Title
Synthetic Studies Toward the Total Synthesis of Maklamicin and Related Spirotetronate Polyketides

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Synthetic Studies Toward the Total Synthesis of Maklamicin and Related Spirotetronate Polyketides

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requirements for the degree
Doctor of Philosophy
in
Chemistry
by
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2016
This dissertation of Michelle Lacoske is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

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List of Symbols and Abbreviations

Ac .............................................. acetyl
AcOH ........................................ acetic acid
Bu .............................................. butyl
t-Bu ........................................... tert-butyl
°C .............................................. degrees Celsius
CDCl₃ ........................................ deuterated chloroform
CHCl₃ ........................................ chloroform
CH₂Cl₂ ........................................ dichloromethane
CH₃OH ......................................... methanol
DCM ............................................ dichloromethane
DIPEA ......................................... diisopropyl ethyl amine
DMS ............................................. dimethylsulfide
DMSO .......................................... dimethylsulfoxide
DMAP .......................................... N,N-dimethylaminopyridine
DMF ............................................. N,N-dimethylformamide
DMP ........................................... Dess-Martin periodinane
eq .............................................. equivalents
Et .............................................. ethyl
EtOAc ......................................... ethyl acetate
EtOH .......................................... ethanol
Et₃N ........................................... triethyl amine
g .............................................. gram
h .............................................. hours
hv .............................................. irradiation with light
HMDS ......................................... hexamethyldisiloxane
HRMS .......................................... high-resolution mass spectrometry
IBX ........................................... o-iodoxybenzoic acid
IC₅₀ ........................................... mean inhibitory concentration
LDA ........................................... lithium diisopropylamide
LiHMDS ...................................... lithium bis(trimethylsilyl)amide
M .............................................. molar
Me ............................................. methyl
MeOH .......................................... methanol
MHz ........................................... megahertz
mL ............................................. milliliter
µL ............................................. microliter
µmol .......................................... micromole
mmol ........................................ millimole
NaHMDS ...................................... sodium bis(trimethylsilyl)amide
NBS ........................................... N-Bromosuccinimide
NHK ........................................... Nozaki-Hiyama-Kishi
NMO ........................................... N-methylmorpholine N-oxide
NMR ............................. nuclear magnetic resonance
NOESY ............................. nuclear overhauser effect spectroscopy
[O] ................................ oxidation
Pd(PPh₃)₄ ......................... tetrakis(triphenylphosphine)palladium(0)
Ph ................................. phenyl
PhH ................................ benzene
PhMe ................................ toluene
PPh₃ ............................... triphenylphosphine
ppm ................................ parts per million
PPTS ............................... pyridinium p-toluenesulfonate
Rf ................................. retention factor
SAR ............................... structure activity relationship
TBAF ............................... tetrabutylammonium fluoride
TBS ............................... t-butyldimethyl silyl
TBDPS ............................. t-butyldiphenyl silyl
THF ............................... tetrahydrofuran
TLC ............................... thin layer chromatography
TPAP ............................. tetrapropylammonium perruthenate
TPP ............................... triphenylphosphine
UV ................................. ultraviolet
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ABSTRACT OF THE DISSERTATION

Synthetic Studies Toward the Total Synthesis of Maklamicin and Related Spirotetronate Polyketides

by

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Spirotetronate polyketides are a class of natural products isolated mostly from Micromonospora bacteria that are highlighted by their complex structures and intriguing biological activities. These molecules have had a major impact in the scientific community over the past few decades from development of novel synthetic methods as well as their study in cancer pathology and development of potential new cancer therapeutics. With the synthetic challenges presented I set out to explore a more efficient method of the synthesis of the decalin moiety. The synthesis is highlighted by an intramolecular Diels-Alder reaction (IMDA) that proceeds through an energetically unfavored endo-axial transition state. With the decalin moiety in hand, I set out to explore methods towards the total synthesis of maklamicin, the first class II
spirotetronate isolated to exhibit biological activity in the absence of glycosylation. With the challenges presented I sought to develop a general synthetic strategy towards class II spirotetronates. This modular approach would allow access to synthesize spirotetronate polyketides with varying ring size of the macrocyclic motif.
Chapter 1: Spirotetronate Polyketides as Leads in Drug Discovery
A. Introduction

Since the beginning of mankind, organisms producing natural products have provided a reservoir of therapeutic remedies and medicines for various diseases. A subset of these drugs has been classified as antitumor antibiotics based on their ability to “block cell growth by interfering with DNA, the genetic material in cells.” Key general features of an antitumor antibiotic include interference with DNA synthesis, membrane transport and production of reactive oxygen species. One of the most notable examples of an antitumor antibiotic is mitomycin C, a microbial metabolite that is used currently for the treatment of breast and bladder cancer. Among other antitumor antibiotics, daunorubicin and its semisynthetic derivative doxorubicin represent chemotherapeutic leukemia agents in clinical settings.

The search for new antitumor antibiotics led to the discovery of chlorothricin (1), a complex polyketide produced by various Streptomyces strains. Its intriguing chemical structure and bioactivity defined a new family of microbial metabolites, commonly referred to as spirotetronate polyketides. This family is identified by the presence of a cyclohexene ring spiro-linked to a tetronic acid moiety (Figure 1, fragment A) that is embedded in a macrocycle (Figure 1, fragment B). In several cases, the structure also contains a trans-decalin ring (Figure 1, fragment C) and is decorated by various deoxy oligosaccharides (Figure 1, fragment D). In terms of biological profile, spirotetronate polyketides exhibit potent antibacterial and antitumor activities and a documented value as tools in the elucidation of new biological pathways. As such, they represent highly promising leads in drug discovery. To appreciate their untapped
potential, in this review we group the known spirotetronates based on common structural elements and biosynthetic considerations. We then discuss the biological profiles and highlight synthetic efforts toward each group.

Figure 1.01: Structure of chlorothricin and general structure of spirotetronate polyketides

**B. Classification**

Recently Süssmuth and co-workers proposed a classification of tetronates based on two main categories: the linear tetronates and the spirotetronates. Based on biosynthetic considerations, the latter subgroup can be divided in two classes: class I (generic structure 4) that contains the spirotetronate moiety within a varying size macrocycle, and class II (generic structure 5) that additionally contains a decalin moiety (Figure 2). Representative members of the class I spirotetronates in order of increasing macrocyclic length are: abyssomicin C (6)\textsuperscript{13,14} (containing a C\textsubscript{11} macrocycle), okilactomycin D (7)\textsuperscript{15} (containing a C\textsubscript{13} macrocycle) and spirohexenolide A/B (8/9)\textsuperscript{16} (containing a C\textsubscript{15} macrocycle). Representative members of the class II spirotetronates include: maklamicin (11)\textsuperscript{17} (containing a C\textsubscript{11} macrocycle), tetronolide (12)\textsuperscript{18} (the
aglycone of tetrocarcin A containing a $C_{13}$ macrocycle) and chlorothricolide (2)\textsuperscript{11} (the aglycon of chlorothricin containing a $C_{13}$ macrolactone). In this class is also included versipelostatin aglycone (13) that contains the largest $C_{17}$ macrocyclic motif isolated to date.\textsuperscript{19} Quartromicins (10), an unusual spirotetronate polyketide containing four spirotetronate subunits, lies outside these two classes due to its peculiar structure\textsuperscript{20-22} and unique biosynthesis.\textsuperscript{23-25} The above classification stems from a common biosynthetic pathway that accounts for construction of these compounds.

Figure 1.02: Spirotetronate polyketides: General structures and representative members

C. Biosynthesis of Spirotetronate Polyketides

In general, the biosynthesis spirotetronates occurs through condensation of acetic acid units via the type I polyketide synthase pathway (Scheme 1).\textsuperscript{26-28} As shown in the biosynthesis of abyssomicin C\textsuperscript{29,30} and okilactomycin,\textsuperscript{31} construction of the class
I spirotetronates proceeds by elongating their carbon chain via incorporation of propanoyl and/or acetyl units (14/15) to the acyl carrier protein (ACP). This iterative operation forms polyketide chain 16. Incorporation of a glyceryl unit, via CoA intermediate 17, forms tetronate 18 likely via a Claisen condensation followed by lactonization. The precise mechanism for the elimination of the C-5 hydroxy group was recently elucidated by the Sun and Leadlay groups and shown to proceed via acetylation and subsequent elimination thereby forming dienophile 19. An intramolecular Diels-Alder (IMDA) reaction then generates the characteristic spirotetronate moiety. The resulting substrates subsequently undergo peripheral oxidations to produce the final structures of the natural products.

The biosynthetic pathways of the class II polyketide spirotetronates have been elucidated for chlorothricin, tetrocarcin A, kijanimicin, and versipelostatin. Following chain elongation, the diene and dienophile groups of 20 undergo an IMDA to construct the characteristic decalin moiety of 21. Glyceryl CoA (17) is then inserted to generate tetronate 22 which following a second IMDA, gives rise to the aglycones of the class II spirotetronates (Figure 2).
Oxidations and/or glycosylations at the periphery of the aglycone lead to various natural products of the class II spirotetronates. For instance, chlorothricolide (2), the aglycone of chlorothricin, contains an acyl-oxy tetronic acid moiety. This functionality (i.e. oxygenation at the C-2 position) is proposed to result from a Baeyer-Villiger oxidation that takes place after formation of the spirotetronate motif. A similar biosynthetic scenario can be proposed for the construction of PA-46101 A and B (see structures 57/58). Another interesting example of post-translational modification is found in the structure of tetronolide (12), the aglycone of tetrocarcin A (see structure 47). Compound 12 is highlighted by an enal functionality at C-22-C-23-
C-32. This functionality was proposed to result from oxidation at C-32 to the corresponding aldehyde followed by double bond migration to C-22-C-23 and further allylic oxidation at C-21.⁴⁴

Several class II spirotetronates are subject to glycosylation mostly with 2-deoxycarbohydrates such as D-tetronitrose (26, D-kijano), amicetose (27), and digitoxose (28). These carbohydrates are proposed to arise from thymidine diphosphate (TDP)-6-deoxy-4-keto-D-glucose (24) that, in turn, is available from D-glucose-1-phosphate (23) (Scheme 2). Biosynthesis of the uncommon tetronitrose is proposed to occur from 25 via aminotransferase and methylation, while the precise mechanism for the carbamate biosynthesis still remains elusive.⁴⁴,⁴⁷,⁴⁸,⁵¹,⁵²

Figure 1.04: Biosynthesis of deoxysugars.

D. Biology of Spirotetronate Polyketides

The majority of spirotetronates have been subjected to biological assays that aim to define their bioactivity as antibiotic and/or anticancer leads as well as compounds that regulate metabolism. With this in mind, we have grouped these molecules in three major classes that describe the commonality of their bioactivities.
1. Spirotetronates as Potential Antibiotic Leads

1.1 The Abyssomicin Family

Isolated from a marine Verrucosispora, abyssomicin C (6) and its atropisomer (29) (Figure 3) are the first known natural products to block para-aminobenzoic acid (pABA, 41) biosynthesis.\textsuperscript{13,14,53} pABA is a biosynthetic precursor of folic acid (vitamin B\textsubscript{9}) and as such, it is essential for DNA synthesis/repair and cell survival (Scheme 3).\textsuperscript{54} On the other hand, lack of folic acid is known to induce mutations in DNA resulting in cell death. Importantly, blocking the pABA pathway is detrimental to bacteria but inconsequential to humans since the latter cannot produce folic acid but only absorb it through their diet.\textsuperscript{55} Studies on the effect of the abyssomicin motif in pABA biosynthesis have been performed with atrop-abyssomicin (29) and are highlighted in Scheme 3. Amino-4-deoxychorismate (ADC) synthase, a heterodimeric protein, catalyzes the biosynthesis of amino-4-deoxychorismate (40) a synthetic precursor of pABA. Compound 29 was found to covalently react with the Cys-263 of the PabB subunit of ADC synthase at the C-9 enone center. The transiently formed C-8 nucleophile then reacts with the spirotetronate subunit at the C-16 center to form compound 39, thus irreversibly binding to ADC synthase.\textsuperscript{53}
Figure 1.05: Representative structures of the abyssomicin family of Spirotetronates.

Several natural products of the abyssomicin family have been tested for their ability to inhibit pABA biosynthesis (Scheme 3). Among them, only abyssomicin C (6), atrop-abyssomicin C (29), and abyssomicin J (31) have shown promising bioactivities.\textsuperscript{13,14,53,56-60} Specifically, 6 and 29 potently inhibit proliferation of methicillin-resistant \textit{Staphylococcus aureus} at MIC values of 5.2 \(\mu\text{g/mL}\) and 3.5 \(\mu\text{g/mL}\) respectively.\textsuperscript{13,14,61-63} Similar cytotoxicities have been reported against various tuberculosis-related mycobacteria.\textsuperscript{57,60} On the other hand, abyssomicin D (32) and related analogues lacking the C-7 C-9 enone motif are inactive attesting to the biological significance of this functionality.\textsuperscript{53,56,58,59,64} Moreover, most studies indicate that 29 is more potent than 6.\textsuperscript{61-63} This increased potency has been attributed to an
increased conjugation between the C-7 carbonyl group and the C-8-C-9 alkene that renders 29 a stronger Michael acceptor than 6. The bioactivity of abyssomicin J (31), a thioether dimer of the abyssomicin scaffold, can be explained by considering that oxidation of the sulfur accelerates a retro-Michael addition, producing the C-7 C-9 enone functionality in situ. In fact, it has been suggested that 31 is a prodrug of 6 and as such, it represents a more attractive drug candidate.  

Figure 1.06: pABA biosynthesis and proposed mode of action of atrop-abyssomicin C

1.2 Kijanimicin (43) and Related Class II C13 Macrocycles

Isolated from various *Micromonospora* bacteria, kijanimicin (43) and lobophorin B (42) are structurally defined by a C13 macrocycle (referred to as kijanolide, 44) in which the C-9 and C-17 hydroxy groups have been glycosylated (Figure 4). Most members of this group show potent activity against gram-positive bacteria as well as cytotoxicity against various cancer cell lines. In
addition, kijanimicin was shown to exhibit robust anticancer\textsuperscript{73} and anti-malarial activities in mouse models.\textsuperscript{69} Moreover, Fenical et al. reported promising anti-inflammatory activities of lobophorins in a mouse ear edema model. Interestingly, this is the first report on the untapped potential of spirotetronates as small molecule leads against inflammation.\textsuperscript{70}

A similar framework is in the structures of pyrrolosporin A (45, C-9-glycosylation)\textsuperscript{74,75} and MM46115 (46, C-17 glycosylation).\textsuperscript{76,77} The glycopyranose motif of pyrrolosporin is also found in the structures of decatromicin A/B\textsuperscript{78,79} and Nai414-A/B\textsuperscript{80} that also exhibit similar antibiotic activity against various strains of gram-positive bacteria. In addition to its potent antibiotic activities MM46115 was found to exhibit promising antiviral activities.\textsuperscript{76} Along these lines, the structurally unrelated quartromicins 9\textsuperscript{20,21} were shown to display potent bioactivity against herpes simplex virus (HSV) and human immunodeficiency virus (HIV) at low µM concentration.\textsuperscript{22}
Figure 1.07: Structures of kijanimicin and related class II C\textsubscript{13} macrocyclic spirotetronates

Recent studies indicate that kijanimicin binds to the TetR family of transcriptional regulators\textsuperscript{81} that control expression of various cytoplasmic proteins in prokaryotes. This binding leads to: (a) C-9-deglycosylation of kijanimicin that results in loss of activity; and (b) overexpression of the receptor thus increasing antibiotic resistance.\textsuperscript{82} The structurally related saccharocarcins\textsuperscript{83,84} are subject to a similar mechanism of deactivation and antibiotic resistance.\textsuperscript{82,85}

Figure 1.08: Binding of kijanimicin to TetR leads to C-9-deglycosylation and antibiotic resistance
2. Spirotetronates as Potential Anticancer Leads

![Cellular signaling diagram](image)

Figure 1.09: Cancer cellular signaling and mode of action of select spirotetronate polyketide

### 2.1 Spirohexenolides A and B (8, 9)

Burkart et al. reported the isolation of spirohexenolides A (8) and B (9) and their potent cytotoxicities against various cancer cell lines (Figure 2).\(^{16}\) Subsequent immunoaffinity-fluorescent labeling studies indicated that 8 targets human macrophage migration inhibitory factor (hMIF).\(^{86}\) This interaction reduces the phosphorylation levels of PI3K/AKT ultimately leading to a reduction of tumor cell growth (Figure 6).\(^{87,88}\) Conjugation of spirohexenolide A with fluorescent tags showed localization in the lysosome of HCT-116 cells, suggesting that spirohexenolides interfere with cellular endocytosis of hMIF.\(^{86}\)
2.2 Tetronolide-containing Natural Products

Isolated from various *Micromonospora* bacteria, tetrocarcin A (47, also known as antlermicin A and AC6D)\(^{89-91}\) represents the archetype of the tetronolide-family of natural products that also includes AC6H (48)\(^{92}\) and arisostatins A (49) and B (50) (Figure 7).\(^ {93,94}\) The antibiotic potential of these spirotetronates against several gram-positive bacteria has been reported.\(^ {46,89,91-95}\) Animal studies have shown that 47 is about four times more potent than the commonly used antibiotic diminazene. Although 47 has a narrow safety margin, it can be used in combination with diminazene providing a beneficial synergistic effect.\(^ {96,97}\)

![Selected structures of tetronolide-containing natural products](image)

Various reports on the potential anticancer profile of tetrocarcin A and related family members have been published. Initial studies showed tumor reduction in a mouse sarcoma model upon administration of 10 mg/kg of 47 over a period of 6 days. Similar treatment in mouse leukemia P388 model led to an increased life expectancy.\(^ {89,90}\) Comparable studies in B16 mouse melanoma showed that the life expectancy more than doubled at a single dose of 27 mg/kg of 47.\(^ {98}\) Moreover, AC6H 48 exhibited cytotoxicity against P388 leukemia and B16 melanoma cells at 6.25 and
25 µg/mL respectively. AC6H also showed a moderate increase in the life expectancy of a P388 leukemia mouse model albeit less active than tetrocarcin A. Studies in U937 cells indicated that arisostatin A (49) is equipotent to tetrocarcin A while arisostatin B (50) was ten fold less active. Arisostatin A was also found to be active in various breast and lung cancer cell lines at low micromolar concentrations.

Mode-of-action studies in HeLa cells showed that tetrocarcin A (47) potently inhibits Bcl-2, an important anti-apoptotic protein that is often overexpressed in cancer cells (Figure 6). Although there is no evidence of direct binding to Bcl-2, the phenotypical response induced by 47 is very promising and suggests that this compound represents an important and unexplored lead against cancer.

Studies in lymphoma cells showed that 47 induces a stress response of the endoplasmic reticulum (ER), resulting in upregulation of the heat shock protein HSP70, ultimately triggering cell apoptosis (Figure 6). Studies in breast cancer cells have suggested an alternative mechanism of action of 47 that proceeds by inhibiting phosphorylation of the PI3K/ Akt signaling cascade. Although the main cellular target of tetrocarcin A is still under investigation, preclinical studies have demonstrated its potential as a drug against chemoresistant cancers. In fact, 47 was reported to be more effective than paclitaxel at inducing cell apoptosis in breast cancer cells.

Arisostatin A (49) was found to induce cell apoptosis by generating reactive oxygen species (ROS), altering mitochondrial transmembrane potential and releasing
cytochrome C (Cyt C) in AMC-HN-4 cells (Figure 6) ultimately leading to activation of caspase-3 and induction of apoptosis. However, Bcl-2 activation was not altered by arisostatin A indicating a different mode of action from that of 47. 111

Screening the potential anticancer and antimicrobial activities of naturally occurring tetrocarcins has produced the main SAR data for this family. These studies have led to the following observations: (a) the number of carbohydrate units (digitoxose and amicetose) attached at the C-9 center of tetrocarcin A is proportional to its antimicrobial activity; 45,46,89-91,112 and (b) C-21 acetylation and C-9 glycosylation of tetrocarcin A did not significantly affect Bcl-2 activation. 112 The results suggest that the attachments of amicetose (27) and digitoxose (28) at the C-9 position of tetrocarcin A enhance its antibacterial profile but have no significant effect on its anticancer potential. 85

2.3 Versipelostatins

Versipelostatin A, (51) was isolated from a strain of Streptomyces versipellis (Figure 8). 19,113 Biological studies showed that 51 is the first known molecule to inhibit gene expression of GRP78. Together with its isoform GRP94, these heat shock proteins are induced by stress responses in the endoplasmic reticulum (ER) and are essential for cancer cell survival. 19,52,114 In addition to its role in cancer, ER stress is considered to play a major role in the pathogenesis of various CNS diseases, such as Alzheimer’s and Parkinson’s disease. 115
Recent studies have shown that versipelostatin A (51) inhibits heat shock proteins and unfolded protein response (UPR) under glucose deprivation conditions.\(^{116,117}\) As such, it appears to operate via a different mechanism as compared to that of rapamycin, an FDA-approved immunosuppressive drug, that activates GRP78 independently of glucose availability.\(^{118}\) Thus, versipelostatin may offer a significant advantage due to its selective effect in hypoglycemic cells.\(^{117,119}\) Although there is no information for direct binding of 51 to a protein target, its effect on UPR signaling pathway offers a novel tool to understand ER-induced stress and pharmacologically regulate related illnesses.\(^{120}\)

SAR studies on this family have been limited to the bioactivities of naturally occurring versipelostatins.\(^{121,122}\) The results show that versipelostatins A (51), E (52), and F (53) are the only biologically active compounds, inhibiting GRP78 expression at low micromolar IC\(_{50}\) values. Interestingly, 53 was found to be ten times more potent than 51 in GRP78 expression with an IC\(_{50}\) of 0.3 µM. The data attest to the significance of the glycosylation motif to the GRP78 expression and bioactivity.\(^{121,122}\) In addition to these studies, Takahashi et al. demonstrated the importance of the L-
oleandrose sugar for the bioactivity and changes in the oxidation state of C-7 had no effect on biological activity.\textsuperscript{123}

![Figure 1.12: Structure of okilactomycin and analogs](image)

**2.4 Okilactomycin (54) and Chrolactomycin (55)**

Okilactomycin (54) was isolated from *Streptomyces griseoflavus* and noted for its potent antitumor activity against Ehrlich ascites carcinoma in vivo at 2.5 mg/kg with a T/C of 145.7\% for mice survival.\textsuperscript{124,125} In addition, 54 exhibited in vitro activity against P388 and L1210 leukemia cells, with IC\textsubscript{50} values of 89 and 216 nM, respectively. Recently, okilactomycin was shown to inhibit rRNA protein synthesis at low \(\mu\)M concentrations,\textsuperscript{126} suggesting potential applications as an antibacterial agent.\textsuperscript{127} Although other natural okilactomycins were found to be inactive,\textsuperscript{15} the related chrolactomycin (55) was reported to exhibit antibacterial and anticancer activity at a low \(\mu\)M concentration.\textsuperscript{128} It has been reported that 55 inhibits telomerase activity thus blocking the ability of cancer DNA to replicate.\textsuperscript{111,128} The most recently isolated 6-hydroxy chrolactomycin was less active than 55 against gram-positive bacteria.\textsuperscript{129}

**2.5 PA-46101A/B (57/58), Maklamicin (11) and Nomimicin (59)**

The potent antibiotic properties of PA-46101A (57) and B (58)\textsuperscript{50} have been reported. Recent efforts by Igarashi and co-workers led to the isolation of maklamicin
(11)\textsuperscript{17} and nomimic (59),\textsuperscript{130} which contain the smallest macrocyclic ring of the class II spirotetronates. Both compounds display potent activity against many gram-positive bacteria, while 11 also exhibits moderate antitumor activity against HeLa and MCF7 breast cancer cells.\textsuperscript{17,130}

![Structures of PA46101 A/B, maklamicin and nomimicin](image)

**3. Spirotetronates as Potential Leads in Metabolism and Digestion**

**3.1 Chlorothricin (1)/ A88696C/F (60/61)/ Tetronothiodin (62).**

Chlorothricin (1) was shown to inhibit the activity of pyruvate carboxylase,\textsuperscript{131,132} a key enzyme that converts pyruvate to oxaloacetate thus allowing consumption of glucose through the Krebs cycle (Figure 11). Inhibition of pyruvate carboxylase leads to increase of pyruvate concentration in liver, which through gluconeogenesis, accounts for accumulation of glucose ultimately leading to diabetes.\textsuperscript{133} Moreover, an inhibitory effect of 1 on malate dehydrogenase, an enzyme
that oxidizes malate to oxaloacetate in the Krebs cycle, has also been reported.\textsuperscript{134} It should be noted, however, that the direct cellular target of 1 is under debate and may involve interaction with components in the cell membrane that may account for the observed downstream effects.\textsuperscript{135}

Figure 1.14: Effects of spirotetronate polyketides on metabolic pathways and digestion

Although the potential anticancer properties of chlorothricin (1) have not been investigated, C-31 hydroxychlorothricin (Figure 1) was shown to exhibit antitumor activity at 40 mg/kg against implanted Ehrlich carcinoma cells in mice with an LD\textsubscript{50} of 295 mg/kg.\textsuperscript{136} C-28 methyl ester of chlorothricolide (2),\textsuperscript{137} the aglycone of 1 (Figure
1), also inhibits pyruvate carboxylase albeit at higher concentrations than 1 suggesting that glycosylation enhances biological activity.\textsuperscript{132}

Efforts to discover new gastric ATP-ase inhibitors\textsuperscript{138} led to the isolation of A88696F (61) and its dehydroxylated counterpart A88696C (60).\textsuperscript{139,140} Hydroxylation at C-3 was found to enhance the biological activities since 61 was the most active with an IC\textsubscript{50} at 0.5 µM while 60 was considered inactive.\textsuperscript{139,140}

![Figure 1.15: Structures of A88696C/F and tetronothiodin](image)

Isolated from a \textit{Streptomyces} species, tetronothiodin (62) was shown to inhibit brain-type cholecystokinin (CCK)-B receptor in rat cerebral cortex with an IC\textsubscript{50} value of 3.6 nM.\textsuperscript{141-143} It is worth noting that CCK receptors are structurally similar to gastrin and are used throughout the central nervous system (CNS) and gastric tract.\textsuperscript{144} Interestingly, 62 has 27,000 times higher affinity for CCK-B over CCK-A in rat models.\textsuperscript{144} Thus, in addition to its pharmaceutical promise, 62 could be used as a tool to study the CCK-B/ CCK-A signaling pathway.\textsuperscript{145,146}

**E. Synthetic Approaches Toward Spirotetronate Polyketides**

In this part of the review, we highlight the key steps toward the synthesis of selected spirotetronates. When possible, we compare the various strategies in terms of overall efficiency.
1. Class I, C₁₁ Spirotetronates: Abyssomicins (6 and 29)

Abyssomicin C (6) and its atropisomer 29 contain a rigid oxabicyclo [2.2.2] octane substructure that encapsulates the spirotetronate moiety. To date, three chemical syntheses of 6 and 29 have been reported. The key transformations are highlighted in Scheme 4. Sorensen’s group used a biomimetic IMDA to construct spirotetronate moiety 65 from diene 63. C-11-C-12 epoxidation of 65 followed by C-16 intramolecular enol epoxide opening produced a 1:1 mixture of abyssomicin C (6) and atrop-abyssomicin (29).¹⁴⁷ A similar strategy has been implemented by the Snider¹⁴⁸ and Couladouros¹⁴⁹ groups.

