Design, Synthesis And Biological Evaluation Of $(+)$-Discodermolide And Synthetic Study Towards $(–)$-Pterocidin

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Design, Synthesis And Biological Evaluation Of (+)-Discodermolide And Synthetic Study Towards (−)-Pterocidin

Abstract
ABSTRACT

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION
OF (+)-DISCODERMOLIDE ANALOGS
AND
SYNTHETIC STUDY TOWARDS (−)-PTEROCIDIN

Nan Zhang
Amos B. Smith, III

Chapter one describes the design and synthesis of novel (+)-discodermolide analogs, that featured different saturation degrees of the terminal diene system and various lactone moieties. Biological evaluation via multiparameter dose-response analysis identified analog B2 as lead congener with superior efficacy towards different cancer cell lines. The high-resolution crystal structure of the B2-tubulin complex was obtained, shedding light on future design of new (+)-discodermolide analogs based on a better understanding of binding mechanism at molecular level.

Chapter two describes a “high-risk” synthetic study towards the natural product (−)-pterocidin. Besides cytotoxicity in different cancer cell lines at the low micromolar level, (−)-pterocidin has potent anti-invasive activity at non-cytotoxic concentration. A “high-risk” synthetic strategy was designed as a showcase of Type II Anion Relay Chemistry comprising a multicomponent union involving an aldehyde fragment, a bifunctional linchpin and a dienyl ether moiety. The key union has been demonstrated and the final step of the synthesis is currently under investigation.

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Subject Categories
Organic Chemistry

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION
OF (+)-DISCODERMOLIDE
AND
SYNTHETIC STUDY TOWARDS (−)-PTEROCIDIN
Nan Zhang
A DISSERTATION
in
Chemistry
Presented to the Faculties of the University of Pennsylvania
in
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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF (+)-DISCODERMOLIDE
AND
SYNTHETIC STUDY TOWARDS (−)-PTEROCIDIN
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2019
Nan Zhang
To Smith Group
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ABSTRACT

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION
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AND
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<th>Description</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ARC</td>
<td>Anion Relay Chemistry</td>
</tr>
<tr>
<td>Arg</td>
<td>Arginine</td>
</tr>
<tr>
<td>Asp</td>
<td>Aspartic Acid</td>
</tr>
<tr>
<td>ASG</td>
<td>Anion stabilizing group</td>
</tr>
<tr>
<td>BCl·DMS</td>
<td>Boron trichloride dimethyl sulfide</td>
</tr>
<tr>
<td>BF₃·Et₂O</td>
<td>Boron trifluoride diethyl etherate</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>CIS</td>
<td>Chemotherapy Induced senescence</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
</tr>
<tr>
<td>CPME</td>
<td>Cyclopentyl methyl ether</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-para-benzoquinone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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<td>-----------</td>
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<tr>
<td>DIPEA</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>d.r.</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>DOS</td>
<td>Diversity-oriented synthesis</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl Acetate</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear multiple quantum correlation</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared spectroscopy</td>
</tr>
<tr>
<td>KO$_t$Bu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>Leu</td>
<td>Leucine</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography–mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>LiAl(OtBu)₃H</td>
<td>Lithium tri-tert-butoxy aluminum hydride</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>Meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxyl methyl</td>
</tr>
<tr>
<td>MPA</td>
<td>Methoxy phenylacetyl</td>
</tr>
<tr>
<td>MTPA</td>
<td>Methoxy trifluoromethyl phenylacetyl</td>
</tr>
<tr>
<td>NaH</td>
<td>Sodium hydride</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear overhauser effect spectroscopy</td>
</tr>
<tr>
<td>PMB</td>
<td>Para-methoxybenzyl</td>
</tr>
<tr>
<td>PIDA</td>
<td>(Diacetoxyiodo)benzene</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pro</td>
<td>Proline</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure-activity relationship</td>
</tr>
<tr>
<td>s-BuLi</td>
<td>Sec-butyllithium</td>
</tr>
<tr>
<td>Ser</td>
<td>Serine</td>
</tr>
<tr>
<td>SFC</td>
<td>Supercritical fluid chromatography</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>$t$-BuLi</td>
<td>Tert-butyllithium</td>
</tr>
<tr>
<td>TBS</td>
<td>Tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethylpiperidine-1-oxyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Thr</td>
<td>Threonine</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
</tbody>
</table>
CHAPTER 1. DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF (+)-DISCODERMOLIDE ANALOGS

1.1 Introduction

1.1.1 Isolation and Structure of (+)-Discodermolide

(+)-Discodermolide (1.1, Figure 1.1) is a polyketide natural product isolated from the Caribbean deep-sea marine sponge *Discodermia dissoluta* by Gunasekera and co-workers in 1990.¹ The isolation yield was only 0.002 % (7 mg from 454 g frozen sponge) and to date fermentation to produce (+)-discodermolide has not been successful.

Figure 1.1 Structure of (+)-Discodermolide
The structure of (+)-discodermolide was determined based on a series of NMR analyses, including $^1$H, $^{13}$C, COSY and a battery of 2D correlation experiments. (+)-Discodermolide is composed of a 24-carbon linear polypropionate chain containing 13 stereogenetic centers (4 hydroxyls and 7 methyl groups). The backbone of the natural product is punctuated by (Z)-olefinic linkages at C-8/C-9, C-13/C-14 and a terminal diene at C-21/C-22. (+)-Discodermolide adopts a U shape in the solution with the internal Z olefins acting as conformational locks by minimizing allylic strain and syn-pentane interactions along the backbone. The structure of (+)-discodermolide also features a carbamate and a tetrasubstituted δ-lactone with a boat-like conformation. The relative stereochemistry of (+)-discodermolide was determined by X-ray crystallographic analysis by Gunasekera and co-workers. However, the absolute stereochemistry of the natural product remained unknown until later confirmed by Schreiber and co-workers when they completed the first total synthesis of (–)-discodermolide in 1993.

1.1.2 Biological Activity of (+)-Discodermolide

Initial biological studies carried out by Gunersekera and co-workers demonstrated that (+)-discodermolide is a potent immunosuppressive compound both in vitro and in vivo. Specifically, (+)-discodermolide can suppress the proliferative response of splenocytes and human peripheral blood leukocytes in the two-way mixed lymphocyte reaction with an IC$_{50}$ at low micromolar level, and as such is equally effective as clinical approved cyclosporin A. In addition, (+)-discodermolide has low nanomolar anti-tumor efficacy towards a variety of human cancer cell lines, as reported by Lonely and co-workers. More importantly, Schreiber and co-workers discovered that (+)-discodermolide retains
the cytotoxicity against both taxol-resistant and multi-drug-resistant cell lines with high water solubility (100-fold greater than taxol), which makes it a promising candidate as anti-tumor drug.\textsuperscript{6,7}

In terms of the mechanism of action, (+)-discodermolide was found by researchers at Harbor Branch, Florida to be a highly potent microtubule-stabilizing agent.\textsuperscript{7} It binds to the taxane pocket of β-tubulin and promotes tubulin polymerization, resulting in mitosis arrest at the G2 and M-phase that eventually leads to cell death. (+)-Discodermolide also promotes assembly of microtubules faster and more potently than any of the other known microtubule-stabilizing agents.\textsuperscript{7,8} In 2000, Horwitz and co-workers discovered the synergistic interaction between (+)-discodermolide and taxol in vitro and in vivo,\textsuperscript{9} suggesting a promising combination for chemotherapy, although it was Schreiber and co-workers who demonstrated that the competitive binding between (+)-discodermolide and taxol.\textsuperscript{10} Finally, the precise binding model of (+)-discodermolide with tubulin at the molecular level was only recently disclosed by the Steinmetz group in 2017.\textsuperscript{11}

1.1.3 Previous Syntheses of (+)-Discodermolide

The impressive biological profile of (+)-discodermolide and the scarce availability from the natural sponge material have over the years stimulated intensive synthetic study towards the natural product. Recognizing the repeating methyl-hydroxy-methyl stereochemical triad embedded in the target, each synthesis disconnected the natural product into three fragments of similar or equivalent complexity.
The first total synthesis of the unnatural antipode (−)-dicodermolide was reported by Schreiber and co-workers in 1993, which established the absolute configuration of the natural product. The synthesis was completed with an overall yield of 3.2% and 24 steps for the longest linear sequence. Later they prepared (+)-discodermolide. Subsequently in 1995, the Smith group published their first-generation synthesis of (−)-dicodermolide with a 2.0% overall yield and a longest linear sequence of 29 steps, that featured a triple convergency strategy from a common precursor. Later in 1999, 1.043 gram of (+)-discodermolide was prepared by the Smith group employing an improved second-generation synthetic route with an overall yield of 6.0% and a longest linear sequence 21 steps. The Smith fourth-generation synthesis was then reported in 2005 with an impressive improvement in overall yield to 9.0% with only 17 steps for longest linear sequence. This approach is both highly efficient and convergent, overcoming the previous problem in the preparation of a Wittig salt fragment. In 2000, the Paterson group reported their first synthesis of (+)-discodermolide employing a stereo-controlled aldol disconnection. They arrived at their third-generation approach via a Still-Gennari olefination with a longest linear sequence 21 steps and in 11.1% overall yield.

