.5, 130.0, 128.4 (2C), 128.3 (2C), 127.8 (2C), 127.5, 126.8, 125.9 (2C), 117.1, 77.7, 70.9, 38.2, 33.5, 28.9; HRMS ES m/z (M + Na)⁺ calcd 315.1719, obsd 315.1707.
4.61 (d, J = 11.4 Hz, 0.46 H), 4.53 (d, J = 11.6 Hz, 0.54 H), 4.41 (d, J = 11.4 Hz, 0.46 H),
3.58-3.48 (m, 1 H), 2.55-2.99 (m, 4 H), 1.83-1.69 (m, 2 H); 13C NMR (100 MHz, CDCl3)
δ; HRMS ES m/z (M + Na)^+ calcd 383.1599, obsd 383.1602.

Preparation of 3.1i.

To a stirred solution of p-NO2PhCH2P(OEt)2 (0.53 g, 1.93 mmol) in dry THF (8 mL), n-BuLi (1.12 mL of 1.6 M solution in hexane, 1.8 mmol) was added at 0 °C under
N2. At this point the solution turned dark purple. The resulting solution was stirred at 0 °C
for 30 min prior to addition of the aldehyde (0.3 g, 1.4 mmol) dissolved in dry THF (5 mL). After the addition was complete, the reaction mixture was stirred at rt overnight and
quenched with 10 mL of saturated NH4Cl solution. The separated aqueous layer was
extracted with ether (2 x 15 mL) and the combined organic layers were dried and
concentrated. The residue was purified by column chromatography on silica gel (elution
with 25:1 petroleum ether: ether) to afford 0.31 g (67%) of 3.1i as a colorless liquid; IR
(neat, cm^-1) 3075, 3030, 2932, 1651, 1596, 1514, 1337; 1H NMR (300 MHz, CDCl 3)
δ 8.17-8.13 (d, J = 8.8 Hz, 2 H), 7.44-7.27 (m, 7 H), 6.42-6.39 (m, 2 H), 5.94-5.80 (m, 1
H), 5.17-5.09 (m, 2 H), 4.64 (d, J = 11.6 Hz, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 3.56-3.49
(m, 1 H), 2.48-2.29 (m, 4 H), 1.78-1.44 (m, 2 H); 13C NMR (75 MHz, CDCl3) δ 146.4,
144.3, 138.6, 136.1, 134.5, 128.4 (2C), 128.3 (2C), 127.8, 127.6, 126.3 (2C), 123.9 (2C),
117.3, 77.6, 70.9, 38.1, 33.1, 29.2; HRMS ES m/z (M + Na)^+ calcd 360.1530, obsd
360.1586.

Anal. Calcd for C21H23NO2: C, 74.75; H, 6.87. Found: C, 75.13; H, 6.81.
**NMR measurement involving 1 mol% of 3.2b.**

A flame-dried 5 mL pear-shaped flask was tared and placed into a glove box. Approximately 1.2 mg of 3.2b was transferred into the flask inside the glove box and the flask was capped. The exact weight of the catalyst was recorded on a more accurate balance after the flask was taken from the glove box. An approximate amount of CD$_2$Cl$_2$ was added to make a 0.0015 M solution of the catalyst and it was kept under N$_2$ protection. At the same time, about 0.6 mL of 0.0375 M of 3.1 in CD$_2$Cl$_2$ was prepared in another flame-dried pear-shaped flask, which was likewise under N$_2$. At this point, 0.1 mL of the freshly prepared catalyst solution was placed in a dry 5 mm NMR tube capped by a rubber septum by way of a 1 mL disposable syringe. With the Bruker 400 MHz NMR spectrometer set up for measurement, 0.4 mL of the substrate solution was introduced by way of another 1 mL syringe and the counting of time began. The progress of reaction was monitored by recording spectra continually until all of the substrate was consumed. The product/substrate ratio at any point in time was defined by integration of appropriate proton signals and this ratio was used to calculate the concentration of substrate at that time.

**NMR measurement involving 5 mol% of catalyst.**

These measurements were made in an entirely analogous manner.

**General preparative procedure.**

The preparative experiments were performed with 5 mol% catalyst in the manner defined above. When the consumption of substrate was judged to be complete by TLC
analysis, 1.5 equiv (relative to the ruthenium catalyst) of Pb(OAc)₄ and the reaction mixture was stirred overnight prior to solvent removal in vacuo. The residue was purified by column chromatography on silica gel (elution with 10% ethyl acetate in hexane) to give the known 3.3.

**Preparation of 4.23**

To a rapidly stirred solution of 4.22 (10.4 g, 0.06 mol) in KH₂PO₄ buffer (250 mL, 0.1 M) was added PLE 20,000 units (0.17 g) at pH 8.0 at rt. The mixture was stirred at rt for 24 h when the pH was maintained at 8.0 by pH stat-controlled addition of 1.0 N aqueous solution of NaOH. The mixture was extracted with CH₂Cl₂ (2 x 800 mL), the combined organic phases were dried over MgSO₄ and evaporated to give a residue, which was purified by column chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to give 3.16 g (61%) of 4.23 as a colorless liquid; [α]₂⁵ D = +109.0 (c 1.0, CHCl₃); IR (neat, cm⁻¹) 2981, 2939, 1714, 1260, 1158; ¹H NMR (300 MHz, CDCl₃) δ 4.24-4.15 (m, 2 H), 2.55-2.45 (m, 3 H), 2.04-2.02 (m, 1 H), 1.75-1.64 (m, 3 H), 1.51-1.44 (1 H), 1.29 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 206.7, 172.2, 60.4, 56.3, 39.9, 37.5, 26.9, 22.0, 20.5, 13.4; HRMS ES m/z (M + Na)⁺ calcd 207.0992, obsd 207.1000.

**Preparation of 4.24**

To a cold (−78 °C) suspension of NaBH₄ (1.23 g, 32.6 mmol) in anhydrous MeOH (30 mL) was added a solution of 4.23 (5.0 g, 27.2 mmol) in anhydrous MeOH (50 mL) via an addition funnel. The mixture was stirred at −78 °C for 2 h before being quenched
by 10% aqueous HCl solution (50 mL). The mixture was warmed to rt and stirred at rt for 15 min. This solution was extracted with CH$_2$Cl$_2$ (3 x 100 mL), the combined organic phases were dried over MgSO$_4$ and evaporated to give a residue as a mixture of diastereomeric alcohols.

To a cold (0 °C) solution of crude alcohols in dry CH$_2$Cl$_2$ (100 mL) was added Et$_3$N (5.49 g, 54.3 mmol) and MsCl (6.22 g, 54.3 mmol) in sequence. The cloudy solution was stirred at 0 °C for 1.5 h before being quenched with 10% aqueous HCl (50 mL) and diluted with H$_2$O (100 mL). The organic phase was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated under vacuum to give a mixture of mesylates as a yellow oil.

To a solution of the above mesylates in MeOH (200 mL) and H$_2$O (25 mL) was added KOH (10.67 g, 190.19 mmol). The mixture was heated to 60 °C for 16 h before it was cooled to rt. The MeOH was evaporated under vacuum and the residue was acidified to pH 1 by careful addition of 1 N HCl solution. The aqueous layer was extracted with CH$_2$Cl$_2$ (4 x 100 mL), the combined organic phases were dried over MgSO$_4$ and evaporated to give a residue which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to give 2.28 g (60% over three steps) of 4.24 as a colorless liquid; $[\alpha]^{25}_D$ = -100.9 (c 1.2, CHCl$_3$); IR (neat, cm$^{-1}$) 2938, 2643, 1697, 1296, 1188; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.85-5.67 (m, 2 H), 2.20-2.14 (m, 1 H), 2.05-1.98 (m, 2 H), 1.70-1.66 (m, 2 H), 1.53-1.48 (m, 1 H), 1.32-1.24 (m, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 183.7, 130.0, 128.3, 42.8, 32.6, 26.1, 24.6, 19.4; HRMS ES m/z (M + Na)$^+$ calcd 140.0832, obsd 140.0824.
Preparation of 4.25

To a cold (0 °C) suspension of LiAlH₄ (1.25 g, 32.86 mmol) in dry THF (40 mL) was added a solution of 4.24 (2.0 g, 14.29 mmol) in dry THF (40 mL) via an addition funnel. After the addition was complete, the cold bath was removed and the reaction mixture was stirred at rt for 14 h. The reaction mixture was cooled to 0 °C and carefully quenched with 1 N NaOH (1.25 mL) followed by the addition of H₂O (3.75 mL). The mixture was stirred at 0 °C for 1 h during which time a white precipitate was formed. The reaction mixture was filtered and the solid was washed with Et₂O (100 mL). The filtrate was concentrated under vacuum to give a light yellow residue which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to give 1.77 g (98%) of the primary alcohol as a colorless oil; [α]²⁵_D = +8.5 (c 1.0, CHCl₃); IR (neat, cm⁻¹) 3355, 3012, 2914; ¹H NMR (300 MHz, CDCl₃) δ 5.90-5.78 (m, 1 H), 5.41-5.37 (m, 1 H), 3.43-3.30 (m, 2 H), 2.00-1.95 (m, 2 H), 1.71-1.60 (m, 2 H), 1.40-1.27 (m, 2 H), 0.96 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 133.0, 128.1, 70.8, 36.7, 31.5, 25.0, 24.1, 18.8.

To a solution of the above alcohol (1.77 g, 14.05 mmol) in dry DMF (7 mL) was added TBDPSCl (4.63 g, 16.86 mmol) and imidazole (2.87 g, 42.15 mmol). The mixture was heated to 50 °C for 2 h before it was cooled to rt. The mixture was diluted with H₂O (100 mL) and the aqueous layer was extracted with Et₂O (5 x 100 mL). The organic layers were combined, dried over MgSO₄, and evaporated to give a residue which was purified by column chromatography on silica gel (elution with 40:1 hexane:ethyl acetate) to obtain 4.65 g (91%) of 4.25 as a colorless oil; [α]²⁵_D = -28.2 (c 1.4, CHCl₃); IR (neat, cm⁻¹) 3049, 2920, 1470, 1361; ¹H NMR (250 MHz, CDCl₃) δ 7.70-7.66 (m, 4 H), 7.46-
7.27 (m, 6 H), 5.71-5.64 (m, 1 H), 5.46-5.31 (m, 1 H), 3.44-3.33 (m, 2 H), 1.97-1.70 (m, 2 H), 1.70-1.53 (m, 3 H), 1.41-1.33 (m, 1 H), 1.08-1.05 (s, 12 H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 135.7 (4C), 134.0 (2C), 133.8, 129.5 (2C), 127.6 (4C), 127.1, 71.5, 37.2, 31.9, 26.9 (3C), 25.4, 24.8, 19.5, 19.0; HRMS ES \(m/z\) (M + Na)\(^+\) calcd 387.2115, obsd 387.2092.