The Nicolaou group synthesis of abyssomicin C is highlighted by an intermolecular Diels-Alder cycloaddition that furnishes cyclohexene 67 with the desired stereochemistry (Scheme 4).⁶¹-⁶³ A ring closing metathesis was used to generate the macrocyclic skeleton of 6 from diene 68. Interestingly, the authors showed that treatment of 29 with lithium selectride led to formation of abyssomicin D (32). Interestingly, this finding supports the notion that abyssomicin C (6) is a biosynthetic progenitor of 32 and further validates the proposed mechanism of abyssomicin C deactivation as presented in Scheme 3.⁶¹-⁶³

More recently, the groups of Bihelovic and Saicic reported a synthesis of 29.¹⁵⁰,¹⁵¹ Key to their approach was a Tsuji-Trost cyclization that constructed cyclohexane 70. The C₁₁ macrocycle of 29 was subsequently formed using an intramolecular Nozaki-Hiyama-Kishi (NHK) coupling. Interestingly, this strategy produces exclusively atrop-abyssomycin C.¹⁵⁰,¹⁵¹ It is likely that the restricted rotation
around the C-2 and C-3 centers, due to the sp² hybridization, affects the formation of the two isomers. In support of this hypothesis, the Nicolaou group has shown that 29 can be converted to 6 by protonating the C-16 oxygen under mild acidic conditions.61-63 Other studies towards the abyssomicin scaffold have been reported in addition to the mentioned total syntheses.152-154

Figure 1.16: Highlights of abyssomicin C syntheses
2. Class I, C₁₃ Spirotetronates: Okilactomycins (54 and 7).

Smith et al. reported the first total synthesis of okilactomycin 54 in 29 steps.¹⁵⁵,¹⁵⁶ Key to the strategy was a Petasis-Ferrier union/rearrangement of 72¹⁵⁷ that yielded the 2,6-cis-tetrahydropyranone-ring 73. Ring closing metathesis of 77 using Hoveyda-Grubbs second-generation catalyst was used to construct the 13-membered macrocycle of 54.¹⁵⁵,¹⁵⁶

More recently, the Scheidt group also reported a synthesis of okilactomycin. Key to this approach was a Prins-type fragment assembly¹⁵⁸ between cyclohexene 75 and β-keto- ester 74 that formed the 2,6-cis-tetrahydropyranone ring of 76. Similarly to the Smith approach, an intramolecular ring closing metathesis using Grubbs second-generation catalyst constructed the macrocycle.¹⁵⁹ Additional synthetic studies toward okilactomycin have been reported by the Yoshii¹⁶⁰ and Paquette¹⁶¹,¹⁶² groups.
Figure 1.17: Highlights of okilactomycin syntheses

Hoye et al. reported the first total synthesis of the (±)/(-)-okilactomycin D (7). Key to this strategy was an IMDA cycloaddition that formed spirotetronate 80 from precursor 79. The overall synthesis proceeds in 13 linear steps (17 total steps) and 17% yield. Remarkably, demethylation of tetronate 80 was efficiently conducted on a 3 gram scale.163
3. Class I, C\textsubscript{15} Spirotetronates: Spirohexenolides A and B (8 and 9)

The Burkart group reported a strategy toward spirohexenolides based on an intermolecular Diels-Alder cycloaddition (Scheme 7).\textsuperscript{164,165} A ring closing Julia-Kocienski coupling was applied for the synthesis of macrocycle 82. Although the projected intramolecular hemiacetalation to 84 failed due to an oxidative rearrangement of 82 to 83, the overall strategy has successfully installed the major skeletal features of spirohexenolides.\textsuperscript{166}
4. Class I, C_{17} Spirotetronates: Tetronothiodin (62)

![Chemical diagram]

Figure 1.20: Synthetic studies toward tetronothiodin

Structurally tetronothiodin is highlighted by an $\alpha$-acyl tetronic acid moiety and tetrahydrothiophene moiety. Page et al. have reported a synthesis of the spirotetronate subunit isomer 87 using a Diels-Alder reaction with propenal and the hydroxyl diene 85 to install the desired stereochemistry of 86 (Scheme 8). Further functional modifications led to the synthesis of spirotetronate 87.167

5. Class II, C_{13} Spirotetronates: Tetronolide (12)/ Kijanolide (44) and Chlorothricolide (2)

To date there are no reported total syntheses of any class II, C_{13} spirotetronates. Several strategies have been employed for the synthesis of tetronolide (12), the aglycone of tetrocarcin A (47), kijanolide (44), the aglycone of kijanimicin (42) and chlorothricolide (2), the aglycone of chlorothricin (1). Tetronolide has been synthesized by Yoshii168 and Boeckman169 while an improved formal synthesis has also been reported by Roush.170 In general, these strategies rely upon independently constructing the spirotetronate and decalin moieties and then connecting them to form the C_{13} macrocycle. A remarkable synthesis of chlorothricolide (2) was reported by the Roush group.171,172
Figure 1.21: Highlights of tetronolide syntheses

The Yoshii and Roush syntheses of the decalin moiety 92, common to both tetronolide and kijanolide, are summarized in Scheme 9. In Yoshii’s approach a
Horner-Wadsworth Emmons olefination between 88 and 89 was used to construct polyene 90, which underwent an IMDA reaction to produce decalin 92. The Roush group implemented a Suzuki coupling between 93 and 94 to form polyene 91 that, following further functionalizations, gave rise to decalin 92 via an IMDA cycloaddition. A similar approach toward decalin 92 has been reported by the Marshall group.

A synthetic approach toward spirotetronate 100 has been reported by Yoshii and subsequently optimized by Roush. This approach is based on constructing triene 97 via a HWE olefination between 95 and 96. An intermolecular Diels-Alder of diene 97 and chiral dienophile 98, followed by oxidative functionalization and double bond migration, yielded enal 99. Coupling of lithiated spirotetronate 100 with aldehyde 92 followed by subsequent functionalizations yielded sulfone 101 that, under Julia coupling conditions, gave rise to the 13-membered macrocycle of 12.

Boeckman’s group synthesis of 12 is highlighted by a tandem ketene-trapping [4+2] cycloaddition of diene 103 and alcohol 102 to form spirotetronate subunit 104. Conversion of 104 to tetronolide 12 was accomplished under Julia conditions. Overall, this approach significantly reduces the amount of steps required for completion of the tetronolide synthesis.

Various synthetic studies toward kijanolide (44) have been reported by the groups of Marshall, Yoshii, and Roush. These strategies rely on intermolecular Diels-Alder reactions and ketene trapping strategy to form the desired
Application of a Julia coupling to the synthesis of 28,29-bisnor-(+)-kijanolide has been reported by the Yoshii group.\textsuperscript{190}

Figure 1.22: Highlights of the Boeckman strategy toward tetronolide

A tandem intra/intermolecular Diels-Alder reaction between polyene 105 and chiral dienophile 98 was implemented for the synthesis of chlorothricolide (2) (Scheme 11). The reaction gave the desired cycloadduct in 40% yield together with partially reacted decalin 107. Upon treatment with dienophile 98, 107 was converted to desired product 106 in 58% yield.\textsuperscript{171,172} Construction of the spirotetronate unit followed by coupling with the allyl ester completed the synthesis of 2.
Figure 1.23: Highlights of the Roush strategy toward chlorothricolide

A late-stage IMDA reaction was used by the Yoshii’s group for the synthesis of (±)-24-O-methylchlorothricolide (Scheme 12). Although the selectivity of the IMDA reaction was moderate, the overall strategy represents a noteworthy bioinspired approach toward these compounds.\textsuperscript{191} The groups of Marshall,\textsuperscript{192} Ireland,\textsuperscript{193-195} Snider,\textsuperscript{196,197} Schmidt,\textsuperscript{198-200} and Meyers\textsuperscript{201} have also reported studies toward the synthesis of 2.
Figure 1.24: Highlights of the Yoshii strategy toward (±)-24-O-methylchlorothricolide

6. Class II, C17 Spirotetronates: Versipelostatin (51)

Figure 1.25: Synthetic studies towards glycosyl moiety of versipelostatin A

Numerous synthetic studies have been reported towards the total synthesis of versipelostatin A (51), but to date its total synthesis has not been completed. Kirschning’s202 and Takahashi’s123 groups provided synthetic strategies to the trisaccharide moiety. A synthesis of the versipelostatin (51) trisaccharide 114 is shown in Scheme 13.123 Key to the synthesis is a Schmidt glycosylation of 110 with trichloroacetimidate 111. The resulting disaccharide 112 was deprotected and coupled...
with L-oleandrosyl imidate 113 to produce 114 (Scheme 13). Further functionalization of glycosyl 114 and Schmidt glycosylation with acetyl C-7-C-9-C-37 versipelostatin aglycone 13 (Figure 2) yielded a versipelostatin derivative used for biological studies. Based on NMR and biological consideration, the oleandrose sugar was structurally reassigned from D to L. An alternate strategy used was adding each sugar individually to the versipelostatin aglycone thus elongating the glycosyl chain. Various approaches toward the spirotetronate unit of the versipelostatin have been reported.

![Chemical Structures](image)

Figure 1.26: Connection of spirotetronates for quartromicins

7. Quartromicins (10)

A stereocontrolled Diels-Alder reaction has been implemented by the Roush group for the synthesis of the quartromicin spirotetronate unit. In addition, this group reported a strategy of connecting subunits 115 and 116 together using lithium halogen exchange and CeCl₃ coupling. Bedel’s group offered an alternative
strategy of constructing the spirotetronate subunits using RCM, but to date no total syntheses of quartromicins have been completed.208

F. Conclusions

The discovery of penicillin revolutionized pharmaceutical research by demonstrating, for the first time, that microorganisms can produce secondary metabolites of value to medicine. Since then, cultured microorganisms have been recognized as prolific producers of secondary metabolites that are used either directly as drugs or have inspired the design of drugs.114,144,209-213 On the other hand, the intricate structures of these compounds represent exceptional tools to explore new biological pathways and unknown mechanisms of action. These qualities, although scattered, are observed in the family of spirotetronate polyketides and provide evidence for their significant but still untapped pharmacological value.

More than forty years after the discovery of chlorothricin, the spirotetronate family has grown to include over 70 macrocycles of various sizes that, in certain cases, are decorated with carbohydrate side chains. In addition to their potent antitumor and antibiotic activities, certain spirotetronates were characterized as “the first” tools to elucidate a biological effect.13,95,114 For example, versipelostatin was found to induce potent and selective cytotoxicity in glucose-deprived tumor cells.116,117 Moreover, abyssomicin C was found to be the first natural product to block pABA biosynthesis, a pathway essential to bacteria but insignificant to humans.13 Impressive synthetic and chemical biology efforts were combined to decipher the mode-of-action of abyssomicins at the molecular level.53,63 This underscores the enormous
significance of the spirotetronate polyketide family to biology in addition to their pharmacological potential.

Several studies have documented the significance of the carbohydrate chains for the observed antibiotic activity of spirotetronates. However, with the exception of abyssomicins, there is no clear understanding of the biological significance of the spirotetronate aglycone core. At present, chemical strategies developed toward the synthesis of spirotetronates have uncovered the value of certain key reactions, such as Diels-Alder cycloaddition, ring closing metathesis and Julia olefination. Nonetheless, the vast majority of these strategies have not yielded sufficient amounts of compound for a methodical structure-activity relationship study, thereby hampering rational drug design. It is evident that a methodical fragment-based approach to this structure, in combination with chemical biology studies, will be highly beneficial as they could reveal the role of the spirotetronate motif, the effect of the macrocyclic size and the role of the decalin system. In turn, this effort would allow a detailed evaluation and optimization of the spirotetronate pharmacophore. In addition to a dearly needed scalable synthesis, advances in microbial biosynthesis should offer a potential solution to large-scale production or semi-synthesis of a lead candidate. Combination of these efforts should unveil the pharmacological value of spirotetronates and would have significant impact in current efforts toward personalized medicine.
Chapter 1, in part, is a reprint of the material as it appears in M. H. Lacoske, E. A. Theodorakis, Spirotetronate Polyketides as Leads in Drug Discovery, *J. Nat. Prod.* 2015, 3, 562-575. The dissertation author was the primary investigator and author of this paper.
Chapter 2: Synthetic strategies toward the decalin motif of maklamicin and related spirotetronates
A. Introduction

Isolated from various *Micromonospora* strains, spirotetronate polyketides constitute a peculiar family of natural products characterized by a complex chemical architecture and intriguing bioactivity as antitumor antibiotics.\(^{12,222}\) Tetrocarcin A, the defining member of this family, contains an aglycone core, referred to as tetronolide (1),\(^{18}\) that is glycosylated at the C9 and C17 centers. This natural product displays promising anticancer properties *in vitro* and in animals\(^ {89-91}\) that may stem from its ability to induce cell stress and inhibit Bcl-2 expression.\(^ {95,99,104,223}\) Tetrocarcin A also exhibits potent cytotoxicity against several Gram-positive bacteria (e.g. MIC: 0.38 µM against *Bacillus subtilis*).\(^ {45,90,91,96,99,104,223,224}\) Interestingly, it has been shown that glycosylation of C9 is essential for antimicrobial activity but inconsequential for anticancer activity.\(^ {45,112}\) The influence of glycosylation to the antimicrobial potency has also been observed in other spirotetronates.\(^ {45,82,85,112}\)

![Figure 2.01: Structures of tetronolide (1) and maklamicin (2)](image)

The biological and pharmacological potential of spirotetronates has fuelled efforts to isolate new family members. Along these lines, Igarashi *et al* reported the isolation of maklamicin (2) from *Micromonospora* sp. GMKU326.\(^ {17}\) This novel
spirotetronate was shown to exhibit both antimicrobial activities against various Gram-positive bacteria (e.g. MIC: 0.30 µM against *Bacillus subtilis*) and anticancer activities (IC$_{50}$: 17-34 µM against various cancer cell lines). Intriguingly, maklamicin exhibits potent antimicrobial activity in the absence of C9 glycosylation, which is essential for other spirotetronate polyketides.$^{45,82,85,112}$

Structurally, maklamicin (2) encapsulates a trans-decalin and a spiro-tetronic acid moieties within a strained 11-membered macrocyclic motif.$^{17,130}$ Herein we describe synthetic approaches towards the decalin moiety of 2.

**B. Background of IMDA Transition States**

Inspired by the biosynthetic pathway of spirotetronates, we envisioned that the decalin moiety of maklamicin would arise from an intramolecular Diels-Alder reaction (IMDA).$^{44,48}$ This strategy has been successfully applied to the synthesis of related natural products.$^{170-172,176,178,179,192,225-235}$ Closer analysis of this IMDA reveals four possible transition states that give rise to four distinct decalin diastereomers (Figure 2). The two *endo* transition states derive from the relative orientation of the C8 methyl group during the transition state of the IMDA reaction that influences the facial selectivity of this cycloaddition. Based on the C8 methyl group orientation, we define these transition states as *endo*-equatorial and *endo*-axial.$^{236-238}$ In a similar fashion, depending on the C8 methyl group orientation, we can have the *exo*-equatorial and *exo*-axial transition states (Figure 2). To obtain the desired stereochemistry of the maklamicin decalin unit (i.e. compound 5), the IMDA should proceed via an *endo*-axial transition state (3: *endo*-ax. TS). Published reports indicate that the facial
selectivity of this type of an IMDA is expected to proceed via an endo-equatorial transition state (3: endo-eq. TS).\textsuperscript{239,240} With this in mind, we sought to explore various methods that could alter the facial selectivity of the IMDA in favor of that encountered in the structure of maklamicin.

![Diagram of possible transition states for the IMDA of compound 3](image)

Figure 2.02: Possible transition states for the IMDA of compound 3 (only selected hydrogens are shown). The terms axial and equatorial refer to the relative orientation of the C8 methyl group.

C. Synthetic Studies of the Decalin Moiety

Our model studies toward the synthesis of the maklamicin decalin core are highlighted in Schemes 1-3. Previously, we demonstrated that triene 3, synthetically available from (−)-citronellal (10) in 3 steps, undergoes an IMDA in the presence of Et\textsubscript{2}AlCl at −78 °C to produce the endo-equatorial product 4.\textsuperscript{241,242} We hypothesized
that an organocatalytic process could overcome the inherent substrate selectivity of this system and favor construction of cycloadduct 5, the one encountered in the structure of maklamicin. These studies are summarized in Scheme 1. We performed this reaction in the presence of various imidazolidinone catalysts (8) under previously optimized conditions (20 mol% HClO₄, 20 mol% catalyst, MeCN or EtOH, –20 °C).²⁴³-²⁴⁶ Under these conditions, the IMDA reaction was slow (3 days for completion) and produced exclusively the endo-equatorial adduct 4.²⁴¹,²⁴² The results indicate that the catalysis was not effective in our substrate, presumably due to the presence of the C4 methyl group adjacent to the carbonyl group. This methyl group likely prevents the transiently formed iminium intermediate from assuming the geometry needed for the desired facial selectivity of IMDA, thus diminishing the ability of the catalyst to direct the stereochemical outcome of this reaction.²⁴³,²⁴⁵-²⁴⁷

Figure 2.03: Studies on the IMDA of 3 under imidazolidinone organocatalysis.

In light of these results, we pursued an alternative strategy, shown in Scheme 2, in which the desired facial stereoselectivity of IMDA could be achieved using Evans oxazolidinones (e.g. compounds 13 and 14) as chiral auxiliaries.²⁴⁸-²⁵⁰ The
modified strategy departed from \((S)-(\text{--})\)-citronellal (10) that, following established protocols, was converted to enal 11.\textsuperscript{241,242,251} The difference in the chemoselectivity between the two carbonyl groups of 11, allowed selective protection of aliphatic aldehyde with ethylene glycol and tosylic acid. The resulting acetal underwent Pinnick oxidation to afford the corresponding carboxylic acid 12 (80% yield over two steps). DCC coupling of 12 with \((R)\)-4-benzyl oxazolidinone or \((S)\)-4-benzyl oxazolidinone followed by acetal deprotection (18% aqueous HCl) yielded aldehydes 15 and 16 (75% yield over two steps). Olefination of aldehyde 15 and 16 with a Wittig ylide, produced \textit{in situ} from phosphonium salt 17 with \(n\)-BuLi, afforded trienes 18 and 19 respectively in about 60% yield. The selectivity of this olefination was moderate \((E:Z = \sim 3:2)\). and could not be improved using related olefination techniques.
Figure 2.04: Synthesis of polyenes 18 and 19 containing benzyl oxazolidinones as chiral auxiliaries.

Figure 2.05: Model system for stereochemical control of IMDA
The \((E,E)\) stereochemistry of the C10 and C13 diene is essential for the desired IMDA. With this in mind, a photoisomerization of 18 and 19 was conducted with 5 mol% of iodine in dichloromethane under sun-lamp photoirradiation, to produce almost exclusively the \(E,E\)-alkenes (Scheme 3). For characterization purposes, these compounds can be isolated after the photoisomerization reaction (see Supporting Information). Nonetheless, these polyenes can undergo the IMDA reaction in one pot, immediately after the photoisomerization.\textsuperscript{252} To this end, polyenes 18 and 19 were each treated with 1.1 eq. of Me\(_2\)AlCl at \(-78\) °C and then the reaction was allowed to warm to \(-20\) °C. Each of these reactions produced two readily separable cycloadducts in a 1:1 isolated yield. NOESY experiments were performed to assign the relative stereochemistry of these compounds (Scheme 3). In compounds 20 and 22 we observed key correlations between the C4 methyl and both protons at C10 and C13 (marked with red arrows in Scheme 3). These correlations, together with the absence of a signal between the C10 and the C5 protons indicate the presence of a \textit{trans}-decalin ring and thus an \textit{endo} IMDA reaction. Compound 20 also displayed NOESY correlations between (a) the C10 proton and C8 methyl; and (b) the C4 methyl and C6\textsubscript{axial} proton (marked with blue arrows in Scheme 3) supporting the notion that the IMDA proceeded through an \textit{endo}-axial tranistion state. This assignment is consistent with the NOESY data reported for the decalin moiety of maklamicin.\textsuperscript{17} In addition to the key correlations of an \textit{endo} adduct (marked with red arrows in Scheme 3), compound 22 displayed NOESY correlation between the protons at C10 and C8 supporting the assignment of the \textit{endo}-equatorial adduct. Similar correlations have
been observed in related equisetin derivatives.\textsuperscript{253-256} In a similar manner, compounds 21 and 23 were identified as \textit{exo} adducts since they displayed a NOESY signal between the protons at C10 and C5 as expected in a \textit{cis}-decalin motif (marked with a red arrow in Scheme 3). Compound 21 displayed additional correlations between: (a) the C4 methyl and protons at C7\textsubscript{axial} and C9\textsubscript{axial}; and (b) protons at C13 and C5 (marked in blue arrows in Scheme 3). These correlations confirm that adduct 21 was produced via an \textit{exo}-axial IMDA transition state. Similar correlations have been reported for the \textit{cis}-decalin ascosalipyrrolidinone.\textsuperscript{257} On the other hand, compound 23 displayed additional correlations between the C4 methyl and protons at both C5 and C13 in support of this IMDA proceeding through an \textit{exo}-equatorial transition state. These correlations have been observed in pyrrolocin B a compound that contains a \textit{cis}-decalin with an equatorial methyl at C8.\textsuperscript{258}

The above data demonstrate that all stereoisomers of the IMDA reaction can be accessible using the chiral auxiliary approach. In the specific case of maklamicin synthesis, formation of the \textit{endo}-axial configuration requires use of the (\textit{R})-4-benzyl oxazolidinone (13). Having established a strategy for the synthesis of the desired decalin moiety, we then turned our attention toward an appropriately functionalized acyclic precursor of the maklamicin decalin core.
Figure 2.06: Synthesis of functionalized Wittig salt

Installation of the C14 methyl group at the polyene precursor of maklamicin was accomplished as highlighted in Scheme 4. Commercially available methyl sorbate (24) underwent allylic bromination to form 25 in 90% yield.\textsuperscript{259} SN\textsubscript{2} methylation at C14 was accomplished in a stereoselective manner using Feringa’s protocol that involves slow addition of 25 to a solution of methyl cuprate and S,S-TANIAPHOS (26). Lowering the amounts of CuBr·DMS and 26 to 2.5 mol% and 3 mol% respectively, maintained the same level of enantioselectivity and afforded skipped diene 27 (91% yield, 97% ee). Due to the volatility of product 27, its isolation yield is maximized when the alkylation reaction takes place on one-gram scale. The slow addition of bromosorbate (25) to a cold solution of the catalyst limits the scalability of this reaction.\textsuperscript{259-262} Reduction of methyl ester 27 with DIBAL-H generated the allylic alcohol, which was converted to the allylic bromide under Appel conditions.\textsuperscript{263-266} The allylic bromide was immediately converted to the Wittig salt in MeCN and PPh\textsubscript{3} to produce 28 (73% over 3 steps).
Figure 2.07: First generation approach to functionalized decalin

Wittig olefination of aldehyde 15 with phosphonium bromide 28 yielded polyene 29 in 59% yield ($E:Z \approx 3:2$). Double bond isomerization of this $E:Z$ mixture was attempted but the previously established conditions promoted isomerisation of the terminal C15-C16 olefin to form the conjugated triene. Thus, the $E:Z$ mixture was subjected to the IMDA reaction that proceeded by adding 5 equivalents of Me$_2$AlCl. Under these conditions we isolated cycloadduct 30 in 42% yield (formed from the $E$-isomer). Not surprisingly, the $Z$-isomer does not undergo cycloaddition under these conditions.$^{267,268}$ NOESY correlation of 30 was compared with compounds 20-23 to confirm that the IMDA proceeded via an endo-axial transition state. Reduction of oxazolidinone 30 with DIBAL-H followed by oxidation of the resulting alcohol with Dess-Martin periodinane yielded decalin aldehyde 31 (78% yield over 2 steps). Albeit short (9 total steps) this strategy has limited scalability due to the following reasons:
(a) difficulties in installing the C14 methyl group in large scale due to limitations of the S_N2' alkylation and the cost of the catalyst; (b) inability to isomerize triene 29 to the desired all trans isomer; and (c) low yielding IMDA reaction that only proceeded from E isomer in 42% yield.

![Chemical Structure](image)

**Figure 2.08: Synthesis of scalable Wittig salt**

To overcome the above difficulties we sought to develop an alternative route to decalin aldehyde starting from commercially available methyl (R)-(−)-3-hydroxyisobutyrate (Roche’s ester). This compound was protected with tert-butyldiphenylsilyl chloride (TBDPSCI) and imidazole in DMF in quantitative yield.\(^{269-271}\) Reduction of the methyl ester to aldehyde 33 was achieved with DIBAL-H administered via syringe pump at −78 °C. Aldehyde 33 was directly subjected to Wittig olefination with (carbethoxymethylene) triphenylphosphorane. The resultant ethyl ester was reduced to the allylic alcohol 34 with DIBAL-H at 0 °C in 81% yield over two steps.\(^ {269-271}\) Appel bromination yielded allylic bromide, which was immediately subjected to PPh\(_3\) in MeCN to generate Wittig salt 35 (84% over two steps). The overall preparation of this Wittig salt is high yielding, scalable, and only
requires one silica column chromatography after TBDPS protection to produce over 30 grams of Wittig salt 35.

![Diagram](image)

Figure 2.09: Synthesis of scalable decalin moiety 38

Wittig salt 35 was treated with n-BuLi to generate the ylide in situ and then aldehyde 15 was added to form polyene 36 (61% yield, $E:Z \approx 3:2$). The double bond isomerization and the subsequent IMDA proceeded smoothly to generate decalin 37 (52% yield on more than 3 grams scale). NOESY correlations of 37 were compared to compounds 20-23, 30, and maklamicin to confirm that the desired stereochemistry was achieved. Reduction of 37 with DIBAL-H followed by IBX oxidation yielded aldehyde 38 (49% yield, 2 steps). The C15 silylated alcohol in 38 allows further derivatization (e.g. olefination protocols) en route to the chemical synthesis of maklamicin.

**D. Conclusions**
In conclusion we have developed an asymmetric approach to the decalin motif of maklamicin. Initial studies on simplified systems confirmed the role of the benzyl oxazolidinone on the facial selectivity of the IMDA. We then applied this information to the synthesis of the unusual endo-axial decalin moiety of maklamicin. The chiral methyl groups at C8 and C14 of the IMDA precursor were introduced from enantiomerically pure starting materials. Overall, the strategy is divergent and allows access to the decalin motif 38 in 10 linear steps and good overall yield. Importantly, decalin 38 is suitably protected for further functionalization towards the synthesis of maklamicin.

Chapter 2, in part, is a reprint of the material as it appears in M. H. Lacoske, J. Xu, N. Mansour, C. Gao, E. A. Theodorakis, Synthetic strategies toward the decalin motif of maklamicin and related spirotetronates, *Org. Chem. Front.* 2015, 2, 388-392. The dissertation author was the primary investigator and author of this paper.