Early in 2004, Novartis prepared 60 grams of (+)-discodermolide for phase I clinical trial. The route they used was the hybrid of the Smith gram-scale route and endgame of the Paterson first-generation synthesis. The most recent synthesis of discodermolide came from Morken and coworkers in 2014. The synthesis featured catalytic stereoselective borylations developed in their group with the longest linear step count of 17 and in 13% overall yield.
1.1.4 The Structure-Activity Relationship Study of (+)-Discodermolide Analogs

More than 200 analogs of (+)-discodermolide have been prepared by researchers from academia and industry for structure-activity relationship (SAR) study since it was isolated in 1990. (+)-Discodermolide could be divided into five regions (A-E) in terms of discussing the SAR study (Figure 1.2). All the analogs feature modifications either in one region or several regions at the same time.

Analogs with modifications in region A were first investigated. Compounds with attachment of linkers or fluorescent probes to the terminal diene moiety displayed similar potency as the parent molecule, indicating that there is space to attach large groups in this domain. The reduction of internal olefins reduced the bioactivity dramatically, suggesting that it may be required for the high potency. A variety of analogs have been made with modifications at the carbamate region in which the aryl or alkyl groups were attach to the nitrogen. Almost all these analogs have equivalent or better (3-10 folds increase) potency, except the loss of activity in the cell lines with the P-glycoprotein efflux pump. Region B thus is another potential domain to introduce substituents to tune the pharmacokinetic properties. The skeleton C-17 through C-11 is necessary to retain the potent cytotoxicity as the acetylation of the hydroxyls or epimerization of stereocenters led to the loss of bioactivity. The 16-demethyl analog has a slight increase of the potency which may be taken advantages of in the design of simplified analogs. The olefins at C-13/C-14 and C-8/C-9 have significant impacts on the activity, possibly because they are required to set the conformation of the molecule. Region E has the most modifications so far with promising results. The alkylation or acetylation of C-7 hydroxy has very positive effect on the potency (2-10 folds increase), suggesting
possibly there is no hydrogen bond interaction involved with this hydroxyl. The substituents on the lactone ring are not necessary which results in simplified analogs with similar or better potency.\textsuperscript{29}

In summary, the diene system, the carbamate and the lactone moiety provide opportunities to design promising analogs with higher potency and better pharmacokinetic parameters. Considering the complexity of the molecule, the SAR study may help to develop simplified analogs which is valuable as total synthesis is the only method to access the molecule so far.

**Figure 1.2 Structure-activity Relationship Study of (+)-Discodermolide Analogs**

![Figure 1.2](image)

**1.2 Rational Design of (+)-Discodermolide Analogs**

Because of the impressive biological profile of (+)-discodermolide as a promising anti-tumor drug, chemists from Novartis prepared 60 gram of the natural product and completed a Phase I clinical oncology trial in 2004. (+)-Discodermolide displayed some
significant efficacy with disease stabilization for seven patients out of thirty. Unfortunately, the trial was discontinued due to the pneumotoxicity in three patients out of thirty-two after 4-5 cycles of drug treatment at higher dose levels.24

In 2005, the Smith and Horwitz groups characterized (+)-discodermolide as a potent inducer of chemotherapy induced senescence (CIS), while taxol was a weak inducer.20 Chemotherapy induced senescence (CIS) is defined as prolonged exit from proliferation that is distinct form quiescence, which has been shown to be a harmful therapeutic fate.21 Later in 2014, Smith and Horwitz hypothesized that the chemotherapy induced senescence contributed to the fatal pneumotoxicity in the Novartis phase I clinical trial of (+)-discodermolide.27 Based on this hypothesis, we set out to look for analogs with lower risk of CIS, but that would have higher anti-tumor efficacy.

According to a metabolic study in human liver microsomes by Day and co-workers, the lactone moiety and terminal diene of (+)-discodermolide were the most metabolically labile sites.28 Specifically, the lactone may undergo net oxidation and form a double bond at C-4 and C-5 position; the terminal diene moiety could also yield a diol after epoxidation followed by hydrolysis. During this metabolic process, the generation of reactive oxygen species may be associated with senescence induction. To this end, we hypothesized that analogs with enhanced metabolically stability may reduce the chemotherapy induced senescence leading to a less toxic drug candidate.

For a structure-activity relationship study of (+)-discodermolide, we were interested in the degree of saturation at the terminal diene system, with different substitutions at the C-7 position and modification of lactone moiety (Figure 1.3). Early studies demonstrated that analogs with a saturated C-(23, 24) terminal system and a simplified lactone moiety
had enhanced cytotoxicity with reduced induction of senescence relative to (+)-discodermolide,\textsuperscript{29} possibly due to the fact that the modified compound is more resistant to oxidative metabolism. Therefore, we chose to prepare analogs with different saturation degrees at the terminal diene system (i.e., diene, monoene and saturated) to investigate the influence on stability and cytotoxicity. In terms of the lactone moiety, we were also interested in a simplified six-member ring lactone, and as well as a more rigid five-member ring lactone.\textsuperscript{30} We also wished to evaluate analogs with one more methyl group at the C-4 position of lactone fragment, potentially blocking possible oxidative metabolism of the C-(4, 5) bond. According to literature precedence, the substitution at the C-7 position also has very positive effects on the cytotoxicity (i.e., 2-10 fold improved activity).\textsuperscript{31} This finding may be explained by the fact that the substitution is situated just above C-(4, 5) bond thus introducing steric hindrance for potential oxidations. To this end, we planned to synthesize analogs with different ether substitutions at the C-7 position, such as alkyls, methoxymethyl ether, acetate or carbamate groups. To summarize, we hypothesized that the potential designed analogs would be more resistant to oxidative metabolism, and thus with reduced senescence induction, but at the same time could retain or have improved cytotoxicity.
1.3 Synthesis of (+)-Discodermolide Analogs

1.3.1 Retrosynthetic Analysis
From the retrosynthetic perspective, disconnection at the C-8/C-9 Z-olefinic linkage of butyrolactone analogs would lead to Wittig phosphonium salt 1.4 and butyrolactone 1.3. The lactone fragment 1.3 could then be tracked back to intermediate epoxide 1.13. Wittig salt fragment 1.4 in turn could be constructed via a Suzuki coupling protocol of alkyl iodide 1.6 and vinyl iodide 1.7.\textsuperscript{14} Importantly, both coupling partners could be derived from the same common precursor 1.5, which would be prepared from the (S)-Roche ester. This common precursor strategy is a notable feature of Smith discodermolide synthesis, permitting access to complex fragments in a highly convergent and efficient way. Novartis employed this strategy in their 60-gram synthesis of (+)-discodermolide.\textsuperscript{17}
1.3.2 Synthesis of Lactone Fragment 1.3

Scheme 1.2 Synthesis of Lactone Fragment (−)-1.3

1.3.2 Synthesis of Lactone Fragment 1.3

Scheme 1.2 Synthesis of Lactone Fragment (−)-1.3

1.3.2 Synthesis of Lactone Fragment 1.3

Scheme 1.2 Synthesis of Lactone Fragment (−)-1.3
The synthesis of lactone fragment \((-\cdot)\text{-1.3}\) began with protection of commercially available \((R)\)-glycidol \((\pm\cdot)\text{-1.8}\) as a benzyl ether. The organocuprate was then prepared in situ to open the epoxide regioselectively,\(^{32}\) followed by TBS protection of the homoallylic alcohol \((\pm\cdot)\text{-1.10}\). Epoxidation of alkene formed two diastereomers \((\text{anti: syn}=1.5:1)\), which were subjected to Jacobsen hydrolytic kinetic resolution\(^{28}\) to provide the desired \(\text{anti}\) diastereomer \((-\cdot)\text{-1.13}\). Opening the epoxide with diethyl malonate followed by spontaneous cyclization afforded \(\alpha\)-ethoxycarbonyl lactone \((-\cdot)\text{-1.14}\). Pleasingly the Krapcho decarboxylation\(^{34}\) mediated by LiCl proceeded in 93% yield with the silyl group removed at the same time. The TBS protective group was then reinstalled, followed by the hydrogenolysis of benzyl ether to deliver primary alcohol \((-\cdot)\text{-1.16}\). Swern oxidation\(^{35}\) of the alcohol was then accomplished to furnish the target aldehyde \((-\cdot)\text{-1.3}\). Alcohol \((-\cdot)\text{-1.15}\) was also subjected to methylation\(^{36}\), hydrogenolysis and an oxidation sequence to provide lactone \((-\cdot)\text{-1.17}\). Other lactones with different alkyl groups on C-7 position can also be prepared following this route for the future synthesis of analogs with different C-7 substitutions.
1.3.3 Synthesis of Wittig Salt Fragment 1.4

Scheme 1.3 Initial Approach to Wittig Salt Fragment

For the synthesis of Wittig salt 1.4, advanced intermediate 1.17, available in the Smith group, required that the two PMB protective groups to be selectively deprotected. The initial strategy involved removal of both PMB groups and the resultant primary hydroxyl 1.18 to be reprotected selectively as pivalate ester (Scheme 1.3). The free secondary alcohol 1.19 was then reprotected using PMB trichloroacetimidate catalyzed by a Lewis acid. Reductive cleavage of pivaloyl group delivered the desired alcohol 1.21. While carrying on with this route, we were pleased to discover that the primary PMB group could be removed selectively with the BCl₃-DMS complex at 0 °C in good yield (Scheme 1.4).³⁷ With alcohol 1.21 in hand, the corresponding iodide 1.22 was then obtained followed by a modified Corey protocol.³⁸ The unstable iodide was next heated with
excess PPh₃ and DIPEA to provide the requisite Wittig phosphonium salt 1.4. Wittig salt fragment 1.24 with a MOM protective group on C-11 hydroxyl was later prepared for the synthesis of other analogs given our concern with the low yielding step from 1.22 due to a cyclization byproduct.³⁹