**Preparation of 4.26**

Ozone was passed through a cold (-78 °C) solution of 4.25 (4.0 g, 10.98 mmol) in a 1:1 mixture of CH\(_2\)Cl\(_2\) and MeOH (130 mL each). After the reaction was done, PPh\(_3\) (3.17 g, 12.09 mmol) was added and the mixture was stirred at rt for 4 h. The solvent was evaporated under vacuum, the residue was further evaporated with PhH (250 mL), and redissolved in PhH (250 mL). To this solution was added \(p\)-TsOH (0.63 g, 3.29 mmol) and the mixture was heated to 65 °C for 20 h. The solvent was removed and the residue was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to give 3.36 g (81% over two steps) of 4.26 as a colorless oil; \([\alpha]^{25}\_D = -40.4 \ (c 0.6, \text{CHCl}_3); \) IR (neat, cm\(^{-1}\)) 3050, 2962, 2929, 1681, 1105; \(^1\text{H}\) NMR (250 MHz, CDCl\(_3\)) \(\delta\) 9.75 (s, 1 H), 7.71-7.63 (m, 4 H), 7.48-7.36 (m, 6 H), 6.90-6.61 (m, 1 H), 3.55 (s, 2 H), 2.58-2.52 (m, 2 H), 2.02-1.94 (m, 1 H), 1.73-1.59 (m, 1 H), 1.17 (s, 3 H), 1.07 (s, 9 H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 190.4, 158.5, 146.3, 135.7 (4C), 133.5 (2C), 129.7 (2C), 127.7 (4C), 70.4, 52.6, 33.4, 27.6, 26.8 (3C), 22.7, 19.3; HRMS ES \(m/z\) (M + Na)\(^+\) calcd 401.1907, obsd 401.1900.
**Preparation of 4.20**

To a stirred mixture of 4.26 (3.0 g, 7.94 mmol) and 2-methyl-2-butene (5.57 g, 79.4 mmol) in t-BuOH (20 mL) was added an aqueous solution of NaClO₂ (2.87 g, 31.76 mmol) and NaH₂PO₄ (3.29 g, 23.82 mmol) in H₂O (20 mL) at rt. The resulting solution was stirred at rt overnight before it was quenched with 10% HCl solution to reach pH 5.0. The aqueous layer was extracted with EtOAc (5 x 50 mL), and the combined organic phases were dried over MgSO₄ and evaporated to give a residue, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to afford 2.94 g (94%) of 4.20 as a colorless liquid; [α]₂⁵⁺ = +18.3 (c 1.3, CHCl₃); IR (neat, cm⁻¹) 3072, 2960, 2858, 1684, 1280; ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.63 (m, 4 H), 7.46-7.35 (m, 1 H), 6.73-6.71 (m, 1 H), 3.53-3.46 (m, 2 H), 2.64-2.58 (m, 2 H), 2.05-1.96 (m, 1 H), 1.71-1.61 (m, 1 H), 1.15 (s, 3 H), 1.06 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 170.6, 152.1, 135.6 (4C), 135.1, 133.5 (2C), 129.6 (2C), 127.6 (4C), 70.4, 52.5, 33.7, 30.3, 26.8 (3C), 22.7, 19.3; HRMS ES m/z (M + Na)⁺ calcd 417.1856, obsd 417.1876.

**Preparation of 4.22**

To a cold (-78 °C), stirred solution of oxazolidinone 4.27 (1.8 g, 6.95 mmol) in dry THF (24 mL) was added NaHMDS (7.3 mL of 1.0 M solution in THF, 7.3 mmol) slowly over 5 min under N₂. After being stirred at −78 °C for 45 min, a solution of iodide 4.28 (1.27 g, 3.42 mmol) in THF (12 mL) was added via an addition funnel. The resulting mixture was stirred for 5 h at −78 °C before it was quenched with a saturated solution of NH₄Cl (30 mL). The mixture was allowed to warm to rt, stirred for an additional 10 min, and diluted with H₂O (50 mL). The organic layer was separated and the aqueous layer
was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to leave a residue which was dissolved in anhydrous MeOH (90 mL). To a cold (0 °C) flask of the previous solution was added NaBH₄ (1.3 g, 34.4 mmol) in portions and the resulting solution was allowed to stir at 0 °C overnight. The reaction mixture was quenched with a saturated solution of NH₄Cl (100 mL) followed by H₂O (100 mL). The mixture was extracted with CH₂Cl₂ (4 x 200 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated to obtain a residue, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to afford 0.68 g (60% over two steps) of alcohol 4.29 as a colorless oil; [α]²⁰ D = +0.3 (c = 1.0, CHCl₃); IR (neat, cm⁻¹) 3424, 3073, 2930, 1721, 1641, 1176; ¹H NMR (250 MHz, CDCl₃) δ 8.07-8.03 (m, 2 H), 7.56-7.52 (m, 1 H), 7.47-7.27 (m, 2 H), 5.84-5.77 (m, 1 H), 5.10-5.01 (m, 2 H), 4.80-4.77 (m, 2 H), 4.32 (t, J = 6.6 Hz, 2 H), 3.55 (d, J = 5.3 Hz, 2 H), 2.13-2.00 (m, 6 H), 1.84-1.75 (m, 3 H), 1.50-1.37 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 148.1, 136.8, 132.8, 130.4, 129.5 (2C), 128.3 (2C), 116.4, 110.9, 65.5, 65.0, 38.14, 38.10, 35.7, 35.4, 28.9, 28.6, 27.4, 25.9; HRMS ES m/z (M + Na)+ calcd 353.2087, obsd 353.2061.

Preparation of 4.30

To a cold (0 °C), stirred solution of 4.29 (1.7 g, 5.15 mmol) in dry CH₂Cl₂ (30 mL) was added pyridine (1.2 g, 15.5 mmol) followed by PivCl (1.24 g, 10.3 mmol). The mixture was stirred at rt overnight before it was quenched with 10% HCl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and
evaporated to obtain a residue, which was purified by column chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to obtain 1.98 g (93%) of 4.30 as a colorless oil; \([\alpha]_{D}^{20} = -3.0 (c = 1.2, \text{CHCl}_3); \ IR (\text{neat, cm}^{-1}) 3074, 2933, 2858, 1724, 1641, 1160; \]

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.06-8.03 (m, 2 H), 7.58-7.53 (m, 1 H), 7.46-7.41 (m, 2 H), 5.82-5.70 (m, 1 H), 5.06-4.99 (m, 2 H), 4.77 (d, \(J = 15.5\) Hz, 2 H), 4.32 (t, \(J = 6.62\) Hz, 2 H), 3.99-3.91 (m, 2 H), 2.13-1.94 (m, 7 H), 1.80-1.73 (m, 2 H), 1.55-1.33 (m, 6 H), 1.21 (s, 9 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 178.2, 166.4, 146.8, 135.8, 132.6 (2C), 131.3, 129.4 (2C), 128.2, 116.7, 111.3, 65.8, 64.8, 38.9, 37.6, 35.4, 35.3, 35.2, 28.8, 28.6, 27.4, 27.1 (3C), 25.8; HRMS ES \(m/\ell\) (M + Na)\(^+\) calcd 437.2662, obsd 437.2681.

**Preparation of 4.31**

Ozone was passed through a cold (-78 °C) solution of 4.30 (0.82 g, 1.99 mmol) in a 1:1 mixture of CH\(_2\)Cl\(_2\):MeOH (20 mL each). After the reaction was complete, PPh\(_3\) (3.17 g, 12.09 mmol) was added and the mixture was stirred at rt for 6 h. The solvent was evaporated under vacuum, the residue was further evaporated with PhH (60 mL), and redissolved in PhH (60 mL). To this solution was added \(p\)-TsOH (0.20 g, 1.04 mmol) and the mixture was heated to 65 °C for 15 h. The solvent was removed and the residue was purified by column chromatography on silica gel (elution with 5:1 hexane:Et\(_2\)O) to afford 0.52 g (65% over two steps) of 4.31 as a colorless oil; \([\alpha]_{D}^{25} = -24.0 (c 0.9, \text{CHCl}_3); \ IR (\text{neat, cm}^{-1}) 2936, 1720, 1674, 1480, 1157; \)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.06-8.03 (m, 2 H), 7.59-7.53 (m, 1 H), 7.47-7.42 (m, 2 H), 6.70-6.68 (m, 1 H), 4.32 (t, \(J = 6.6\) Hz, 2 H), 4.03-4.00 (m, 2 H), 2.60-2.53 (m, 1 H), 2.46-2.39 (m, 2 H), 2.28-2.18 (m, 4 H), 1.81-1.77 (m, 2 H), 1.48-1.43 (m, 4 H), 1.22 (s, 9 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.0,
178.2, 166.6, 143.2, 139.7, 132.8 (2C), 130.5, 129.5 (2C), 128.3, 66.9, 64.9, 41.2, 38.8, 34.9, 29.2, 28.8, 28.5, 28.2, 27.2 (3C), 25.7; HRMS ES m/z (M + Na)$^+$ calcd 423.2142, obsd 423.2112.

**Preparation of 4.32**

To a mixture of 4.31 (1.0 g, 2.5 mmol) and CeCl$_3$·7H$_2$O (1.4 g, 3.8 mmol) in anhydrous MeOH (20 mL) was added NaBH$_4$ (0.12 g, 3.0 mmol) in portions at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with a saturated solution of NH$_4$Cl (40 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave a residue, which was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ethyl acetate) to afford 0.93 g (92%) of the allylic alcohol as colorless oil; $[\alpha]^{20}_D$ = -24.1 ($c = 1.1$, CHCl$_3$); IR (neat, cm$^{-1}$) 3503, 2935, 1721, 1480, 1277, 1162; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.07-8.03 (m, 2 H), 7.59-7.53 (m, 1 H), 7.48-7.42 (m, 2 H), 5.49-5.46 (m, 1 H), 4.36-4.28 (m, 3 H), 3.97 (d, $J = 6.0$ Hz, 2 H), 2.30-2.28 (m, 1 H), 2.16-2.00 (m, 5 H), 1.82-1.78 (m, 3 H), 1.49-1.31 (m, 4 H), 1.21 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.6, 165.8, 139.5, 131.9 (2C), 130.2, 128.6 (2C), 127.4, 121.5, 67.5, 67.2, 64.1, 38.0, 35.4, 32.1, 31.5, 27.8, 27.7, 26.5, 26.3 (3C), 24.9; HRMS ES m/z (M + Na)$^+$ calcd 425.2298, obsd 425.2285.

To a cold (0 °C), stirred mixture of the above alcohol (2.15 g, 5.35 mmol) and PMBImid (2.27 g, 8.02 mmol) in dry Et$_2$O (72 mL) was added TfOH (0.16 mL, 0.16 mmol). The resulting mixture was stirred at rt for 5 h before it was quenched with a saturated solution of NaHCO$_3$ (20 mL) followed by H$_2$O (100 mL). The organic layer
was separated and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to obtain a residue, which was purified by column chromatography on silica gel (elution with 10:1 petroleum ether:ethyl acetate) to afford 2.23 g (80%) of 4.32 as colorless oil; [α]²⁰_D = -34.8 (c = 0.8, CHCl₃); IR (neat, cm⁻¹) 2935, 2859, 1721, 1612, 1160; ¹H NMR (250 MHz, CDCl₃) δ 8.07-8.03 (m, 2 H), 7.57-7.53 (m, 1 H), 7.47-7.41 (m, 2 H), 7.29-7.25 (m, 2 H), 6.89-6.85 (m, 2 H), 5.52-5.49 (m, 1 H), 4.59 (d, J = 11.3 Hz, 1 H), 4.40 (d, J = 11.3 Hz, 1 H), 4.38-4.29 (m, 2 H), 4.03-3.98 (m, 3 H), 3.79 (s, 3 H), 2.30-1.76 (m, 8 H), 1.49-1.36 (m, 5 H), 1.21 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.5, 166.6, 159.0, 139.2, 132.8, 130.7, 130.4, 129.5 (2C), 129.2 (2C), 128.3 (2C), 123.0, 113.7, (2C), 74.4, 70.1, 68.2, 65.0, 55.2, 38.8, 32.73, 32.70, 31.5, 28.6, 28.5, 27.4, 27.2 (3C), 25.8; HRMS ES m/z (M + Na)+ calcd 545.2874, obsd 545.2842.