**E. Experimental Section**

**1. General Procedures**

Unless indicated, all commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and
dimethylformamide (DMF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using Hexanes-EtOAc or CH₂Cl₂-MeOH mixtures of increasing polarity. The progress of all the reactions were monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F₂₅₄ to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of KMnO₄ stain or Seebach’s stain followed by heating. ¹³C NMR and ¹H NMR spectra were recorded on either 500 MHz Varian instrument or 500 MHz JEOL instrument. CDCl₃ was treated with flame dried K₂CO₃, chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference (CDCl₃), with the abbreviations s, br s, d, t, q, m, td, dt and qd denoting singlet, broad singlet, doublet, triplet, quartet, multiplet, quartet of doublets, triplet of doublets, doublet of triplets and quartet of doublets respectively. J = coupling constants given in Hertz (Hz). IR spectras were collected on a Jasco 4100 FTIR. High resolution Mass spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade anhydrous CHCl₃.

2. Preparation of Compounds

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**Dialdehyde (11) (Method 1):** To a solution of (S)-(−)-citronellal (1.45 mL, 1.23 g, 8.0 mmol, purchased from TCI America, > 96.0%, [α]D20 = −15.5, neat) in CH2Cl2 (150 mL) was added methacrolein (1.32 mL, 16.0 mmol) and Grubbs catalyst (2nd generation, 340 mg, 0.4 mmol). The reaction mixture was refluxed for 24 hours under argon atmosphere. The reaction was allowed to cool to room temperature and concentrated. The residue was purified via silica column chromatography (hexanes:EtOAc, 100:1 to 10:1) to recover the (S)-(−)-citronellal (205 mg, 17%) and yield the di-aldehyde 11 (1.01 g, 75%, 90% brsm) as a pale yellow oil.

**Dialdehyde (11) (Method 2):** To a solution of SeO2 (416 mg, 3.7 mmol) and salicylic acid (1.99 g, 12.4 mmol) in CH2Cl2 (40 mL) was added t-butyl hydrogen peroxide slowly (70% in H2O, 71.0 mL, 496 mmol). The mixture was stirred for 15 min then (S)-(−)-citronellal (18.8 g, 122 mmol) was added. The reaction was stirred at room temperature for 36 hours. The reaction was diluted with benzene (100 mL) and concentrated. The residue was diluted with ether (400 mL) and washed with 10% NaOH (2 x 130 mL) and brine (120 mL). The organic layer was dried over MgSO4, filtered, concentrated and purified through silica column chromatography (hexanes:EtOAc, 200:1 to 5:1) to recover the (S)-(−)-citronellal (3.23 g, 17%) and yield the di-aldehyde 11 (2.80 g, 14%) and corresponding allylic alcohol (9.10 g, 44%) as a clear oil. To a solution of this allylic alcohol (1.60 g, 9.4 mmol) in DMSO (35 mL) was added IBX (3.76 g, 13.4 mmol) in one portion. The reaction was stirred for 1.5 hours, then was diluted with water (180 mL) and filtered through Celite® to remove the precipitate. The filtrate was extracted with diethyl ether (5 x 100 mL). The
combined organic layers were washed with brine (100 mL) and 10% NaOH (2 x 100 mL), dried over MgSO₄, filtered and concentrated to yield 11 (1.35 g, 87 %) as a pale yellow oil. The analytical data were identical with the one obtained from method 1. Characterization of this compound matched to the literature.

(2E,4E)-Hexa-2,4-dien-1-yltriphenylphosphonium bromide (17): To a stirred solution of (2E,4E)-hexadien-1-ol (9.80 g, 100 mmol) in CH₂Cl₂ (20 mL) at –10 ºC was slowly added a solution of phosphorus tribromide (9.20 g, 34.0 mmol) in CH₂Cl₂ (20 mL) dropwise via an addition funnel. After all the phosphorous tribromide was added, the reaction mixture was stirred for 3 hours before it was diluted with ether (150 mL) and quenched with a saturated NaHCO₃ (100 mL) solution. The mixture was separated with diethyl ether with the aid of brine. The aqueous phase was extracted with ether (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford crude (2E,4E)-hexadienylbromide (10.4 g, 65%) as a brown oil. The crude (2E,4E)-hexadienylbromide was then dissolved in anhydrous toluene (90 mL), followed by the addition of triphenyl phosphine (18.9 g, 72.0 mmol). This reaction was then stirred for 72 hours at room temperature, and the resulting crystalline product was collected by suction filtration, rinsing the solids with a small amount of toluene. After pumping under high vacuum at room temperature for 12 hours, the phosphonium salt 17 were obtained (27.2 g, 99%, 64% from (2E,4E)-hexadien-1-ol). mp: 159–160 ºC. Characterization of this compound matched to the literature.
**Triene (3):** To a suspension of (2E,4E)-hexa-2,4-dien-1-yltriphenylphosphonium bromide 17 (20.6 g, 48.7 mmol) in THF (240 mL) was added dropwise n-BuLi (30.4 mL, 48.7 mmol, 1.6 M in hexane) via addition funnel at –78 °C. The mixture was stirred for 1 hour at –60 °C then re-cooled to –78 °C and transferred via cannula, slowly dropwise to a solution of aldehyde 11 (8.2 g, 48.7 mmol) in THF (240 mL) at –78 °C over 2 hours. After completion of addition, the reaction mixture was stirred at this temperature for 10 min, quenched with saturated NH₄Cl solution (250 mL), diluted with ethyl ether (350 mL) and allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated and purified through neutralized (Et₃N, 5%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 50:1) to yield polyene 3 (6.8 g, 61%) as a pale yellow oil as an inseparable E/Z isomeric mixture (E:Z = ca. 3:2). To a solution of the (E/Z) 3 (113 mg, 0.28 mmol) in CH₂Cl₂ (5.6 mL) at RT was added iodine (3.5 mg, 14 µmol) in CH₂Cl₂ (0.2 mL). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). Then the reaction was quenched with saturated sodium thiosulfate (11 mL). The mixture was extracted with CH₂Cl₂ (3 x 15 mL). All organic layers were washed with brine (15 mL), dried over Na₂SO₄ and concentrated to yield polyene 3 (112 mg, 99%)
as a clear oil and inseparable E/Z isomeric mixture (E:Z = ca. 95:1). Characterization of this compound matched to the literature.\textsuperscript{241,242}

**Decalin aldehyde (4):** To a mixture of MacMillan’s catalyst (20 mol\%) (listed in Scheme 1) in MeCN or ethanol (0.86 mL) was added triene (3) (10 mg, 43 µmol) in ethanol (0.1 mL) followed by perchloric acid (0.52 µl, 8.61µmol, 0.2 eq, 70\% in water) at –20°C. This reaction continued to stir at this temperature for 3 days and then was concentrated and purified via preparative thin layer chromatography (hexanes:EtOAc, 9:1) to yield decalin aldehyde 4 (6.0 mg, 60\%) as a clear oil. Characterization of this compound matched to the literature.\textsuperscript{241,242}

**Acetal aldehyde (11_1):** To a solution of the dialdehyde 11 (14 g, 83 mmol) in ethylene glycol (93 mL, 20 eq.) was added p-toluenesulfonic acid, p-TsOH (1.583 g, 8.32 mmol, 0.1 eq.) and stirred for 5 minutes. Then reaction was diluted with water (500 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 500 mL). All organic layers were washed with water (2 x 750 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to yield 11_1 (17.67 g, 100\%). This compound was used directly to the next step without further purification. \(R_t= 0.65\) (silica gel, hexanes:EtOAc, 3:1); \([\alpha]_D^{23} = -5.5\) (c = 0.34, CHCl\textsubscript{3}); \(^{1}\text{H} \text{NMR (500 MHz, CDCl}_3\) \(\delta 9.37\) (s, 1H), 6.47 (t, \(J = 7.5\) Hz, 1H), 4.88 (t, \(J = 5.2\) Hz, 1H),
3.95 (m, 2H), 3.83 (m, 2H), 2.35 (m, 2H), 1.72 (s, 3H), 1.66-1.37 (m, 5H), 0.98 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 195.4, 154.8, 139.3, 103.6, 64.8, 64.8, 40.6, 35.7, 29.1, 26.6, 19.8, 8.9; HRMS (ESI) m/e 235.1301 [M+Na$^+$] calcd for C$_{12}$H$_{20}$O$_3$Na$^+$: 235.1305.

Carboxylic acid (12): To aldehyde 11-1 (17.67 g, 83 mmol) in THF (357 mL) was added at 0°C sulfamic acid (11.31 g, 117 mmol) dissolved in water (170 mL) followed by sodium chlorite (10.54 g, 117 mmol) dissolved in water (170 mL) and stirred for 30 minutes at room temperature. The reaction was acidified to pH 2 with 2N HCl (50 mL) and extracted with ethyl acetate (3 x 500 mL). All organic layers were washed with brine (500 mL), dried over Na$_2$SO$_4$ and concentrated. The resultant product was then purified through silica column chromatography (hexanes:EtOAc, 100:1 to 1:1) to yield carboxylic acid 12 (15.20 g, 80%) as a clear oil. $R_f$ = 0.22 (silica gel, hexanes:EtOAc, 3:1); [$\alpha$]$_D^{23}$ = −28.5 (c = 0.32, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.88 (t, J = 7.5 Hz, 1H), 4.88 (t, J = 4.9 Hz, 1H), 3.95 (m, 2H), 3.82 (m, 2H), 2.19 (m, 2H), 1.81 (s, 3H), 1.66 (m, 2H), 1.50 (m, 2H), 1.32 (m, 1H), 0.95 (d, J = 6.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.7, 145.3, 127.0, 103.6, 64.8, 64.7, 40.7, 35.8, 29.2, 26.4, 19.8, 12.0; HRMS (ESI) m/e 251.1256 [M+Na$^+$] calcd for C$_{12}$H$_{20}$O$_4$Na$^+$: 251.1254.
Acetal (12_1): To a suspension of (R)-4-benzyl-2-oxazolidinone (12.98 g, 73.2 mmol), 4-dimethylaminopyridine, DMAP (1.057 g, 8.66 mmol), and carboxylic acid 12 (15.20 g, 66.6 mmol) in CH$_2$Cl$_2$ (89 mL) at 0°C was added N,N'-dicyclohexylcarbodiimide, DCC (17.86 g, 87 mmol). The reaction stirred at this temp for 10 min and then rt overnight. The reaction was filtered through a fritted funnel to remove the urea byproduct and rinsed with 500 mL CH$_2$Cl$_2$. The organic layer was washed with saturated NaHCO$_3$ (500 mL), dried over Na$_2$SO$_4$, and concentrated. The crude compound was purified by silica chromatography (hexane:EtOAc, 100:1 to 1:1) to yield 12_1 (19.35 g, 75%) as a clear oil. $R_f$ = 0.42 (silica gel, hexanes:EtOAc, 7:3); $[\alpha]_D^{23} = -40.5$ (c = 0.27, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33-7.18 (m, 5H), 6.07 (t, $J$ = 7.5 Hz, 1H), 4.90 (t, $J$ = 5.2 Hz, 1H), 4.71 (m, 1H) 4.22 (t, $J$ = 8.6 Hz, 1H), 4.14 (dd, $J$ = 5.2, 8.6 Hz, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 3.33 (dd, $J$ = 3.5, 13.8 Hz, 1H), 2.82 (dd, $J$ = 9.2, 13.8 Hz, 1H), 2.20 (m, 2H), 1.90 (s, 3H), 1.71-1.17 (m, 5H), 0.98 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.0, 153.3, 140.2, 135.3, 130.5, 129.6, 129.0, 127.4, 103.7, 66.4, 64.8, 64.7, 55.6, 40.8, 37.6, 35.8, 29.2, 26.0, 19.8, 13.6; HRMS (ESI) m/e 388.2119 [M+H$^+$] calcd for C$_{22}$H$_{30}$O$_5$N$^+$: 388.2118.
**Acetal (12_2):** To a suspension of (S)-4-benzyl-2-oxazolidinone (0.77 g, 4.3 mmol), 4-dimethylaminopyridine, DMAP (0.06 g, 0.5 mmol), and carboxylic acid 12 (0.9 g, 3.9 mmol) in CH₂Cl₂ (5.3 mL) at 0°C was added N,N’-dicyclohexylcarbodiimide, DCC (1.06 g, 5.1 mmol). The reaction stirred at this temp for 10 min and then rt overnight. The reaction was filtered through a fritted funnel to remove the urea byproduct and rinsed with CH₂Cl₂ (20 mL). The organic layer was washed with saturated NaHCO₃ (15 mL), dried over Na₂SO₄, and concentrated. The crude compound was purified by silica chromatography (hexane:EtOAc, 100:1 to 1:1) to yield 12_2 (1.15 g, 75%) as a clear oil. \( R_f = 0.5 \) (silica gel, hexanes:EtOAc, 3:2); \( [\alpha]_D^{22} = +6.9 \) (c = 0.32, CHCl₃); \(^1\text{H} \) NMR (500 MHz, CDCl₃) \( \delta \) 7.36-7.20 (m, 5H), 6.10 (t, \( J = 7.3 \) Hz, 1H), 4.92 (t, \( J = 5.1 \) Hz, 1H), 4.72 (m, 1H), 4.26 (t, \( J = 8.5 \) Hz, 1H), 4.16 (dd, \( J = 5.6, 9.0 \) Hz, 1H), 3.99 (m, 2H), 3.86 (m, 2H), 3.36 (dd, \( J = 3.4, 13.5 \) Hz, 1H), 2.83 (dd, \( J = 9.3, 13.5 \) Hz, 1H), 2.24 (m, 2H), 1.92 (s, 3H), 1.71-1.30 (m, 5H), 1.00 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\text{C} \) NMR (125 MHz, CDCl₃) \( \delta \) 172.0, 153.2, 140.1, 135.2, 130.4, 129.5, 128.9, 127.3, 103.6, 66.4, 64.8, 64.7, 55.5, 40.7, 37.5, 35.7, 29.2, 25.9, 19.8, 13.5; HRMS (ESI) m/e 410.1940 [M+Na⁺] calcd for C₂₂H₃₀NO₅Na⁺: 410.1938.

![Acetal Structure](image)

**Aldehyde 15:** To a solution of the acetal 12_1 (19.35 g, 49.9 mmol) in THF (333 mL) was added 18% aqueous HCl solution (333 mL). After 2 hrs the reaction was carefully quenched with saturated NaHCO₃ solution (1 L) and extracted with EtOAc (3 x 800 mL). All organic layers were washed with brine (700 mL), dried over Na₂SO₄ and...
concentrated to yield aldehyde 15 (17.15 g, 100%) as a clear oil. \( R_f = 0.42 \) (silica gel, hexanes:EtOAc, 7:3); \( [\alpha]_D^{23} = -48.0 \) (c = 2.17, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)

9.72 (s, 1H), 7.30-7.16 (m, 5H), 6.00 (t, \( J = 7.5 \) Hz, 1H), 4.68 (m, 1H), 4.22 (t, \( J = 8.6 \) Hz, 1H), 4.12 (dd, \( J = 5.8, 9.2 \) Hz, 1H), 3.30 (d, \( J = 13.2 \) Hz, 1H), 2.80 (dd, \( J = 9.2, 13.2 \) Hz, 1H), 2.38 (dd, \( J = 5.8, 16.1 \) Hz, 1H), 2.23 (m, 2H), 2.10 (m, 1H), 1.88 (s, 3H), 1.71-1.30 (m, 3H), 0.96 (d, \( J = 6.9 \) Hz, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)

202.8, 171.8, 153.2, 138.8, 135.2, 131.1, 129.5, 129.0, 127.4, 66.5, 55.5, 50.9, 37.6, 35.3, 27.7, 25.9, 19.8, 13.6; HRMS (ESI) m/e 344.1859 [M+H\(^+\)] calcd for C\(_{20}\)H\(_{26}\)O\(_4\)N\(^+\): 344.1856.

**Aldehyde 16:** To a solution of the acetal 12_2 (1.15 g, 2.97 mmol) in THF (20 mL) was added 18% aqueous HCl solution (20 mL). After 2 hrs the reaction was carefully quenched with saturated NaHCO\(_3\) solution (100 mL) and extracted with EtOAc (3 x 20 mL). All organic layers were washed with brine (70 mL), dried over Na\(_2\)SO\(_4\) and concentrated to yield aldehyde 16 (1.02 g, 100%) as a clear oil. \( R_f = 0.5 \) (silica gel, hexanes: EtOAc, 3:2); \( [\alpha]_D^{24} = +2.1 \) (c = 0.37, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)

9.77 (t, \( J = 2.2 \) Hz, 1H), 7.37-7.20 (m, 5H), 6.05 (t, \( J = 7.3 \) Hz, 1H), 4.72 (m, 1H), 4.26 (t, \( J = 8.5 \) Hz, 1H), 4.17 (dd, \( J = 5.4, 9.0 \) Hz, 1H), 3.36 (dd, \( J = 3.4, 13.5 \) Hz, 1H), 2.84 (dd, \( J = 9.3, 13.5 \) Hz, 1H), 2.43 (dd, \( J = 5.7, 16.3 \) Hz, 1H), 2.25 (m, 2H), 2.14 (m, 1H), 1.93 (s, 3H), 1.65-1.37 (m, 3H), 1.01 (d, \( J = 6.7 \) Hz, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \)

202.8, 171.8, 153.2, 138.9, 135.1, 131.0, 129.5, 128.9, 127.4, 66.4, 55.5,

**Polyene (18):** To a stirred solution of phosphonate 17 (0.77 g, 1.8 mmol) in THF (9.7 mL) at -78°C was added n-butyl lithium (n-BuLi) (1.15 mL, 1.8 mmol, 1.6 M) dropwise and this solution turned deep red in color and continued to stir for 1 hr at this temperature. Then aldehyde 15 (0.63 g, 1.8 mmol) in THF (9.6 mL) was added to this solution dropwise. After stirring at -78°C for 5 minutes the reaction was quenched with sat. NH₄Cl solution (10 mL) and warmed to RT. The reaction was extracted with ether (3 x 30 mL). All organic layers were washed with brine (30 mL), dried over Na₂SO₄, and concentrated. The resulting product was purified through neutralized (Et₃N, 5%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 3:1) to yield polyene 18 (0.47 g, 63%) as a clear oil and inseparable E/Z isomeric mixture (E:Z = ca. 3:2). Rₜ = 0.63 (silica gel, hexanes:EtOAc, 7:3); [α]D²³ = -18.2 (c = 0.52, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (E:Z = ca. 3:2) δ 7.37-7.20 (m, 5H), 6.51-6.04 (m, 5H), 5.75-5.41 (m, 2H), 4.72 (m, 1H), 4.26 (t, J = 8.5 Hz, 1H), 4.16 (dd, J = 5.6, 8.9 Hz, 1H), 3.35 (dd, J = 3.5, 13.5 Hz, 1H), 2.84 (dd, J = 9.3, 13.5 Hz, 1H), 2.27-2.10 (m, 4H), 1.92 (s, 3H), 1.78 (m, 3H), 1.60-1.41 (m, 3H), 0.92 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) (E:Z = ca. 3:2) δ 171.9, 153.2, 152.1, 140.4, 140.4, 140.4, 140.3,
Polyene (18) isomerized: To a solution of the \((E/Z)\) 18 (113 mg, 0.28 mmol) in CH\(_2\)Cl\(_2\) (5.6 mL) at RT was added iodine (3.5 mg, 14 µmol) in CH\(_2\)Cl\(_2\) (0.2 mL). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). Then the reaction was quenched with saturated sodium thiosulfate (11 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). All organic layers were washed with brine (15 mL), dried over Na\(_2\)SO\(_4\) and concentrated to yield polyene 18 (112 mg, 99%) as a clear oil and inseparable \(E/Z\) isomeric mixture \((E:Z = \text{ca. 95:1})\). \(R_f = 0.63\) (silica gel, hexanes:EtOAc, 7:3); \([\alpha]_D^{24} = -21.4\) (c = 3.04, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37- 7.20 (m, 5H), 6.51-6.04 (m, 5H), 5.75-5.41 (m, 2H), 4.72 (m, 1H), 4.26 (t, \(J = 8.5\) Hz, 1H), 4.16 (dd, \(J = 5.6, 8.9\) Hz, 1H), 3.35 (dd, \(J = 3.5, 13.5\) Hz, 1H), 2.84 (dd, \(J = 9.3, 13.5\) Hz, 1H), 2.27-2.10 (m, 4H), 1.92 (s, 3H), 1.78 (d, \(J = 5.9, 3\)H), 1.60-1.41 (m, 3H), 0.92 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.0, 153.2, 152.1, 140.4, 135.3, 132.5, 132.0, 131.9, 131.0, 130.6, 130.5,
129.6, 129.0, 127.4, 66.4, 55.6, 40.3, 37.6, 35.1, 33.1, 26.2, 19.5, 18.4, 13.6; HRMS (ESI) m/e 344.1859 [M+H+] calcd for C_{26}H_{33}O_3N+: 344.1856.

Polyene (19): To a stirred solution of phosphonate 17 (1.00 g, 2.36 mmol) in THF (12.4 mL) at –78°C was added n-butyl lithium (n-BuLi) (1.47 mL, 2.36 mmol, 1.6M in hexanes) dropwise and this solution turned deep red in color and continued to stir for 1 hr at this temperature. Then aldehyde 16 (0.81 g, 2.36 mmol) in THF (12.4 mL) was added to this solution dropwise. After stirring at -78°C for 5 minutes the reaction was quenched with saturated NH_4Cl solution (40 mL) and warmed to RT. The reaction was extracted with ether (3 x 40 mL). All organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The resulting product was purified through neutralized (Et_3N, 5%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 3:1) to yield polyene 19 (0.61 g, 63%) as a clear oil and inseparable E/Z isomeric mixture (E:Z = ca. 3:2). R_f = 0.65 (silica gel, hexanes:EtOAc, 7:3); [α]_D^{23} = +38.1 (c = 2.13, CHCl_3); ^1H NMR (500 MHz, CDCl_3) (E:Z = ca. 3:2) δ 7.31- 7.18 (m, 5H), 6.51-5.19 (m, 7H), 4.69 (m, 1H), 4.23 (t, J = 8.3 Hz, 1H), 4.14 (m, 1H), 3.33 (d, J = 13.7 Hz, 1H), 2.82 (dd, J = 9.2, 13.2 Hz, 1H), 2.25-1.94 (m, 4H), 1.90 (s, 3H), 1.75 (m, 3H), 1.60-1.45 (m, 3H), 0.89 (m, 3H); ^13C NMR (125 MHz, CDCl_3) (E:Z = ca. 3:2) δ 171.9, 153.2, 152.1, 140.4, 140.4, 140.4, 140.3, 135.2, 133.2,
132.9, 132.5, 131.9, 131.7, 130.9, 130.5, 130.4, 130.1, 129.7, 129.7, 129.5, 129.0, 128.9, 127.3, 125.9, 125.8, 105.0, 66.4, 55.5, 40.2, 40.2, 37.5, 35.1, 35.0, 34.9, 33.2, 33.0, 26.2, 26.1, 19.4, 19.4, 18.4, 18.4, 13.5, 13.5; HRMS (ESI) m/e 408.2535 [M+H]⁺ calcd for C₂₆H₃₄O₃N⁺: 408.2533.

**Polyene (19) isomerized:** To a solution of the (E/Z) 19 (68 mg, 0.17 mmol) in CH₂Cl₂ (3.3 mL) at RT was added iodine (2.1 mg, 8.3 µmol) in CH₂Cl₂ (0.1 mL). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). Then the reaction was quenched with saturated sodium thiosulfate (7 mL). The mixture was extracted with CH₂Cl₂ (3 x 7 mL). All organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated to yield polyene 19 (67 mg, 99%) as a clear oil and inseparable E/Z isomeric mixture (E:Z = ca. 95:1). Rᵋ = 0.63 (silica gel, hexanes:EtOAc, 7:3); [α]D²⁵ = +44.9 (c = 2.49, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.31- 7.18 (m, 5H), 6.51-5.19 (m, 7H), 4.69 (m, 1H), 4.23 (t, J = 8.3 Hz, 1H), 4.14 (m, 1H), 3.33 (d, J = 13.7 Hz, 1H), 2.82 (dd, J = 9.2, 13.2 Hz, 1H), 2.25-1.94 (m, 4H), 1.90 (s, 3H), 1.75 (d, J = 6.9, 3H), 1.60-1.45 (m, 3H), 0.89 (d, J =6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.9, 153.2, 140.3, 135.2, 132.5, 131.9, 131.7, 130.9, 130.5, 130.4, 129.5, 129.0, 128.9, 127.3, 66.4, 55.5, 40.2, 37.5, 35.0,
Decalin (22/23): Then to a stirred solution of polyene 19 (0.18 g, 0.44 mmol) in CH$_2$Cl$_2$ (6.3 mL) was added iodine (5.6 mg, 22 µmol, 0.05 eq.). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). The mixture was cooled to -78°C at which time Me$_2$AlCl (0.49 mL, 0.49 mmol, 1M in hexanes) was added dropwise. The reaction mixture was then warmed to -20°C and continued to stir at this temperature for 2 days. The reaction mixture was quenched with a 1:1 sat. NaHCO$_3$/sodium thiosulfate solution (20 mL) and the mixture was ran through a Celite® plug followed by rinse with CH$_2$Cl$_2$ (50 mL). The reaction was extracted with CH$_2$Cl$_2$ (3 x 20 mL). All organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude compound was purified by silica column chromatography (hexanes:EtOAc, 200:1 to 5:1) to yield decalin 23 (74 mg, 41%) and decalin 22 (74 mg, 41%) as a white foam. Characterization of decalin 22: $R_f$ = 0.47 (silica gel, hexanes: EtOAc, 9:1); $[\alpha]_D^{24} = +168.1$ (c = 1.8, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.24 (m, 5H), 5.51 (m, 1H), 5.40 (m, 2H), 5.26 (m, 1H), 4.47 (m, 1H), 4.08 (m, 2H), 3.86 (dd, $J = 3.4, 9.7$ Hz, 1H), 3.38 (d, $J = 13.2$ Hz, 1H), 2.46 (t, $J = 12.3$ Hz, 1H), 1.91- 0.99 (m, 9H), 1.58 (d, $J = 6.3$ Hz, 3H), 1.36 (s, 3H), 0.93 (d, $J =
6.3 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.8, 152.3, 136.5, 132.2, 129.9, 129.6, 129.0, 127.2, 127.0, 126.7, 65.9, 59.2, 50.6, 44.5, 42.5, 42.4, 38.0, 37.2, 35.8, 33.5, 28.1, 22.6, 17.9, 14.0; HRMS (ESI) m/e 408.2536 \([\text{M+H}^+]\) calcd for C\(_{26}\)H\(_{34}\)NO\(_3\)^\(+\): 408.2533.