**Scheme 1.4 Synthesis of Wittig Salt Fragment 1.4**
1.3.4 Wittig Union and Final Elaborations

Scheme 1.5 Wittig Union and Final Elaborations

Having access to lactone 1.3 and Wittig salt 1.4, we turned to the key union and final elaborations of the butyrolactone analog. Pleasingly, Wittig union of fragment 1.3 and fragment 1.4 mediated by MeLiLiBr furnished advanced intermediate 1.23 with a high level of Z selectivity (>19:1) without epimerization or elimination (Scheme 1.5).29 The base sensitivity of the lactone and bulky complex phosphonium fragment provides a rationalization for the modest yield of this challenging union reaction. Having established the full carbon skeleton of the desired analog, removal of the secondary PMB group afforded secondary alcohol 1.24. Subsequent installation of the carbamate moiety,
followed by global deprotection completed the synthesis of the butyrolactone analog 1.2. Pleasingly, analog 1.2 displayed comparative biological activity across a range of cancer cell lines compared to (+)-discodermolide according to data from the biological assays.

1.4 Biological Evaluation of (+)-Discodermolide Analogs

Figure 1.4 Analogs Prepared for Biological Evaluations

<table>
<thead>
<tr>
<th>Diene</th>
<th>Monoene</th>
<th>Saturated</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram A1" /></td>
<td><img src="image" alt="Diagram A2" /></td>
<td><img src="image" alt="Diagram A3" /></td>
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<tr>
<td><img src="image" alt="Diagram B1" /></td>
<td><img src="image" alt="Diagram B2" /></td>
<td><img src="image" alt="Diagram B3" /></td>
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<tr>
<td><img src="image" alt="Diagram C1" /></td>
<td><img src="image" alt="Diagram C2" /></td>
<td><img src="image" alt="Diagram C3" /></td>
</tr>
</tbody>
</table>
Working together with Dr. Boying Guo who prepared the other eight novel analogs, a series of (+)-discodermolide analogs (Figure 1.4) with different degrees of saturation in the terminal diene system and with different lactone fragments have now been prepared for biological evaluation. In collaborations with professors Susan B. Horwitz and Hayley M. McDaid at the Albert Einstein College of Medicine, all analogs have been evaluated in cell proliferation assays with different cancer cell lines (especially triple negative breast and ovarian cancer cell lines which are typically taxane-resistant) employing multiparameter dose-response analysis (EC$_{50}$, E$_{max}$, AUC) to compare the pharmacologic properties.$^{40}$ According to these results, saturated analogs (A3, B3 and C3, Figure 1.4) had weaker anti-tumor activity compared to the monoene (A2, B2 and C2) and diene (A1, B1 and C1) series; however monoenes (A2 and B2) have superior activity compared to diene analogs (A1 and B1). In terms of the lactone, the geminal dimethyl analogs (A1-A3) only have a subtle difference in activity relative to the B series with one methyl at the C-4 position in the lactone ring, while analogs with a butyrolactone group have reduced anti-tumor activity compared to the A or B series. Together with additional analysis of activity in taxol-resistant cell models, compound B2 with the monoene and a simplified lactone was identified as the lead analog for future study. Importantly, B2 displayed superior long-term anti-tumor efficacy and anti-metastatic properties relative to (+)-discodermolide and to Taxol in cell proliferation assay.

An equally important goal of this project is to evaluate the chemotherapy induced senescence (CIS) response of novel (+)-discodermolide analogs. Lead analog B2 had significantly reduced CIS compared with (+)-discodermolide at 50 nm, although the phenotype activity was detectable at a lower dose.$^{40}$ As we hypothesized that
chemotherapy induced senescence contributes to the fatal pneumotoxicity in the phase I clinical trial of (+)-discodermolide, we believed that analog B2 with lower risk of CIS but superior anti-tumor efficacy is a promising lead drug.

1.5 Future Directions

As one of the most potent types of microtubule-stabilizing agents, the outlook of (+)-discodermolide and the analogs therefore remain promising, and thus continues to stimulate research from chemists and biologists.

In 2017, Steinmetz group reported the first high-resolution crystal structure of (+)-discodermolide in complex with tubulin (Figure 1.5) that revealed detailed binding modes of this natural product in the taxane pocket of β-tubulin.11

According to the crystal structure published by Steinmetz and co-workers, (+)-discodermolide was buried deeply in the taxane site of β-tubulin (A, Figure 1.5), possessing a very similar hairpin conformation as was observed in solid-state and solution NMR studies. However, the lactone ring in the crystal structure of the complex is a in half-chair conformation. There are five main hydrogen bonds: C-1 ester carbonyl and Ser232; C-3 hydroxy and Arg369; C-11 hydroxy and Asp226; C-17 hydroxy and Pro274/Thr276; carbamate with Leu371. In addition, the terminal diene system of (+)-discodermolide has a weak hydrogen bond to Thr276 and a π-π interaction to Arg278. The detailed binding model lends some support to the previous structure-activity relationship studies (i.e. hydroxyls at C-11 and C-17 are important, and the lactone and
the carbamate moiety are required for high potency) and permits rationalization of the retention of cytotoxicity again taxol-resistant cancer cell lines.

**Figure 1.5 Crystal Structure of (+)-Discodermolide-tubulin Complex**

A) Overall view of (+)-discodermolide-tubulin complex  
B) Detailed view of (+)-discodermolide-tubulin complex

Having identified B2 (Figure 1.4) as a lead compound, we hoped to gain insights into the molecular binding mechanism of this analog in the taxane pocket for the future design of novel (+)-discodermolide analogs. In collaboration with professor Michel O. Steinmentz, we were pleased very recently to learn of the crystal structure of the B2 analog in complex with β-tubulin at a level of 2.0 Å resolution (Figure 1.6). In the taxane pocket, the B2 analog adopted a very similar hairpin structure and conserved most
of the interactions as (+)-discodermolide (A, Figure 1.6). However, the simplified six-member lactone led to the loss of one hydrogen bond to Arg369 (B, Figure 1.6). Reorientation of the lactone ring in the taxane site was also observed. Moreover, there is a small reorientation of monoene moiety in the B2 analog resulting in a minor shift of Arg278 sidechain. These observations may rationalize the superior bioactivity of B2 analog due to a more favorable occupation in the binding site of β-tubulin relative to (+)-discodermolide.

**Figure 1.6 Crystal Structure of B2-Tubulin Complex**

A) Detailed view of B2 analog-tubulin complex

B) Close-up view of superimposed (+)-discodermolide-tubulin complex (violet purple)

Although we have gained some structural insights into the binding modes, we still cannot yet completely understand the better bonding affinity of B2 analog. To this end, Dr. Boying Guo has designed two new analogs 1.26 and 1.27 (Figure 1.6) for better understanding of binding mechanism. Compared with the B2 analog, both 1.26 and 1.27
have a monoene system but different lactone fragments: one has one methyl on C-2 (1.26, Figure 1.6) and the other has a hydroxy group on C-3 (1.27, Figure 1.6). Once synthesized, we would like to obtain the crystal structure of analog 1.26 and 1.27 complexed with tubulin to understand which (monoene moiety or lactone fragment) causes the more favorable binding of B2 with tubulin. Only with better understanding of the binding modes, will we be able to design new analogs of (+)-discodermolide as drug candidate by fully exploiting the landscape of the taxane site.

Figure 1.7 Novel (+)-Discodermolide Analogs
1.6 Reference


O. Unpublished Results
CHAPTER 2. SYNTHEtic Study towards (−)-pterocidin: a “high-risk” venture

2.1 Introduction

2.1.1 Isolation and Structure Elucidation of (−)-Pterocidin

2.1.1.1 Isolation of (−)-Pterocidin

(−)-Pterocidin (2.1, Figure 2.1), a cytotoxic compound from endophytic Streptomyces hygroscopicus TP-A0451 strain, was isolated by Igarashi and co-workers in 2006.1 In 2012, they rediscovered (−)-pterocidin from Streptomyces sp. TP-A0879 in a marine sediment sample collected at Otsuchi Bay in Japan.2 With sufficient material (36 mg natural product after HPLC purification) in hand, Igarashi and co-workers established the absolute stereo-configuration of (−)-pterocidin based on a series of NMR analyses and chemical derivatizations.

Figure 2.1 Structure of (−)-Pterocidin 2.1
(-)-Pterocidin\(^1\) (2.1, Figure 2.1) is a linear polyketide featuring an \(\alpha, \beta\)-unsaturated \(\gamma\)-oxygenated \(\delta\)-lactone terminus with five stereogenetic centers. It also has a highly unsaturated aliphatic chain with a dienyl ether moiety. Although the chiral \(\alpha, \beta\)-unsaturated \(\delta\)-lactone motif is not unusual in bioactive natural products, (-)-pterocidin is the first in this class to have a methoxy substitution on the lactone ring. The structure of (-)-pterocidin is closely related to several other members in this class of natural products isolated from *Streptomyces* species, including fostriecin\(^3\), cytostatin\(^4\) and pironetin\(^5\) et al.