**Preparation of 4.33**

To a stirred solution of 4.32 (1.3 g, 2.49 mmol) in 1:1 mixture of CH₂Cl₂:MeOH (30 mL each) was passed O₃ at −78 °C. After reaction was complete, PPh₃ (0.72 g, 2.74 mmol) was added and the resulting mixture was stirred at rt for 4 h. Solvent was evaporated under vacuum, the residue was further evaporated with Et₂O (75 mL), and redissolved in Et₂O (75 mL). To this solution was added piperidine (78 mg, 0.92 mmol) and the resulting mixture was stirred at rt before HOAc (97 mg, 1.62 mmol) was added. The mixture was heated to reflux for 20 h, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ether) to afford 1.06 g (80%) of 4.33 as colorless liquid; [α]²⁰_D = +7.1 (c
= 0.7, CHCl₃); IR (neat, cm⁻¹) 2934, 1719, 1671, 1611, 1159; ¹H NMR (250 MHz, CDCl₃) δ 10.04 (s, 1 H), 8.06-8.02 (m, 2 H), 7.57-7.54 (m, 1 H), 7.48-7.42 (m, 2 H), 7.28-7.24 (m, 2 H), 6.90-6.86 (m, 2 H), 4.60 (d, J = 11.5 Hz, 1 H), 4.51-4.48 (m, 1 H), 4.42-4.29 (m, 4 H), 4.20-4.13 (m, 1 H), 3.79 (s, 3 H), 3.20-3.12 (m, 1 H), 2.79-2.54 (m, 2 H), 2.35-2.21 (m, 1 H), 1.76-1.45 (m, 7 H), 1.18 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 188.7, 178.3, 166.5, 165.1, 137.7, 132.9, 130.3, 129.9, 129.54 (2C), 129.50 (2C), 128.3 (2C), 113.8 (2C), 82.7, 71.4, 65.5, 64.5, 55.2, 41.4, 38.8, 32.2, 28.4, 28.1, 27.1 (3C), 26.0, 25.8; HRMS ES m/z (M + Na)⁺ calcd 559.2666, obsd 559.2646.

Preparation of 4.34

To a cold (0 °C), stirred solution of aldehyde 4.33 (0.49 g, 0.91 mmol) in anhydrous MeOH (25 mL) was added NaBH₄ (70 mg, 1.85 mmol) in portions. The resulting mixture was stirred at 0 °C for 20 min before it was quenched with a saturated solution of NH₄Cl (30 mL). The mixture was extracted with CH₂Cl₂ (4 x 50 mL). The organic layers were combined, dried over MgSO₄, filtered and evaporated to obtain a residue which was purified by column chromatography on silica gel (elution with 4:1 petroleum ether:ethyl acetate) to afford 0.49 g (100%) of allylic alcohol as a colorless oil; [α]²₀° = -20.0 (c = 0.1, CHCl₃); IR (neat, cm⁻¹) 3475, 2937, 1722, 1612, 1172; ¹H NMR (300 MHz, CDCl₃) δ 8.06-8.03 (m, 2 H), 7.59-7.54 (m, 1 H), 7.47-7.42 (m, 2 H), 7.27-7.23 (m, 2 H), 6.89-6.84 (m, 2 H), 4.54 (d, J = 11.4 Hz, 1 H), 4.44-4.11 (m, 8 H), 3.79 (s, 3 H), 3.00-2.95 (m, 1 H), 2.33-2.18 (m, 3 H), 1.77-1.72 (m, 3 H), 1.47-1.42 (m, 4 H), 1.21 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.2, 166.3, 158.8, 141.8, 138.0, 132.5 (2C), 130.5, 130.1, 129.2 (2C), 128.9 (2C), 128.0 (2C), 113.4, 83.3, 70.4, 66.7, 64.5,
To a stirred solution of above alcohol (0.88 g, 1.63 mmol) in dry CH₂Cl₂ (15 mL) was added imidazole (0.33 g, 4.89 mmol) followed by TBSCl (0.37 g, 2.44 mmol). The mixture was stirred at rt for 1 h before it was quenched with H₂O (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to leave a residue which was purified by column chromatography on silica gel (elution with 15:1 petroleum ether:ethyl acetate) to afford 1.0 g (94%) of 4.34 as a colorless oil; [α]²⁰^D = -17.4 (c = 0.06, CHCl₃); IR (neat, cm⁻¹) 2952, 1713, 1613, 1169; ¹H NMR (300 MHz, CDCl₃) δ 8.09-8.03 (m, 2 H), 7.57-7.53 (m, 1 H), 7.47-7.41 (m, 2 H), 7.27-7.24 (m, 2 H), 6.88-6.85 (m, 2 H), 4.53 (d, J = 11.6 Hz, 1 H), 4.38-4.27 (m, 6 H), 4.16 (d, J = 12.5 Hz, 1 H), 4.08-3.91 (m, 1 H), 3.79 (s, 3 H), 3.02-3.95 (m, 1 H), 2.29-2.12 (m 3 H), 1.78-1.70 (m, 2 H), 1.64-1.55 (m, 1 H), 1.48-1.39 (m, 4 H), 1.19 (s, 9 H), 0.88 (s, 9 H), 0.07-0.03 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 178.4, 166.5, 159.0, 140.5, 138.2, 132.7 (2C), 130.9, 130.4, 129.4, 129.2 (2C), 128.2 (2C), 113.6 (2C), 83.8, 70.4, 66.6, 64.6, 58.1, 54.9, 43.5, 38.6, 32.6, 28.4, 27.6, 27.0 (3C), 25.9, 25.7 (3C), 25.6, 18.0, -5.6 (2C); HRMS ES m/z (M + Na)⁺ calcd 675.3688, obsd 675.3660.

Preparation of 4.35

To a stirred solution of 4.34 (1.0 g, 1.53 mmol) in anhydrous MeOH (60 mL) was added K₂CO₃ (1.06 g, 7.65 mmol). The mixture was stirred at rt overnight before it was quenched with a saturated solution of NH₄Cl (30 mL). The mixture was extracted with
EtOAc (4 x 40 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to obtain a residue that was purified by column chromatography on silica gel (elution with 2:1 petroleum ether:ethyl acetate) to afford 0.78 g (93%) of the primary alcohol as a colorless oil; \([\alpha]_{D}^{20} = -21.3 \ (c = 0.08, \text{CHCl}_3)\); IR (neat, cm\(^{-1}\)) 3443, 2955, 1731, 1613, 1166; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.28-7.23 (m, 2 H), 6.89-6.84 (m, 2 H), 4.53 (d, \(J = 11.5\ \text{Hz}, 1\ \text{H}\)), 4.43-4.26 (m, 4 H), 4.15 (d, \(J = 12.4\ \text{Hz}, 1\ \text{H}\)), 4.05-3.80 (m, 1 H), 3.80 (s, 3 H), 3.62-3.57 (m, 2 H), 2.99-2.95 (m, 1 H), 2.30-2.20 (m, 1 H), 2.15-2.11 (m, 2 H), 1.64-1.50 (m, 3 H), 1.37-1.18 (m, 13 H), 0.88 (s, 9 H), 0.06-0.03 (m, 6 H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) 178.4, 159.0, 140.6, 138.1, 130.9, 129.2 (2C), 113.6 (2C), 83.8, 70.5, 66.7, 62.6, 58.2, 55.1, 43.5, 38.7, 32.7, 32.5, 27.8, 27.1 (3C), 26.0, 25.76 (3C), 25.70, 18.1, -5.5 (2C); HRMS ES \(m/z\) (M + Na)^+ calcd 571.3425, obsd 571.3434.

To a stirred solution of the above alcohol (1.29 g, 2.35 mmol) in dry CH₂Cl₂ (7 mL) was added \(i\)-Pr₂NEt (0.91 g, 7.05 mmol) followed by MEMCl (0.59 g, 4.70 mmol) at 0 °C under N₂. The resultant solution was stirred at rt for 18 h before it was quenched with 10% HCl solution (10 mL). The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (2 x10 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to obtain a residue, which was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ether) to afford 1.39 g (93%) of **4.35** as colorless oil; \([\alpha]_{D}^{20} = -15.06 \ (c = 1.7, \text{CHCl}_3)\); IR (neat, cm\(^{-1}\)) 3030, 2929, 1726, 1612, 1251; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.29-7.27 (m, 2 H), 6.94-6.90 (m, 2 H), 4.76 (s, 2 H), 4.60-4.56 (m, 1 H), 4.49-4.31 (m, 4 H), 4.23-4.19 (m, 1 H), 4.10-4.04 (m, 1 H), 3.86 (s, 3 H), 3.79-3.73 (m, 2 H), 3.64-3.45 (m, 4 H), 3.45 (s, 3 H), 3.11-2.94 (m, 1 H), 2.35-2.25 (m, 1 H), 2.20-2.16 (m, 2 H), 1.70-1.60 (m, 3 H), 1.49-1.27 (m, 4 H), 1.00...
1.24 (s, 9 H), 0.93 (s, 9 H), 0.12-0.08 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.4, 159.0, 140.6, 138.1, 131.0, 129.1 (2C), 113.6 (2C), 95.4, 83.9, 71.7, 70.5, 67.8, 66.8, 66.6, 58.9, 58.2, 55.2, 43.6, 38.7, 32.8, 29.5, 28.1, 27.2 (3C), 26.3, 26.1, 25.8 (3C), 18.2, -5.4, -5.5; HRMS ES m/z (M + Na)$^+$ calcd 659.3949, obsd 659.3914.

**Preparation of 4.21**

To a stirred solution of 4.35 (0.62 g, 0.97 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added Dibal-H (2.43 mL of 1.0 M solution in hexane, 2.43 mmol) at –78 ºC under N$_2$.