Characterization of decalin 23: \(R_f= 0.29\) (silica gel, hexanes: EtOAc, 9:1); \(\alpha_D^{24} = – 26.8\) (c = 1.4, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.20 (m, 5H), 5.66 (m, 1H), 5.50 (m, 2H), 5.42 (d, \(J = 10.3\) Hz, 1H), 4.75 (m, 1H), 4.15 (t, \(J = 8.6\) Hz, 1H), 4.10 (dd, \(J = 3.5, 9.2\) Hz, 1H), 3.50 (br s, 1H), 3.20 (dd, \(J = 3.5, 13.2\) Hz, 1H), 2.68 (dd, \(J = 9.8, 13.2\) Hz, 1H), 2.59 (m, 1H), 2.24 (br s, 1H), 1.69 (d, \(J = 5.2\) Hz, 3H), 1.67-0.86 (m, 7H), 1.42 (s, 3H), 0.82 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 178.6, 152.7, 135.6, 131.3, 130.6, 129.5, 129.5, 129.0, 128.1, 127.3, 66.2, 58.0, 51.4, 44.9, 40.6, 38.2, 37.9, 35.5, 34.9, 28.4, 22.8, 22.6, 18.3, 18.2; HRMS (ESI) m/e 408.2535 \([\text{M+H}^+]\) calcd for C\(_{26}\)H\(_{34}\)NO\(_3\)^\(+\): 408.2533.

Decalin (20/21): Then to a stirred solution of 18 (0.37 g, 0.91 mmol) in CH\(_2\)Cl\(_2\) (13 mL) was added iodine (12.0 mg, 45 \(\mu\)mol, 0.05 eq.). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). The mixture was cooled to -78°C at which time Me\(_2\)AlCl (1.00 mL, 1.0 mmol, 1M in
hexanes) was added dropwise. The reaction mixture was then warmed to -20°C and continued to stir at this temperature for 2 days. The reaction mixture was quenched with a 1:1 sat. NaHCO$_3$/sodium thiosulfate solution (40 mL) and the mixture was ran through a Celite® plug followed by a rinse with CH$_2$Cl$_2$ (80 mL). The reaction was extracted with CH$_2$Cl$_2$ (3 x 30 mL). All organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude compound was purified by silica column chromatography (hexanes:EtOAc, 200:1 to 5:1) to yield decalin 20 (0.15 g, 41%) and decalin 21 (0.15 g, 41%) as a white foam. Characterization for 20: $R_f = 0.47$ (silica gel, hexanes:EtOAc, 9:1); $[\alpha]_D^{25} = -19.2$ (c = 0.58, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35-7.24 (m, 5H), 5.51 (m, 1H), 5.40 (m, 2H), 5.25 (m 1H), 4.47 (m, 1H), 4.08 (m, 2H), 3.86 (m, 1H), 3.37 (d, J = 12.6 Hz, 1H), 2.44 (t, J = 12.0 Hz, 1H), 2.08 (m, 2H), 1.80-1.19 (m, 7H), 1.58 (d, J = 6.3 Hz, 3H), 1.39 (s, 3H), 1.03 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.8, 152.3, 136.5, 132.2, 130.2, 129.6, 129.0, 127.3, 127.2, 126.7, 65.8, 59.2, 50.6, 44.4, 43.4, 39.7, 37.2, 32.7, 31.9, 27.9, 22.7, 18.8, 17.9, 14.1; HRMS (ESI) m/e 408.2534 [M+H$^+$] calcd for C$_{26}$H$_{34}$NO$_3$: 408.2533.

Characterization for 21: $R_f = 0.10$ (silica gel, hexanes:EtOAc, 9:1); $[\alpha]_D^{24} = +10.5$ (c = 3.67, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.31-7.12 (m, 5H), 6.10 (m, 2H), 5.75 (m, 1H), 5.42 (dd, J = 8.0, 14.3 Hz, 1H), 4.45 (m, 1H), 4.32 (t, J = 8.3 Hz, 1H), 4.01 (t, J = 8.3 Hz, 1H), 3.51 (br s, 1H), 2.98 (dd, J = 6.3, 13.8 Hz, 1H), 2.73 (dd, J = 7.5, 13.8 Hz, 1H), 1.95-0.40 (m, 9H), 1.77 (d, J = 6.9 Hz, 3H), 1.58 (s, 3H), 0.88 (d, J = 6.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.2, 155.2, 136.2, 134.3, 130.9, 130.8, 129.1, 128.7, 128.0, 127.0, 106.9, 81.4, 67.8, 55.7, 43.6, 42.6, 40.0, 36.7, 35.2, 32.6,
29.5, 22.6, 18.2, 14.1; HRMS (ESI) m/e 408.2535 [M+H\(^+\)] calcd for C\(_{26}\)H\(_{34}\)NO\(_3\)\(^+\): 408.2533.

6-bromo methyl sorbate (25): A mixture of methyl sorbate (20.2 g, 160 mmol) and N-bromosuccinimide (29.6 g, 167 mmol) in dry chlorobenzene (136 mL) was heated to 100 °C over 1 hour. Benzoylperoxide (1.75 g, 7.21 mmol) was then cautiously added portionwise. After the addition was complete, the reaction mixture was heated under reflux for 3 hr. The reaction was cooled and the chlorobenzene was concentrated. The residual paste was dissolved with Et\(_2\)O (300 mL) and was washed with sodium hydroxide (75 mL of a 5% aqueous solution) until the washings were colorless. The organic layer was then dried over MgSO\(_4\), filtered, and concentrated. The crude residue was purified by silica column chromatography (0 to 10% ethyl acetate in hexane) to afford bromide 25 (29.5 g 90 %) as light yellow oil. This material matched what was previously reported in the literature.\(^{258}\)

Skipped Diene (27): Optimization of literature protocol: Copper (I) bromide dimethylsulfide complex (25 mg, 0.12 mmol, 2.5 mol%) and S,S-TANIAPHOS (100 mg, 0.15 mmol, 3 mol%, purchased from Strem Chemicals Inc.) were dissolved in CH\(_2\)Cl\(_2\) (49 mL) at room temperature and stirred for 15 minutes. Then the reaction was cooled to -78°C and methyl magnesium bromide, MeMgBr (2 mL, 5.85 mmol, 3M in diethyl ether) was added dropwise. Then the bromo methyl sorbate (25) (1 g, 4.88
mmol) was dissolved in CH₂Cl₂ (20 mL) and was added to reaction dropwise at a rate of 1mL/hr. The reaction was stirred at –60 °C for additional 48 hours and then was quenched with saturated NH₄Cl solution (100 mL). This mixture was then warmed up to room temperature, extracted with CH₂Cl₂ (100 mL x 2), dried over MgSO₄ and carefully concentrated at reduced pressure (150 torr). The residue was purified via silica column (pentane:ether, 100:1 to 20:1) to afford the skipped diene 27 as colorless oil (0.615 g, 91%, ee > 97%). The skipped diene ester matched characterization data provided in the literature with our optimized preparation.

Skipped Diene Wittig Salt (28): The skipped diene ester 27 (0.615 g, 4.39 mmol) was dissolved in CH₂Cl₂ (25 mL) and cooled to 0 °C. A solution of DIBAL-H (17.6 mL, 17.6 mmol, 1M in hexanes) was added in dropwise. After 5 min the reaction was diluted with ether (50 mL), and sequentially added water (0.8 mL), aqueous 15% NaOH solution (0.8 mL), and water (0.5 mL). The reaction was warmed to RT and stirred at this temperature for 30 minutes. Some MgSO₄ was added and continued to stir for another 15 min. The reaction was filtered and carefully concentrated at reduced pressure (150 torr). The afforded allylic alcohol was essentially pure to be used directly in next step. The allylic alcohol (0.492 g, 4.39 mmol) was dissolved in CH₂Cl₂ (25 mL) and cooled to 0°C. PPh₃ (1.265 g, 4.82 mmol, 1.1 eq.) and CBr₄ (1.60 g, 4.82 mmol, 1.1 eq.) were added subsequently. After stirring for 5 min the reaction was diluted with pentane (100 mL) and filtered through a short Celite® pad, which was washed with pentane (200 mL). The filtrate was carefully concentrated at reduced
pressure (350 torr). The resultant residue was dissolved in pentane (150 mL) and the mixture was sonicated for 2 min, which was filtered through a short Celite® pad and washed with pentane (200 mL). The filtrate was carefully concentrated at reduced pressure (350 torr). The resultant allylic bromide was essentially pure and was dissolved in acetonitrile (30 mL) and triphenylphosphine (1.5 g, 5.70 mmol, 1.3 eq.) was added. The clear mixture stirred for 16 hours at RT. The reaction was extracted with hexanes (6 x 50 mL) to remove excess PPh₃ and the acetonitrile layer was dried over MgSO₄ and concentrated. The compound was dissolved in benzene (15 mL) and concentrated to yield Wittig salt 28 (1.40 g, 73% over 3 steps) as a white foam. Note: Precursor compounds were carried through with residual solvent to avoid removing compound during concentration and yields are based on total isolated yield of Wittig salt 28 at the end. [α]D²³ = +4.7 (c = 0.17, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.86-7.59 (m, 15H), 5.79 (m, 1H), 5.54 (m, 1H), 5.27 (m, 1H), 4.86-4.55 (m, 4H), 2.77 (m, 1H), 0.92 (d, J = 8.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.8 (d, J = 13.1 Hz), 141.0 (d, J = 3.3 Hz), 134.9 (d, J = 5.5 Hz), 134.1, 134.0, 132.9 (d, J = 2.7 Hz), 132.5, 132.4, 130.3, 130.2, 129.1, 128.9, 128.8, 118.6, 117.9, 113.7, 113.1 (d, J = 9.8 Hz), 40.7 (d, J = 2.4 Hz), 28.0 (d, J = 48.2 Hz), 19.2; HRMS (ESI) m/e 357.1769 [M–Br⁺] calcd for C₂₅H₂₆P⁺: 357.1767.
Polyene (29): To a stirred solution of phosphonate 28 (1.40 g, 2.72 mmol) in THF (13.6 mL) at -78°C was added n-butyl lithium (n-BuLi) (1.8 mL, 2.72 mmol, 1.6M in hexanes) dropwise and this solution turned deep red in color and continued to stir for 1 hr at this temperature. Then aldehyde 15 (0.93 g, 2.72 mmol) in THF (13.6 mL) was added to this solution dropwise. After stirring at -78°C for 5 minutes the reaction was quenched with sat. NH₄Cl solution (40 mL) and warmed to RT. The reaction was extracted with ether (3 x 100 mL). All organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The resulting product was purified through neutralized (Et₃N, 5%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 3:1) to yield polyene 29 (0.68 g, 59%) as a clear oil and inseparable E/Z isomeric mixture (E:Z = ca. 3:2). R₁ = 0.50 (silica gel, hexanes:EtOAc, 5:1); [α]D²³ = -19.5, (c = 2.67, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (E:Z = ca. 3:2) δ 7.35-7.25 (m, 5H), 7.18 (d, J = 6.9 Hz, 2H), 6.10-5.97 (m, 2H), 5.77 (m, 1H), 5.56 (m, 1H), 5.38-4.92 (m, 2H), 4.70 (m, 1H), 4.23 (t, J = 8.6 Hz, 1H), 4.14 (dd, J = 5.8, 9.2 Hz, 1H), 3.33 (dd, J = 3.5, 13.8 Hz, 1H), 2.88 (m, 1H), 2.81 (dd, J = 9.7, 13.8 Hz, 1H), 2.23-1.90 (m, 4H), 1.90 (s, 3H), 1.55-1.24 (m, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) (E:Z = ca. 3:2). δ 171.9, 153.1, 152.1, 142.6, 142.5, 140.3, 140.2, 138.0, 135.7, 135.2, 131.7, 131.2, 130.4, 129.5, 129.4, 129.1, 128.9, 128.9, 127.3, 124.4, 113.1, 112.9, 105.9, 66.3, 55.5, 40.5, 40.3, 40.0, 37.6, 35.0, 35.0, 34.7, 33.2, 33.0, 26.1, 26.1, 19.8, 19.7, 19.4, 19.4, 13.5, 13.5; HRMS (ESI) m/e 444.2510 [M+Na⁺] calcd for C₂⁷H₃₅NO₃Na⁺: 444.2509.
Decalin (30): To a stirred solution of 29 (0.68 g, 1.61 mmol) in CH₂Cl₂ (161 mL) at -78°C was added Me₂AlCl (8.1 mL, 8.06 mmol, 1M in hexanes, 5 eq.) dropwise. The reaction mixture was then warmed to 0°C and continued to stir at this temperature for 3 hrs. The reaction was quenched with saturated NaHCO₃ solution (100 mL) and the mixture was ran through a Celite® plug followed by a rinse with CH₂Cl₂ (100 mL). The reaction was extracted with CH₂Cl₂ (3 x 50 mL). All organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by silica column chromatography (hexanes: EtOAc, 200:1 to 3:1) to yield decalin 30 (171 mg, 42% from the E isomer) as a white foam. $R_f = 0.50$ (silica gel, hexanes:EtOAc, 4:1); $[\alpha]_D^{23} = -75.5, (c = 0.5, CHCl₃)$; $^1$H NMR (500 MHz, CDCl₃) δ 7.30 (m, 5H), 5.92 (m, 1H), 5.44 (m, 2H) 4.97 (m, 2H), 4.48 (m, 1H), 4.14 (m, 2H), 3.57 (d, $J = 13.2$ Hz, 1H), 3.28 (br s, 1H), 2.71 (dd, $J = 10.9, 13.2$ Hz, 1H), 2.22 (s, 1H), 2.08-1.90 (m, 3H), 1.82-1.31 (m, 6H), 1.34 (s, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 176.7, 152.6, 144.1, 136.1, 132.0, 129.6, 129.0, 127.3, 123.6, 113.3, 66.3, 59.5, 52.0, 45.8, 44.9, 39.9, 39.3, 37.2, 32.9, 31.8, 27.8, 23.4, 18.8, 16.4, 13.8; HRMS (ESI) m/e 444.2510 [M+Na⁺] calcd for C₂₇H₃₅NO₃Na⁺: 444.2509.
Decalin aldehyde (31): To a stirred solution of 30 (170 mg, 0.40 mmol) in CH₂Cl₂ (5 mL) at 0°C was added diisobutylaluminum hydride (DIBAL-H) (2.02 mL, 2.02 mmol, 1M in hexanes) dropwise. This solution stirred at room temperature for 3 hours before being cooled down to 0°C. The reaction was diluted with ether (15 mL) and then water (0.1 mL), aqueous 15% NaOH (0.1 mL), and water (0.2 mL) were added subsequently dropwise. The solution was warmed to room temperature and stirred for 30 minutes. Then magnesium sulfate was added and stirred for an additional 15 minutes. The solution was filtered, concentrated and ran through a short silica plug (hexanes:EtOAc, 4:1) to yield the crude alcohol. The resultant crude alcohol was dissolved in CH₂Cl₂ (5 mL) and sodium bicarbonate (203 mg, 2.42 mmol) and Dess-Martin periodinane (341 mg, 0.81 mmol) were subsequently added at room temperature. After stirring for 30 minutes the reaction was diluted with a 1:1 mixture of water and saturated sodium thiosulfate solution (10 mL) and stirred at rt for 30 minutes. Then the solution was extracted with CH₂Cl₂ (3 x 20 mL), dried over Na₂SO₄, and concentrated. The crude product was purified by silica column chromatography (pure hexanes, then hexanes:EtOAc, 100:1 to 5:1) to yield aldehyde 31 (77 mg, 78% over 2 steps) as a clear oil. R<sub>f</sub> = 0.55 (silica gel, hexanes:EtOAc, 4:1); [α]<sub>D</sub><sup>24</sup> = -46.6 (c = 0.22, CHCl₃); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 9.70 (s, 1H), 5.79 (m, 1H), 5.50 (m, 2H), 4.97 (m, 2H), 2.43 (m, 1H), 2.07 (m, 2H), 1.70-1.16 (m, 8H), 1.04 (d, J = 6.9 Hz, 3H), 1.03 (s, 3H), 0.99 (d, J = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ 208.4, 143.9, 133.0, 124.5, 114.0, 50.8, 50.2, 41.3, 38.9, 38.5, 32.2, 31.0, 27.7, 21.9, 18.3, 17.2, 15.8; HRMS (ESI) m/e 247.2054 [M+H<sup>+</sup>] calcd for C<sub>17</sub>H<sub>27</sub>O<sup>+</sup>: 247.2056.
**TBDPS Roche ester (32_1):** To methyl (R)-(−)-3-hydroxy-2-methylpropionate (10.00 g, 85 mmol) in DMF (106 mL) at 0°C was added imidazole (11.53 g, 169 mmol) followed *tert*-butyldiphenylchlorosilane (23.1 mL, 89 mmol) dropwise. After stirring at RT for 2 hrs the reaction was diluted water (75 mL) and hexanes (200 mL). The aqueous layer was extracted with hexanes (3 × 75 mL), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude compound was purified by silica column chromatography (hexanes:Et$_2$O, 200:1 to 5:1) to yield 32_1 (30.2 g, 100%) as a clear oil. $R_f$ = 0.50 (silica gel, hexanes:EtOAc, 9:1); [α]$_D^{23}$ = −9.8 (c = 0.2, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67-7.37 (m, 10H), 3.83 (dd, $J$ = 7.0, 9.8 Hz, 1H), 3.73 (dd, $J$ = 5.8, 9.8 Hz, 1H), 3.70 (s, 3H), 2.73 (m, 1H), 1.17 (d, $J$ = 7.1 Hz, 3H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 175.4, 135.6, 133.4, 129.7, 127.7, 65.9, 51.6, 42.4, 26.7, 19.2, 13.5; HRMS (ESI) m/e 379.1705 [M$^+$Na$^+$] calcd for C$_{21}$H$_{28}$O$_3$SiNa$: 379.1700$.\(^{269-271}\)

**Aldehyde (33):** To methyl ester 32_1 (30.2 g, 85 mmol) dissolved in hexanes (607 mL) at -78°C was added DIBAL-H (93 mL, 93 mmol, 1M in hexanes) via a syringe pump over 3 hours. This reaction continued to stir at -78°C for 2 hrs until the reaction was diluted with ether (300 mL) and water (3.7 mL), aqueous 15% NaOH (3.7 mL), and water (4.8 mL) were added slowly. The mixture warmed to rt for 30 minutes and then MgSO$_4$ was added and stirred for an additional 15 minutes. The solution was
filtered and concentrated to yield aldehyde 33 (24.89 g, 90%). This compound was used as is to the next step. $R_f = 0.50$ (silica gel, hexanes:EtOAc, 9:1); $[\alpha]_{D}^{23} = -11.1$ ($c = 0.8$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.76 (d, $J = 1.8$ Hz, 1H), 7.64-7.36 (m, 10H), 3.90 (dd, $J = 4.0$, 9.8 Hz, 1H), 3.84 (dd, $J = 6.9$, 10.3 Hz, 1H), 2.56 (m, 1H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.03 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 204.6, 135.7, 133.2, 129.9, 127.9, 64.2, 48.9, 26.8, 19.3, 10.4; HRMS (ESI) m/e 349.1602 [M+Na$^+$] calcd for C$_{20}$H$_{26}$O$_2$SiNa$^+$: 349.1600.

Ethyl ester (33_1): To a solution of aldehyde 33 (24.89 g, 76 mmol) in CH$_2$Cl$_2$ (305 mL) was added (carbethoxymethylene)triphenylphosphorane (27.9 g, 80 mmol) portionwise at RT. The reaction stirred overnight and upon completion the reaction was concentrated and then taken up in hexanes (500 mL) and sonicated for 2 minutes before filtering the solution through a Celite® plug. The Celite® plug was rinsed with hexanes (200 mL) and concentrated. This procedure was repeated 1-2 more times until the triphenylphosphine oxide was removed to yield ethyl ester 33_1 (26.9 g, 89%) as a clear oil. $R_f = 0.50$ (silica gel, hexanes:EtOAc, 9:1); $[\alpha]_{D}^{23} = -10.1$ ($c = 0.5$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67-7.36 (m, 10H), 6.97 (dd, $J = 7.2$, 15.8 Hz, 1H), 5.84 (dd, $J = 1.2$, 15.8 Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.58 (m, 2H), 2.56, (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.7, 151.4, 135.6, 133.5, 129.7, 127.7, 121.0, 67.5, 60.2, 39.1, 26.8, 19.3,
15.6, 14.3; HRMS (ESI) m/e 419.2010 [M+Na\(^+\)] calcd for C\(_{24}\)H\(_{32}\)O\(_3\)SiNa\(^+\): 419.2013.\(^{269-271}\)

![TBDPSO](image)

**Allylic alcohol (34):** To a solution of ethyl ester 33_1 (26.9 g, 67.8 mmol) in CH\(_2\)Cl\(_2\) (136 mL) at 0°C was added DIBAL-H (203 mL, 203 mmol, 1M in hexanes) dropwise via an addition funnel. About 5 minutes later the reaction was diluted with ether (400 mL) and water (8.1 mL), aqueous 15% NaOH (8.1 mL), and water (10 mL) were added slowly. The mixture warmed to rt for 30 minutes and then MgSO\(_4\) was added and stirred for an additional 15 minutes. The solution was filtered and concentrated to yield alcohol 34 (21.88 g, 91%). This compound was used as is to the next step. \(R_f=0.39\) (silica gel, hexanes:EtOAc, 4:1); \([\alpha]_D^{23} = -9.2\) (c = 0.3, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.67-7.34 (m, 10H), 5.62 (m, 2H), 4.06 (t, \(J = 5.2\) Hz, 2H), 3.55 (dd, \(J = 6.3, 10.3\) Hz, 1H), 3.50 (dd, \(J = 6.3, 9.7\) Hz, 1H), 2.40, (m, 1H), 1.05 (s, 9H), 1.03 (d, \(J = 6.9\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 135.7, 133.9, 132.3, 129.5, 128.7, 127.6, 68.5, 63.9, 39.0 26.7, 19.3, 16.4; HRMS (ESI) m/e 377.1899 [M+Na\(^+\)] calcd for C\(_{22}\)H\(_{30}\)O\(_2\)SiNa\(^+\): 377.1907.\(^{269-271}\)

![TBDPSO](image)

**Bromide (34_1):** To a solution of alcohol 34 (21.88 g, 61.7 mmol) in CH\(_2\)Cl\(_2\) (617 mL) at 0°C was added PPh\(_3\) (17.80 g, 67.9 mmol) and CBr\(_4\) (22.51 g, 67.9 mmol) portionwise. After 10 minutes the reaction was diluted with hexanes (500 mL) and filtered through a Celite\(^\circledR\) plug, which was rinsed with additional hexanes (200 mL)
and concentrated. The crude extract dissolved in hexanes (400 mL) and sonicated for 2 minutes before being filtered through a Celite® plug which was rinsed with additional hexanes (100 mL) and concentrated. This procedure was repeated 1-2 more times until the triphenylphosphine oxide was removed to yield bromide 34_1 (22.67 g, 88%) as a light yellow oil. $R_t = 0.62$ (silica gel, hexanes: EtOAc, 9:1); $[\alpha]_D^{23} = -8.7$ ($c = 0.7$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67-7.36 (m, 10H), 5.72 (m, 2H), 3.95 (dd, $J = 1.6$, 3.7 Hz, 2H), 3.53 (dd, $J = 1.2$, 6.5 Hz, 2H), 2.43 (m, 1H), 1.06 (s, 9H), 1.03 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 138.9, 135.6, 133.7, 129.6, 127.6, 126.1 68.2, 38.9, 33.6, 26.9, 19.3, 16.1; HRMS (ESI) m/e 439.1070 [M+Na$^+$] calcd for C$_{22}$H$_{29}$OSiBrNa$^+$: 439.1069.

**Wittig salt (35):** To a solution of bromide 34_1 (22.67 g, 54.3 mmol) in MeCN (272 mL) was added PPh$_3$ (15.67 g, 59.7 mmol) and stirred for 18 hours at rt. Then the reaction was extracted with hexanes (6 x 300 mL) and the MeCN layer was dried over Na$_2$SO$_4$ and concentrated. The compound was dissolved in benzene (50 mL) and concentrated to yield Wittig salt 35 (35.1 g, 95%) as a white foam. $[\alpha]_D^{23} = -4.3$ ($c = 0.26$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83-7.60 (m, 25H), 5.71 (m, 1H), 5.34 (m, 1H), 4.74 (m, 2H), 3.36 (dd, $J = 5.8$, 9.9 Hz, 1H), 3.26 (dd, $J = 7.2$, 10.0 Hz, 1H), 2.29 (m, 1H), 0.98 (s, 9H), 0.89 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 135.5, 135.5, 134.9, 134.9, 134.0, 134.0, 130.3, 130.2, 129.7, 128.3, 127.7, 127.7, 118.6, 117.9, 67.8 (d, $J = 4.4$ Hz), 39.8 (d, $J = 2.5$ Hz), 28.1 (d, $J = 48.2$ Hz), 26.8, 19.2, 16.4; HRMS (ESI) m/e 599.2896 [M–Br$^-$$]$ calcd for C$_{40}$H$_{44}$O$_2$P$_2$Si$^2$+: 599.2899.
Polyene 36: To a stirred solution of phosphonate 35 (11.6 g, 17.1 mmol) in THF (90 mL) at -78°C was added n-butyl lithium (n-BuLi) (6.83 mL, 17.1 mmol, 2.5M in hexanes) dropwise and this solution turned deep red in color and continued to stir for 1 hr at this temperature. Then aldehyde 15 (5.86 g, 17.1 mmol) in THF (90 mL) was added to this solution dropwise. After stirring at -78°C for 5 minutes the reaction was quenched with sat. NH₄Cl solution (160 mL) and warmed to rt. The reaction was extracted with ether (3 x 300 mL). All organic layers were washed with brine (200 mL), dried over Na₂SO₄, and concentrated. The resulting product was purified through neutralized (Et₃N, 5%) silica column chromatography (pure hexanes, then hexanes:EtOAc, 500:1 to 5:1) to yield polyene 36 (6.91 g, 61%) as a clear oil and inseparable isomeric mixture (E:Z = ca. 3:2). Rᵣ = 0.63 (silica gel, hexanes:EtOAc, 7:3); [α]D²³ = -10.0, (c = 0.75, CHCl₃); ¹H NMR (500 MHz, CDCl₃) (E:Z = ca. 3:2) δ 7.65-7.18 (m, 15H), 6.30-5.97 (m, 3H), 5.62-5.46 (m, 2H), 4.70 (m, 1H), 4.22 (m, 1H), 4.13 (m, 1H), 3.56-3.44 (m, 2H), 3.33 (m, 1H), 2.80 (m, 1H), 2.53 (br s, 1H), 2.44-2.00 (m, 5H), 1.90 (s, 3H), 1.72-1.30 (m, 2H), 1.05 (d, J=7.5 Hz, 3H), 1.04 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) (E:Z = ca. 3:2) δ 171.9, 153.2, 140.4, 135.6, 135.2, 134.8, 134.6, 134.0, 133.9, 131.9, 131.0, 130.4, 130.0, 129.7, 129.5, 129.5, 128.9, 127.7, 127.6, 127.3, 68.6, 66.3, 55.5, 40.0, 39.3, 37.5, 35.0, 33.0, 26.9, 26.6,

Decalin (37): To a stirred solution of 36 (6.91 g, 10.41 mmol) in CH₂Cl₂ (210 mL) was added iodine (132 mg, 0.52 mmol). The reaction mixture was irradiated with visible light (sunlamp, visible light) for 10 minutes. (caution: keep the flask a few feet from the light source to avoid the heating-induced IMDA reaction). The mixture was further diluted with CH₂Cl₂ (830 mL) and cooled to -78°C at which time Me₂AlCl (52 mL, 52.0 mmol, 1M in hexanes) was added dropwise. The reaction mixture was then warmed to 0°C and continued to stir at this temperature for 2 hrs. The reaction mixture was quenched with sat. NaHCO₃ solution (300 mL) and the mixture was ran through a Celite® plug followed by a rinse with CH₂Cl₂ (300 mL). The reaction was extracted with CH₂Cl₂ (2 x 100 mL). All organic layers were dried over Na₂SO₄ and concentrated. The crude extract was purified by silica column chromatography (hexanes:EtOAc, 200:1 to 2:1) to yield decalin 37 (3.67 g, 52%) as a white foam. Rᵣ = 0.66 (silica gel, hexanes:EtOAc, 4:1); [α]D²⁴ = -70.5 (c = 0.63, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.72-7.31 (m, 15H), 5.44 (d, J = 9.7 Hz, 1H), 5.32 (m, 1H), 4.51 (m, 1H), 4.11 (m, 2H), 3.64 (dd, J = 5.2, 9.7 Hz, 1H), 3.56 (d, J = 13.2 Hz, 1H), 3.46 (t, J = 9.2 Hz, 1H), 3.38 (s, 1H), 2.59 (t, J = 12.6 Hz, 1H), 2.19 (s, 1H), 2.07-1.43 (m, 9H), 1.36 (s, 3H), 1.07 (s, 9H), 1.02 (d, J = 7.5 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H); ¹³C NMR
79

(125 MHz, CDCl₃) δ 176.3, 152.1, 136.1, 135.6, 134.8, 134.1, 133.9, 131.9, 129.5, 128.9, 127.1, 123.8, 68.7, 66.0, 59.1, 51.7, 44.8, 42.6, 39.7, 39.0, 36.9, 32.9, 31.9, 27.8, 26.8, 23.4, 19.3, 18.8, 15.9, 13.1; HRMS (ESI) m/e 686.3637 [M+Na⁺] calcd for C₄₂H₅₃O₄SiNa⁺: 686.3636.