### 2.1.1.2 Structure Elucidation of (-)-Pterocidin

The molecular formula of (-)-pterocidin 2.1 was first established by \(^{13}\)C NMR and HRFAB-MS analysis.\(^1\) According to the \(^1\)H, \(^{13}\)C, HMQC, DEPT NMR spectra and IR/UV absorption spectra, the molecular composition and functional groups of 2.1 were determined. DQF-COSY and HMBC correlations studies revealed the connectivity along the carbon skeleton. Coupling constants were then used to establish the *trans* configurations for C-6/C-7, C-8/C-9, and C-16/C-17, as well as the *cis* configurations for C-2/C-3. Equally important, strong NOESY correlations suggested the *cis* configuration for C-4/C-5.

In terms of the absolute configurations,\(^2\) Igarashi and co-workers began with Mosher’s ester derivatization analysis to establish and confirm the absolute configurations of C-13 as \(S\). Based on a series of *J*-based analyses and NOESY analyses, they assigned the C-10 as \(S\) and C-12 as \(R\) configuration. The coupling constant between protons at C-4 and C-5 as well as the NOE between these protons suggested the *syn* relationship. (-)-Pterocidin
2.1 was also reduced with Ca(BH₄)₂ and the corresponding tris-mpa ester was prepared, permitting establishment of the R configurations for C-5 and thus the R configurations for C-4.

2.1.2 Biological Activity of (−)-Pterocidin

Similar to other polyketides with δ-lactone rings isolated from actinomycetes, (−)-pterocidin¹ has antiproliferative activity towards different cancer cell lines with IC₅₀ values ranging from 2.9 to 7.1 μM (Table 2.1). More importantly, (−)-pterocidin has potent anti-invasive activity at non-cytotoxic concentrations. Specifically, the invasion of murine colon 26-L5 carcinoma cells across the Matrigel-fibronectin membrane can be inhibited by (−)-pterocidin with an IC₅₀ value of 0.25 μM, while the cytotoxicity is not apparent with concentrations up to 7 μM.

Tumor cell invasion comprises a key feature of metastasis, which significantly reduces survival rates and the prognosis of patients, and thus is the most common cause of death in cancer patients. However, the current market is still without this type of effective drug. That is, anti-invasion agents are in great demand as a complement to and improved options for innovative cancer therapy. As the first example with potent anti-invasive activity in this class of natural products, we were very interested in the possibility of a structure-activity relationship study of (−)-pterocidin for future drug development.
Table 2.1 Cytotoxicity of (−)-Pterocidin Against Different Cancer Cell Lines

<table>
<thead>
<tr>
<th>Cancer Cell Line</th>
<th>NCI-H522</th>
<th>OVCAR-3</th>
<th>SF539</th>
<th>LOX-IMVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ (μM)</td>
<td>2.9</td>
<td>3.9</td>
<td>5.0</td>
<td>7.1</td>
</tr>
</tbody>
</table>

2.2 Retrosynthetic Analysis of (−)-Pterocidin

2.2.1 Strategic Disconnection of (−)-Pterocidin

Retrosynthetically, we envisioned the endgame construction of (−)-pteroicidin to comprise methylation, desulfurization and TMS removal of the dithiane precursor (+)-2.2. This advanced intermediate in turn would be constructed via a late-stage union of aldehyde fragment (−)-2.3, bifunctional linchpin (−)-2.5 and a dienyl ether fragment 2.4 employing the Type II Anion Charge Relay (ARC) tactic (Scheme 2.1) developed in the Smith group. Continuing with this analysis, disconnection of the diene side chain and lactone moiety in aldehyde fragment (−)-2.3 leads to alkene (−)-2.16. The Smith group$^6$ has developed a six-step synthesis of enantiopure linchpin (−)-2.5 from commercially available (S)-Roche ester. The 1,3-dienyl ether 2.4 in turn would derive from olefin 2.26 via a 1,4-elimination.$^7$
Scheme 2.1 Retrosynthetic Analysis of (−)-Pterocidin 2.1

Such a convergent strategy would hold the promise not only to access (−)-pterocidin but potentially other analogs for a structure-activity relationship study, via late-stage assembly of carbon skeleton and early-stage flexible adjustment of each coupling fragment. This strategy exploiting the Type II ARC tactic can also be applied to the synthesis of other members in this class of natural products, featuring a δ-lactone terminus and unsaturated polyene chains such as cytostatin† (Scheme 2.2).
2.2.2 Key Union: A Showcase for Type II Anion Relay Chemistry (ARC)

In the above proposed retrosynthetic disconnection of (−)-pterocidin, the key fragment union was clearly designed as a “high-risk” showcase for Type II Anion Relay Chemistry (ARC) exploiting the bifunctional linchpin (−)-2.5 recently developed in the Smith group (Scheme 2.3).
Scheme 2.3 Key Fragment Union Employing Type II ARC Tactic

Addition of a metallated dienyl ether such as 2.4 to the enantiopure linchpin aldehyde \((-)-2.5\) (Scheme 2.3) was anticipated to proceed via Felkin-Anh\(^8\) diastereoselective control to form the \textit{syn} addition product, lithium alkoxide 2.41. Upon addition of HMPA, a 1,4-Brook rearrangement\(^9\) could then be triggered to reveal the dithiane-stabilized carbanion 2.42, which would be trapped in situ by aldehyde fragment \((-)-2.3\) to furnish the highly functionalized intermediate \((+)-2.2\) as the tricomponent adduct.
2.2.3 Type II Anion Relay Chemistry and Its Application in Natural Product Synthesis

Over the past decade, the Smith group has reported extensive studies on the development and application of the highly efficient, multicomponent Anion Relay Chemistry (ARC)$^{10}$ tactic. Anion relay chemistry features in “one-flask” a multiple fragment union tactic by controlling the migration of negative charge, employing a linchpin as the center component. This strategy permits the formation of multiple C-C bonds in a “single” flask reaction, thus having access to the rapid and efficient assembly of highly functionalized intermediates found in architecturally complex biologically active molecules synthesis. Equally important, with facile structural variations pre-installed in each fragment prior to their union, the anion relay chemistry can lead to a convergent synthetic route that holds considerable potential for diversity-oriented synthesis (DOS)$^{11}$.

Anion relay chemistry has more recently evolved into Type I and Type II ARC union tactics (Scheme 2.4)$^{10}$. In Type I ARC, an anion is first generated in the linchpin with anion-stabilizing group followed by addition of an electrophile (i.e., an epoxide) to generate the lithium alkoxide. Upon triggering a Brook rearrangement by changes of solvent polarity, temperature and/or counterion, the negative charge on the oxygen is relayed back to the original carbon site, followed by electrophilic termination to provide the tricomponent adduct. In Type II ARC, an external nucleophile first adds to a bifunctional linchpin to form the lithium alkoxide. The negative charge on the oxygen is then migrated to a new distal carbon center via a Brook rearrangement, which is further captured by electrophiles to deliver tricomponent adducts in a single flask.
Recently, our group has developed a new aldehyde linchpin\(^6\) for the synthesis of propionate subunits in complex molecules exploiting the Type II ARC tactic (Scheme 2.5). In this event, an external nucleophile first adds to the enantiopure aldehyde linchpin \((-\text{-}2.5\) to form the lithium alkoxide. With an alpha substituent on the aldehyde, the nucleophilic attack is controlled by the Felkin-Anh model\(^8\) to furnish the \textit{syn} adduct. Upon triggering the \textit{1,4}-Brook rearrangement, the negative charge on oxygen migrates to a distal carbon site leading to the dithiane anion, which is then trapped by electrophiles to deliver the tricomponent adduct with propionate units present.
Scheme 2.5 New Aldehyde Linchpin for Type II ARC

The Type II ARC tactic featuring this new aldehyde linchpin has been employed to great advantage recently by our group. In 2015, Dr. Mellilo and co-workers demonstrated the synthetic utility of this new protocol in the synthetic study toward C-16-C-19 fragment of rhizopodin (A, Scheme 2.6). In this convergent synthetic route, the vinyl species derived from iodide 2.42 was added to the aldehyde linchpin (+)-2.5, followed by 1,4-Brook rearrangement triggered by addition of HMPA and terminating the process with epoxide 2.43 to provide the desired tricomponent adduct 2.44 featuring the C-16-C-19 carbon skeleton of rhizopodin. Later in 2017, Dr. Liu and co-workers completed the first total synthesis of nahuoic acid C₁ (B₃), in which the side chain was constructed via the Type II ARC tactic employing the new bifunctional linchpin (B, Scheme 2.6). In
this event, isopropyl lithium 2.45 first attacked aldehyde linchpin (+)-2.5 to form the lithium alkoxide. Upon 1,4-Brook rearrangement triggered by addition of HMPA, the generated carbon anion was trapped by epichlorohydrin 2.46 to furnish the intermediate 2.47 as single diastereomer with a 76% yield on gram scale.