The resultant solution was stirred at –78 ºC for 0.5 h and at 0 ºC for 1 h before it was quenched with a saturated solution of potassium sodium tartrate (10 mL). The resultant cloudy solution was stirred at rt overnight. It was diluted with water (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and evaporated to obtain a yellow residue that was purified by column chromatography on silica gel (elution with 2:1 petroleum ether:ethyl acetate) to get 0.42 g (78%) of 4.21 as colorless oil; $[\alpha]_{20}^{20}$D = -31.53 (c = 0.72, CHCl$_3$); IR (neat, cm$^{-1}$) 3457, 2928, 1612, 1514, 837; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.28-7.23 (m, 2H), 6.91-6.84 (m, 2H), 4.71 (s, 2H), 4.58-4.53 (m, 1H), 4.39-4.29 (m, 3H), 4.15-4.11 (m, 1H), 3.80 (s, 3H), 3.74-3.66 (m, 2H), 3.57-3.48 (m, 6H), 3.40 (s, 3H), 2.82-2.68 (m, 1H), 2.27-2.09 (m, 3H), 1.61-1.50 (m, 3H), 1.43-1.29 (m, 4H), 0.88 (s, 9H), 0.09 (m, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.8, 141.7, 138.7, 130.5, 129.3 (2C), 113.6 (2C), 95.4, 82.9, 71.7, 70.6, 67.7, 66.6, 64.5, 58.9, 58.5, 55.2, 47.6, 32.5, 29.5, 28.0, 26.3, 26.0, 25.8 (3C), 18.2, -5.4, -5.5; HRMS ES m/z (M + Na)$^+$ calcd 575.3375, obsd 575.3362.
Preparation of 4.38

To a cold (−78 °C), stirred solution of oxalyl chloride (48.2 g, 0.38 mol) in dry CH₂Cl₂ (400 mL) was added a solution of DMSO (44.5 g, 0.57 mol) in dry CH₂Cl₂ (300 mL) via an addition funnel under N₂. After 30 min of stirring, a solution of 4.37 (48.0 g, 0.19 mol) in dry CH₂Cl₂ (300 mL) was added over 30 min at −78 °C. The resulting cloudy solution was stirred at −78 °C for 1 h before Et₃N (96.0 g, 0.95 mol) was added via addition funnel. The cold bath was removed and the mixture was allowed to warm to 0 °C before being quenched with a saturated solution of NH₄Cl (500 mL). The organic layer was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 500 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to obtain a yellow residue, which was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ethyl acetate) to afford 42.4 g (90%) of the saturated aldehyde as colorless oil.

A mixture of above aldehyde (13.0 g, 52.4 mmol), Et₂NH·HCl (5.6 g, 68.2 mmol), and CH₂O (5.53 mL of 37% aqueous solution, 68.2 mmol) was heated to 110 °C for 16 h. The mixture was cooled to rt and diluted with H₂O (200 mL). The mixture was extracted with CH₂Cl₂ (4 x 200 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to leave a yellow residue, which was purified by column chromatography on silica gel (elution with 10:1 petroleum ether:ethyl acetate) to yield 10.6 g (74%) of 4.38 as colorless oil; IR (neat, cm⁻¹) 2934, 2858, 1718, 1692, 1117; ¹H NMR (300 MHz, CDCl₃) δ 9.53 (s, 1 H), 8.05-8.02 (m, 2 H), 7.58-7.53 (m, 1 H), 7.46-7.41 (m, 2 H), 6.25 (s, 1 H), 5.99 (s, 1 H), 4.33-4.29 (m, 2 H), 2.28-2.23 (m, 2 H), 1.79-1.72 (m, 2 H), 1.51-1.35 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 194.4, 166.3, 149.9,
133.8, 132.6, 130.2, 129.3 (2C), 128.1 (2C), 64.7, 28.7, 28.4, 27.5, 27.4, 25.6; HRMS ES m/z (M + Na)^+ calcd 283.1305, obsd 283.1306.

**Preparation of 4.39**

To a cold (-20 °C), stirred solution of 4.38 (31.7 g, 115.8 mmol) in anhydrous MeOH (250 mL) was added NaBH₄ (4.4 g, 115.8 mmol) in portions. The resulting mixture was stirred at -20 °C for 30 min before being quenched by 10% HCl solution (200 mL). The mixture was extracted with CH₂Cl₂ (4 x 300 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to obtain a residue, which was purified by column chromatography (elution with 4:1 petroleum ether:ethyl acetate) to afford 31.0 g (91%) of 4.39 as colorless oil; IR (neat, cm⁻¹) 3422, 2932, 2856, 1720, 1118; ¹H NMR (300 MHz, CDCl₃) δ 8.07-8.03 (m, 2 H), 7.57-7.54 (m, 1 H), 7.48-7.42 (m, 2 H), 5.02 (s, 1 H), 4.88 (s, 1 H), 4.33 (t, J = 6.6 Hz, 2 H), 4.08 (d, J = 5.8 Hz, 2 H), 2.12-2.06 (m, 2 H), 1.81-1.76 (m, 2 H), 1.54-1.40 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 148.7, 132.5, 130.0, 129.2 (2C), 128.0 (2C), 108.5, 65.1, 64.7, 32.5, 28.7, 28.3, 27.2, 25.5; HRMS ES m/z (M + Na)^+ calcd 285.1461, obsd 285.1473.

**Preparation of 4.40**

To a cold (-78 °C), stirred solution of 4.39 (14.7 g, 53.15 mmol) in dry CH₂Cl₂ (150 mL) was added Et₃N (10.8 g, 106.3 mmol) followed by MsCl (12.2 g, 106.3 mmol) under N₂. The resulting solution was slowly warmed to 0 °C and stirred at 0 °C for 1.5 h before being quenched by 10% HCl solution (100 mL). The organic layer was separated
and the aqueous layer was extracted with CH$_2$Cl$_2$ (4 x 100 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and evaporated to obtain a residue.

The residue obtained above was dissolved in dry THF (100 mL) followed by the addition of anhydrous LiBr (9.2 g, 106.2 mmol) at 0 °C. The mixture was stirred at rt for 2 h before it was filtered through a pad of silica gel. The solid was washed with Et$_2$O (4 x 100 mL) and the combined filtrates were evaporated under vacuum to afford a yellow residue, which was purified by column chromatography on silica gel (elution with 40:1 hexane:ethyl acetate) to obtain 14.60 g (81% over two steps) of 4.40 as a light yellow oil; IR (neat, cm$^{-1}$) 2934, 2859, 1721, 1451, 1275, 1116, 711; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.07-8.03 (m, 2 H), 7.59-7.53 (m, 1 H), 7.47-7.41 (m, 2 H), 5.16 (s, 1 H), 4.96 (s, 1 H), 4.32 (t, $J = 6.64$ Hz, 2 H), 3.97 (s, 2 H), 2.25-2.20 (m, 2 H), 1.83-1.74 (m, 2 H), 1.56-1.35 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.4, 145.3, 132.6 (2C), 130.3, 129.4, 128.2 (2C), 114.8, 64.8, 36.7, 33.0, 28.7, 28.5, 27.0, 25.7.

**Preparation of 4.28**

To a stirred solution of 4.40 (10.0 g, 30.77 mmol) in acetone (50 mL) was added NaI (6.92 g, 46.15 mmol) at rt. The resulting cloudy solution was stirred under dark for 24 h before it was quenched with H$_2$O (50 mL). The resulting solution was extracted with Et$_2$O (3 x 100 mL). The combined organic layers were evaporated under vacuum to give 11.0 g of crude 4.28 as an orange oil; IR (neat, cm$^{-1}$) 3063, 2934, 2856, 1716, 1451, 1271, 1115; $^1$H NMR (250 MHz, CDCl$_3$) δ 8.08-8.04 (m, 2 H), 7.57-7.54 (m, 1 H), 7.48-7.42 (m, 2 H), 5.24 (s, 1 H), 4.92 (s, 1 H), 4.34 (t, $J = 6.61$ Hz, 2 H), 3.94 (s, 2 H), 2.27-2.24 (m, 2 H), 1.80-1.78 (m, 2 H), 1.55-1.43 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.0,
145.9, 132.4 (2C), 130.1, 129.1, 128.0 (2C), 113.1, 64.6, 33.5, 28.5, 28.3, 26.8, 25.5;
HRMS ES m/z (M + Na)+ calcd 395.0478, obsd 395.0475.

**Preparation of 4.41**

To a mixture of alcohol 4.21 (0.25 g, 0.46 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (0.26 g, 1.38 mmol) and DMAP (0.06 g, 0.46 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added a solution of 4.20 (0.18 g, 0.46 mmol) in dry CH$_2$Cl$_2$ (3 mL) via cannula. The resulting mixture was stirred at rt for 24 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether:ethyl acetate) to give 0.30 g (70%) of 4.41 as colorless oil; IR (neat, cm$^{-1}$) 3072, 2929, 2858, 1714, 1613, 1514, 1251, 1110; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66-7.63 (m, 4 H), 7.44-7.34 (m, 6 H), 7.26-7.22 (m, 2 H), 6.89-6.84 (m, 2 H), 6.57 (s, 1 H), 4.71 (s, 2 H), 4.55-4.16 (m, 6 H), 4.08-4.02 (m, 1 H), 3.80 (s, 3 H), 3.71-3.68 (m, 2 H), 3.58-3.47 (m, 6 H), 3.40 (s, 3 H), 3.09-2.98 (m, 1 H), 2.61-2.56 (m, 2 H), 2.28-2.23 (m, 1 H), 2.14-2.11 (m, 2 H), 1.99-1.95 (m, 1 H), 1.69-1.54 (m, 4 H), 1.34-1.26 (m, 4 H), 1.12 (s, 3 H), 1.05 (s, 9 H), 0.88 (s, 9 H), 0.05-0.04 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.3, 158.9, 148.9, 140.7, 138.3, 135.7, 135.6 (4C), 133.48, 133.40, 130.8, 129.52, 129.49, 129.1 (2C), 127.5 (4C), 113.6 (2C), 95.3, 83.7, 71.7, 70.4, 67.7, 67.1, 66.5, 58.9, 58.2, 55.1, 52.1, 43.6, 33.7, 32.8, 30.6, 30.2, 29.5, 27.9, 26.7 (3C), 26.3, 26.1, 25.8 (3C), 22.7, 19.2, 18.1, -5.5 (2C); HRMS ES m/z (M + Na)$^+$ calcd 951.5233, obsd 951.5210.
Preparation of 4.42

To a stirred solution of 4.41 (0.57 g, 0.61 mmol) in a 1:1 mixture of CH₂Cl₂:MeOH (10 mL each) at 0 °C was added CSA (0.14 g, 0.61 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with a saturated NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The organic layers were combined, dried over MgSO₄, filtered, and evaporated to obtain a colorless oil. The crude oil was purified by column chromatography on silica gel (elution with 1:1 petroleum ether:ether) to afford 0.46 g (92%) of 4.42 as a colorless oil; [α]₂⁰_D = -24.5 (c = 1.08, CHCl₃); IR (neat, cm⁻¹) 3482, 2930, 2857, 1714, 1613, 1514, 1249, 1112; ¹H NMR (300 MHz, CDCl₃) δ 7.65-7.61 (m, 4 H), 7.44-7.34 (m, 6 H), 7.26-7.23 (m, 2 H), 6.91-6.83 (m, 2 H), 6.60-6.59 (m, 1 H), 4.70 (s, 2 H), 4.55-4.51 (m, 1 H), 4.41-4.16 (m, 6 H), 3.79 (s, 3 H), 3.70-3.66 (m, 2 H), 3.57-3.48 (m, 6 H), 3.39 (s, 3 H), 3.08-2.92 (m, 1 H), 2.61-2.56 (m, 2 H), 2.27-2.26 (m, 1 H), 2.20-2.15 (m, 2 H), 2.00-1.96 (m, 1 H), 1.66-1.55 (m, 4 H), 1.44-1.26 (m, 3 H), 1.26 (s, 3 H), 1.06 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.3, 159.1, 149.5, 142.3, 138.6 (2C), 135.5 (2C), 133.5, 130.8, 129.5 (4C), 129.2 (4C), 127.6 (2C), 113.7 (2C), 95.4, 83.4, 71.8, 70.6, 70.4, 67.7, 67.3, 66.7, 58.9, 57.7, 55.2, 52.2, 43.5, 33.7, 32.8, 30.6, 29.6, 27.7, 26.8 (3C), 26.0, 25.7, 22.7, 19.3 (2C); HRMS ES m/z (M + Na)⁺ calcd 837.4368, obsd 837.4348.