Decalin (38): To a solution of 37 (600 mg, 0.9 mmol) in CH₂Cl₂ (18.1 mL) at -78°C was added DIBAL-H (4.52 mL, 4.52 mmol, 1M in hexanes) dropwise. This solution continued to stir at this temperature for 1 hr and then at 0°C for 1 hr before being diluted with ether (20 mL) and then water (0.18 mL) was added dropwise and then warmed to RT for 30 minutes. Then some MgSO₄ was added and stirred for an additional 15 minutes before being filtered and ran through a silica plug (hexanes, then hexanes:EtOAc 9:1) to isolate the crude alcohol (244 mg). Then the alcohol was dissolved in DMSO (2.2 mL) and cooled to 0°C and IBX (209 mg, 0.75 mmol) was added in one portion. The reaction continued to stir at RT for 1 hrs before being diluted with water (5 mL). Then the solution was filtered through a Celite® plug which was rinsed with ether (10 mL). The filtrate was extracted with ether (5 x 5 mL) and all organic layers were washed with brine (10 mL) and 10% NaOH solution (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to yield decalin aldehyde 38 (216 mg, 49% over two steps) as a clear oil. Rf = 0.57 (silica gel, hexanes:EtOAc, 9:1); [α]D₂₃ = -54.4 (c = 1.29, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.65 (s, 1H), 7.69-7.38 (m, 10H), 5.52 (d, J = 10.3 Hz, 1H), 5.36 (m, 1H), 3.43 (m,
2H), 2.50 (m, 1H), 2.19 (s, 1H), 2.07 (m, 1H), 2.01-1.22 (m, 9H), 1.08 (s, 3H), 1.06 (s, 9H), 1.02 (d, J = 7.3 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 208.3, 135.6, 133.6, 133.2, 129.7, 127.7, 123.2, 67.3, 50.6, 44.6, 41.6, 38.9, 36.7, 32.3, 31.1, 27.7, 26.9, 22.0, 19.3, 18.4, 16.1, 14.2; HRMS (ESI) m/e 511.3009 [M+Na$^+$] calcd for C$_{32}$H$_{44}$O$_2$SiNa$^+$: 511.3008.

3. List of Spectra
Spectrum 2.01: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 11_1
Spectrum 2.02: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 11_1
Spectrum 2.03: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 12
Spectrum 2.04: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 12
Spectrum 2.05: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 12_1
Spectrum 2.06: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 12_1
Spectrum 2.07: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 12_2
Spectrum 2.08: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 12_2
Spectrum 2.09: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 15
Spectrum 2.10: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 15
Spectrum 2.11: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 16
Spectrum 2.12: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 16
Spectrum 2.13: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 18
Spectrum 2.14: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 18
Spectrum 2.15: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 18 isomerized
Spectrum 2.16: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 18 isomerized
Spectrum 2.17: ^1^H NMR (CDCl₃, 500 MHz) of compound 19
Spectrum 2.18: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 19
Spectrum 2.19: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 19 isomerized
Spectrum 2.20. $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 19 isomerized
Spectrum 2.21: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 22
Spectrum 2.22: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 22
Spectrum 2.23: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 22
Spectrum 2.24: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 23
Spectrum 2.25: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 23
Spectrum 2.26: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 23
Spectrum 2.27: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 20
Spectrum 2.28: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 20
Spectrum 2.29: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 20
Spectrum 2.30: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 21
Spectrum 2.31: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 21
Spectrum 2.32: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 21
Spectrum 2.33: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 28
Spectrum 2.34: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 28
Spectrum 2.35: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 29
Spectrum 2.36: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 29
Spectrum 2.37: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 30
Spectrum 2.38. $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 30
Spectrum 2.39: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 30
Spectrum 2.40: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 31
Spectrum 2.41: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 31
Spectrum 2.42: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 32_1
Spectrum 2.43: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 32_1
Spectrum 2.44: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 33
Spectrum 2.45: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 33
Spectrum 2.46: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 33_1
Spectrum 2.47: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 33_1
Spectrum 2.48: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 34
Spectrum 2.49: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 34
Spectrum 2.50: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 34_1
Spectrum 2.51: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound $34_1$
Spectrum 2.52: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 35
Spectrum 2.53: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 35
Spectrum 2.54: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 36
Spectrum 2.55: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 36
Spectrum 2.56: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 37
Spectrum 2.57: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 37
Spectrum 2.58: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 37
Spectrum 2.59: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 38
Spectrum 2.60: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 38
Chapter 3: Synthetic Studies Towards the Total Synthesis of Maklamicin
A. Introduction

In 1990, Masumota et al. isolated PA-46101A (4) and B (5), figure 3.01, as the first example of a spirotetronate containing a C\textsubscript{11} macrocycle and exhibited an unusual acyl-oxy functionality connecting the decalin moiety to the spirotetronate ring\textsuperscript{50} with chlorothricin\textsuperscript{11} being the only other example. More recently Igarashi et al. has isolated more examples of the spirotetronates containing the C\textsubscript{11} macrocycle: maklamicin (1),\textsuperscript{17} 29-deoxymaklamicin (2),\textsuperscript{272} and nomimicin (3)\textsuperscript{130}. These compounds and in particular maklamicin have excited the scientific community as these class II spirotetronates exhibit biological activity in the absence of glycosylation.\textsuperscript{17,130,272} Maklamicin (1) was isolated from the bacteria Micromonospora sp. GMKU326 found on the roots of the plant Abrus pulchellus in Thailand. Maklamicin exhibits strong to moderate activity in multiple bacterial lines including the following bacteria with MIC values: Micrococcus luteus 0.2 µg/ml, Bacillus subtilis 1.7 µg/ml, and Bacillus cereus 6.5 µg/ml. Maklamicin also exhibited potent anticancer activity in the following cell lines: IC\textsubscript{50}: HeLa cells 17 µM and MCF7 cells 34 µM.\textsuperscript{17} This data is consistent with the history of spirotetronate polyketides being known as antitumor antibiotics.\textsuperscript{222} Maklamicin’s isolation has peaked the interest of chemists with 55 papers citing its isolation but the only synthetic study towards this molecule has been my own illustrated in chapter 2.\textsuperscript{273} Herein this chapter I will go through a few of my strategies in my attempts to complete the first total synthesis of maklamicin and my insight on certain structural features that inhibited the completion of this molecule in the laboratory.
Figure 3.01: Examples of class II spirotetronates containing an 11-membered macrocycles

**B. Biosynthesis of Maklamicin**

Igarashi et al. elucidated the exact biosynthetic sequence of maklamicin (1) last year. Maklamicin’s biosynthesis follows in form with the generalized biosynthetic process presented in figure 1.03 in chapter 1. Polyketide synthase type I (PKS I) elongates the chain adding units of acetyl CoA and propionyl CoA. As soon as the carbon chain elongation completes, an IMDA reaction occurs forming the decalin ring 7 in figure 3.02. Incorporation of 9 under guidance of MakB1 constructed tetronate 10. Elimination across C4-C5 bond forms the olefin on the tetronate ring in 11. With the defined dienophile in 11, a second IMDA occurs to form the spirotetronate ring in 12.
Oxidation at C29 under direction of MakC2 relinquishes the final structure of maklamicin (I). \(^{274}\)

Figure 3.02: Biosynthesis of maklamicin

The exact mechanism of how the Diels-Alder reaction occurs biosynthetically has been a mystery that has plagued scientists for the past few decades. Kuzuyama and coworkers showed protein VstJ in spirotetronate biosynthesis of the Diels-Alderase protein facilitating the IMDA of the spirotetronate moiety. \(^{276}\) Race and coworkers elaborated on this discovery got the first X-ray crystal structure of spirotetronate cyclase AbyU and in conjugation with molecular simulations got a more definitive
look on how these proteins actually catalyze the IMDA reaction. Additionally they used different IMDA precursors of abyssomicin to illustrate that this protein can catalyzed the IMDA reaction on substrates that researchers couldn’t force to cyclize on the benchtop in the laboratory. This discovery could help facilitate the use of biological systems in the synthesis of the spirotetronates in the laboratory setting.\textsuperscript{277}

C. First Generation Synthesis Towards Maklamicin

![Image of retrosynthesis diagram]

Figure 3.03: Retrosynthesis of nature-inspired route towards maklamicin

Inspired by the proposed biosynthesis, my retrosynthetic approach to maklamicin proposed a late stage IMDA to generate the spirotetronate unit of maklamicin. To build this framework I proposed utilizing an anionic coupling between the spirotetronate template and the decalin aldehyde. The skipped triene could attach to the handle off the decalin moiety through a cross-metathesis reaction that could
dramatically reduce the number of steps required to install the diene template. The key
formation of the decalin moiety template would be formed via an IMDA reaction
(illustrated in chapter 2\textsuperscript{273}). The skipped triene would be rapidly assembled by a one
pot hydrostannylation/ Stille coupling sequence from known compounds.

![Chemical structure diagram]

Figure 3.04: Synthesis of known precursors.

The synthesis of vinyl iodide 16 was prepared from known sequence illustrated
in figure 3.04.\textsuperscript{278} Commercially available 13 and 14 are coupled to synthesize pent-en-
yne 15 with a time consuming distillation to remove THF from the reaction.\textsuperscript{279} The
methyl zirconation/iodination sequence was initially troublesome to make the vinyl
iodide due to an incorrect time table from the literature procedure. After alterations
though, the reaction worked as expected and on gram scale.\textsuperscript{278} The synthesis of the
alkynyl ester 19 proceeded smoothly on decagram scale through an epoxide opening
Synthesis of the tetronate moiety 21 proceeded through a high yielding Hofmann elimination sequence.\(^{186}\)

![Synthesis diagram]

Figure 3.05: Synthesis of triene template

I was looking for a rapid assembly of triene 25 (figure 3.05), which will lay the framework for the diene that will be utilized in the second IMDA. Past syntheses of related spirotetronates most commonly used a HWE reaction, which increased the step count through installation of phosphonate esters.\(^{171,172,281}\) With inspiration from the work of Cai and coworker I sought to use alkyne 19 and undergo a one-pot hydrostannylation with palladium tetrakis and tributyltin hydride followed by a Stille coupling with known vinyl iodide 16 and copper (I) bromide.\(^{282}\) This reaction proceeded in the laboratory to yield a ~1:1 mixture the lactone 24 and ethyl ester 23 in 42% yield on multi-gram scale. The reaction performed 2 transformations with only 2 mol % of palladium. NOESY correlation confirmed the desired (E,Z) conformation of...
the newly formed diene. This mixture was reduced with DIBAL-H to the corresponding diol, which protected with TBS yielding 25 (77% over 2 steps).

Decalin aldehyde 26 and triene 25 were refluxed in DCM with 5 mol% of Grubbs second generation catalyst to yield 27 in 45% yield. The cross metathesis reaction worked as expected, but this reaction experienced scalability issues. The purification of the cross-metathesis product was only possible on preparative TLC due to the polarity of the product and the excess triene being very similar in Rf. Nucleophilic attack of the aldehyde 27 with lithiated butenolide 21 yielded a 1:1 diasteromeric mixture of alcohols. Oxidation of the alcohols with Dess-Martin periodinane yielded tetronate 28 in 51% yield over two steps. With challenges in the scalability of this route I sought to build a model system to test the conditions of the late stage IMDA with more sufficient material. This way I could screen many
conditions without wasting the precious late stage material after a few failed test reactions of the IMDA reaction.

![Chemical structures and reaction scheme]

Figure 3.07: Synthesis of model system for late-stage IMDA

The synthesis of the allyl aldehyde 30 was prepared through known protocols involving a Wittig reaction and alkylation chemistry (figure 3.07). Triene 25 and aldehyde 30 were refluxed with Grubbs second-generation catalyst to give 31 in 57% yield. The cross-metathesis for this model system was easier to purify than for the real system of 27 with the ability to purify on a silica column chromatography on hundreds of milligram scale and higher yield. The higher yield is likely due to an easier cross-metathesis without the adjacent methyl group to the allyl system. Anionic coupling
with lithiated tetronate 21 and subsequent oxidation yielded 32 (45% over two steps). With the set system for investigation of the IMDA, I screened many conditions to force any reaction on 5 mg scale. Lewis acid catalysis only resulted in the deprotection of the silyl groups with no observed cycloaddition even upon heating these systems. Upon traditional heating of 32, at 220°C I observed decomposition of the starting material with stabilizer m-cresol. In addition to the conditions above, I sought to also try different reaction concentrations of 0.07M, 0.01M, 0.006M, and 0.003M due to learning the importance of concentration for the facilitation of an IMDA from synthesis of the decalin moiety. I started heating these reaction at 110°C and slowly raising the temperature until I observed a reaction or decomposition of the starting materials. The silyl deprotected compound 33 unfortunately didn’t reveal more fruitful results and decomposed at 140°C in the presence of stabilizer. Demethylation of the tetronate moiety was not performed although this would be the biomimetic precursor for this reaction. Hoye and coworker tried this approach in their synthesis of okilactomycin D noting that the demethylated tetronate did not undergo cycloaddition reaction and decomposed more readily due to the instability of the tetronate moiety.163

Unsatisfied with these results I sought to look at the reactivity of this diene and dienophile of the Diels-Alder reaction in an intermolecular reaction. I was in disbelief that reaction did not work and I was curious if the length of the tether to make the 11-membered macrocycle was to blame for the difficulty in the IMDA reaction even though molecular models appeared that the diene and dienophile should line up perfectly for the cycloaddition.
Figure 3.08: Model system testing the reactivity of the diene and dienophile for Diels-Alder reaction

For the intermolecular case of the IMDA of this tetronate, I wanted to have a simple system that would match the electronics of the dienophile that I had been using for my previous studies. Using commercially available cyclohexyl aldehyde 36, I methylated the alpha position to yield 37. Anionic coupling with butenolide 21 and subsequent oxidation gave 38 in 45% yield. With 38 and 25 in hand, I tried varying equivalence of the dienophile and diene at 1.0M or 0.5M to force a Diels-Alder reaction. The intermolecular case suffered experimental limitations since the terminal olefin on 25 would migrate upon heating at 100°C. Using Lewis acid catalysis only resulted in deprotection of the TBS group and unfortunately no observed cycloaddition product 39. The limitations to this system I believe was due to the highly substituted (E,Z) diene being less reactive in Diels-Alder reactions. Similar dienes have shown reactivity in Diels-Alder reactions only with highly reactive acrolein derivatives being used as the dienophile.\textsuperscript{206,284} The tetronate as a dienophile is not as electron
withdrawing in character in comparison to an acrolein derivative. The electron density remains on the oxygens surrounding the tetronate carbon and would not delocalization as well from the double bond participating in the IMDA. Additionally, the methyl group attached to this diene creates more of a gauche interaction with the dienophile, which also makes it difficult for the orbitals of the diene to interact with those of the dienophile. These factors I believe inhibited the ability to lower the HOMO-LUMO energy gap for the IMDA reaction to occur.

**D. Second Generation Synthesis Toward Maklamicin**

![Image of retrosynthetic approach for ring-closing metathesis (RCM) method](image)

Figure 3.09: Retrosynthetic approach for ring-closing metathesis (RCM) method

For a second-generation approach to maklamicin (1), I sought to use a fragmented approach by building the spirotetronate 44 and decalin 26 separately and then connecting the 2 structures together via an anionic coupling followed by a ring closing metathesis (RCM).
Figure 3.10: Synthesis of exo spirotetronate

The Roush group pioneered the synthetic efforts of spirotetronate polyketides and using their methodology, I synthesized my exo spirotetronate using triene 25\textsuperscript{164,206}. α-Bromo-acrolein and triene 25 were treated with MeAlCl\textsubscript{2} at -78°C to produce the Diels-Alder product 40 (7:1 dr, 77% yield). Aldehyde 40 was reduced to the corresponding alcohol in quantitative yield and subsequently treated with NaOMe to close epoxide 41 (77% over two steps). Epoxide 41 was opened with thiophenol and the resultant sulfide was oxidized to the sulfoxide using mCPBA. The sulfone was dissolved in Ac\textsubscript{2}O and treated with 5 eq. of NaOAc and heated to 125°C to undergo a Pummer rearrangement to yield aldehyde 42 (36% over three steps). Aldehyde 42 was oxidized the carboxylic acid utilizing the Pinnick oxidation that was converted to
methyl ester 43 using Meerwein’s reagent (79% over two steps). Then methyl ester 43 was treated with LiHMDS to undergo a Dieckmann condensation followed by methylation with methyl sulfate to yield spirotetronate 44 in 71% yield. The overall process proceeded as expected from Roush’s protocols and similar yields to their work.

![Chemical structures and reactions](image)

**Figure 3.11:** Anionic coupling and ring closing metathesis (RCM)

With tetronate 44 and decalin 26 in hand I sought to connect the two compounds together. For this lithiation, LDA was not strong enough for this system and literature examples used tBuLi at -78°C.\(^{166}\) Spirotetronate 44 was deprotonated with tBuLi and the addition of decalin 26 to the prepared solution of 45 yielded a (1:1) diasteromeric mixture of the decalin alcohol. This mixture was subjected to a Dess-Martin periodinane oxidation and was surprised by the lack of reaction. Upon analysis
of the lowest energy conformer, it appears the resultant alcohol sits in a perfect position for hydrogen bonding to the carbonyl oxygen. The steric bulk of the spirotetronate moiety seems to favor this interaction over my previous studies using just the butenolide ring in the lithiation chemistry. For the tetronolide synthesis, which was the most similar to mine, they used a Ley oxidation so I decided to use these conditions. This reaction surprisingly took 6 days at room temperature in acetonitrile to yield 46 (64% over two steps). With 46 in hand I sought to perform the RCM reaction. Based on literature conditions, I screened all available Grubbs catalyst in the lab, Grubbs 1st and 2nd generation catalyst and the Grubbs-Hovedya 2nd generation catalyst at different catalyst loading on 2 mg scale reaction. Catalyst loading started at 2mol% at reflux 40°C and more catalyst was added to try to push reaction in DCM. I subjected the same reaction in toluene at 80 and 100°C with while increasing amount of catalyst. As a last resort I did subject this reaction at 150°C under microwave radiation and still could not force the RCM reaction. In fact no reaction was observed and noticed the decomposition of the starting material. Further reading prompted switching the reaction solvent to C₆F₆. This fluorinated solvent has been used in the literature to make the Grubbs catalyst even more reactive but no RCM product 48 was observed.

The system I developed for the RCM reaction is quite rigid. I was hoping that by using the alcohol I synthesized from the coupling on the spirotetronate 44 and decalin aldehyde 26 that this would have better axis of rotation. I tried the conditions above with no success on the alcohol substrate. I removed the silyl groups to give 47
to see if I could alter any steric constraints to make this reaction work but was unsuccessful. Despite the coupling of 2 terminal alkenes, the substrate for the intramolecular ring closing metathesis is quite rigid. Also the terminal alkenes are quite sterically hindered if you look at the structure of this molecule. With the large Grubbs catalyst with this rigid structure, it may have been difficult for both alkenes to come together.

E. Conclusions

I approached the total synthesis of maklamicin through 2 major routes. My first generation approach towards maklamicin’s synthesis revolved around a nature-inspired double IMDA strategy. This strategy unfortunately failed three steps away from the natural product due to the inability to force the IMDA reaction to form the spirotetronate ring. The second-generation approach involved a fragmented approach that synthesized the decalin and spirotetronate moieties separately followed by connecting the 2 pieces to form of the macrocyclic motif. Anionic coupling proceeded as expected, but unfortunately the RCM did not work in my hand. I had one last strategy planned out for the synthesis of maklamicin. This route would include an intramolecular Julia olefination as the final step to close the macrocyclic ring of maklamicin as opposed to a ring closing metathesis. This strategy ultimately was not pursued to do the lacking novelty of strategy since this was heavily based on methodology developed by Yoshii and Roush. Also the Julia coupling would add an additional 8 steps to the synthesis due to setting up the functionalities of the sulfone and aldehyde.
F. Experimental Information

1. General Procedures

Unless indicated, all commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH2Cl2), and dimethylformamide (DMF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using Hexanes-EtOAc or CH2Cl2-MeOH mixtures of increasing polarity. The progress of all the reactions were monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F254 to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of KMnO4 stain or Seebach’s stain followed by heating. 13C NMR and 1H NMR spectra were recorded on either 500 MHz Varian instrument or 500 MHz JEOL instrument. CDCl3 was treated with flame dried K2CO3, chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference (CDCl3), with the abbreviations s, br s, d, t, q, m, td, dt and qd denoting singlet, broad singlet, doublet, triplet, quartet, multiplet, quartet of doublets, triplet of doublets, doublet of triplets and quartet of doublets respectively. J = coupling constants given in Hertz (Hz). IR spectras were collected on a Jasco 4100 FTIR. High resolution Mass
spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade anhydrous CHCl₃.

2. Preparation of Compounds

\[ \text{Pentenyne 15:} \] To a solution of 0.5 M ethynylmagnesium bromide in THF (400 ml, 200 mmol) was added copper (I) bromide (1.4 g, 10 mmol) and allyl bromide (17.8 ml, 210 mmol) at 0°C. After stirring overnight at 23°C, the reaction mixture was quenched with aqueous NH₄Cl (300 ml), extracted with decalin (3 x 150 ml), washed with brine (100 ml), and dried over MgSO₄. The filtrate was subjected to a fractional distillation to give a mixture of pent-1-en-4-yn and THF. To this resultant mixture was added decalin (300 ml) and was washed with water (100 ml x 20). The organic layer was then washed with brine (100 ml), dried over MgSO₄, and filtered. A fractional distillation gave pent-1-en-4-yn 15 (6.6 g, 50%, bp 39°C). This material matched what was previously reported in the literature.²⁸⁶,²⁸⁷

\[ \text{Vinyl Iodide 16:} \]
To a solution of bis(cyclopentadienyl)zirconium dichloride, ZrCl₂Cp₂ (1.747 g, 5.98 mmol) in dichloroethane, DCE (37 ml) at 0°C was added trimethylaluminum, Me₃Al (37.2 ml, 2M in hexanes, 74.7 mmol) dropwise and stirred at this temp for 10 minutes. Then the pent-1-en-4-yn (2.5 g, 29.9 mmol) was added dropwise to the solution and stirred at room temperature overnight. Then the reaction
was cooled to -78 and iodine (15.17 g, 59.8 mmol) in THF (17 ml) was added dropwise and stirred for 30 minutes at this temperature. Then the reaction was warmed to 0°C and stirred for 30 minutes. Then the reaction was quenched carefully with sodium thiosulfate (50 ml) until a white precipitate formed and filtered through a celite® plug and washed with 200 ml ether. To this solution was added 50 ml of water and extracted with ether (3 x 150 ml). All organic layers were washed with brine (100 ml) and dried over Na₂SO₄ and concentrated. The crude compound was purified by silica column chromatography (hexanes: Et₂O, 100% hexanes then 200:1, 10:1) to yield 16 (4.54 g, 73%) as yellow oil. This material matched what was previously reported in the literature.286

Alkynyl Alcohol 19: To a solution of ethyl propiolate (33.8 g, 344 mmol) in THF (594 ml) at -78°C was added n-BuLi (138 ml, 2.5M in hexanes, 344 mmol) dropwise and stirred at this temp for 30 minutes. Then (R)-propylene oxide (10 g, 172 mmol) was added dropwise followed by boron trifluoride diethyl etherate (42.4 ml, 344 mmol) dropwise. After 2 hrs at -78°C, the solvents were concentrated, diluted with CH₂Cl₂ (400 ml), and washed with saturated NH₄Cl solution (500 ml). The aqueous layer was extracted with CH₂Cl₂ (3 x 400 ml). Combined organic layers were dried over Na₂SO₄, and concentrated. The crude compound was purified by silica chromatography (hexanes: EtOAc, 10:1 to 1:1) to yield alkynyl alcohol 19 (22.05 g, 82%) as yellow oil. This material matched what was previously reported in the literature.288,289
**Diol 25_1:** To an RBF with the alkynyl alcohol 19 (15.0 g, 96 mmol) dissolved in benzene (384 ml), tetrakis(triphenylphosphine)palladium (0), Pd(PPh₃)₄ (2.22 g, 1.92 mmol, 2 mol%) and tributyltin hydride, Bu₃SnH (29.4 g, 101 mmol, 1.05 eq.) were added. This reaction stirred at rt for 4 hours. The solution was concentrated and dissolved in DMF (769 ml). Vinyl iodide 16 (10.79 g, 51.9 mmol), and copper (I) iodide (4.12 g, 21.6 mmol) were added and the reaction was heated to 70°C for 16 hours. The reaction was diluted with ether (500 ml), saturated KF solution (1L) and filtered through celite®. The reaction was extracted with ether (3 x 500 ml). The combined organic layers were washed with brine (750 ml), dried over Na₂SO₄, and concentrated. The crude residue was purified through column chromatography (hexanes:EtOAc, 200:1 to 2:1) to yield a mixture of lactone 24 and ethyl ester 23. To this mixture in CH₂Cl₂ (290 ml) at 0°C was added diisobutylaluminum hydride (DIBAL-H) (114 ml, 1M) dropwise. 1.5 hrs later the reaction was diluted with 300 ml ether and water (4.6 ml), 15% aq. sodium hydroxide (4.6 ml), and water (2.3 ml) were added sequentially and warmed to room temperature for 30 minutes. Then anhydrous magnesium sulfate was added and stirred 15 minutes, filtered, and concentrated to yield diol 25_1 (5.11 g, 45% over two steps) as a clear oil. *R*<sub>t</sub> = 0.15 (silica gel, hexanes: EtOAc, 2:1); [α]<sub>D</sub><sup>24.5</sup> = −12.8 (c = 0.5, CHCl₃); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 5.81 (m, 2H), 5.49 (t, *J* = 10.0, 1H), 5.04 (m, 2H), 4.21 (d, *J* = 14.4, 1H), 4.05 (d, *J* = 14.4, 1H), 3.88 (m, 1H), 2.79 (d, *J* = 8.75, 2H), 2.34 (m, 2H), 1.79 (s, 3H), 1.25 (d, *J* = 7.5, 3H); <sup>13</sup>C NMR (125
MHz, CDCl$_3$) $\delta$ 139.6, 136.9, 136.6, 128.4, 126.5, 116.3, 66.9, 60.2, 44.9, 37.4, 23.4, 17.9; HRMS (ESI) m/e 195.1387 [M$^+$H$^-$] calcd for C$_{12}$H$_{19}$O$_2$: 195.1391.