Scheme 2.6 Recent Application of linchpin 2.5

A. Key Union in the Synthesis of rhizopodin

B. Side Chain Preparation of Nahuoic Acid C₁ (B₁i)
2.3 Synthetic Studies Towards (-)-Pterocidin

2.3.1 Synthesis of Aldehyde Fragment (-)-2.3

2.3.1.1 First-Generation Synthetic Approach To Aldehyde Fragment (-)-2.3

Retrosynthetically, aldehyde fragment (-)-2.3 can be accessed from alkene (-)-2.11 via ring-closing metathesis\(^{13}\) reaction. Alkene (-)-2.11 in turn could be assembled via a Brown\(^{14}\) alkoxyallylation of aldehyde 2.9 with subsequent acylation. Boeckman\(^{15}\) et al. has reported a scalable protocol for the synthesis of aldehyde 2.9 from commercially available sorbaldehyde 2.6 (Scheme 2.7).

![Scheme 2.7 First-Generation Retrosynthetic Analysis of Aldehyde (-)-2.3](image)

Our synthesis thus began with commercially available 2,4-hexdienal 2.6 (E/Z mixture 5:1) involving a condensation with diisopropyl tert-butylphosphonoacetate (Scheme 2.8). The Horner-Wadsworth-Emmons\(^{16}\) reaction was then successfully employed to afford the sensitive and unstable triene 2.7. The crude triene was next subjected to a regioselective
Sharpless catalytic dihydroxylation\textsuperscript{17} to furnish diol ester 2.8 which was converted to the aldehyde 2.9 by oxidation employing NaIO\textsubscript{4}. Followed Brown’s asymmetric alkoxyallylation\textsuperscript{14} technology, the γ-methoxyallyl borane reagent generated in situ was added to the aldehyde 2.9 which resulted in the construction of the syn-stereocenters in 2.10 both with good yield and stereoselectivity. Subsequent acylation led to ring-closing-metathesis precursor (−)-2.11.

Scheme 2.8 First-Generation Synthetic Approach to Aldehyde (−)-2.3
With alkene (–)-2.11 in hand, various conditions for the metathesis reaction were investigated including different temperatures (r.t. – 110 °C), solvents (DCM, toluene, CPME) and catalysts (A1 - A4, Table 2.2). However, the ring-closing metathesis reaction aiming to access α,β-unsaturated lactone 2.12 proceeded in unsatisfactory yields (10% - 15%). We reasoned that the methoxy group and the diene moiety in (–)-2.11 may chelate with the Ru carbene competitively resulting low conversion of the reaction. Unfortunately, no significant improvements were observed with either additives such as Ti(OiPr)$_4$ and/or fast initiating catalysts (A3, A4, Table 2.2). We therefore decided to construct the lactone ring in 2.12 via ring-closing metathesis before the diene chain was installed.

**Table 2.2 Catalysts Screen of Ring-Closing Metathesis Reaction**

![Catalysts](image)

2.3.1.2 Second-Generation Synthetic of Aldehyde Fragment (–)-2.3

With this possibility in mind, we envisioned that the diene chain in aldehyde fragment (–)-2.3 could be installed via Horner-Wadsworth-Emmons reaction from aldehyde 2.19,
and that the aldehyde in turn could be constructed from alkene \((-\)-2.16) via ring-closing metathesis, which would derive from aldehyde 2.14.

**Scheme 2.9 Second-Generation Retrosynthetic Analysis of Aldehyde \((-\)-2.3)**

A second route was thus designed that begins with the commercially available aldehyde 2.14, which can also be synthesized via a two-step transformation beginning with ethylene glycol 2.13 (Scheme 2.9). Followed Brown’s asymmetric alkoxyallylation\(^{14}\) technology, the \(\gamma\)-methoxyallyl borane reagent was generated in situ and added to the aldehyde 2.14 to construct the \(\text{syn}\)-stereocenters in \((-\)-2.15) with good yield and stereoselectivity (\(\text{dr}>95\%\), \(\text{ee}>90\%\)). Subsequent acylation (a migration byproduct was observed, see experimental section) and ring-closing metathesis with the Hoveyda-Grubbs II generation catalyst\(^{18}\) (loading can be as low as 1.5\% mmol) in toluene successfully delivered lactone \((-\)-2.17). Acidic removal of the TBS protecting group revealed the primary alcohol in good yield. However, oxidation of alcohol 2.22 to access the desired aldehyde 2.23 under various conditions (Swern/Parikh-Doering oxidation\(^{21a}\), Dess-Martin\(^{21b}\), TPAP\(^{21c}\)) proved to be problematic. Elimination product\(^{22}\) 2.24 was always preferred due to aromaticity.
To obtain the aldehyde precursor necessary to install the diene side chain, an alternative route was developed via the conversion of lactone (-)-2.17 to the corresponding ethyl acetal 2.18 followed by oxidation (Scheme 2.10). Lactone (-)-2.17 was then reduced by DIBAL-H to the lactol followed by conversion to the corresponding ethyl acetal 2.18. An alternative method to prepare acetal 2.18 via transketalization\textsuperscript{23} of (-)-2.15 with acrolein diethyl acetal followed by ring-closing metathesis proved unrewarding, which was mostly attributed to the modest conversion (40% - 60%) of transketalization on large scale. To this end, deprotection with TBAF, followed by TEMPO mediated oxidation\textsuperscript{24} furnished the desired aldehyde 2.19.

We next turned to explore the elaboration of aldehyde 2.19 into \(\alpha,\beta\)-unsaturated ester 2.20. Initial efforts here to add aldehyde 2.19 to the deprotonated phosphonate using LiHMDS, NaH, \(n\)-BuLi et al.\textsuperscript{25} as base gave unsatisfactory yields (Entry 1-3, Table 2.3),
likely because the product is unstable under those conditions. Reverse addition of deprotonated phosphonate to aldehyde or premixing aldehyde with phosphonate led to better yields (Entry 3, 6, Table 2.3). We next turn to investigate modified conditions with inorganic bases such as LiOH·H₂O²⁶ and Ba(OH)₂·8H₂O²⁷ (Entry 7, 8, Table 2.3). Pleasingly, installation of the E, E-diene moiety in dienoate 2.20 was achieved using LiOH·H₂O in the present of 4 Å molecular sieves with 60% yield. The tert-butyl dienoate proved advantageous for the following formation of the acid in the presence of a lactone; initially we prepared the corresponding methyl dienoate which proved to be problematic in the subsequent hydrolysis of the α,β-unsaturated lactone to form the acid (i.e., 1,2-addition at the double bond of the unsaturated lactone or leading to decomposition).

Table 2.3 Optimization of Horner-Wadsworth-Emmons Olefination

![Diagram of the reaction](image-url)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp.</th>
<th>Conditions</th>
<th>Result</th>
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<tbody>
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<td>1</td>
<td>LiHMDS</td>
<td>0 °C</td>
<td>Normal addition&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>Normal addition&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>Reverse addition&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>NaH</td>
<td>0 °C</td>
<td>Reverse addition&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi</td>
<td>-78 °C</td>
<td>Reverse addition&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>-78 °C</td>
<td>Premix 2.19 with phosphonate</td>
<td>30%</td>
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<tr>
<td>7</td>
<td>LiOH·H₂O</td>
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<td>Reflux with 4 Å molecular sieves</td>
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<tr>
<td>8</td>
<td>Ba(OH)₂·8H₂O</td>
<td>70 °C</td>
<td>Reflux with 4 Å molecular sieves</td>
<td>55%</td>
</tr>
</tbody>
</table>

<sup>a</sup>The phosphonate was deprotonated at -78 °C, stirred for 20 min at 0 °C.

<sup>b</sup>The aldehyde substrate 2.19 was added to deprotonated phosphonate.

<sup>c</sup>The deprotonated phosphonate was added to aldehyde substrate 2.19.

Lactal 2.12 was therefore next converted to corresponding lactone (−)-2.12 with purified m-CPBA<sup>28</sup> as oxidant mediated by BF₃·Et₂O<sup>29</sup>. Next, a TFA assisted tert-butyl group removal led to the carboxylic acid (−)-2.21 (Scheme 2.11). This acid was then treated with the Ghosez chloroenamine reagent<sup>30</sup> to form the acid chloride, which was reduced in-situ to afford aldehyde fragment (−)-2.3. Pleasingly this route can be processed on the gram scale level with an 8% overall yield for the 11 steps from commercially available aldehyde 2.13.
Scheme 2.11 Second-Generation Synthesis of Aldehyde (−)-2.3

2.3.2 Synthesis of 1,3-Dienyl Ether Fragment 2.4

Turning next to the synthesis of dienyl ether 2.4, the third component for the ARC protocol, we began with lithiation of 3-methoxypropyne 2.23 followed by addition of propanal to afford propargyl alcohol 2.24. Subsequent semi-hydrogenation using Lindlar’s catalyst led to Z-alkene 2.25 as a diastereomeric mixture (Scheme 2.12). Alkene 2.25 was then subjected to O-methylation, followed by treatment with n-BuLi to provide the desired (1Z, 3E)-dienyl ether 2.4 as a single isomer in 70% yield over the two
steps. The resultant olefin geometry of the product can be rationalized by the fact that complex A is favored relative to complex B in the reaction (Scheme 2.12).