Preparation of 4.43

To a solution of 4.42 (30 mg, 0.036 mmol) in dry CH₂Cl₂ (1 mL) was added freshly distilled Et₃N (0.01 mL, 0.074 mmol) followed by MsCl (6 µL, 0.074 mmol) at 0 °C under N₂. The mixture was stirred at 0 °C for 30 min and quenched with aqueous 1N
HCl solution (2 mL) followed by H₂O (1 mL). The organic layer was separated and the aqueous phase was washed with CH₂Cl₂ (2 x 5 mL). The CH₂Cl₂ layers were combined, dried over anhydrous MgSO₄, filtered, and concentrated under vacuum to obtain the allyl mesylate as a yellow oil.

This crude oil was dissolved in dry THF (2 mL) and anhydrous LiBr (5 mg, 0.06 mmol) was added at rt. The mixture was stirred at rt for 1.5 h and filtered through a pad of silica, where the pad was further washed with ether (50 mL). The filtrate was concentrated under vacuum to afford a yellow oil, which was purified by column chromatography on silica gel (elution with 3:1 petroleum ether:ethyl acetate) to get 27 mg (86%) of bromide 4.43 as a colorless liquid; [α]²⁰_D = -47.0 (c = 0.83, CHCl₃); IR (neat, cm⁻¹) 2932, 1711, 1658, 1513, 1249, 1112; ¹H NMR (300 MHz, CDCl₃) δ 7.66-7.61 (m, 4 H), 7.45-7.34 (m, 6 H), 7.27-7.23 (m, 2 H), 6.89-6.84 (m, 2 H), 6.63-6.62 (m, 1 H), 4.71 (s, 2 H), 4.55-4.51 (m, 1 H), 4.43-4.34 (m, 2 H), 4.27-4.14 (m, 3 H), 4.05-4.02 (m, 1 H), 3.80 (s, 3 H), 3.71-3.68 (m, 2 H), 3.58-3.48 (m, 6 H), 3.39 (s, 3 H), 3.15-3.08 (m, 1 H), 2.63-2.57 (m, 2 H), 2.37-2.33 (m, 1 H), 2.21-2.18 (m, 2 H), 2.04-1.95 (m, 1 H), 1.68-1.54 (m, 4 H), 1.40-1.32 (m, 4 H), 1.12 (s, 3 H), 1.05 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.3, 159.2, 149.8, 146.1, 135.7 (2C), 135.6, 133.6 (2C), 130.6, 129.6 (4C), 129.3 (4C), 127.6 (2C), 113.8 (2C), 95.5, 82.9, 71.8, 70.8, 70.5, 67.8, 66.7, 66.6, 59.0, 55.3, 52.3, 42.7, 38.9, 33.7, 32.5, 30.7, 29.7, 27.7, 26.9 (3C), 26.8, 26.4, 26.2, 22.8, 19.4; HRMS ES m/z (M + Na)⁺ calcd 899.3524, obsd 899.3547.
**Preparation of compound 5.7**

To a stirred solution of optically active hydroxyester 5.6 (4.7 g, 27.33 mmol) in dry CH$_2$Cl$_2$ (100 mL) was added Et$_3$N (6.91 g, 68.33 mmol) followed by MsCl (6.26 g, 54.66 mmol) at 0 °C. Stirring was continued at 0 °C for 45 min prior to quenching with 10% HCl solution (20 mL) and dilution with H$_2$O (200 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to obtain a yellow oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to give the mesylate as a colorless oil.

To a stirred solution of the above mesylate in dry CH$_2$Cl$_2$ (100 mL) was added Dibal-H (69 mL of 1.0 M solution in hexane, 68.33 mmol) at –78 °C under N$_2$. After being stirred at –78 °C for 1 h, the solution was slowly warmed to 0 °C before it was carefully quenched with a saturated solution of Na-K-tartrate (20 mL) followed by H$_2$O (100 mL). The resulting suspension was stirred at rt overnight. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 2:1 hexane:ethyl acetate) to afford the primary alcohol as a colorless oil.

To a solution of above alcohol in dry DMF (10 mL) was added imidazole (4.60 g, 67.56 mmol) and TBDPSCl (7.43 g, 27.02 mmol). The resulting solution was then heated to 50 °C for 1.5 h, cooled to rt, and diluted with H$_2$O (100 mL). The aqueous layer was extracted with ether (4 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated under vacuum to obtain an oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to afford the desired product.
chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to afford 9.14 g (75% over 3 steps) of 5.7 as a colorless oil; [α]_{D}^{25} = +19.5 (c 0.64, CHCl₃); IR (neat, cm⁻¹) 3048, 2964, 2860, 1590, 1472, 1428, 1360, 1177, 1113, 957; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.62 (m, 4 H), 7.47-7.36 (m, 6 H), 5.0 (t, J = 5.41 Hz, 1 H), 3.45-3.36 (m, 2 H), 2.92 (s, 3 H), 2.09-1.44 (m, 6 H), 1.08 (s, 9 H), 1.03 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.7 (4 C), 133.2 (2 C), 129.8 (2 C), 127.7 (4 C), 86.2, 68.4, 47.8, 38.0, 33.0, 31.5, 26.9 (3 C), 20.4, 18.4, 15.3; HRMS ES m/z (M + Na)⁺ calcd 469.1839, obsd 469.1854.

Preparation of compound 5.8

To a stirred solution of compound 5.7 (6.36 g, 14.24 mmol) in dry DMF (50 mL) was added DBU (10.84 g, 71.19 mmol). The resulting solution was then heated to 100 °C for 2 d, cooled to room temperature, and diluted with H₂O (500 mL). The aqueous layer was extracted with ether (5 x 300 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave a brown oil, which was purified by column chromatography on silica gel (elution with hexane) to yield 4.3 g (86%) of 5.8 as a colorless oil; [α]_{D}^{25} = -36.64 (c 0.11, CHCl₃); IR (neat, cm⁻¹) 3048, 2964, 1590, 1472, 1428, 1360; ¹H NMR (300 MHz, CDCl₃) δ 7.69-7.65 (m, 4 H), 7.42-7.34 (m, 6 H), 5.70-5.67 (m, 1 H), 5.58-5.54 (m, 1 H), 3.48-3.41 (m, 2 H), 2.37-2.30 (m, 2 H), 1.91-1.82 (m, 1 H), 1.57-1.47 (m, 1 H), 1.11 (s, 3 H), 1.06 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 137.8, 135.7 (4 C), 133.2 (2 C), 130.1, 129.4 (2 C), 127.5 (4 C), 71.2, 51.3, 33.8, 31.8, 26.9 (3 C), 23.7, 19.4; HRMS ES m/z (M + Na)⁺ calcd 373.1958, obsd 373.1935.
Preparation of compound 5.9

Ozone was purged through a solution of 5.9 (4.16 g, 11.89 mmol) in 1:1 mixture of CH₂Cl₂:MeOH (50mL of each) at –78 °C. After the reaction was complete, PPh₃ (4.1 g, 15.45 mmol) was added and the reaction mixture was stirred at rt for 6 h. The reaction mixture was then cooled to 0 °C and NaBH₄ (1.35 g, 35.67 mmol) was added in portions. The resulting mixture was stirred at 0 °C for 0.5 h before being quenched carefully with 10% HCl solution (50 mL). The solution was further diluted with H₂O (100 mL) and the resultant solution was extracted with CH₂Cl₂ (4 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave a brown oil, which was purified by column chromatography on silica gel (elution with 3:2 hexane:ethyl acetate) to afford 4.4 g (96%) of 5.9 as a colorless gel; [α]²⁵D = +8.47 (c 0.59, CHCl₃); IR (neat, cm⁻¹) 3372, 2931, 1112; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.64 (m, 4 H), 7.48-7.37 (m, 6 H), 3.64-3.47 (m, 6 H), 1.50-1.27 (m, 4 H), 1.07 (s, 9 H), 0.80 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 135.6 (4 C), 132.9 (2 C), 129.8 (2 C), 127.8 (2 C), 70.7, 69.2, 63.4, 39.2, 29.6, 26.8 (3 C), 26.4, 19.2, 18.5; HRMS ES m/z (M + Na)⁺ calcd 409.2169 obsd 409.2152.

Preparation of compound 5.10

To a cold (-10 °C), stirred solution of diol 5.9 (0.3 g, 0.78 mmol) and pyridine (0.12 g, 1.56 mmol) in dry CH₂Cl₂ (5 mL) was added PivCl (0.11 g, 0.94 mmol) under N₂. Stirring was continued at –10 °C for 24 h before it was quenched with 10% aqueous HCl solution (1.0 mL), and stirring was continued for another 0.5 h at rt. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The
combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to obtain an oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to afford the mono-pivaloyl ester as a colorless oil.

To a cold (-78 °C), stirred solution of the above alcohol in dry CH₂Cl₂ (5 mL) were added 2,6-lutidine (0.25 g, 2.34 mmol) and TBSOTf (0.27 g, 1.01 mmol) under N₂. The mixture was stirred at –78 °C for another 1 h before being quenched with a saturated aqueous solution of CuSO₄ (10 mL). The resulting solution was stirred at rt for another 1 h. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to afford the desired compound as a colorless oil.

To a cold (-78 °C) solution of above compound in CH₂Cl₂ (10 mL) was added Dibal-H (2.34 mL of 1.0 M in hexane, 2.34 mmol) under N₂. The solution was stirred at –78 °C for 45 min before it was slowly warmed to 0 °C when it was carefully quenched with a saturated aqueous solution of K-Na-tartrate (1 mL) followed by H₂O (20 mL). Stirring was continued at rt overnight. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to obtain 0.28 g (71% over three steps) of 5.10 as a colorless oil; [α]²⁵_D = +3.82 (c 0.55, CHCl₃); IR (neat, cm⁻¹) 3325, 3072, 2932, 2859, 1428, 1251, 1117; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.64 (m, 4 H), 7.45-7.34 (m, 6 H), 3.57-3.54 (m, 2 H), 3.49-3.40 (m, 4 H), 1.29-1.19 (m, 4 H), 1.06 (s, 9 H), 0.88 (s, 9 H), 0.82 (s, 3 H), 0.03 (s, 6 H); ¹³C NMR (75 MHz,
Preparation of compound 5.11

To a cold (0 °C), stirred solution of 5.10 (0.42 g, 0.84 mmol) in dry CH₂Cl₂ (5 mL) were added Et₃N (0.17 g, 1.68 mmol) and TsCl (0.32 g, 1.68 mmol). The mixture was slowly warmed to rt and stirred for 5 h before being quenched by a saturated aqueous solution of NH₄Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to obtain 0.52 g (95%) of 5.11 as a colorless oil; [α]_{25} = +4.32 (c 0.44, CHCl₃); IR (neat, cm⁻¹) 3072, 2933, 2858, 1472, 1178, 1099, 835; ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.75 (m, 2 H), 7.64-7.60 (m, 4 H), 7.45-7.29 (m, 8 H), 3.97-3.93 (m, 2 H), 3.36-3.33 (m, 4 H), 2.42 (s, 3 H), 1.63-1.48 (m, 2 H), 1.26-1.17 (m, 2 H), 1.06 (s, 9 H), 0.86 (s, 9 H), 0.75 (s, 3 H), -0.01 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 144.5, 135.6 (2C), 133.7 (2C), 133.3, 129.7 (4C), 129.5 (2C), 127.9 (2C), 127.6 (4C), 71.4, 67.2, 66.5, 40.0, 29.6, 26.9 (3C), 25.9 (3C), 23.2, 21.6, 19.3, 18.5, 18.2, -5.6 (2C); HRMS ES m/z (M + Na)⁺ calcd 677.3123, obsd 677.3147.
**Preparation of compound 5.15**

To a cold (0 °C), stirred solution of diol 5.9 (1.40 g, 3.62 mmol) and Et₃N (0.73 g, 7.24 mmol) in dry CH₂Cl₂ (15 mL) was added TsCl (0.90 g, 4.71 mmol) under N₂. Stirring was continued at 0 °C for 36 h before it was quenched with 10% aqueous HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 3:1 hexane:ethyl acetate) to afford mono-tosylate as a colorless liquid.