**TBS Diol 25:** To solution of the diol (5.11 g, 26.2 mmol) in CH$_2$Cl$_2$ (262 ml) at 0°C was added imidazole (9.11 g, 134 mmol) and the TBSCI (19.77 g, 131 mmol) in CH$_2$Cl$_2$ (50 ml). After stirring at room temperature for 1 hr, the reaction was quenched with saturated NH$_4$Cl (300 ml). The reaction was extracted with CH$_2$Cl$_2$ (3 x 300 ml), dried over Na$_2$SO$_4$, and concentrated. The crude product was purified by silica column chromatography (hexanes:EtOAc, 200:1 to 9:1) to isolate TBS diol 25 (9.14 g, 82%) as a clear oil. $R_f$ = 0.7 (silica gel, hexanes: EtOAc, 4:1); $\left[a\right]_D^{23} = -1$ (c = 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.81 (m, 1H), 5.76 (s, 1H), 5.36 (t, $J$ = 7.8, 1H) 5.04 (m, 2H), 4.19 (q, $J$ = 11.7, 2H), 3.85 (m, 1H), 2.78 (d, $J$ = 6.3, 2H), 2.28 (m, 2H), 1.75 (s, 3H), 1.14 (d, $J$ = 5.9, 3H), 0.88 (s, 18 H), 0.04 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.9, 136.9, 135.5, 126.9, 126.7, 116.0, 68.9, 61.5, 45.0, 38.2, 26.1, 23.7, 18.3, 18.0, -4.4, -4.6, -5.0; HRMS (ESI) m/e 447.3086 [M$^+$Na$^+$] calcd for C$_{24}$H$_{48}$O$_2$Si$_2$Na$^+$: 447.3085.

**Butenolide 25:** To a flask containing 4-methoxy-2(5H)-furanone (5 g, 43.8 mmol), was added N,N dimethylformamide dimethylacetal (25 ml). The mixture was heated at 120°C for 3 hrs with a distillation setup. The compound was then concentrated and
purified by silica column chromatography (hexanes: EtOAc, 20:1 to 1:1) yielding the intermediate amine in a quantitative yield. The amine was dissolved in dichloroethane, DCE (400 ml) and acetic acid (5.01 ml, 87 mmol, 2 eq) was added dropwise at room temperature and the solution stirred for 15 minutes. Sodium triacetoxyborohydride, NaBH(OAc)$_3$ (46.4 g, 219 mmol, 5 eq) was added at room temperature and refluxed for 2 days. The reaction was quenched with saturated NH$_4$Cl solution (200 ml) and extracted with CH$_2$Cl$_2$ (3 x 300 ml) and dried over Na$_2$SO$_4$, and concentrated. The crude compound was purified by silica column chromatography (hexanes: EtOAc, 5:1 to 1:5) to yield butenolide 25 (3.80 g, 69%, 86% brsm) as a white solid. This material matched what was previously reported in the literature.$^{24,290}$

$R_f= 0.5$ (silica gel, hexanes: EtOAc, 1:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.23 (s, 1H), 5.01 (d, $J = 10.3$, 2H), 3.91 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.8, 168.4, 149.7, 92.6, 90.0, 59.4; HRMS (ESI) m/e 127.0391 [M$^+$$H^+$$]$ calcd for C$_6$H$_7$O$_3$: 127.0390.

**Triene 27:** To a solution of decalin aldehyde 26 (30 mg, 0.122 mmol) in CH$_2$Cl$_2$ (1.5 ml) was added triene 25 (207 mg, 0.487 mmol, 4 eq.) and Grubbs catalyst (2$^{nd}$ generation, 5.17 mg, 6.09 µmol, 0.05 eq.). The solution was degassed bubbling with
argon for 30 minutes and then was refluxed for 24 hours under argon atmosphere. The reaction was allowed to cool to room temperature and concentrated. The residue was purified via preparative TLC (hexanes: Et$_2$O 100:1 ran 4x) to yield the decalin triene 27 (44 mg, 56%, 8:1 $E$:$Z$) as a clear oil. $R_f$ = 0.24 (silica gel, hexanes: Et$_2$O, 50:1); $[\alpha]_D^{23}$ = -32.9 ($c$ = 0.42, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.69 (s, 1H), 5.71 (s, 1H), 5.50 (s, 2H), 5.42 (dd, $J$ = 6.9, 15.5, 1H) 5.33 (m, 2H), 4.16 (q, $J$ = 11.45, 2H), 3.83 (m, 1H), 2.69 (d, $J$ = 6.3, 2H), 2.41 (m, 1H), 2.28 (m, 2H), 2.05 (m, 2H), 1.95-1.17 (m, 8H) 1.71 (s, 3H), 1.12 (d, $J$ = 5.75, 3H), 1.02 (d, $J$ = 8, 3H), 1.02 (s, 3H), 0.99 (d, $J$ = 6.85, 3H), 0.87 (s, 18 H), 0.03 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 208.3, 137.7, 137.2, 135.9, 132.7, 127.8, 126.9, 126.3, 124.8, 68.7, 61.3, 50.9, 50.8, 43.6, 41.3, 39.0, 38.1, 37.6, 32.3, 31.0, 27.7, 25.9, 25.8, 25.8, 23.6, 21.9, 18.3, 18.1, 17.9, 17.8, 15.8, -4.5, -4.7, -5.2, -5.2; HRMS (ESI) m/e 665.4757 [M$^+$Na$^+$] calcd for C$_{39}$H$_{70}$O$_3$Si$_2$Na$: 665.4756.

**Tetronate 28:** To a solution of THF (0.32 ml) and diisopropylamine (14 $\mu$l, 0.142mmol) was added $n$-BuLi (0.10 ml, 1.4 M in hexanes) at -78°C. This solution stirred for 1 hr at this temperature. Then the butenolide 21 (18 mg, 0.14 mmol) in THF (0.16 ml) and DMPU (20 $\mu$l) was added to the lithium diisopropylamine (LDA) dropwise to make a lemon yellow solution. After 5 minutes, a solution of decalin
aldehyde 27 (30 mg, 0.05 mmol) in THF (0.20 ml) was added to the lithiated butenolide dropwise. After 5 minutes at -78°C the reaction was quenched with saturated NH₄Cl (3 ml). The reaction mixture was extracted with EtOAc (3 x 10 ml). All organic layers were washed with brine (5 ml), dried over Na₂SO₄, and concentrated. A silica plug (hexanes:EtOAc, 70:30) was used to recover a 1:1 diasteromeric mixture of alcohols and butenolide 21. This mixture was carried through to the next step. Rf = 0.44 and .32 (silica gel, hexanes: EtOAc, 7:3) To the diasteromeric mixture of alcohols and the butenolide crude in DCM (1 ml) was added sodium bicarbonate (24 mg, 0.28 mmol) and Dess-Martin Periodinane (40 mg, 0.09 mmol) at room temperature. The reaction mixture continued to stir for 30 minutes and a 1:1 mixture of saturated sodium thiosulfate and saturated sodium bicarbonate (5 ml) was added and that solution stirred for 30 minutes until all layers became clear. Then the solution was extracted with DCM (3 x 10 ml), dried over Na₂SO₄, and concentrated. The crude mixture was purified by silica column chromatography (hexanes:EtOAc, 200:1 to 3:1) to yield ketone 28 (18 mg, 51% over two steps) as a clear oil. Rf= 0.62 (silica gel, hexanes: EtOAc, 4:1); [α]D²³ = -45.0 (c = 0.25, CHCl₃);

¹H NMR (500 MHz, CDCl₃) δ 5.70 (s, 1H), 5.62 (dd, J = 5.2, 15.5, 1H) 5.45 (m, 2H), 5.30 (m, 2H), 5.20 (d, J = 2.9, 1H), 5.14 (d, J = 2.9, 1H), 4.19 (d, J = 12.0, 1H), 4.12 (d, J = 12.0, 1H), 3.81 (m, 1H), 3.18, (br s, 1H), 2.71 (d, J = 6.9, 2H), 2.34-2.20 (m, 2H), 2.12 (m, 1H), 2.04, (m, 1H), 1.96-1.81 (m, 2H), 1.70 (s, 3H), 1.69-1.24 (m, 9H), 1.28 (s, 3H), 1.13 (d, J = 6.3, 3H), 0.98 (d, J = 7.45, 3H), 0.90 (d, J = 6.9, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (125
MHz, CDCl$_3$) $\delta$ 203.2, 168.3, 165.3, 149.3, 137.8, 137.4, 136.6, 131.7, 130.9, 128.8, 126.7, 125.9, 124.2, 108.5, 94.6, 68.8, 63.2, 61.4, 54.9, 47.6, 43.9, 42.7, 39.5, 38.1, 38.0, 32.6, 31.3, 27.5, 25.9, 25.8, 23.6, 21.9, 18.4, 18.3, 18.1, 17.9, 13.7, -4.6, -4.7, -5.2, -5.2; HRMS (ESI) m/e 789.4917 [M$^{+}$Na$^{+}$] calcd for C$_{45}$H$_{74}$O$_6$Si$_2$Na$^+$: 789.4916.

SI_1_29: To a solution of methoxymethylenetriphenylphosphine chloride (25.4 g, 74.2 mmol) in THF (362 ml) was added a solution of sodium hexamethyldisilazane (72.4 ml, 1M in THF, 72.4 mmol) dropwise at 0°C and stirred at this temperature for 30 minutes. The solution of 2-allyl-cyclohexanone (5 g, 36.2 mmol) in THF (30 ml) was added dropwise and warmed to rt and stirred overnight. The reaction was then quenched with saturated NH$_4$Cl (300 ml) and extracted with Et$_2$O (3 x 400 ml). All organic layers were washed with brine (300 ml), dried over Na$_2$SO$_4$, and concentrated. The crude mixture was purified by column chromatography (hexanes:Et$_2$O, 200:1 to 4:1) to yield methoxenyol SI_1_29 (5.29 g, 88%) as a clear oil. This material matched what was previously reported in the literature.$^{291}$

SI_2_29: Methoxenyol SI_1_29 (2.5 g, 15.0 mmol) was dissolved in a 4:1 THF: 5% aq. HCl solution (250 ml, 0.06M) and was refluxed for 3 hrs. After the solution cooled to rt, the reaction was carefully quenched with saturated NaHCO$_3$ (300 ml). The reaction was extracted with ether (3 x 150 ml), washed with brine (200 ml), dried over
Na₂SO₄, and concentrated. The mixture of aldehydes was then dissolved in 1:1 MeOH: 5% KOH aq. (118 ml, 0.13M) and was refluxed for 3 hrs. After cooling, the reaction was extracted with Et₂O (3 x 150 ml). All organic layers were washed with brine (100 ml), dried over Na₂SO₄, and concentrated to afford aldehyde SI_2_29 (2.20 g, 96%). This material matched what was previously reported in the literature.²⁹¹

**Aldehyde 30:** To a solution of the aldehyde (3.00g, 19.71 mmol) and iodomethane (24.6 ml, 394 mmol) in THF (66 ml) at 0°C was added NaOtBu (3.79 g, 39.4 mmol) portionwise and stirred overnight. The next morning the reaction was quenched with saturated NH₄Cl (75 ml) and extracted with ether (3 x 75 ml). All organic layers were washed with brine (70 ml), dried over Na₂SO₄ and concentrated. The compound was purified via silica chromatography (hexanes: Et₂O, 200:1 to 9:1) to yield aldehyde 30 (2.326 g, 71%) as a clear liquid. This material matched what was previously reported in the literature.²⁹²

**Triene 31:** To a solution of aldehyde 30 (410 mg, 2.47 mmol) in CH₂Cl₂ (29 ml) was added triene 25 (3.14 g, 7.4 mmol) and Grubbs catalyst (2nd generation, 105 mg, 0.12 mmol, 0.05 eq.). The solution was degassed with argon for 30 minutes and then was
refluxed for 24 hours under argon atmosphere. The reaction was allowed to cool to room temperature and concentrated. The crude reaction mixture was purified by silica column chromatography (pentane: CH₂Cl₂, 200:1 to 1:1). The isolated compound was ran through a silica plug (hexanes: EtOAc, 4:1) to yield 31 (861 mg, 62%, E/Z, 3:1) as a clear oil. \( R_f = 0.83 \) (silica gel, hexanes: EtOAc, 4:1); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \)
9.70 and 9.39 (s, 1H), 5.74 (s, 1H), 5.40 (m, 3H), 4.21 (d, \( J = 11.9 \), 1H), 4.16 (d, \( J = 13.0 \), 1H), 3.85 (m, 1H), 2.73 (d, \( J = 6.05 \), 2H), 2.36-2.23 (m, 3H), 2.00 (m, 1H), 1.91-1.23 (m, 9H), 1.75 (s, 3H), 1.14 (d, \( J = 5.9 \), 3H), 1.11 (s, 3H), 0.88 (s, 18H), 0.04 (s, 12H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 207.3, 137.8, 136.0 130.6 130.0, 126.8, 126.2, 68.7, 61.3, 48.9, 43.6, 38.1, 33.3, 29.7, 29.7, 27.4, 25.9, 25.2, 23.5, 22.2, 20.7, 18.3, 18.1, 17.9, -4.5, -4.7, -5.2; HRMS (ESI) m/e 585.4132 [M\(^+\)Na\(^+\)] calcd for C\(_{33}\)H\(_{62}\)O\(_3\)Si\(_2\)Na\(^+\): 585.4130.

**Tetronate 32**: To a solution of THF (8.4 ml) and diisopropylamine (0.54 ml, 3.79 mmol) was added \( n \)-BuLi (2.33 ml, 1.6M in hexanes) at -78°C. This solution stirred for 1 hr at this temperature. Then the butenolide 21 (470 mg, 3.72 mmol) in THF (4.2 ml) and DMPU (0.2 ml) was added to the prepared LDA dropwise to make a lemon yellow solution. After 5 minutes, a solution of cyclohexane aldehyde 31 (710 mg, 1.24 mmol) in THF (5.2 ml) was added to the lithiated butenolide dropwise. After 5
minutes at -78°C the reaction was quenched with saturated NH₄Cl (20 ml). The reaction mixture was extracted (3 x 20 ml) with EtOAc. All organic layers were washed with brine (20 ml), dried over Na₂SO₄, and concentrated. A silica plug (hexanes:EtOAc, 7:3) was ran to recover a 1:1 diasteromeric mixture of alcohols and butenolide 21. This mixture was carried through to the next step.

To the diasteromeric mixture of alcohols and the butenolide crude in DCM (12.4 ml) was added sodium bicarbonate (625 mg, 7.44 mmol) and Dess-Martin Periodinane (1.05 g, 2.48 mmol) at room temperature. The reaction mixture continued to stir for 30 minutes and a 1:1 mixture of saturated sodium thiosulfate and saturated sodium bicarbonate (30 ml) was added and that solution stirred for 30 minutes until all layers became clear. Then the solution was extracted with DCM (3 x 30 ml), dried over Na₂SO₄ and concentrated. The crude mixture was purified through silica chromatography (hexanes:EtOAc, 200:1 to 4:1) to yield ketone 32 (453 mg, 53% over two steps) as a clear oil. $R_f = 0.7$ (silica gel, hexanes: EtOAc, 4:1); ¹H NMR (500 MHz, CDCl₃) $\delta$ 5.73 (s, 1H), 5.39 (m, 3H), 5.15 (d, $J = 13.3$, 2H), 4.19 (q, $J = 13.4$, 2H), 3.95 (s, 3H), 3.85 (m, 1H), 2.72 (m, 2H), 2.31 (m, 3H), 2.17 (m, 1H), 2.05-1.23 (m, 9H), 1.73 (s, 3H), 1.45 (s, 3H), 1.15 (s, 3H), 0.89 (s, 18H), 0.04 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) $\delta$ 205.0, 165.8, 165.5, 149.2, 137.8, 136.2, 131.0, 129.6, 126.7, 126.1, 108.0, 94.3, 68.8, 61.8, 61.4, 53.3, 51.8, 43.7, 38.1, 33.3, 29.7, 25.9, 25.9, 24.7, 24.3, 23.5, 21.8, 18.4, 18.1, 17.9, -4.5, -4.7, -5.2; HRMS (ESI) m/e 709.4291 [M⁺Na⁺] calcd for C₃⁹H₆₆O₆Si₂Na⁺: 709.4290.
Alcohols 33: To the TBS diene (75 mg, 0.11 mmol) in DCM (1 ml) was added triethylamine trihydrofluoridic acid (0.12 ml, 0.33 mmol) dropwise at rt. The reaction stirred for 2 hrs and was quenched with saturated NaHCO$_3$ (10 ml). Then the solution was extracted with DCM (3 x 7 ml), dried over Na$_2$SO$_4$ and concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 20:1 to 1:1) to yield the diol 33 (38 mg, 76%) as a clear oil. $R_f=0.6$ (silica gel, hexanes: EtOAc, 1:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.75 (s, 1H), 5.52-5.35 (m, 3H), 5.17-5.15 (m, 2H), 4.22 (d, $J=11.7$, 1H), 4.07 (d, $J=11.7$, 1H), 3.94 (s, 3H), 3.90 (m, 1H), 2.74 (m, 2H), 2.34 (m, 3H), 2.19 (m, 1H), 2.10-1.23 (m, 9H), 1.75 (s, 3H), 1.41 (s, 3H), 1.26 (d, $J=11.7$, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 205.1, 165.9, 165.6, 149.2, 139.8, 138.1, 131.5, 129.1, 127.9, 125.7, 125.7, 107.8, 94.4, 67.1, 61.8, 60.4, 53.3, 51.9, 51.8, 43.6, 39.9, 37.3, 33.2, 29.7, 23.4, 21.7, 18.0; HRMS (ESI) m/e 457.2591 [M$-$H]$^-$ calcd for C$_{27}$H$_{37}$O$_6$: 457.2590.

Aldehyde 40: To a solution 25 (1.574 g, 3.70 mmol) and 2-bromoacrylaldehyde (1.1 g, 8.15 mmol) in toluene (106 mL) at -78°C was added dimethylaluminum chloride (3.70 ml, 3.70 mmol, 1 M). After 3 hours the solution was quenched with sat. NH$_4$Cl
(50 mL) and filtered through a celite plug. The solution was extracted with DCM (3 x 50mL), dried over Na$_2$SO$_4$, and concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 200:1 to 9:1) to yield 40 (1.597 g, 2.85 mmol, 77 % yield) as a clear oil. $R_f = 0.7$ (silica gel, hexanes: EtOAc, 9:1); $[\alpha]_D^{23} = -63$ ($c = 1.61$, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.69 (s, 1H), 5.71 (m, 1H), 5.32 (s, 1H), 5.05 (m, 2 H), 4.12 (q, $J = 14.6$ Hz, 2H), 3.94 (m, 1H), 2.73 (m, 1H), 2.44-1.88 (m, 6H), 1.39 (s, 3H), 1.17 (d, $J = 6.5$ Hz, 3H), 0.90 (s, 18H), 0.09 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 191.90, 138.53, 133.57, 127.08, 118.93, 78.35, 65.24, 64.36, 44.78, 43.04, 40.84, 33.44, 31.25, 25.96, 25.94, 18.41, 17.98, -3.77, -4.57, -5.17, -5.27; HRMS (ESI) m/e 581.2457 [M$^{+}$Na$^+$] calcd for C$_{27}$H$_{51}$BrO$_3$Si$_2$Na: 581.2452.

**Epoxide 41:** To a solution of 40 (1.6 g, 2.86 mmol) in MeOH (42 mL) at 0°C was added sodium borohydride (0.108 g, 2.86 mmol). After 30 minutes the reaction was quenched with sat. NH$_4$Cl (30 mL) and concentrated. The residue was extracted with ether (3 x 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO$_4$ and concentrated to give the alcohol (1.606 g, 2.86 mmol, 100 % yield), which was carried directly to the next step. To a solution of the alcohol (1.6 g, 2.85 mmol) in MeOH (47.5 mL) at 0°C was added sodium methoxide solution (11.39 mL, 5.70 mmol, 0.5M). After 2 hours the reaction was quenched with sat. NH$_4$Cl (30 mL) and
concentrated. The residue was extracted with ether (3 x 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO$_4$ and concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 200:1 to 5:1) to yield 41 (1.068 g, 2.221 mmol, 78 % yield) as a clear oil. $R_f$ = 0.6 (silica gel, hexanes: EtOAc, 5:1); $[\alpha]_D^{23}$ = -60.4 (c = 2.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.83 (m, 1H), 5.45 (s, 1H), 4.99 (m, 2 H), 4.10 (s, 2H), 3.87 (m, 1H), 2.77-1.44 (m, 9H), 1.39 (s, 3H), 1.12 (d, $J$ = 6.6 Hz, 3H), 0.94 (s, 18H), 0.09 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.59, 138.02, 135.76, 131.40, 130.46, 129.55, 123.90, 117.53, 76.08, 65.93, 64.90, 44.40, 42.46, 36.39, 31.76, 26.21, 25.03, 18.22, -3.42, -4.24, -5.16; HRMS (ESI) m/e 503.3348 [M$^+$Na$^+$] calcd for C$_{27}$H$_{52}$O$_3$Si$_2$Na: 503.3347.

**Sulfone 42_1:** To a solution of 41 (1.068 g, 2.221 mmol) in tBuOH (12.97 mL) at 0°C was added benzenethiol (0.729 g, 6.61 mmol) and NaOH (0.353 g, 8.82 mmol) and this solution was heated at 80°C overnight. The reaction was cooled and quenched with sat. NH$_4$Cl (20 mL). The reaction was extracted with ether (3 x 40 mL). The combined organic layers were washed with brine (30mL), dried over MgSO$_4$ and concentrated. The residue was ran through a silica plug (hexanes:EtOAc, 4:1) and resulted in the sulfide (1.094 g, 1.852 mmol, 84 % yield). To solution of the sulfide (1.09 g, 1.844 mmol) in DCM (18.44 mL) at -78°C was added $m$CPBA (0.318 g, 1.844 mmol) and stirred for 30 minutes. The solution was quenched with sat. Na$_2$S$_2$O$_3$
(20 mL) and the solution was extracted with ether (3 x 50 mL). The combined organic layers were washed with sat. NaHCO₃ (20 mL). Then the organic layer was washed with brine (30mL), dried over MgSO₄ and concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 200:1 to 5:1) to yield 42₁ (1.008 g, 1.660 mmol, 90 % yield) as a clear oil. Rᵣ= 0.5 (silica gel, hexanes: EtOAc, 4:1); [α]D²³ = -49.6 (c = 2.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.55 (m, 5H), 5.78 (m, 1H), 5.28 (m, 1H), 5.02 (m, 2H), 4.11 (m, 2H), 4.10 (m, 1H), 3.02-1.92 (m, 7H), 1.22 (d, J = 6.4 Hz, 3H), 0.89 (s, 18H), 0.09 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 143.59, 138.02, 135.76, 131.40, 130.46, 129.55, 123.90, 117.53, 76.08, 65.93, 64.90, 44.40, 42.46, 36.39, 31.76, 26.21, 25.03, 18.22, -3.42, -4.24, -5.16.; HRMS (ESI) m/e 629.3486 [M⁺Na⁺] calcd for C₃₃H₅₈O₄SSi₂Na: 629.3487.

**Aldehyde 42:** To a solution of 42₁ (1 g, 1.647 mmol) in Ac₂O (9.15 mL) was added sodium acetate (0.676 g, 8.24 mmol) and heated at 125°C overnight. The next morning the reaction was diluted with toluene (3 times 10 mL) and concentrated to azeotrope off the Ac₂O. The crude mixture was purified via column chromatography (hexanes:EtOAc, 200:1 to 4:1) to yield 42 (0.275 g, 0.511 mmol, 31 % yield) as a clear oil. Rᵣ= 0.7 (silica gel, hexanes: EtOAc, 5:1); [α]D²³ = -36.1 (c = 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.72 (s, 1H), 5.71 (m, 1H), 5.31 (s, 1H), 4.99 (m, 2H), 4.12 (s, 2H), 3.94 (m, 1H), 2.59-1.88 (m, 7H), 2.07 (s, 3H), 1.19 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H), 0.89 (s, 18H), 0.08 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ 199.78, 170.58,
Butenolide 44: To a solution of 42 (0.275 g, 0.403 mmol) in tBuOH (5.10 mL) at 0°C was added NaH₂PO₄ (0.097 g, 0.816 mmol), 2-methyl-2-butene (0.108 ml, 1.021 mmol) and sodium chlorite (0.069 g, 0.765 mmol). The solution stirred at rt overnight and diluted with water (10 mL). The reaction was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated to yield carboxylic acid (0.224 g, 0.403 mmol, 79 % yield) essentially clean as a clear oil. The resultant carboxylic acid was diluted in DCM (4.02 mL) and trimethyloxonium tetrafluoroborate (0.065 g, 0.442 mmol) followed by DIPEA (0.077 ml, 0.442 mmol) were added. After 5 minutes, the reaction was diluted with water (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to yield the methyl ester (0.229 g, 0.402 mmol, 100 % yield). To a solution of the methyl ester in THF (8.09 mL) was added LiHMDS (1.213 mL, 1.213 mmol, 1M) at -78°C. The reaction stirred at this temp for 30 minutes then methyl sulfate (0.5mL) was added and warmed to rt over 3 hours. The reaction was quenched with sat. NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and...
concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 200:1 to 1:1) to yield 44 (0.158 g, 0.287 mmol, 71 % yield). \( R_f = 0.59 \) (silica gel, hexanes: EtOAc, 7:3); \([\alpha]_D^{23} = -17.5 \) (c = 0.2, CHCl₃); \(^1\text{H NMR} \) (500 MHz, CDCl₃) \( \delta \) 5.77 (m, 1H), 5.39 (s, 1H), 5.04 (m, 2 H), 4.12 (q, \( J = 14.7 \) Hz, 2H), 3.87 (m, 1H), 3.86 (s, 3H), 2.70-1.91 (m, 6H), 1.39 (s, 3H), 1.14 (d, \( J = 6.6 \) Hz, 3H), 0.95 (s, 3H), 0.89 (s, 18H), 0.05 (s, 12H); \(^{13}\text{C NMR} \) (125 MHz, CDCl₃) \( \delta \) 184.51, 171.66, 137.94, 134.58, 127.32, 117.78, 89.64, 87.55, 65.74, 64.63, 59.25, 44.50, 41.02, 34.19, 30.11, 25.93, 25.77, 19.79, 17.96, -3.92, -4.84, -5.28.; \( \text{HRMS (ESI)} m/e 573.3404 \) [M\(^+\)Na\(^+\)] calcld for C\(_{30}\)H\(_{54}\)O\(_5\)Si\(_2\)Na: 573.3402.