Scheme 2.12 Synthesis of 1,3-Dienyl Ether Fragment 2.4

![Diagram showing the synthesis process]
2.3.3 Fragment Union to Complete the Carbon Skeleton of (-)-Pterocidin

2.3.3.1 Generation of α-Lithiated 1,3-Dienyl Ether

Having procured all three required fragments on reasonable scale, we began to explore the key union reaction exploiting Type II ARC strategy. We first investigated the metalation of the 1,3-dienyl ether 2.4 at α position. Preliminary results using s-BuLi/TMEDA or t-BuLi as base\textsuperscript{33} proved unsatisfactory; no deuterium incorporation was observed upon a D\textsubscript{2}O quenching experiment. However, when dienyl ether 2.4 was treated with Schlosser’s base (n-BuLi/KOt-Bu) in THF at -78 °C, more than 90% deuterium incorporation at α position was observed.\textsuperscript{34} The methoxy group in dienyl ether 2.4 presumably directs the lithiation reagent to the adjacent α-H, which has greater acidity due to the presence of the electronegative oxygen atom, resulting in regioselective deprotonation at the α position.
Having generated the α-metalated dienyl ether, we proceeded to investigate the nucleophilic addition with linchpin aldehyde 2.5. Initial results proved unrewarding, possibly given that the aldehyde is not compatible with the very basic anion generated with Schlosser’s base (Scheme 2.13). Although transmetalation aiming to reduce the basicity is possible, it may complicate the subsequent Brook rearrangement process. In turn, we prepared both organostannane 2.29 and iodide 2.30 as possible precursors to generate α-lithiated 1,3-dienyl ether. Pleasingly, Li-I exchange with two equivalents of t-BuLi proved to be optimal, with inconsistent Li-Sn exchange using n-BuLi, which is possibly limited by the transmetalation equilibrium.
2.3.3.2 First Stage of ARC Union: Nucleophilic Addition and Brook Rearrangement

Having successfully generated the α-lithiated dienyl ether required for the nucleophilic addition of ARC union tactic, the subsequent 1,4-Brook rearrangement was examined (Table 2.4). Using less dissociating solvents such as diethyl ether for Li-I exchange and nucleophilic addition to aldehyde (−)-2.5, pre-Brook intermediate (+)-2.27 was captured in good yield (Entry 1, Table 2.4). As expected, addition of HMPA to increase the solvent polarity or the use of KOtBu for countercation exchange\(^37\) triggers the 1,4-Brook rearrangement at -78 °C to afford product (+)-2.28 (Entry 2-3, Table 2.4). Alternatively, in the presence of the more polar solvent THF, only Brook product (+)-2.28 was observed (Entry 4, Table 2.4). Both pre-Brook product (+)-2.27 and Brook product (+)-2.28 were isolated as single diastereomer. The relative configuration of the pre-Brook product (+)-2.27 was assigned as syn according to Mosher ester NMR analysis\(^38\) confirming the Felkin-Ahn control in the nucleophilic addition between the anion precursor 2.30 and linchpin aldehyde (−)-2.5. The dithiane anion derived from Brook rearrangement was further validated with allylbromide as a terminating electrophile; very pleasingly tricomponent adduct (+)-2.31 was isolated in 80% yield.

**Table 2.4 Investigation of First Stage of ARC Union**

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td></td>
<td>(+)-2.27 pre-Brook product</td>
</tr>
<tr>
<td>2-3</td>
<td>b</td>
<td>HMPA</td>
<td>(+)-2.28 Brook product</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>KOtBu</td>
<td>(+)-2.28 Brook product</td>
</tr>
</tbody>
</table>
### Table 2.27

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent a</th>
<th>Solvent b</th>
<th>Additive</th>
<th>Product 2.27</th>
<th>Product 2.28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_2$O</td>
<td>Et$_2$O</td>
<td>-</td>
<td>89%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Et$_2$O</td>
<td>Et$_2$O</td>
<td>HMPA</td>
<td>-</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>Et$_2$O</td>
<td>Et$_2$O</td>
<td>KO$_t$Bu</td>
<td>-</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>THF</td>
<td>-</td>
<td>-</td>
<td>75%</td>
</tr>
</tbody>
</table>

2.3.3.3 Second Stage of ARC Union: Dithiane Anion Capture by Electrophiles

With the encouraging results from the first stage of ARC union tactic achieved, we turned to investigate different electrophiles as the terminating component. Originally, we proposed acid chloride 2.32 as terminating electrophile for the ARC union (Scheme 2.14). On the one hand, an acid chloride is a highly reactive electrophile towards many organometallic reagents for ketone synthesis. Thus, we hope to achieve chemoselective addition of fragment 2.32 in the present of other reactive functionalities such as α, β-unsaturated lactone, diene and the acidic proton at C-5 in consideration of the potential elimination. More importantly, we might have the chance to control the stereochemistry at C-10 via a subsequent diastereoselective reduction if the desired adduct ketone 2.33 could be obtained.
The reaction of acid chlorides with organometallic reagents often provide versatile ketone syntheses. The most useful synthetic methods generally employ organocopper species prepared from organolithium, Grignard reagent or organozinc reagents.\(^{39}\) Also possible, palladium catalyzed acylation with organozinc or organostannanes have been well developed as acid chlorides undergo facile oxidative addition to Pd(0).\(^{40}\) We first prepared the organocuprate utilizing different copper salts from the organolithium dithiane anion derived from the 1,4-Brook rearrangement (Entry 1-3, Table 2.5). Unfortunately, no desired tri-component adduct was observed. We further perform transmetalation with ZnCl\(_2\) to form functionalized organozinc species (Entry 4, Table 2.5). However, upon addition of Pd(PPh\(_3\))\(_4\), only the corresponding carboxylic acid was isolated. Organoaluminium reagents were also examined, but did not prove fruitful. In the interim, we adopted alternative electrophiles as coupling partners (e.g., imidazole,
pentafluorophenol or the Weinreb amide, Entry 6-8, Table 2.5) to construct ketone 2.33.
However, nucleophilic acyl substitutions proved unsatisfactory.

Table 2.5 Alternative Electrophiles Coupling Partners

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lithium 2-thienylcyanocuprate</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CuCN2LiCl, -78 °C</td>
<td>Cl</td>
<td>decomposition or acid isolated</td>
</tr>
<tr>
<td>3</td>
<td>CuI, -78 to -40 °C</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ZnCl2, -78 to 0 °C then Pd(PPh3)4</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>AlCl3, -78 °C</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MgBr2, -78 °C</td>
<td>-</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
To this end, we turned to aldehyde (−)-2.3 as the terminating electrophile for the ARC union. When aldehyde was added to the dithiane anion derived from the Brook rearrangement, the nucleophilic addition proved unrewarding with an elimination byproduct isolated (see experimental section). This result may be attributed to the high reactivity of dithiane anion and the sensitivity of aldehyde fragment. We then reverse the addition order; that is, the dithiane anion was added to the aldehyde fragment, aiming to suppress side reactions with the electrophile. Pleasingly, we isolated a diastereomeric mixture of tri-component adduct 2.34 albeit the yield was ca. 40%. The diastereomeric ratio was approximately 1:1.5 and importantly the two diastereomers could be separated via medium pressure liquid chromatography. The absolute configuration of C-10 in the major diastereomer (+)-2.2 was determined via Mosher ester analysis (Table 2.7). To reduce the basicity of dithiane anion, we also tested transmetalation with LaCl3·2LiCl or ZnCl2, however the results were not rewarding due to concomitant retro-Brook rearrangements (Entry 5-6, Table 2.6).

Table 2.6 Aldehyde (−)-2.3 as Terminating Electrophile
<table>
<thead>
<tr>
<th>Entry</th>
<th>Anion Equivalent</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>THF, -78 °C</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>THF, -78 °C</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>3</td>
<td>2, aTHF,-78 °C</td>
<td>38~42%, 52% brsm</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>aTHF, -78 °C</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>5</td>
<td>2, aLaCl3 2LiCl, -78 °C</td>
<td>&lt;5%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2, aZnCl2, -78 °C to 0 °C</td>
<td>&lt;5%</td>
<td></td>
</tr>
</tbody>
</table>

*Reverse addition: after linchpin was added, the reaction mixture was cannulated to aldehyde 2.3 (see SI)*

Table 2.7 Mosher Ester Analysis of (+)-2.2
<table>
<thead>
<tr>
<th>Nucleus</th>
<th>S-ester δ&lt;sub&gt;S&lt;/sub&gt; (ppm)</th>
<th>R-ester δ&lt;sub&gt;R&lt;/sub&gt; (ppm)</th>
<th>δ&lt;sub&gt;S&lt;/sub&gt;–δ&lt;sub&gt;R&lt;/sub&gt; (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6.18</td>
<td>6.17</td>
<td>+0.01</td>
</tr>
<tr>
<td>3</td>
<td>6.97</td>
<td>6.96</td>
<td>+0.01</td>
</tr>
<tr>
<td>4</td>
<td>4.03</td>
<td>4.02</td>
<td>+0.01</td>
</tr>
<tr>
<td>5</td>
<td>4.99</td>
<td>4.97</td>
<td>+0.02</td>
</tr>
<tr>
<td>6</td>
<td>5.96</td>
<td>5.80</td>
<td>+0.16</td>
</tr>
<tr>
<td>7</td>
<td>6.44</td>
<td>6.38</td>
<td>+0.06</td>
</tr>
<tr>
<td>8</td>
<td>6.53</td>
<td>6.16</td>
<td>+0.37</td>
</tr>
<tr>
<td>9</td>
<td>6.10</td>
<td>6.07</td>
<td>+0.03</td>
</tr>
<tr>
<td>12</td>
<td>1.91</td>
<td>2.13</td>
<td>–0.04</td>
</tr>
<tr>
<td>13</td>
<td>5.05</td>
<td>5.05</td>
<td>0.00</td>
</tr>
<tr>
<td>15</td>
<td>5.59</td>
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<td>–0.01</td>
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<td>17</td>
<td>5.65</td>
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<td>–0.01</td>
</tr>
<tr>
<td>18</td>
<td>2.11</td>
<td>2.13</td>
<td>–0.02</td>
</tr>
<tr>
<td>19</td>
<td>1.02</td>
<td>1.02</td>
<td>0.00</td>
</tr>
<tr>
<td>22</td>
<td>0.95</td>
<td>0.96</td>
<td>–0.01</td>
</tr>
<tr>
<td>24</td>
<td>0.19</td>
<td>0.22</td>
<td>–0.03</td>
</tr>
</tbody>
</table>