To a stirred solution of above compound in dry CH₂Cl₂ (15 mL) was added pyridine (0.57 g, 7.24 mmol) and PivCl (0.65 g, 5.43 mmol) at 0 °C under N₂. The reaction mixture was slowly warmed to rt and the stirring was continued for 24 h. The reaction mixture was quenched with 10% aqueous HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to afford 1.63 g (2.61 mmol, 72% over two steps) of 5.15 as colorless oil; [α]²⁵_D = +3.83 (c 1.07, CHCl₃); IR (neat, cm⁻¹) 3070, 2935, 1731, 1472, 1178, 1099, 835; ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.74 (m, 2 H), 7.62-7.59 (m, 4 H), 7.45-7.30 (m, 8 H), 3.98-3.92 (m, 4 H), 3.36 (s, 2 H), 2.43 (s, 3 H), 1.59-1.49 (m, 3 H), 1.31-1.19 (m, 1 H), 1.13 (s, 9 H), 1.04 (s, 9 H), 0.83 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 177.9, 144.5, 135.4 (4 C), 133.03 (2 C), 132.9, 129.7 (4 C), 127.7 (4 C), 127.5
HRMS ES m/z (M + Na)+ calcd 647.2833, obsd 647.2826.

Preparation of compound 5.16

To a stirred solution of Ph₂Se₂ (0.42 g, 1.36 mmol) in absolute ethanol (5 mL) was added NaBH₄ (0.10 g, 2.72 mmol) at 0 °C. The yellow solution turned colorless after 15 min of stirring at 0 °C. At this point, a solution of 5.15 (0.57 g, 0.91 mmol) in dry THF (4 mL) was added via cannula. The mixture was stirred at rt for 10 h before being quenched with a saturated aqueous solution of NaHCO₃ (20 mL). It was diluted with Et₂O (20 mL) and the organic layer was separated. The aqueous layer was extracted with Et₂O (5 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave a yellow oil, which was purified by flash chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to obtain a yellow oil.

Ozone was passed through a cold (-78 °C) solution of the above oil in dry CH₂Cl₂ (10 mL). After reaction was complete, the mixture was slowly warmed to rt and then heated under reflux for 3 h. Solvent was evaporated under vacuum and the crude oil was purified by column chromatography on silica gel (elution with 25:1 hexane:ether) to afford 0.29 g (70% over three steps) of 5.16 as a yellow oil; [α]$_{25}^{20}$ = +4.12 (c 0.85, CHCl₃); IR (neat, cm$^{-1}$) 3072, 2961, 2859, 1732, 1473, 1428, 1160, 1112, 826, 703; $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.67-7.64 (m, 4 H), 7.46-7.35 (m, 6 H), 5.81-5.67 (m, 1 H), 5.05-4.99 (m, 2 H), 4.03-3.94 (m, 2 H), 3.47-3.40 (m, 2 H), 2.13-2.10 (d, $J = 7.52$ Hz, 2 H), 1.16 (s, 9 H), 1.06 (s, 9 H), 0.85 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 178.1, 135.6

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(4 C), 133.6, 133.03 (2 C), 129.6 (2 C), 127.6 (4 C), 117.9, 67.4 (2 C), 39.4, 38.8, 27.1 (3 C), 26.8 (3 C), 19.3 (2 C), 18.7; HRMS ES \( m/\ell \) (M + Na)\(^+\) calcd 475.2639, obsd 475.2631.

**Preparation of compound 5.13**

To a stirred solution of 5.16 (0.81 g, 1.79 mmol) in dry CH\(_2\)Cl\(_2\) (15 mL) was added Dibal-H (5.4 mL of 1.0 M solution in hexane, 5.37 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 1.5 h before it was quenched with K-Na-tartrate solution (5 mL) followed by the addition of H\(_2\)O (20 mL). The mixture was slowly warmed to rt and stirring was continued overnight. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and evaporated to leave an oil, which was purified by flash chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to yield the primary alcohol as a colorless liquid.

To a cold (–78 °C) solution of above liquid in dry CH\(_2\)Cl\(_2\) (5 mL) were added 2,6-lutidine (0.96 g, 8.95 mmol) and TBSOTf (1.42 g, 5.37 mmol). Stirring was continued for 1 h at –78 °C before being quenched with 10% aqueous HCl solution (10 mL). The mixture was warmed to rt and stirred for an additional 0.5 h at rt. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and evaporated to leave an oil, which was purified by column chromatography on silica gel (elution with hexane) to get 0.83 g (1.72 mmol, 96% over two steps) of 5.13 as a colorless oil; \([\alpha]^{25}_D = +1.82\) (c 0.77, CHCl\(_3\)); IR (neat, cm\(^{-1}\)) 3073, 2957, 2931, 2895, 2858, 1640, 1472, 1112, 836, 701; \(^1\)H
NMR (300 MHz, CDCl$_3$) $\delta$ 7.68-7.65 (m, 4 H), 7.44-7.35 (m, 6 H), 5.82-5.68 (m, 1 H), 5.05-4.99 (m, 2 H), 3.46-3.38 (m, 4 H), 2.05-2.00 (m, 2 H), 1.06 (s, 9 H), 0.87 (s, 9 H), 0.81 (s, 3 H), 0.02 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.7 (4 C), 134.9, 133.8 (2 C), 129.5 (2 C), 127.5 (4 C), 117.1, 67.4, 66.4, 40.8, 38.4, 26.9 (3 C), 25.9 (3 C), 19.4, 18.6, 18.3, -5.5 (2 C); HRMS ES $m/z$ (M + Na)$^+$ calcd 505.2929, obsd 505.2925.

**Preparation of compound 5.17**

Ozone was passed through a stirred solution of 5.13 (0.83 g, 1.72 mmol) in dry CH$_2$Cl$_2$ (10 mL) at –78 °C. After the reaction was complete, PPh$_3$ (0.54 g, 2.06 mmol) was added and the mixture was warmed up to rt. Stirring was continued at rt for 6 h before the solvent was evaporated and the crude solid was purified by flash chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to leave the intermediate aldehyde as a colorless oil.

The aldehyde obtained above was dissolved in t-BuOH (8 mL) followed by the addition of 2-methyl-2-butene (1.21 g, 17.2 mmol) at rt. To this solution was added a mixture of NaClO$_2$ (0.16 g, 6.88 mmol) and NaH$_2$PO$_4$·H$_2$O (0.71 g, 5.16 mmol) in H$_2$O (8 mL) at rt. The cloudy yellow solution was stirred at rt for 2 h before it was quenched with 10% aqueous HCl solution (10 mL). The layer was extracted with ethyl acetate (5 x 25 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated under vacuum to obtain the carboxylic acid as yellow oil.

The crude carboxylic acid obtained above was dissolved in dry DMF (4.5 mL) followed by the addition of MeI (2.44 g, 17.2 mmol) and K$_2$CO$_3$ (1.2 g, 8.6 mmol). The mixture was stirred at rt for 12 h and diluted with H$_2$O (25 mL) and Et$_2$O (10 mL). The
organic layer was separated and the aqueous layer was extracted with Et₂O (5 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to leave an oil, which was purified by column chromatography on silica gel (elution with 20:1 hexane:ethyl acetate) to afford 0.70 g (1.35 mmol, 78% over three steps) of 5.17 as a colorless oil; [α]²⁵_D = -1.2 (c 3.5, CHCl₃); IR (neat, cm⁻¹) 2957, 2857, 1738, 1428, 1113, 836, 701; ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.64 (m, 4 H), 7.45-7.34 (m, 6 H), 3.59 (s, 3 H), 3.57-3.48 (m, 4 H), 2.40-2.29 (m, 2 H), 1.05 (s, 9 H), 0.95 (3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 135.6 (4 C), 133.6 (2 C), 129.5 (2 C), 127.6 (4 C), 67.2, 66.3, 51.1, 40.6, 38.1, 26.8 (3 C), 25.9 (3 C), 19.4, 18.6, 18.3, -5.6 (2 C); HRMS ES m/z (M + Na)⁺ calcd 537.2827, obsd 537.2836.

Preparation of compound 5.4

To a cold (−78 °C), stirred solution of (EtO)₂P(O)Et (0.67 g, 4.05 mmol) in dry THF (15 mL) was added n-BuLi (2.53 mL of 1.6 M solution in hexane, 4.05 mmol) under N₂. After 30 min of stirring at −78 °C, a solution of 5.17 (0.70 g, 1.35 mmol) in dry THF (15 mL) was added via cannula at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was warmed to 0 °C and stirring was continued at 0 °C for 0.5 h prior to quenching with saturated NH₄Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 2:1 hexane:ethyl acetate) to afford 0.81 g (1.24 mmol, 92%) of 5.4 as a colorless oil as 1:1 diastereomeric mixture; IR (neat, cm⁻¹) 3447, 3072, 2950, 2740, 1712; ¹H NMR (300
MHz, CDCl₃) δ 7.66-7.61 (m, 4 H), 7.44-7.34 (m, 6 H), 4.11-4.04 (m, 4 H), 3.59-3.42 (m, 4 H), 3.30-3.20 (m, 1 H), 2.76-2.53 (m, 2 H), 1.32-1.20 (m, 9 H), 1.05-1.04 (m, 9 H), 0.98-0.95 (m, 3 H), 0.87-0.84 (m, 9 H), 0.01 -0.02 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 205.3, 135.4 (4 C), 133.4 (2 C), 129.4 (2 C), 127.4 (4 C), 67.5, 66.5, 62.2 (2 C), 48.5, 46.7, 45.9, 41.1, 26.7 (3 C), 25.7 (3 C), 19.2, 18.4, 18.1, 16.2, 10.7, -5.7 (2 C); HRMS ES m/z (M + Na)+ calcd 671.3323, obsd 671.3331.