**Butenolide 46:** To a solution 44 in THF (0.609 mL) at -78°C was added tBuLi (0.051 mL, 0.064 mmol, 1.25M) dropwise and stirred for 30 minutes. Then 26 (.015 g, 0.061 mmol) in THF (0.152 mL) was added and stirred at this temperature for 30 minutes before being quenched with sat. NH₄Cl (5 mL). The reaction was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated. The crude mixture was purified via column chromatography (hexanes:EtOAc, 100:1 to 1:1) to yield alcohol (0.029 g, 0.037 mmol, 60 % yield). To a solution of the alcohol (0.029 g, 0.036 mmol) in MeCN (0.727 mL)
was added TPAP (1.278 mg, 3.64 µmol) and NMO (0.017 g, 0.145 mmol). After 5 days the reaction was purified via silicia column chromatography (hexanes:EtOAc, 200:1 to 1:1) to yield 46 (0.023 g, 0.029 mmol, 80 % yield). $R_f = 0.41$ (silica gel, hexanes: EtOAc, 3:1); $[\alpha]_{D}^{23} = -70.6$ (c = 0.1, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.90 (m, 1H), 5.77 (s, 1H), 5.45 (m, 3H), 5.04-4.89 (m, 4H), 4.14 (q, $J = 14.7$ Hz, 2H), 4.09 (s, 3H), 3.91 (m, 1H), 3.19 (s, 1H), 2.70 (m, 1H), 2.25-1.89 (m, 7H), 2.07 (s, 3H), 1.59-0.80 (m, 9H), 1.59 (s, 3H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.98 (s, 3H), 0.94 (s, 18H), 0.05 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.37, 171.23, 145.45, 137.96, 134.66, 131.83, 127.38, 125.65, 117.86, 111.97, 106.40, 86.62, 65.74, 60.44, 48.81, 46.52, 44.89, 42.41, 41.33, 39.38, 35.67, 33.61, 32.83, 30.30, 29.73, 27.32, 25.92, 25.81, 24.32, 21.11, 20.07, 18.61, 18.01, 16.08, 14.22, -3.87, -3.88, -5.26.; HRMS (ESI) m/e 817.5231 [M$^+$Na$^+$] calcd for C$_{47}$H$_{78}$O$_6$Si$_2$Na: 817.5229.

3. List of Specta
Spectrum 3.01: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 19
Spectrum 3.02. $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 19
Spectrum 3.03: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 21
Spectrum 3.04: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 21
Spectrum 3.05: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 25_1
Spectrum 3.06: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 25_1
Spectrum 3.07: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 25
Spectrum 3.08: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 25_1
Spectrum 3.09: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 27
Spectrum 3.10: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 27
Spectrum 3.11: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 28
Spectrum 3.12: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 28
Spectrum 3.13: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 31
Spectrum 3.14: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 31
Spectrum 3.15: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 32
Spectrum 3.16: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 32
Spectrum 3.17: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 33
Spectrum 3.18: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 33
Spectrum 3.19: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 40
Spectrum 3.20: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 40
Spectrum 3.21: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 41
Spectrum 3.22: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 41
Spectrum 3.23: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 42
Spectrum 3.24: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 42
Spectrum 3.25: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 44
Spectrum 3.26: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 44
Spectrum 3.27: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 46
Spectrum 3.28: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 46
Chapter 4: General Strategy Towards the Spirotetronate Polyketides
A. Introduction

Looking over the history of the spirotetronate polyketides, I was surprised to find how inefficient some the synthetic strategies were for this class of molecules. Maklamicin (1) and versipelostatin (4), which contains a C_{11} macrocycle, has no synthetic strategy presented thus far. The total synthesis of tetronolide (2) despite best efforts contains over 40 linear steps to complete the molecule (over 60 in total). Chlorothricolide (3) has the best synthetic record with about about 25 steps towards its total synthesis via a tandem double IMDA. I was wondering if a generalized approach to the spirotetronate polyketides could be developed. This
method would go towards the synthesis of the basic skeleton of a spirotetronate polyketide. Also this strategy would be modular, so minor changes in the synthetic strategy should hopefully be able to access other spirotetronates of varying ring size of their macrocycle. This strategy will revolved around the rapid assembly of the decalin moiety. Functionalization of the decalin would install the would set the template for the installation of the diene and the dienophile (tetronate moiety) using a less sterically hindered diene to facilitate the IMDA reaction to form the spirotetronate moiety. Examples of this biomimetic transformation has occurred in the total synthesis of abyssomicin C\textsuperscript{147} and okilactomycin D\textsuperscript{163} using these dienes.

**B. First Generation Approach**

![Figure 4.02: Retrosynthetic strategy towards the natural products spirotetronate polyketides](image)

For the generalized approach to the spirotetronate polyketides key to my synthetic approach is a nature-inspired double IMDA approach with the first IMDA assembling the decalin moiety (figure 4.02). The second IMDA would assemble the spirotetronate moiety. So to start this synthetic approach I decided to use the chemistry
of the fusarisetin A synthesis of the rapid assembly of the decalin moiety through a substrate controlled IMDA.\textsuperscript{241,242} Differing in my strategy would be the Wittig salt used. I needed a functionalized handle off my decalin to elongate the carbon chain to synthesize the diene. The aldehyde of this decalin could then be used in an anionic coupling to install the butenolide.

Figure 4.03: Synthesis of Wittig salt (8)

To start this synthetic plan off, I first sought to use readily available starting materials. I was able to mono silyate 1,3 propanediol (5) in 99% yield after small modifications to literature protocols (figure 4.03).\textsuperscript{293} A one-pot Swern [O] and Wittig olefination yielded ester 6 in 85% yield. This reaction could be performed on 40 gram scale. Ester 6 was subsequently reduced to alcohol 7 with DIBAL-H in 89% yield. Alcohol 7 was converted to the allylic bromide under Appel conditions and then converted to phosphonium salt 8 (80% over two steps). This process overall was scalable and high yielding which is important for continuation is the synthetic sequence.
The synthesized Wittig salt 8 was deprotonated with nBuLi to generate the ylide in situ at 0°C and this solution was slowly added dropwise into a solution of dialdehyde 9 at -78°C (figure 4.04). This similar reaction was performed in the lab, but my Wittig salt suffered in these conditions due to poor solubility at low temperatures. I modified the protocol to be performed at 0°C as opposed to -78°C and also decreased the overall concentration of that reaction for optimal solubility. This reaction on scale of 50 grams Wittig salt 8 gave 10 in 52% yield. The IMDA reaction proceeded smoothly using 1.5 eq. of Me₂AlCl added at -78°C with the reaction stirring at 0°C overnight to give decalin 11 in 77% yield. This reaction could be perform in 3 hours by using BF₃·Et₂O albeit a lower yield of 50%. Only one stereoisomer is present
by NMR of decalin 11. In effort to avoid protecting group strategy my synthetic strategy was to install the tetronate first followed by installation of the diene. Decalin 11 underwent nucleophilic attack by butenolide 12 which result in alcohol 13 (60% yield 1:1 dr). Subsequent oxidation with IBX yielded ketone 14 (80% yield). The silyl protecting group was removed using HF and subsequent oxidation resulted in aldehyde 15 (69% over two steps). My compound decomposed when using a Wittig olefination to elongate the carbon chain. I monitored this reaction closely at -78°C, but observed disappearance of my starting material. With these results in hand, I sought to use a softer method to carbon chain elongation via NHK coupling with vinyl iodide 16, which also decomposed 15. After these results I thought the tetronate might be acting as a very strong Michael acceptor so I had to alter my synthetic strategy to avoid this complication. The mode of action of abyssomicin C supports this conclusion.294

![Chemical structure](image)

Figure 4.05: Acetate protected tetronate and chain elongation of triene
In efforts to make the tetronate ring a weaker Michael acceptor, I protected alcohol 13 with an acetate group (figure 4.05). Subsequent TBDPS deprotection and oxidation with IBX yielded aldehyde 17 (63% over three steps). I treated 17 under Wittig conditions and still noted the same decomposition as before. However this time using NHK conditions with aldehyde 17 and vinyl iodide 16 resulted in diasteromeric mixture 18 from the alcohols and the E:Z mixture present in starting material 16 in 42% yield. The essential component to this strategy would be the fully oxidized form of the tetronate for the IMDA chemistry. Unfortunately 18 decomposed upon deprotection of the acetate group as well as trying to oxidize the resultant alcohol or in the reverse order. This prompted changing the synthetic strategy.

C. Second Generation Approach

![Chemical diagram](image)

Figure 4.06: Synthesis of decalin moiety using a double protecting group strategy.
Since the installation of the tetronate ring early in the synthesis was problematic, I rerouted my approach to leave this portion at the end of the synthesis. Starting with decalin 11 (figure 4.06) reduction with DiBAL-H resulted in the alcohol that was subsequently protected with Ac₂O to yield ester 20 (96% over two steps). Desilylation with HF and oxidation with IBX gave aldehyde 21 (66% over two steps). This altered strategy thus far was overall high yielding with stable intermediates throughout.

Aldehyde 21 was reacted under Wittig condition to yield 1:1 dr of the methoxy-olefin. This compound was hydrolyzed with water and tosyl acid to yield aldehyde 22 (76% over two steps) with the carbon chain extended by one carbon. Wittig olfination of 22 with phoshonium salt 23⁴¹,⁴² and subsequent I₂ double bond isomerization gave triene 24 (69% yield over two steps). Deprotection of the acetate group of 24 and subsequent oxidation with IBX gave decalin aldehyde 25 (77% yield over two steps). This overall process was high yielding to this important synthetic intermediate.
Figure 4.07: Synthesis of spirotetronate framework with 11-membered macrocycle

The lithiated tetronate (26) reaction was optimized due to issues with consistency of this reaction. For the optimization of this reaction I tested a few different bases including tBuLi, LiHMDS, and LDA which was the most successful in
this reaction. This reaction needs to be as cold as you can make it, since the lithiated tetronate is unstable and needs to be used quickly. The brown color of the reaction that is explained by other protocols is directly related to poorer yields.\textsuperscript{147} The decomposition cannot be seen on NMR and is baseline material. By quenching the tetronate as the limiting reagent seemed to reduce decomposition and provided a higher yield. With these modifications I can isolate the alcohol in about 20\% high yield than other literature protocols.\textsuperscript{147} Oxidation with IBX yielded ketone 27 (61.2\% over two steps). The IMDA reaction proceeded smoothly at 110°C in a sealed tube with degassed toluene heating overnight to give 1 new spot, but the crude NMR clearly showed two diasteromers. Through trial and error I found that 200:1 toluene acetone can separate the 2 diasteromers on a preparative TLC to yield 28 and 29 (75\% 1.5:1 dr). Preliminary assignment of the stereochemistry from NOESY correlation of an endo adduct (28) and an exo adduct (29) as seen in figure 4.07. The key assignment was whether or not if the distal methyl group off the spirotetronate ring could see the methoxy group on the butenolide ring. Presence of this signal indicated the endo adduct and the absence of this signal indicated an exo adduct.

**D. Conclusions**

In conclusion I have presented a strategy toward the skeleton of a class II, $C_{11}$ spirotetronate. Despite a few failed strategies, the second IMDA cycloaddition was successful and validated this approach towards the synthesis class II spirotetronate polyketides. In the laboratory, the synthesis of a class II, $C_{17}$ macrocycle is under
investigation. If this approach is successful, this will be the first example of an intramolecular IMDA reaction in the formation of a 17-membered ring and validating a convergent route.

E. Experimental Section

1. General Procedure

Unless indicated, all commercially available reagents and anhydrous solvents were purchased at the highest commercial quality and were used as received without further purification. All non-aqueous reactions were carried out under argon atmosphere using dry glassware that had been flame-dried under a stream of argon unless otherwise noted. Anhydrous tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and dimethylformamide (DMF) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) using Hexanes-EtOAc or CH$_2$Cl$_2$-MeOH mixtures of increasing polarity. The progress of all the reactions were monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F$_{254}$ to a thickness of 0.5 mm (Merck), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of KMnO$_4$ stain or Seebach’s stain followed by heating. $^{13}$C NMR and $^1$H NMR spectra were recorded on either 500 MHz Varian instrument or 500 MHz JEOL instrument. CDCl$_3$ was treated with flame dried K$_2$CO$_3$, chemical shifts (δ) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak reference (CDCl$_3$), with the abbreviations s, br s, d, t, q, m, td, dt and qd denoting singlet, broad
singlet, doublet, triplet, quartet, multiplet, quartet of doublets, triplet of doublets, doublet of triplets and quartet of doublets respectively. $J =$ coupling constants given in Hertz (Hz). IR spectras were collected on a Jasco 4100 FTIR. High resolution Mass spectra (HRMS) were recorded on a trisector WG AutoSpecQ spectrometer. Optical rotation data were collected on a Jasco P-1010 polarimeter using HPLC grade anhydrous CHCl$_3$.

2. Preparation of Compounds

**Alcohol 6_1**: To a solution of the propane-1,3-diol (47.0 ml, 655 mmol) in CH$_2$Cl$_2$ (437 mL) was added triethylamine (45.6 mL, 327 mmol) dropwise. After which the reaction was cooled to 0°C and tert-butyldiphenylchlorosilane (56.1 mL, 218 mmol) was added dropwise and reaction continued to stir at rt overnight. The reaction was diluted with CH$_2$Cl$_2$ and then the organic layer was washed with water, sat. NaHCO$_3$, and brine. The organic layer was dried over Na$_2$SO$_4$, concentrated and purified via silica column chromatography (hexanes:Et$_2$O, 200:1 to 20:1) to yield 6_1 (67 g, 213 mmol, 98 % yield) as a white solid. $R_f =$ 0.41 (silica gel, hexanes:EtOAc, 4:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70-7.40 (m, 10H), 3.85 (t, $J =$ 5.6 Hz, 4H), 1.82 (m, 2H), 1.05 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.8, 133.4, 130.0, 128.0, 63.5, 62.2, 34.4, 27.0, 19.3; HRMS (ESI) m/e 337.1591 [M$^+$Na$^+$] calcd for C$_{19}$H$_{26}$O$_2$SiNa$^+$: 337.1594.
Ester 6: To a solution of CH$_2$Cl$_2$ (294 mL) and DMSO (27.1 ml, 382 mmol) at -78°C was added oxalyl chloride (22.27 ml, 254 mmol) dropwise. The reaction continued to stir at this temp for 30 minutes and then 5-1 (40 g, 127 mmol) in CH$_2$Cl$_2$ (23.55 mL) was added dropwise and then stirred at this temperature for 1 hr. Then triethylamine (70.9 mL, 509 mmol) was added dropwise, stirred at -78°C for 5 minutes and was then warmed to room temperature over 45 minutes. TLC was checked at this point to make sure that the oxidation was completed. Then ethyl 2-(triphenylphosphoranylidene)acetate (66.5 g, 191 mmol) was added to the reaction in one portion and the reaction was stirred at room temperature overnight. The reaction was quenched with water and was extracted with CH$_2$Cl$_2$ (3 x mL). The combined organic layer were dried over Na$_2$SO$_4$, concentrated and then purified via silica column chromatography (hexanes: Et$_2$O, 200:1, 50:1) to yield 6 (41.5 g, 108 mmol, 85 % yield) pure and light yellow oil. $R_f$ = 0.57 (silica gel, hexanes:EtOAc, 9:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66-7.30 (m, 10H), 6.97 (m, 1H), 5.86 (d, $J$ = 15.7 Hz, 1H), 4.20 (d, $J$ = 7.0 Hz, 2H), 3.77 (t, $J$ = 6.4 Hz, 2H), 2.44 (m, 2H), 1.29 (d, $J$ = 6.9 Hz, 1H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.7, 146.0, 135.8, 133.8, 129.9, 127.9, 123.3, 62.5, 60.4, 35.7, 27.0, 19.4, 14.5; HRMS (ESI) m/e 383.1964 [M$^+$H$^+$] calcd for C$_{23}$H$_{31}$O$_3$Si$: 383.1962$. 
**Alcohol 7:** To a solution of 6 (55.38 g, 145 mmol) in CH$_2$Cl$_2$ at -78°C was added DIBAL-H (290 mL, 290 mmol) dropwise. After 5 minutes the reaction was diluted with ether and 2 mL water, 2 mL 15% NaOH, and 4 mL water were added and the reaction warmed to room temperature over 30 minutes. Then some MgSO$_4$ was added and stirred for an additional 15 minutes. The reaction was filtered and concentrated to yield the clean 7 (44.1 g, 130 mmol, 89% yield), which was used as is to the next step as clear oil. $R_f = 0.38$ (silica gel, hexanes:EtOAc, 4:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.66-7.37 (m, 10H), 6.97 (m, 1H), 5.67 (m, 2H), 4.06 (m, 2H), 3.70 (t, $J = 6.9$ Hz, 2H), 2.30 (m, 2H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.8, 134.1, 131.2, 129.9, 129.8, 127.9, 64.0, 63.7, 35.8, 27.1, 19.5; HRMS (ESI) m/e 341.1859 [M$^+$H$^+$] calcd for C$_{21}$H$_{29}$O$_2$Si$: 341.1857$.

**Bromide 8_1:** To a solution of 7 (32 g, 94 mmol) in CH$_2$Cl$_2$ (470 mL) at 0°C was added triphenylphosphine (34.5 g, 132 mmol) and carbon tetrabromide (34.3 g, 103 mmol) and continued to stir at this temperature for 15 minutes. Upon completion the reaction was diluted with hexanes and concentrated. Then the crude compound retaken up in hexanes and sonicated for 3 minutes before being run through a celite plug,
which was rinsed with an additional portion of hexanes. This process was continued until the triphenylphosphine oxide was removed visibly to yield 8_1 (33.5 g, 83 mmol, 88 % yield), which was essentially pure and used as is to the next step as light yellow oil. $R_f = 0.88$ (silica gel, hexanes:EtOAc, 4:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67-7.37 (m, 10H), 5.74 (m, 2H), 3.93 (d, $J = 5.8$ Hz, 2H), 3.70 (t, $J = 6.9$ Hz, 2H), 2.31 (m, 2H), 1.04 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.7, 133.9, 133.2, 129.7, 128.3, 127.8, 63.2, 35.5, 33.4, 27.0, 19.3; HRMS (ESI) m/e 403.1015 [M$^+$H$^+$] calcd for C$_{21}$H$_{28}$BrOSi$^+$: 402.1013.

**Wittig salt 8:** To a solution of MeCN (407 mL) and 8_1 (32.8 g, 81 mmol) at room temperature was added triphenylphosphine (23.46 g, 89 mmol) in one portion and stirred at this temperature overnight. This solution was extracted with hexanes (5 x 150 mL) and the MeCN layer was dried over Na$_2$SO$_4$ and concentrated. The resultant oil was taken up in minimum amount of benzene and concentrated to yield 8 (49.2 g, 73.9 mmol, 91 % yield) as white foam. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76-7.29 (m, 25H), 5.80 (m, 1H), 5.33 (m, 1H), 4.59 (m, 2H), 3.45 (t, $J = 6.7$ Hz, 2H), 2.16 (m, 2H), 0.91 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.9 (d, $J = 13.3$ Hz), 135.4, 135.0, 133.8 (d, $J = 9.7$ Hz), 130.3 (d, $J = 12.5$ Hz), 129.7, 127.7, 118.3, 117.6, 115.9 (d, $J = 9.8$ Hz), 62.8 (d, $J = 4.3$ Hz), 36.0 (d, $J = 2.5$ Hz), 28.0 (d, $J = 49.3$ Hz), 26.8, 19.0; HRMS (ESI-TOFMS) m/e 585.2732 [MBr$^+$] calcd for C$_{39}$H$_{42}$OPSi$^+$: 585.2737.
**Aldehyde 10:** To a solution of 8 in THF (386 mL) was added at 0°C BuLi (15.38 mL, 38.5 mmol, 2.2M) dropwise this solution stirred at 0°C for 30 minutes. This solution was then transferred via a cannula to a solution of 9 (6.81 g, 40.5 mmol) in THF (193 mL), which was at -78°C over the span of 3.5 hrs. The solution was warmed to room temperature afterwards for 45 minutes and then was quenched with sat. NH₄Cl. The resulting solution was extracted with Et₂O (4 x mL) and the combined organic layers were washed with brine (500 mL), dried over Na₂SO₄ and concentrated. The crude compound was columned on a 2% Et₃N buffered column to yield 10 (9.99 g, 21.05 mmol, 52 % yield) as light yellow oil. Rf = 0.50 (silica gel, hexanes:EtOAc, 4:1); [α]D²³ = +8.1 (c = 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.39 (s, 1H), 7.70-7.36 (m, 10H), 6.47 (t, J = 8.8 Hz, 1H), 6.37-5.28 (m, 4H), 3.70 (m, 2H), 2.38 (m, 5H), 2.03 (m, 2H), 1.75 (s, 3H), 1.59-1.27 (3H), 1.05 (s, 9H), 0.92 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 195.6, 155.2, 135.8, 134.2, 132.4, 132.2, 130.8, 129.8, 128.9, 127.8, 63.9, 40.1, 36.2, 35.2, 33.2, 27.1, 26.9, 26.9, 19.6, 9.4; HRMS (ESI) m/e 497.2850 [M⁺Na⁺] calcd for C₃₁H₄₂O₂SiNa⁺: 497.2846.

![Decalin 11](image)

**Decalin 11:** To a solution of 10 in CH₂Cl₂ (92 mL) was added diiodine (0.094 g, 0.369 mmol), which was irradiated under sunlamp UV for 5-10 minutes. Then the reaction was cooled to -78°C and dimethylaluminum chloride (11.06 mL, 11.06 mmol, 1M) was added dropwise. The reaction stirred at this temperature for 1 hour and then at -5°C overnight. The reaction was quenched with saturated NaHCO₃ (mL) and
saturated Na₂S₂O₃ (mL) and then filtered through a celite plug. The reaction was then extracted with CH₂Cl₂ (3 x 20 mL) and all organic layers were dried over Na₂SO₄ and concentrated. The compound was purified via silica column chromatography (hexanes:Et₂O, 500:1 to 20:1) to yield 11 (2.7 g, 5.69 mmol, 77 % yield) as clear oil. 

$R_f = 0.59$ (silica gel, hexanes:EtOAc, 9:1); $[\alpha]_D^{23} = +49$ ($c = 0.85$, CHCl₃); $^1$H NMR (500 MHz, CDCl₃) δ 9.57 (s, 1H), 7.66-7.38 (m, 10H), 5.55 (m, 1H), 5.42 (d, $J = 10.1$ Hz, 1H), 3.70 (m, 2H), 2.20 (m, 2H), 1.83-1.46 (m, 11H) 1.05 (s, 9H), 1.02 (s, 3H), 0.92 (d, $J = 6.6$Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 208.7, 135.5, 135.5, 133.7, 131.1, 129.6, 127.7, 127.0, 61.7, 49.6, 41.6, 41.2, 39.2, 37.9, 35.4, 35.1, 33.2, 26.9, 26.8, 22.5, 19.2, 14.6; HRMS (ESI) m/e 475.3029 [M⁺H⁺] calcd for C₃₁H₄₃O₂Si⁺: 475.3027.

**Tetronate 13:** To THF (7.1 mL) in a round bottom flask was added diisopropylamine (0.233 mL, 1.632mmol). The flask was cooled to -78°C and BuLi (1.02 mL, 1.58 mmol, 1.55M) was added dropwise. The reaction stirred for 1 hour at this temperature then a solution of butenolide 26 in THF (3.5 mL) was added the reaction dropwise. After 5 minutes, decalin 11 (0.5 g, 1.05 mmol) in THF (4.5 mL) was added to the reaction. After 30 minutes, the reaction was quenched with sat. NH₄Cl (20 mL) and warmed to rt. The reaction was extracted with EtOAc (5 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated.
The crude residue was purified via silica column chromatography (hexanes:EtOAc 200:1 to 2:1) to yield 13 (0.32g, 0.52mmol, 50%) as a white foam. \( R_f = 0.32 \) (silica gel, hexanes:EtOAc, 7:3); \( [\alpha]_D^{23} = +18.4 \ (c = 2.65, \text{CHCl}_3) \); \(^1\)H NMR (500 MHz, CDCl\(_{3}\)) \( \delta \) 7.71-7.37 (m, 10H), 5.58 (m, 1H), 5.30 (m, 1H), 5.19 (d, \( J = 2.3 \) Hz, 1H), 5.09 (d, \( J = 2.3 \) Hz, 1H), 4.76 (d, \( J = 6.9 \) Hz, 1H), 4.08 (s, 3H), 3.29 (m, 1H), 2.49-1.01 (m, 10H), 1.06 (s, 9H), 1.03 (s, 3H), 0.92 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_{3}\)) \( \delta \) 169.03, 163.14, 148.72, 135.61, 133.95, 133.90, 130.40, 129.63, 129.51, 127.60, 112.79, 94.68, 70.82, 62.65, 60.97, 44.80, 41.88, 41.07, 40.19, 35.88, 35.30, 32.91, 26.85, 26.22, 22.49, 19.20, 16.70; HRMS (ESI) m/e 623.3163 \([M^+Na^+]\) calcd for C\(_{37}\)H\(_{48}\)O\(_5\)SiNa\(^+\): 623.3165.