2.3.4 Late-Stage Elaboration of (−)-Pterocidin

Having established the carbon skeleton and all stereocenters of the natural product, we proceeded to late stage elaboration to complete the synthesis. The advanced intermediate 2.34 proved base and acid sensitive, due to the presence of the dienyl ether and lactone moiety. Indeed, methylation tactics under basic or acidic conditions (Entry 1–4, Table 2.8) all failed. The mild and almost neutral condition employing silver oxide and
methyl iodide, however, was promising. In fact, we were able to achieve the methylation with excess silver oxide even in consideration of the steric hindrance around C-10 hydroxyl group in advanced intermediate 2.34.

Table 2.8 Optimization of Late Stage Methylation Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Methylation Reagent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>MeI</td>
<td>messy</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>MeI</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>2,6-di-tert-butyl-pyridine</td>
<td>MeOTf</td>
<td>messy</td>
</tr>
<tr>
<td>4</td>
<td>proton sponge</td>
<td>Me₃OBF₄</td>
<td>messy</td>
</tr>
<tr>
<td>5</td>
<td>Ag₂O (5eq)</td>
<td>MeI (excess)</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>Ag₂O (50eq)</td>
<td>MeI (excess)</td>
<td>60%</td>
</tr>
</tbody>
</table>

Next, TBAF mediated removal of silyl ether protective group delivered compound 2.36 (Scheme 2.15). The last step to complete the synthesis is now to reduce dithiane moiety at C-11 to methylene. However, this transformation is quite formidable given the
presence of multiple double bonds, α, β-unsaturated and a dienyl ether. We first explored Raney nickel\textsuperscript{43} as reducing agent, but this tactic only leads to decomposition. Currently the \textit{t-Bu}\textsubscript{3}SnH\textsuperscript{44} and NiCl\textsubscript{2}/NaBH\textsubscript{4} system are under investigation for final desulfurization.

\textbf{Scheme 2.15 Late Stage Elaboration of (−)-Pterocidin}

\textbf{2.4 Summary}

To date, the aldehyde fragment (−)-2.3, the bifunctional linchpin (−)-2.5 and the dienyl ether 2.30 fragment have been prepared on significant scale. The key union of the three fragments via ARC has also been achieved resulting in advanced intermediate (+)-2.2 with all correct stereogenicities established for the natural product (Scheme 2.15). However, the yield of the union reaction is currently only 40%; optimization of this
reaction is ongoing. The synthesis of aldehyde fragment \((-)-2.3\) takes 11 steps from a commercially available aldehyde with an overall yield of 8\%. The synthesis of linchpin 
\((-)-2.5\) aldehyde comprised a six-step transformation from \((S)\)-Roche ester with an overall yield of 55\%. The dienyl ether fragment \(2.30\) was next prepared via modification of a literature procedure, which takes five steps with a total yield of 49\%.

Current studies are directed at the optimization of the tri-component union reaction to improve the yield and stereoselectivity. The late-stage desulfurization is under investigation followed by completion of the total synthesis of \((-)\)-pterocidin \(2.1\).

Concerning the potent anti-invasive activity of \((-)\)-pterocidin, more analogs will be designed and synthesized for further biological and medicinal study. The lactone moiety can be replaced by de-methoxy six/five-member ring lactone or aryl rings with different substituents. The simple enol ether analogs will also be investigated.
2.5 Reference


3.1 Experimental Section Relevant to Chapter One

3.1.1 Materials and Methods

Reactions were performed either in flame or oven-dried glassware under a nitrogen atmosphere unless noted otherwise. Anhydrous diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂) and toluene were obtained from a solvent purification system. Triethylamine, diisopropylethylamine and pyridine were freshly distilled from calcium hydride under a nitrogen atmosphere. All chemicals were purchased from commercial vendors, unless otherwise referenced. Reactions were magnetically stirred unless stated otherwise and monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates. Silica gel chromatography was performed utilizing ACS grade solvents and silica gel. Preparatory TLC was performed using 500 μm pre-coated silica gel plates and ACS grade solvents. Medium pressure liquid chromatography was conducted by using a medium pressure pump equipped with a high pressure glass column (350 mm ÅL 35 mm or 350 mm Å~ 10 mm) packed with silica gel (Standard Grade, porosity 60 Å, particle size 32-63 μm). Infrared spectra were obtained using a FT/IR plus spectrometer. Optical rotations were obtained using a polarimeter at 589 nm. CD spectra were obtained using a circular dichroism spectrometer in a 1 mm quartz cell. ¹H NMR spectra (500 MHz field strength) and ¹³C NMR spectra (125 MHz field strength) were obtained on a 500 MHz spectrometer or a cryomagnet (500MHz/52mm) with a 5 mm dual cryoprobe. Chemical shifts are reported relative to chloroform (δ 7.26), benzene (δ 7.16) or methanol (δ 3.31) for ¹H NMR spectra and chloroform (δ 77.16), benzene (δ
128.06) or methanol (δ 49.15) for $^{13}$C spectra. The following abbreviations are used to describe multiplicities in 1H NMR spectra: s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), t (triplet), td (triplet of doublets), m (multiplet) and q (quartet), app (apparent). High-resolution mass spectra (HRMS) were measured on a LC-TOF mass spectrometer.

3.1.2 Experimental Procedures

\[ \text{HO}_{\text{OBn}} \]

**Alcohol (+)-1.10**: To glycidol benzyl ether (600 mg, 3.65 mmol, 1.0 equiv., prepared according to literature procedure\(^1\)) in THF (36.5 ml, 0.1 M) at -20 °C, CuI (696 mg, 3.65 mmol, 1.0 equiv.) was added. Next vinyl magnesium bromide (1 M in THF, 9.14 ml, 9.14 mmol, 2.5 equiv.) was added quickly to the suspension. After stirring for 2 hours at the same temperature, the reaction was quenched by saturated aqueous NH$_4$Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO$_4$, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil, which was used directly for next step without purification.
**Alkene (+)-1.11:** To crude alcohol (+)-1.10 (1 g, 5.2 mmol, 1.0 equiv.) in DCM (52 ml, 0.1 M), DMAP (63.5 mg, 0.52 mmol, 0.1 equiv.), imidazole (1.77 g, 26 mmol, 5.0 equiv.) and TBSCl (3.92 g, 26 mmol, 5.0 equiv.) were added at room temperature. The reaction mixture was stirred overnight before it was quenched by saturated aqueous NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (1.43 g, 90%) as colorless oil. The ¹H NMR and ¹³C NMR of the title compound matched with the literature report.²

**Epoxide 1.12:** To homoallylic alcohol (+)-1.11 (500 mg, 1.63 mmol, 1.0 equiv.) in DCM (11 ml, 0.15 M), m-CPBA (731.2 mg, 3.26 mmol, 2.0 equiv.) was added portionwise at 0 °C. The reaction then warmed up to room temperature and stirred for overnight. Upon completion, the mixture was quenched by saturated aqueous NaHCO₃ solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The
filtrate was concentrated in vacuo to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (473 mg, 90%) as colorless oil. IR (film) 2927.41 2855.1 1471.9 1253.5 1110.8 836.473 776.208 734.746 697.623 666.767 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.26 (m, 5H), 4.59 – 4.53 (m, 2H), 4.08 (dp, J = 11.3, 5.7 Hz, 1H), 3.58 – 3.39 (m, 2H), 3.13 – 3.02 (m, 1H), 2.79 (ddd, J = 21.4, 5.2, 4.0 Hz, 1H), 2.50 (ddd, J = 14.8, 5.2, 2.7 Hz, 1H), 1.76 (dt, J = 25.2, 5.9 Hz, 2H), 0.92 (d, J = 1.6 Hz, 9H), 0.14 – 0.08 (m, 6H); ¹³C NMR (126 MHz, Chloroform-d) δ 138.45, 138.38, 128.48, 127.77, 127.75, 127.72, 127.70, 74.78, 74.47, 73.53, 73.45, 69.86, 69.45, 49.75, 49.50, 47.93, 46.91, 38.22, 38.08, 25.99, 25.97, 18.25, -4.25, -4.31, -4.77, -4.79; HRMS (ESI) m/z 345.1895 [(M+Na)⁺; calcd for C₁₈H₃₀O₃SiNa: 345.1862].