**Preparation of compound 5.20**

To a stirred suspension of (-)-DET (67 mg, 0.33 mmol) and 4 Å MS (1.40 g) in dry CH₂Cl₂ (30 mL) was added Ti(O-i-Pr)₄ (77 mg, 0.27 mmol) at –20 °C under N₂. Stirring was continued for 15 min at –20 °C before a solution of 5.19 (1.0 g, 2.71 mmol) in dry CH₂Cl₂ (20 mL) was added via cannula. The resulting solution was stirred at –20 °C for another 1.5 h before t-BuOOH (3.13 mL of 2.6 M solution in CH₂Cl₂, 8.14 mmol) was added via syringe under N₂. Stirring was continued at –20 °C for 6 h before the reaction mixture was quenched with Me₂S (0.8 mL, 10.84 mmol). The mixture was stirred at –20 °C for 1 h before it was filtered through a pad of silica and the solid was washed with CH₂Cl₂ (100 mL). The filtrate was stirred with 2.7 mL of 30% (w/v) NaOH saturated with NaCl for 1 h at 0 °C. The solution was diluted with H₂O (100 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 3:1 hexane:ethyl acetate) to afford 0.9 g (86%) of 5.20 as colorless oil; [α]²⁵_D = +10.8 (c 0.76, CHCl₃); IR (neat, cm⁻¹) 3433, 3071, 2932, 2858, 1590, 1428, 1390, 1111;
$^1$H NMR (300 MHz, CDCl$_3$) δ 7.68-7.64 (m, 4 H), 7.44-7.35 (m, 6 H), 3.84-3.79 (m, 1 H), 3.57-3.49 (m, 3 H), 2.96-2.92 (m, 1 H), 2.85-2.82 (m, 1 H), 1.91-1.86 (m, 1 H), 1.80-1.72 (m, 1 H), 1.47-1.38 (m, 1 H), 1.08-0.98 (m, 12 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 135.5 (2 C), 133.7 (2 C), 129.6 (4 C), 127.6 (4 C), 68.2, 61.6, 58.4, 54.9, 35.3, 34.2, 26.8 (3 C), 19.2, 17.2; HRMS ES m/z (M + Na)$^+$ calcd 407.2013, obsd 407.2014.

Preparation of compound 5.21

To a stirred solution of 5.20 (0.9 g, 2.34 mmol) in THF (7 mL) were added PPh$_3$ (0.80 g, 3.04 mmol), imidazole (0.48 g, 7.02 mmol), and I$_2$ (0.83 g, 3.28 mmol) in sequence at 0 °C. The resultant dark red solution was stirred at 0 °C for 1 h before being quenched by a saturated aqueous solution of Na$_2$S$_2$O$_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated under vacuum to leave an oil, which was purified by column chromatography on silica gel (elution with 15:1 hexane:ethyl acetate) to afford the epoxy iodide as an intermediate.

To a stirred solution of the above iodide in dry THF (15 mL) was added n-BuLi (1.8 mL of 1.6 M solution in hexane, 2.81 mmol) dropwise at −78 °C under N$_2$. The resulting solution was stirred at −78 °C for 1 h before it was slowly warmed to −10 °C. The reaction mixture was quenched by a saturated aqueous solution of NH$_4$Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave an oil, which was purified by column chromatography on silica gel (elution with 5:1 hexane:ethyl acetate) to obtain the 0.81 g (94% over 2 steps) of allylic alcohol; [$\alpha$]$^\text{D}$
= -7.06 (c 0.51, CHCl₃); IR (neat, cm⁻¹) 3374, 3070, 2956, 1590, 1462, 1390, 1112; ¹H NMR (300 MHz, CDCl₃) δ 7.69-7.65 (m, 4 H), 7.46-7.26 (m, 6 H), 5.91-5.80 (m, 1 H), 5.27-5.20 (m, 1 H), 5.12-5.08 (m, 1 H), 4.23-4.19 (m, 1 H), 3.73-3.47 (m, 2 H), 2.27 (d, J = 4.4 Hz, 1 H), 1.88-1.84 (m, 1 H), 1.72-1.63 (m, 1 H), 1.58-1.43 (m, 1 H), 1.06 (s, 9 H), 0.92 (d, J = 6.83 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 141.3, 135.6 (2 C), 133.5 (2 C), 129.6 (4 C), 127.6 (4 C), 114.4, 71.1, 68.9, 41.4, 32.1, 26.8 (3 C), 19.2, 17.5; HRMS ES m/z (M + Na)⁺ calcd 391.2064, obsd 391.2078.

**Preparation of compound 5.22**

To a stirred solution of 5.21 (0.87 g, 2.36 mmol) in dry THF (10 mL) was added NaHMDS (3.54 mL of 1.0 M solution in THF, 3.54 mmol) dropwise at 0 °C under N₂. The resultant solution was stirred at 0 °C for 0.5 h before a solution of PMBBBr (0.85 g, 4.25 mmol) in dry THF (2 mL) was added via cannula followed by the addition of catalytic amount of n-Bu₄NI (50 mg). The reaction mixture was stirred at rt overnight before being quenched by a saturated solution of NH₄Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 25:1 hexane:ethyl acetate) to obtain the PMB ether.

To a solution of the above PMB ether in dry THF (10 mL) was added TBAF (4.72 mL of 1.0 M solution in THF, 4.72 mmol) at rt and the resultant solution was stirred for 8 h at rt. The solvent was evaporated and the crude red oil was purified by column
chromatography on silica gel (elution with 3:1 hexane:ethyl acetate) to afford the primary alcohol as a colorless oil.

To a solution of the above alcohol in dry THF (10 mL) were added PPh$_3$ (0.87 g, 3.30 mmol), imidazole (0.48 g, 7.08 mmol), and I$_2$ (0.90 g, 3.54 mmol) in sequence at 0 °C. The resultant dark red solution was stirred at 0 °C for 1 h before it was quenched with a saturated solution of Na$_2$S$_2$O$_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave an oil which was purified by column chromatography on silica gel (elution with 30:1 hexane:ethyl acetate) to afford 0.75 g (88% over 3 steps) of 5.22 as a colorless oil; [$\alpha$]$^\text{D}_{25} = +56.2$ (c 1.6, CHCl$_3$); IR (neat, cm$^{-1}$) 2958, 2932, 2868, 1615, 1514, 1457, 1248, 1037; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.26-7.22 (m, 2 H), 6.91-6.86 (m, 2 H), 5.77-5.66 (m, 1 H), 5.26-5.11 (m, 2 H), 4.53 (d, $J = 11.5$ Hz, 1 H), 4.25 (d, $J = 11.5$ Hz, 3.81 (s, 3 H), 3.78-3.71 (m, 1 H), 3.21-3.03 (m, 2 H), 1.66-1.43 (m, 3 H), 0.96 (d, $J = 8.74$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.1, 138.7, 130.4, 129.3 (2 C), 117.3, 113.8 (2 C), 77.5, 69.6, 55.2, 42.0, 30.5, 21.2, 17.7; HRMS ES $m/z$ (M + Na)$^+$ calcd 383.0478, obsd 383.0479.

**Preparation of compound 5.23**

To a solution of 5.22 (1.18 g, 3.28 mmol) and 18-C-6:CH$_3$CN complex (1.51 g, 4.92 mmol) in dry CH$_3$CN (10 mL) was added KCN (0.32 g, 4.92 mmol). The resultant solution was heated to 80 °C for 2 h. It was cooled to rt, diluted with H$_2$O (100 mL), extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave a yellow oil, which was purified by column
chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to afford the intermediate cyanide as a colorless oil.

To a solution of the above cyanide in dry CH₂Cl₂ (10 mL) was added Dibal-H (8.2 mL of 1.0 M solution in hexane, 8.2 mmol) slowly over 10 min at –78 °C under N₂. After the addition was complete, the reaction mixture was stirred at –78 °C for 5 h before being quenched with a saturated aqueous solution of K-Na-tartrate (2 mL) followed by H₂O (20 mL). The resultant suspension was stirred at rt overnight. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated to obtain a yellow oil, which was purified by column chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to afford 0.76 g of 5.23 (88% over 2 steps) as a colorless oil; [α]²⁵

Preparation of compound 5.24

To a stirred solution of 5.23 (0.41 g, 1.56 mmol) in CH₂ClCH₂Cl (45 mL) were added paraformaldehyde (0.47 g, 15.6 mmol) and Et₂NH·HCl (0.64 g, 7.81 mmol) at rt. The resulting suspension was heated to 75 °C overnight under N₂. The reaction mixture
was cooled to rt, and filtered through a pad of silica. The solid was washed with CH$_2$Cl$_2$
(3 x 30 mL). The combined filtrates were evaporated under vacuum to leave an oil which
was purified by column chromatography on silica gel (elution with 12:1 hexane:ethyl acetate) to afford 0.39 g (91%) of **5.24** as a colorless oil; $[\alpha]^{25}_D = +35.87$ (c 1.67, CHCl$_3$);
IR (neat, cm$^{-1}$) 2961, 2837, 1693, 1613, 1248, 1036; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.73
(s, 1 H), 7.26-7.21 (m, 2 H), 6.88-6.84 (m, 2 H), 6.38 (s, 1 H), 5.93 (s, 1 H), 5.77-5.65
(m, 1 H), 5.30-5.14 (m, 2 H), 4.47 (d, $J = 11.2$ Hz, 1 H), 4.19 (d, $J = 11.2$ Hz, 1 H), 3.80
(s, 3 H), 3.69-3.62 (m, 1 H), 2.96-2.84 (m, 1 H), 1.55 (t, $J = 8.6$ Hz, 2 H), 1.04 (d, $J = 9.8$
Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.3, 159.0, 154.8, 138.7, 133.3, 130.6, 129.4
(2C), 117.2, 113.7 (2C), 78.4, 69.7, 55.2, 40.9, 28.6, 20.1; HRMS ES $m/z$ (M + Na)$^+$
calcd 297.1461, obsd 297.1455.

*Preparation of compound 5.25*

To a mixture of **5.24** (0.42 g, 1.55 mmol) and CeCl$_3$$\cdot$7H$_2$O (0.58 g, 1.55 mmol) in
anhydrous MeOH (10 mL) was added NaBH$_4$ (58 mg, 1.55 mmol) in portions at 0 °C.
After being stirred at 0 °C for 1 h, the reaction mixture was quenched with a saturated
solution of NH$_4$Cl (20 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 mL).
The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave a
residue, which was purified by column chromatography on silica gel (elution with 4:1
hexane:ethyl acetate) to afford 0.38 g (89%) of the allylic alcohol as colorless oil; $[\alpha]^{25}_D$
= +40.52 (c 0.58, CHCl$_3$); IR (neat, cm$^{-1}$) 3406, 2957, 2932, 2872, 1613, 1514, 1248,
1036; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.26-7.22 (m, 2 H), 6.89-6.84 (m, 2 H), 5.80-5.68
(m, 1 H), 5.24-5.18 (m, 2 H), 5.06-5.04 (m, 1 H), 4.87-4.86 (m, 1 H), 4.48 (d, $J = 11.3$
Hz, 3 H), 3.80 (s, 3 H), 3.69-3.62 (m, 1 H), 2.96-2.84 (m, 1 H), 1.55 (t, $J = 8.6$ Hz, 2 H), 1.04 (d, $J = 9.8$
Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 194.3, 159.0, 154.8, 138.7, 133.3, 130.6, 129.4
(2C), 117.2, 113.7 (2C), 78.4, 69.7, 55.2, 40.9, 28.6, 20.1; HRMS ES $m/z$ (M + Na)$^+$
calcd 297.1461, obsd 297.1455.
Hz, 1 H), 4.19 (d, J = 11.1 Hz, 1 H), 4.05-4.04 (m, 2 H), 3.80-3.72 (m, 4 H), 2.49-2.37 (m, 1 H), 1.75-1.58 (m, 3 H), 1.05 (d, J = 7.03 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.0, 153.3, 138.9, 130.5, 129.4 (2 C), 116.8, 113.7 (2 C), 108.4, 78.5, 69.8, 64.4, 55.1, 41.6, 33.1, 20.8; HRMS ES m/z (M + Na)$^+$ calcd 299.1618, obsd 299.1629.