**Ketone 14:** To a solution of 13 (0.63 g, 1.048 mmol) in DCM (10.48 mL) was added Dess-Martin Periodinane (0.889 g, 2.097 mmol) then sodium bicarbonate (0.528 g, 6.29 mmol). This solution stirred at rt for 30 minutes and was quenched with a (1:1:1) mixtures of sat. Na\(_2\)S\(_2\)O\(_3\), sat. NaHCO\(_3\), and water mixture (10 mL) and stirred until clear. The solution was extracted with DCM (3 x 15 mL) and dried over Na\(_2\)SO\(_4\) andd concentrated. The compound was purified via silica column chromatography (hexanes:EtOAc, 20:1 to 3:1) and yielded 14 (0.580 g, 0.97 mmol, 90% yield) as a white foam. \( R_f = 0.68 \) (silica gel, hexanes:EtOAc, 4:1); \( [\alpha]_D^{23} = +23.1 \ (c = 1.1, \text{CHCl}_3) \); \(^1\)H NMR (500 MHz, CDCl\(_{3}\)) \( \delta \) 7.67-7.36 (m, 10H), 5.59 (m, 1H), 5.37 (d, \( J = \))
5.9 Hz, 1H), 5.20 (d, J = 2.2 Hz, 1H), 5.16 (d, J = 2.2 Hz, 1H), 3.94 (s, 3H), 3.73 (m, 2H), 3.12 (m, 1H), 1.91-1.01 (m, 12H), 1.26 (s, 3H), 1.03 (s, 9H), 0.91 (d, J = 6.5 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.44, 167.25, 165.05, 149.21, 135.61, 134.03, 129.96, 129.39, 127.52, 127.44, 108.34, 94.38, 62.94, 62.32, 54.18, 41.85, 40.33, 39.33, 38.53, 36.67, 35.61, 33.11, 26.83, 26.78, 22.46, 19.15, 17.08.; HRMS (ESI) m/e 621.3007 [M\(^+\)Na\(^+\)] calcd for C\(_{37}\)H\(_{46}\)O\(_5\)SiNa\(^+\): 621.3005.

**Alcohol 15_1:** To a solution of 14 in THF (8.35 mL) was added hydrofluoric acid (1.200 ml, 33.4 mmol) dropwise in a plastic tube and stirred at rt overnight. The next morning the reaction was quenched with sat. NaHCO\(_3\) (100 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated. The crude compound was purified via silicia column chromatography (hexanes: EtOAc 20:1 to 1:1) to give alcohol (0.22 g, 0.610 mmol, 73.1 % yield) as a white foam. \(R_f = 0.48\) (silica gel, hexanes:EtOAc, 1:1); \([\alpha]_D^{23} = +26.3\) (c = 1.1, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.73 (m, 1H), 5.44 (d, J = 5.9 Hz, 1H), 5.21 (d, J = 2.2 Hz, 1H), 5.17 (d, J = 2.2 Hz, 1H), 3.92 (s, 3H), 3.68 (m, 2H), 3.68 (m, 2H), 3.10 (m, 1H), 1.91-1.01 (m, 12H), 1.27 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.76, 166.80, 165.83, 149.00, 130.42, 127.01, 108.17, 95.06, 62.82, 60.55, 54.36, 41.81, 40.04, 38.76, 38.61, 36.73, 35.58, 33.08, 26.69, 22.40, 17.74; HRMS (ESI) m/e 383.1829 [M\(^+\)Na\(^+\)] calcd for C\(_{21}\)H\(_{28}\)O\(_3\)Na\(^+\): 383.1826.
Aldehyde 15: To a solution of alcohol in DCM (1.110 mL) was added sodium bicarbonate (0.047 g, 0.555 mmol) and Dess-Martin Periodinane (0.071 g, 0.166 mmol). After stirring for 10 minutes, the reaction was quenched with a 1:1:1 solution of sat. NaHCO₃, water, sat. Na₂S₂O₃ and stirred for 30 minutes. The resultant solution was extracted with DCM (3 x 15 mL). The combined organic layers were then dried over Na₂SO₄ and concentrated. The crude compound was purified via silcia column chromatography (hexanes: EtOAc 50:1 to 3:1) to yield 15 (0.038 g, 0.106 mmol, 96 % yield) as a white foam. Rₚ = 0.67 (silica gel, hexanes:EtOAc, 7:3); ¹H NMR (500 MHz, CDCl₃) δ 9.72 (m, 1H), 5.60 (m, 1H), 5.45 (d, J = 6.1 Hz, 1H), 5.20 (d, J = 2.3 Hz, 1H), 5.17 (d, J = 2.3 Hz, 1H), 3.92 (s, 3H), 3.53 (m, 1H), 2.43-1.01 (m, 12H), 1.33 (s, 3H), 0.91 (d, J = 6.5 Hz, 3H); ¹HRMS (ESI) m/e 358.1780 [M+Na⁺] calcd for C₂₁H₂₆O₅Na⁺: 358.1782.

Acetate 17: To a solution of 13 (0.6 g, 0.999 mmol) in DCM (4.99 mL) was added triethylamine (0.278 mL, 1.997 mmol), acetic anhydride (0.188 mL, 1.997 mmol) and DMAP (0.012 g, 0.100 mmol). This solution stirred for 3 hr before being quenched with sat. NaHCO₃ solution that stirred for 10 min. Then the solution was extracted
with DCM (3 x 30 mL). The combined organic layer were then dried over Na2SO4 and concentrated. The crude compound was purified via silcia column chromatography (hexanes: EtOAc 20:1 to 3:1) to yield acetate protected alcohol (0.507 g, 0.789 mmol, 79 % yield) as a white foam. To a solution of the previous product (0.5 g, 0.778 mmol) in THF (3.89 mL) was added HF (1.118 mL, 31.1 mmol) dropwise. The solution stirred at rt overnight and was then quenched with sat. NaHCO3 (50 mL). The solution was extracted with DCM (3 x 30 mL). The combined organic layers were dried over Na2SO4 and concentrated. The crude compound was purified via silica column chromatography (hexanes:EtOAc 50:1 to 1:2) to yield alcohol (0.232 g, 0.572 mmol, 73.6 % yield) as a white foam. To a solution of the alcohol in DCM (5.74 mL) was added sodium bicarbonate (0.289 g, 3.44 mmol) and Dess-Martin periodinane (0.487 g, 1.147 mmol). The reaction stirred at rt for 10 mintues before being quenched with a 1:1:1 water, sat. NaHCO3, sat Na2SO3 mixture that stirred for 30 minutes. Then the soluton was extracted with DCM (3 x 10 mL). The combine organic layers were dried over Na2SO4 and concentrated. The crude compound was purified via silica column chromatography (hexanes:EtOAc 100:1 to 3:1) to yield 17 (0.208 g, 0.516 mmol, 90 % yield) as a white foam. \(R_t = 0.77\) (silica gel, hexanes:EtOAc, 6:4); \([\alpha]_{D}^{23} = +19.9\) (c = 2.8, CHCl3); \(^1\)H NMR (500 MHz, CDCl3) \(\delta\) 9.79 (m, 1H), 5.57 (m, 2H), 5.33 (d, \(J = 5.9\) Hz, 1H), 5.19 (d, \(J = 2.3\) Hz, 1H), 5.12 (d, \(J = 2.3\) Hz, 1H), 4.20 (s, 3H), 4.10 (m, 1H), 2.49-1.01 (m, 12H), 2.08 (s, 3H), 0.91 (d, \(J = 6.9\) Hz, 3H), 0.87 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl3) \(\delta\) 203.48, 170.41, 166.65, 165.68, 148.33, 130.20, 130.09, 107.27, 95.82, 71.23, 60.84, 49.98, 43.06, 41.69, 40.48, 40.44, 38.44, 35.95, 33.17,

**Triene 18:** A mixture of chromium (II) chloride (0.168 g, 1.367 mmol) and (1,2-dimethoxyethyl)nickel(IV) dichloride hydride (6.01 mg, 0.027 mmol) was flamed dried under vacuum. The mixture was sealed under argon and THF (0.577 mL) was added. Then a mixture of (3E,5E)-1-iodohepta-1,3,5-triene (0.075 g, 0.342 mmol) and 17 (0.055 g, 0.137 mmol) in THF (1.153 mL) was added dropwise to the metal mixture at 0°C. The reaction then stirred at rt overnight. The next morning the reaction was filtered through celite and extracted with ether (3 × 15 mL). The combine organic layers were washed with brine (20mL), dried over Na₂SO₄ and concentrated. The crude compound was purified via silica column chromatography (hexanes:EtOAc 100:1 to 3:1) to yield 18 (0.035 g, 0.070 mmol, 51.6 % yield) as a yellow oil. Rᵋ = 0.35 (silica gel, hexanes:EtOAc, 7:3); [α]D²³ = +17.5 (c = 0.9, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.50-5.13 (m, 11H), 4.22 (s, 3H), 4.20 (m, 1H), 3.52-0.85 (m, 24H); HRMS (ESI) m/e 519.2707 [M⁺Na⁺] calcd for C₃₀H₄₀O₆Na⁺: 519.2717. Mixture of diasteromers.
Acetate 20: To a solution of 11 (3.5 g, 7.37 mmol) in CH₂Cl₂ (73.7 mL) was added DIBAL-H (8.11 mL, 8.11 mmol) dropwise at 0°C. The reaction stirred at this temp for 5 min and was then diluted with ether and fieser method workup. After filtration and concentration, the alcohol (3.4 g, 7.13 mmol, 97 % yield) was isolated as clear oil and moved to the next step. To a solution of the alcohol (3.4 g, 7.13 mmol) in DCM (47.5 mL) was added triethylamine (1.988 ml, 14.26 mmol), acetic anhydride (1.346 mL, 14.26 mmol) and DMAP (0.087 g, 0.713 mmol). The reaction stirred at room temperature for 2 hrs before being quenched with sat. NaHCO₃ and that stirred for 10 min. The solution was extracted with DCM (3 x 25 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated to yield 20 (3.65 g, 7.04 mmol, 99 % yield) at a clear oil that was carried to next step as is. \( R_f = 0.57 \) (silica gel, hexanes:EtOAc, 9:1); \( [α]_D^{23} = +23.5 \) (c = 2.4, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) δ 7.69-7.37 (m, 10H), 5.57 (m, 1H), 5.35 (d, \( J = 10.1 \) Hz, 1H), 4.01 (d, \( J = 11.1 \) Hz, 1H), 3.84 (d, \( J = 11.1 \) Hz, 1H), 3.74 (m, 2H), 2.11 (m, 1H), 2.02 (s, 3H), 1.85-1.72 (m, 4H), 1.57-0.90 (m, 7H), 1.06 (s, 9H), 0.90 (s, 3H), 0.89 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 171.5, 135.5, 133.9, 131.0, 129.6, 128.3, 127.6, 70.0, 62.1, 41.6, 41.0,
39.8, 38.4, 37.0, 35.5, 34.4, 32.8, 26.9, 25.4, 22.6, 21.0, 19.3, 17.5; HRMS (ESI) m/e 541.3107 [M$^+$Na$^+$] calcd for C$_{33}$H$_{46}$O$_3$SiNa$^+$: 541.3108.

**Alcohol 21_1:** To a solution of 20 (3.65 g, 7.04 mmol) in THF (35.2 mL) was added HF (10.11 mL, 281 mmol) and the solution stirred at room temperature overnight. The reaction was quenched with sat. NaHCO$_3$ and then extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude extract was purified via silica column chromatography (hexanes:EtOAc 50:1 to 1:1) to yield 21_1 (1.49 g, 5.31 mmol, 76 % yield) as clear oil. $R_f$ = 0.13 (silica gel, hexanes:EtOAc, 4:1); $[\alpha]_D^{23} = +39.7$ (c = 0.37, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.65 (m, 1H), 5.45 (d, $J = 10.0$ Hz, 1H), 4.05 (d, $J = 11.1$ Hz, 1H), 3.88 (d, $J = 11.1$ Hz, 1H), 3.78 (m, 1H), 3.72 (m, 1H), 2.10 (s, 3H), 2.06 (m, 1H), 1.78 (m, 4H), 1.53-0.90 (m, 7H), 0.92 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.5, 131.5, 127.9, 69.9, 61.4, 41.5, 41.0, 40.2, 38.4, 37.1, 35.5, 34.7, 32.8, 25.3, 22.5, 21.1, 17.4; HRMS (ESI) m/e 303.1930 [M$^+$Na$^+$] calcd for C$_{17}$H$_{28}$O$_3$Na$^+$: 303.1931.
**Aldehyde 21:** To a solution of 21-1 (1.49 g, 5.31 mmol) in DMSO (22.81 mL) was added IBX (2.232 g, 7.97 mmol) and this solution stirred at room temperature for 2 hrs. The solution was diluted with water and filtered through a celite plug which was subsequently rinsed with ether. The filtrate was then extracted with ether (5 x 30 mL). The combined organic layers were then washed with 10% NaOH (2 x 20mL), water (20 mL) and brine (20 mL). The organic layer was then dried over Na₂SO₄ and concentrated to yield 21 (1.32 g, 4.74 mmol, 89 % yield) as light yellow oil used directly in the next step. \( R_f = 0.75 \) (silica gel, hexanes:EtOAc, 2:1); \([\alpha]_D^{23} = +38.5 \) (\( c = 1.0 \), CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 9.75 \) (m, 1H), 5.54 (m, 1H), 5.43 (d, \( J = 9.8 \) Hz, 1H), 3.99 (d, \( J = 11.4 \) Hz, 1H), 3.77 (d, \( J = 11.4 \) Hz, 1H), 2.53 (m, 2H), 2.33 (m, 1H), 2.04 (s, 3H), 1.75 (m, 4H), 1.50-0.90 (m, 5H), 0.92 (s, 3H), 0.88 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta 202.1, 171.1, 131.9, 127.6, 69.4, 46.5, 41.4, 40.8, 38.6, 37.9, 37.0, 35.3, 32.7, 25.2, 22.5, 21.0, 17.4; \) HRMS (ESI) m/e 301.1772 \([\text{M}^+\text{Na}^+]\) calcd for C₁₇H₂₆O₃Na⁺: 301.1774.
Aldehyde 22: To a solution of chloro(methoxymethyl)triphenylphosphorane (4.88 g, 14.22 mmol) in THF (63.2 mL) at 0°C was added KHMDS (13.75 mL, 13.75 mmol, 1M in THF) and stirred at this temp for 30 min then a solution of 21 (1.32 g, 4.74 mmol) in THF (31.6 mL) was added dropwise. After stirring for 5 minutes the reaction was quenched with sat. NH₄Cl and extracted with ether (3 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude compound was then purified via silica column chromatography to yield methoxy-olefin (1.08 g, 3.52 mmol, 74.3 % yield) as clear oil. *R*ₚ = 0.68 (silica gel, hexanes:EtOAc, 4:1) To a solution of methoxy-olefin (1.08 g, 3.52 mmol) in acetone (70.5 mL) was added p-TsOH (2.011 g, 10.57 mmol). After 30 minutes the reaction was quenched with sat. NaHCO₃ and concentrated. The crude mixture was then extracted with ether (3 x 30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄ and concentrated to yield 22 (0.98 g, 3.35 mmol, 95 % yield) as clear oil that was used as is to the next step. *R*ₚ = 0.21 (silica gel, hexanes:EtOAc, 9:1); [α]ᵦ₂₃ = +39.6 (c = 0.85, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.77 (m, 1H), 5.57 (m, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 4.05 (d, *J* = 11.1 Hz, 1H), 3.88 (d, *J* = 11.1 Hz, 1H), 2.50 (m, 2H), 2.07 (s, 3H), 1.80 (m, 6H), 1.53-0.90 (m, 6H), 0.89 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 202.9, 171.6, 132.5, 127.5, 69.9, 42.8, 42.1, 41.7, 41.1, 38.6, 37.7, 35.7, 33.0, 25.5, 24.4, 22.7, 21.3, 17.7; HRMS (ESI) m/e 315.1928 [M⁺Na⁺] calcd for C₁₈H₂₈O₃Na⁺: 315.1931.
Triene 24: To a solution of bromo((2E,4E)-hexa-2,4-dien-1-yI)triphenylphosphorane (4.26 g, 10.05 mmol) in THF (18.6 mL) at -78°C was added BuLi (3.89 ml, 9.72 mmol, 2.5M) and stirred at this 30 min. Then a solution of 22 (0.98 g, 3.35 mmol) in THF (18.62 mL) was added dropwise. After 5 min the reaction was quenched with sat. NH₄Cl and warmed to room temperature. The solution was extracted with ether (3 x 30 mL). The combined organic layers were washed withe brine, dried over Na₂SO₄ and concentrated. The crude compound was purified via buffer 3% Et₃N silica column chromatography to yield 24 (0.81 g, 2.272 mmol, 67.8% yield) as clear oil. Rᵥ = 0.74 (silica gel, hexanes:EtOAc, 4:1); [α]D²⁴ = +56.8 (c = 0.46, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.45-5.40 (m, 8H), 4.00 (d, J = 11.1 Hz, 1H), 3.86 (d, J = 11.1 Hz, 1H), 2.24 (m, 1H), 2.07 (s, 3H), 2.04 (m, 2H), 1.85 (m, 1H), 1.75 (d, J = 6.8 Hz, 3H), 1.74 (m, 3H), 1.54-0.91 (m, 7H), 0.89 (s, 3H), 0.89 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 134.1, 131.7, 131.1, 130.9, 130.6, 130.4, 129.0, 128.3, 70.0, 42.6, 41.6, 41.1, 38.4, 35.5, 32.8, 31.4, 30.6, 25.4, 21.1, 18.3, 17.5; HRMS (ESI) m/e 379.2606 [M⁺Na⁺] calcd for C₂₄H₃₆O₂Na⁺: 379.2608.
**Alcohol 25_1**: To a solution of 24 (0.81 g, 2.272 mmol) in THF (22.72 mL) at 0°C was added sodium methoxide (9.09 mL, 4.54 mmol, 0.5M) dropwise. 7 hours later the reaction was quenched with sat. NH₄Cl and extracted with ether (3 x 20 mL). The combine organic layers were washed with brine and dried over Na₂SO₄ and concentrated to yield 25_1 (.638 g, 2.029 mmol, 89 % yield) as a white wax, which was pushed to the next step. Rₜ = 0.26 (silica gel, hexanes:EtOAc, 9:1); [α]D²³ = +66.1 (c = 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 6.56-5.38 (m, 8H), 3.50 (s, 2H), 2.26 (m, 1H), 2.07 (m, 1H), 1.80-1.65 (m, 4H), 1.75 (d, J = 6.7 Hz, 3H), 1.50-0.92 (m, 8H), 0.87 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 134.6, 132.0, 131.4, 131.1, 130.8, 130.8, 129.1, 128.9, 68.6, 42.9, 41.9, 41.3, 38.8, 35.8, 33.1, 31.9, 31.0, 29.9, 25.6, 22.8, 18.5, 17.3; HRMS (ESI) m/e 315.2689 [M+H⁺] calcd for C₂₂H₃₅O⁺: 315.2688.
**Aldehyde 25:** To a solution of 25-1 (0.638 g, 2.029 mmol) in CH$_2$Cl$_2$ (20.29 mL) was added sodium bicarbonate (1.022 g, 12.17 mmol) then Dess-Martin Periodinane (1.291 g, 3.04 mmol). The reaction stirred for 15 minutes and was then quenched with a 1:1:1 solution of saturated NaHCO$_3$ (5 mL), saturated Na$_2$SO$_3$ (5 mL), and water (5 mL) that stirred for 30 minutes. Then the solution was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, and concentrated to yield 25 (.554 g, 1.773 mmol, 87 % yield) as clear oil. R$_f$ = 0.60 (silica gel, hexanes:EtOAc, 9:1); [α]$_D^{23}$ = +76.7 (c = 0.34, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.63 (s, 1H), 6.16-5.44 (m, 8H), 2.31- 1.76 (m, 5H), 1.74 (d, $J$ = 8.9 Hz, 3H), 1.68-1.02 (m, 9H), 0.98 (s, 3H), 0.90 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.3, 133.2, 131.9, 131.5, 131.5, 131.3, 130.4, 129.4, 127.2, 50.1, 44.6, 41.8, 39.6, 38.1, 35.6, 33.4, 32.4, 30.9, 27.1, 22.7, 18.5, 14.8; HRMS (ESI) m/e 313.2522 [M$^+$H$^+$] calcd for C$_{22}$H$_{33}$O$^+$: 313.2522.

![Chemical structure of Aldehyde 25](image)

**Tetronate 27:** To a solution of diisopropylamine (0.025 ml, 0.177 mmol) in toluene (1.232 mL) at -78°C was added BuLi (0.110 ml, 0.170 mmol) (1.55M) dropwise and this solution stirred at this temperature for 1 hr. Then a solution of 4-methoxy-5-methylenefuran-2(5H)-one (0.017 g, 0.131 mmol) in THF (0.616 mL) was added.
dropwise over the span of 5 minutes and stirred at this temperature for 10 minutes to create a yellow solution. Then a solution of 25 (0.045 g, 0.144 mmol) was added dropwise over the span of 5 minutes and the yellow color persisted. (If the reaction color darkens, the material was added too quickly to the reaction mixture and will lead to partial decomposition of material and significantly lower reaction yield) This reaction continued to stir at this temperature for 30 minutes before being quenched with sat. NH₄Cl. Then the reaction mixture slowly warmed up to room temperature.

The reaction was extracted with EtOAc (5 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄ and concentrated. The crude compound was purified via a 2% Et₃N buffered column to yield 27_1 (39 mg, 89 µmol, 68% yield) as 1:1 dr alcohols that was carried together to the next step. To the mixture of 27_1 in DMSO (0.2 mL) was added IBX (7 mg, 0.15 mmol) and the reaction continued to stir at room temperature for 3 hrs. Then the reaction was diluted with water (2 mL) and filtered through a celite plug, which was then rinsed with ether (10 mL). The resulting solution was then extracted with ether (5 x 5 mL). The combined organic layers were washed with 10% NaOH (2 x 5 mL), water (5 mL), and brine (5 mL). The organic layer was dried over Na₂SO₄ and concentrated to yield 27 (30 mg, 81%) essentially pure as light yellow oil. The compound was run through a silica plug to purify for characterization. $R_f=0.75$ (silica gel, hexanes:EtOAc, 4:1); $[\alpha]_D^{22}=+40.5$ (c = 0.40, CHCl₃); $^1$H NMR (500 MHz, CDCl₃) δ 6.49-5.42 (m, 8H), 5.20 (d, $J=2.7$ Hz, 1H), 5.15 (d, $J=2.7$ Hz, 1H), 3.94 (s, 3H), 3.03 (m, 1H), 2.23 (m, 1H), 2.08 (m, 1H), 1.87-1.70 (m, 4H), 1.74 (d, $J=14.2$ Hz, 3H), 1.46-0.93 (m, 7H),
1.27 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 167.2, 165.3, 152.0, 149.2, 134.4, 131.9, 130.8, 130.6, 130.3, 130.2, 128.6, 127.4, 108.3, 94.5, 94.5, 54.6, 41.9, 41.7, 40.3, 38.5, 35.0, 33.1, 30.4, 26.8, 22.4, 18.3, 17.4; HRMS (ESI) m/e 437.2690 [M$^+$H$^{+}$] calcd for C$_{28}$H$_{37}$O$_4^+$: 437.2686.

**Spirotetronate 28/29:** A solution of 27 (.030 g, 0.009 mmol) in toluene (1.145 mL) was degassed with bubbling argon for 30 minutes and was then heated at 110°C (temp 160 setting on yellow stir plate) overnight. Upon completion, the reaction was concentrated to yield a 1.5:1 dr of 28/29 (.023 g, 8.70 µmol, 76 % yield). The diasteromeric mixture was separated via preparative TLC (200:1 toluene/acetone ran 3x) to yield to clean diasteromers as white solids. **Compound 28** $R_f$ = 0.47 (silica gel, hexanes:EtOAc, 9:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.89 (m, 1H), 5.76 (dt, J = 3.1, 9.8 Hz, 1H), 5.56 (dt, J = 2.0, 10.2 Hz, 1H), 5.32 (dd, J = 2.4, 9.7 Hz, 1H), 5.16 (m, 2H), 4.09 (s, 3H), 3.01 (m, 1H), 2.60-2.28 (m, 5H), 1.95-1.68 (m, 8H), 1.53 (s, 3H), 1.46-1.01 (m, 4H), 1.19 (d, J = 7.4 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 184.3, 169.1, 167.8, 132.6, 132.5, 130.9, 130.6, 129.8, 128.8, 123.9, 84.5, 68.2, 62.9, 41.7, 41.1, 38.7, 36.1, 33.4, 28.9, 28.2, 27.7, 23.8, 23.0, 22.6, 21.6, 15.5, 14.1, 11.0.; HRMS (ESI) m/e 437.2683 [M$^+$H$^{+}$] calcd for C$_{28}$H$_{37}$O$_4^+$: 437.2686.
**Compound 29** $R_f = 0.47$ (silica gel, hexanes:EtOAc, 9:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.15 (m, 1H), 5.93 (m, 1H), 5.83 (dt, $J = 3.2$, 9.5 Hz, 1H), 5.65 (dt, $J = 2.6$, 9.6 Hz, 1H), 5.33 (m, 2H), 3.90 (s, 3H), 3.16 (m, 1H), 2.56-1.67 (m, 13H), 1.87-1.70 (m, 4H), 1.74 (d, $J = 14.2$ Hz, 3H), 1.47 (s, 3H), 1.14 (d, $J = 7.2$ Hz, 3H); 0.91 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 180.4, 169.4, 167.8, 151.9, 135.1, 130.9, 130.4, 129.9, 128.8, 105.0, 86.9, 68.2, 61.7, 53.9, 41.8, 36.2, 33.2, 30.4, 28.9, 28.4, 27.9, 23.8, 23.0, 22.5, 20.4, 16.7, 14.1, 11.0.; HRMS (ESI) m/e 437.2683 [M$^+$H$^+$] calcd for C$_{28}$H$_{37}$O$_4$$^+$: 437.2686.

3. List of Spectra
Spectrum 4.01: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 6_1
Spectrum 4.02: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 6_1
Spectrum 4.03: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 6
Spectrum 4.04: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 6
Spectrum 4.05: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 7
Spectrum 4.06: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 7
Spectrum 4.07: $^1\text{H}$ NMR (CDCl$_3$, 500 MHz) of compound 8_1
Spectrum 4.08: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 8_1
Spectrum 4.09: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 8
Spectrum 4.10: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 8
Spectrum 4.11: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 10
Spectrum 4.12: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 10
Spectrum 4.13: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 11
Spectrum 4.14: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 11
Spectrum 4.15: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 13
Spectrum 4.16: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 13
Spectrum 4.17: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 14
Spectrum 4.18: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 14
Spectrum 4.19: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 15_1
Spectrum 4.20: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 15_1
Spectrum 4.21: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 15
Spectrum 4.22: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 17
Spectrum 4.23: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 17
Spectrum 4.24: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 18
Spectrum 4.25: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 20
Spectrum 4.26: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 20
Spectrum 4.27: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 21_1
Spectrum 4.28: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 21_1
Spectrum 4.29: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 21
Spectrum 4.30: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 21
Spectrum 4.31: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 22
Spectrum 4.32: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 22
Spectrum 4.33: $^1$H NMR ($\text{CDCl}_3$, 500 MHz) of compound 24
Spectrum 4.34: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 24
Spectrum 4.35: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 25_1
Spectrum 4.36: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 25_1
Spectrum 4.37: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 25
Spectrum 4.38: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 25
Spectrum 4.39: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 27
Spectrum 4.40: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 27
Spectrum 4.41: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 28
Spectrum 4.42: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 28
Spectrum 4.43: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 28
Spectrum 4.44: $^1$H NMR (CDCl$_3$, 500 MHz) of compound 29
Spectrum 4.45: $^{13}$C NMR (CDCl$_3$, 125 MHz) of compound 29
Spectrum 4.46: $^1$H NOESY NMR (CDCl$_3$, 500 MHz) of compound 29
Reference


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