The second generation Grubbs catalyst (58 mg, 0.0069 mmol) was carefully weighed in a dry box and placed in a flame-dried flask inside the dry box. A 0.03 M stock solution of above allylic alcohol (0.38 g, 1.37 mmol) in dry CH$_2$Cl$_2$ (46 mL) was added to the catalyst at rt. The mixture was heated to 45 °C for 3 h, cooled to rt, stirred overnight in the presence of air. The solvent was evaporated and the residue was purified by column chromatography on silica gel (elution with 3:1 hexane: ethyl acetate) to get 0.31 g (91%) of 5.25 as a colorless oil; IR (neat, cm$^{-1}$) 3408, 2955, 2930, 1614; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.29-7.25 (m, 2 H), 6.91-6.84 (m, 2 H), 5.78-5.76, 4.55-4.42 (m, 3 H), 4.32-4.04 (m, 2 H), 3.80 (s, 3 H), 2.67-2.61 (m, 1 H), 2.54-2.44 (m, 1 H), 1.55-1.46 (m, 1 H), 1.17 (d, J = 7.0 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.9, 152.5, 130.7, 129.2 (2 C), 124.5, 113.6 (2 C), 82.4, 77.2, 70.2, 60.1, 55.1, 39.6, 38.0, 19.8; HRMS ES m/z (M + Na)$^+$ calcd 271.1305, obsd 271.1326.

**Preparation of compound 5.5**

To a suspension of IBX (0.28 g, 1.0 mmol) in DMSO (0.5 mL) was added a solution of allylic alcohol (50 mg, 0.20 mmol) in THF (5 mL) at rt. The resultant suspension was stirred for 10 h at rt before being quenched by hexane (1 mL). Stirring was continued for another 1 h at rt and the reaction mixture was filtered through a pad of Celite. The solid was washed with ether (2 x 20 mL). The organic layer was diluted with
H₂O (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under vacuum to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to afford 41.0 mg (85%) of 5.5 as a colorless oil; [α]₂⁵° = +133.1 (c 1.5, CHCl₃); IR (neat, cm⁻¹) 2959, 2871, 2837, 1613, 1464, 1249, 1162, 1075, 822; ¹H NMR (300 MHz, CDCl₃) δ 9.81 (s, 1 H), 7.29-7.26 (m, 2 H), 6.98-6.87 (m, 2 H), 6.74-6.73 (m, 1 H), 4.67-4.61 (m, 1 H), 4.54-4.47 (m, 2 H), 3.81 (s, 3 H), 2.97-2.85 (m, 1 H), 2.58-2.49 (m, 1 H), 1.61-1.52 (m, 1 H), 1.25 (d, J = 6.95 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 190.4, 159.3, 151.8, 149.2, 130.1, 129.4 (2 C), 113.9 (2 C), 81.8, 71.2, 55.2, 39.4, 35.8, 20.2; HRMS ES m/z (M + Na)+ calcd 269.1148, obsd 269.1151.

Preparation of compound 5.27

To a stirred solution of 5.4 (95 mg, 0.146 mmol) in dry CH₃CN (2 mL) were added DBU (93 mg, 0.609 mmol) and anhydrous LiCl (31 mg, 0.731 mmol) at rt. To this mixture was added a solution of aldehyde 5.5 (30 mg, 0.122 mmol) in dry CH₃CN (2 mL) via syringe. The mixture was stirred at rt for 6.5 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel (elution with 10:1 hexane:ethyl acetate) to afford 81 mg (89%) of 5.27 as a colorless liquid; [α]₂⁵° = -22.9 (c 1.53, CHCl₃); IR (neat, cm⁻¹) 2957, 2857, 1738, 1428, 1113, 836, 701; ¹H NMR (300 MHz, CDCl₃) δ 7.66-7.63 (m, 4 H), 7.44-7.39 (m, 6 H), 7.36-7.26 (m, 2 H), 6.91-6.87 (m, 3 H), 5.93 (s, 1 H), 4.62-4.58 (m, 1 H), 4.56-4.46 (m, 2 H), 3.81 (s, 3 H), 3.59-3.52 (m, 4 H), 2.74-2.66 (m, 3 H), 2.50-2.43 (m, 1 H), 1.91 (s, 3 H), 1.51-1.44 (m, 1 H), 1.13-1.09
(d, J = 12.5 Hz, 3 H), 1.05 (s, 9 H), 0.98 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.6, 159.2, 147.1, 140.5, 135.6 (4 C), 133.7 (2 C), 133.0, 132.4, 130.9, 129.5 (2 C), 129.3 (2 C), 127.5 (4 C), 113.8 (2 C), 82.8, 70.7, 67.9, 66.7, 55.2, 41.3, 40.8, 39.4, 38.9, 26.9 (3 C), 25.9 (3 C), 20.9, 19.4, 18.9, 18.2, 13.6, 1.0, -5.6 (2 C); HRMS ES $m/z$ (M + Na)$^+$ calcd 763.4184, obsd 763.4194.

**Preparation of compound 5.32**

To a cold (–78 °C), stirred solution of ketone 5.27 (81.0 mg, 0.11 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added Dibal-H (0.22 mL of 1.0 M solution in hexane, 0.22 mmol) under N$_2$. Stirring was continued for 1.5 h at –78 °C before being quenched by a saturated aqueous solution of K-Na-tartrate (1-2 drops) followed by the addition of H$_2$O (15 mL). The mixture was slowly warmed to rt and stirring was continued for 3 h. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave an oil.

To a cold (0 °C) solution of the above oil in dry CH$_2$Cl$_2$ (5 mL) were added Py (17.2 mg, 8.95 mmol), DMAP (1 crystal) and BzCl (23.2 mg, 0.17 mmol). The reaction mixture was stirred at rt for 24 h before being quenched by a saturated aqueous solution of CuSO$_4$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and evaporated to leave a yellow oil, which was purified by column chromatography on silica gel (elution with 8:1 hexane:ethyl acetate) to afford 64.6 mg (70% over two steps) of 5.32 as a colorless oil; IR (neat, cm$^{-1}$) 2957, 2857, 1738, 1428, 1113, 836, 701; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.66-7.63 (m, 4 H), 7.44-7.39 (m, 6 H), 7.36-7.26 (m, 2 H), 126
6.91-6.87 (m, 3 H), 5.93 (s, 1 H), 4.62-4.58 (m, 1 H), 4.56-4.46 (m, 2 H), 3.81 (s, 3 H),
3.59-3.52 (m, 4 H), 2.74-2.66 (m, 3 H), 2.50-2.43 (m, 1 H), 1.91 (s, 3 H), 1.51-1.44 (m, 1
H), 1.13-1.09 (d, J = 12.5 Hz, 3 H), 1.05 (s, 9 H), 0.98 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 6
H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 201.6, 159.2, 147.1, 140.5, 135.6 (4 C), 133.7 (2 C),
133.0, 132.4, 130.9, 129.5 (2 C), 129.3 (2 C), 127.5 (4 C), 113.8 (2 C), 82.8, 70.7, 67.9,
66.7, 55.2, 41.3, 40.8, 39.4, 38.9, 26.9 (3 C), 25.9 (3 C), 20.9, 19.4, 18.9, 18.2, 13.6, 1.0,
-5.6 (2 C); HRMS ES $m/z$ (M + Na)$^+$ calcd 869.4603, obsd 869.4655.
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APPENDIX

$^1$H NMR SPECTRA
$^1$H NMR Spectrum of Precursor of Compound 1.18
$^1H$ NMR Spectrum of Compound 1.19
$^1H$ NMR Spectrum of Compound 1.20
$^1$H NMR Spectrum of Compound 1.16a
$^1$H NMR Spectrum of Compound 1.16b
$^1$H NMR Spectrum of Compound 1.16c
\textbf{H NMR Spectrum of Compound 1.16d}
$^1H$ NMR Spectrum of Compound 1.16f
$^1$H NMR Spectrum of Compound 1.16g
$^1H$ NMR Spectrum of Compound 1.16h
$^1$H NMR Spectrum of Compound 1.22
$^1$H NMR Spectrum of Compound 1.23
\[ \text{H NMR Spectrum of a mixture of Compound 1.24 and 1.25} \]
$^{1}H$ NMR Spectrum of Compound 1.26
$^1$H NMR Spectrum of Compound 1.28
$^1$H NMR Spectrum of Compound 1.29
$^1$H NMR Spectrum of Compound 1.31
$^1$H NMR Spectrum of Compound 1.32
$^1$H NMR Spectrum of Compound 2.14
$^1$H NMR Spectrum of benzyl ether of Compound 2.14
$^1$H NMR Spectrum of Compound 2.15
$^1$H NMR Spectrum of Compound 2.16
$^1$H NMR Spectrum of Compound 2.10a
$^1$H NMR Spectrum of Compound 2.10c
$^1H$ NMR Spectrum of Compound 2.10d
$\text{H NMR Spectrum of Compound 2.10e}$
$^1$H NMR Spectrum of Compound 2.11
TBSO COOE
$^1$H NMR Spectrum of Compound 3.6
$^1$H NMR Spectrum of benzyl ether of Compound 3.6
$^1$H NMR Spectrum of Compound 3.7
$^1$H NMR Spectrum of Compound 3.1a
$^1H$ NMR Spectrum of Compound 3.1b
$^1H$ NMR Spectrum of Compound 3.1c
$^1$H NMR Spectrum of Compound 3.1d
$^{1}H$ NMR Spectrum of Compound 3.1e
$^1H$ NMR Spectrum of Compound 3.1f
$^1$H NMR Spectrum of Compound 3.1g
$^1$H NMR Spectrum of Compound 3.11
$^1$H NMR Spectrum of Compound 2.10d
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$^1$H NMR Spectrum of Compound 2.10d
\textbf{H NMR Spectrum of Compound 5.7}
$^1$H NMR Spectrum of Compound 5.8
$^1$H NMR Spectrum of Compound 5.9
$^1$H NMR Spectrum of Compound 5.10
$^1$H NMR Spectrum of Compound 5.11
$^1$H NMR Spectrum of Compound 5.15
$^1H$ NMR Spectrum of Compound 5.16
$^1$H NMR Spectrum of Compound 5.13
$^1$H NMR Spectrum of Compound 5.17
$^1$H NMR Spectrum of Compound 5.4
$^1$H NMR Spectrum of Compound 5.20
$^1$H NMR Spectrum of Compound 5.21


$^1H$ NMR Spectrum of Compound 5.22
$^1$H NMR Spectrum of Compound 5.23
$^{1}H$ NMR Spectrum of Compound 5.24
\textsuperscript{1}H NMR Spectrum of precursor of Compound 5.25
$^1$H NMR Spectrum of Compound 5.25
$^1$H NMR Spectrum of Compound 5.5
$^1H$ NMR Spectrum of Compound 5.27
$^1$H NMR Spectrum of Compound 5.32