Epoxide (−)-1.13: Epoxide 1.12 (250 mg, 0.78 mmol, 1.0 equiv.) in THF (0.05 ml + 0.05 ml) was added to (S,S)-Jacobsen’s catalyst (603 mg, 0.016 mmol, 2.2% equiv., the catalyst was pre-activated according to literature procedure³) at 0 °C and stirred for 5 min. Then H₂O (7.7 μl, 0.43 mmol, 0.55 equiv.) was added, and the reaction mixture was warmed up to room temperature. The reaction was monitored by ¹H NMR. After the reaction was completed (about 60 hours), the mixture was concentrated in vacuo to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (145 mg,
58%) as colorless oil. [α]D 22 = −52.0 (c 1.0, CH2Cl2); IR (film) 2927.41 2856.06 1683.07 1652.21 1557.72 1471.42 1255.91 1109.83 834.544 777.654 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.29 (m, 5H), 4.54 (d, J = 3.0 Hz, 2H), 4.08 (dq, J = 7.4, 5.4 Hz, 1H), 3.43 (qd, J = 9.6, 5.6 Hz, 2H), 3.06 (ddddd, J = 6.5, 5.6, 3.9, 2.7 Hz, 1H), 2.80 (dd, J = 5.1, 4.0 Hz, 1H), 2.51 (dd, J = 5.1, 2.7 Hz, 1H), 1.73 (ddd, J = 7.3, 5.0, 3.2 Hz, 2H), 0.91 (s, 9H), 0.10 (d, J = 8.7 Hz, 6H); ¹³C NMR (126 MHz, Chloroform-d) δ 138.37, 128.47, 127.74, 127.70, 74.77, 73.45, 69.43, 49.75, 47.93, 38.21, 25.96, 18.23, -4.28, -4.81; HRMS (ESI) m/z 323.2045 [(M+H)⁺; calcd for C₁₈H₃₁O₅Si: 345.2042].

**Lactone** (−)-1.14: To anhydrous ethanol (26 ml, 0.13 M) at 0 °C, NaH (546 mg, 13.64 mmol, 4 equiv., 60% in mineral oil) was added portionwise (gas generated). The mixture was then warmed up to room temperature and stirred for 5 min. Diethyl malonate (2.18 g, 13.64 mmol, 4 equiv.) was added to above suspension dropwise resulting white cloudy mixture. After stirred for 30 min, epoxide (−)-1.13 (1.1 g, 3.4 mmol, 1.0 equiv.) was added dropwise. After refluxed for 3 hours, the reaction mixture was cooled to room temperature and was quenched by saturated aqueous NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as orange-red oil. This oil was then
purified with silica gel flash column chromatography (9:1 hexane/EtOAc) to afford the title compound (1.24 g, 84%) as colorless oil. \([\alpha]_D^{22} = -42.7 (c 1.0, \text{CH}_2\text{Cl}_2)\); IR (film) 2930.31 1780.94 1737.07 1472.87 1370.18 1253.99 836.473 776.69 697.623 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 7.39 – 7.31 (m, 5H), 4.92 (dtd, \(J = 10.2, 7.1, 3.1\) Hz, 1H), 4.69 (tdd, \(J = 9.5, 6.2, 3.0\) Hz, 1H), 4.30 – 4.22 (m, 2H), 4.09 (dp, \(J = 12.5, 4.4, 3.7\) Hz, 1H), 3.69 – 3.57 (m, 1H), 3.48 – 3.33 (m, 2H), 2.72 (ddd, \(J = 13.1, 6.9, 4.9\) Hz, 1H), 2.59 (ddd, \(J = 12.9, 9.3, 6.2\) Hz, 0H), 2.36 (ddd, \(J = 13.0, 10.9, 9.3\) Hz, 0H), 2.15 (ddd, \(J = 13.2, 9.5, 7.3\) Hz, 0H), 2.01 (ddd, \(J = 14.5, 9.9, 2.8\) Hz, 0H), 1.93 – 1.73 (m, 1H), 1.33 (td, \(J = 7.1, 2.9\) Hz, 3H), 0.90 (d, \(J = 3.8\) Hz, 9H), 0.13 – 0.05 (m, 6H); \(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 171.84 (d, \(J = 15.3\) Hz), 167.96, 138.23, 128.51, 127.78, 76.98, 76.16, 74.73, 74.70, 73.48, 73.47, 68.22, 68.16, 62.34, 62.26, 47.57, 47.24, 41.11, 41.03, 32.77, 32.64, 26.01, 25.99, 18.23, 18.21, 14.20, -4.20, -4.26, -4.75, -4.78; HRMS (ESI) \(m/z\) 459.2190 [(M+Na)]\(^+\); calcd for C\(_{23}\)H\(_{36}\)O\(_6\)SiNa: 459.2179.

**Alcohol (−)-1.15**: A solution of malonate (−)-1.14 (200 mg, 0.46 mmol, 1.0 equiv.) and LiCl (38.8 mg, 0.92 mmol, 2.0 equiv.) in DMSO (2.5 ml, 0.18 M) and H\(_2\)O (0.03 ml, 1.6 mmol, 3.5 equiv.) was heated and refluxed at 155 °C for 5 hours. The reaction mixture was cooled to room temperature and was quenched by saturated aqueous NH\(_4\)Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The
combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (2:3 hexane/EtOAc) to afford the title compound (112 mg, 93%) as colorless oil. [α]_D^22 = −36.8 (c 1.0, CH₂Cl₂); IR (film) 3852.11 3445.69 2864.74 1770.81 1558.2 1455.51 1361.98 1183.6 1091.03 916.50 cm⁻¹; ^1H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.28 (m, 5H), 4.79 (tdd, J = 8.5, 6.5, 4.0 Hz, 1H), 4.56 (d, J = 1.2 Hz, 2H), 4.08 (dp, J = 10.6, 3.4 Hz, 1H), 3.54 (dd, J = 9.5, 3.3 Hz, 1H), 3.36 (dd, J = 9.5, 7.3 Hz, 1H), 2.58 – 2.50 (m, 2H), 2.43 – 2.31 (m, 1H), 1.89 (dt, J = 12.8, 9.5, 8.3 Hz, 1H), 1.82 – 1.68 (m, 2H); ^13C NMR (126 MHz, Chloroform-d) δ 177.21, 137.88, 128.64, 128.03, 127.89, 78.01, 74.44, 73.48, 67.47, 39.48, 29.02, 28.69; HRMS (Cl) m/z 251.1284 [(M+Na)^+]; calcd for C₁₄H₂₀O₄: 251.1283.

**Lactone (−)-1.26:** To alcohol (−)-1.15 (112 mg, 0.045 mmol, 1.0 equiv.) in DCM (4.5 ml, 1.0 M) at room temperature, 2, 6-lutidine (0.16 ml, 1.34 mmol, 3.0 equiv.) was added followed by dropwise addition of TBSOTf (0.2 ml, 0.89 mmol, 2.0 equiv.). The light-yellow solution was stirred for 1 h and then was quenched by saturated aqueous NH₄Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil.
This oil was then purified with silica gel flash column chromatography (9:1 hexane/EtOAc) to afford the title compound (138.7 mg, 85%) as colorless oil. \([\alpha]_D^{22} = -52.0 \text{ (c 1.0, CH}_2\text{Cl}_2\text{)}\); IR (film) 2928.38 2855.58 1778.53 1471.9 1361.98 1252.54 1180.7 1096.82 914.575 836.473 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 7.39 – 7.28 (m, 5H), 4.72 (dtd, J = 10.1, 7.5, 3.1 Hz, 1H), 4.53 (d, J = 1.7 Hz, 2H), 4.08 (dtd, J = 10.0, 5.2, 2.7 Hz, 1H), 3.44 (dd, J = 9.7, 4.9 Hz, 1H), 3.37 (dd, J = 9.6, 5.6 Hz, 1H), 2.55 (dd, J = 9.4, 7.1 Hz, 2H), 2.40 – 2.32 (m, 1H), 1.94 – 1.84 (m, 2H), 1.76 (ddd, J = 14.2, 9.8, 3.0 Hz, 1H), 0.89 (s, 9H), 0.08 (d, J = 12.2 Hz, 6H); \(^13\)C NMR (126 MHz, Chloroform-d) \(\delta\) 177.27, 138.27, 128.49, 127.76, 77.55, 74.79, 73.44, 68.23, 41.26, 28.95, 28.53, 26.01, 18.23, -4.23, -4.74; HRMS (ESI) \(m/z\) 364.2148 [M+H]+; calcd for C\(_{20}\)H\(_{34}\)O\(_4\)Si: 364.2148.

Alcohol (\(\rightarrow\))-1.16: To lactone (\(\rightarrow\))-1.26 (290 mg, 0.795 mmol, 1.0 equiv.) in THF/MeOH (7.5 ml/7.5 ml, 0.05 M), Palladium on carbon (58 mg, 20% weight) was added in one portion at room temperature. Then the reaction mixture was purged by hydrogen gas three times. After stirred for 1 hour, the mixture was filtered via a pad of Celite and washed by EtOAc. The filtrated was concentrated in vacuo to provide the crude product as light-yellow oil. This oil was then purified with silica gel flash column chromatography (3:2 hexane/EtOAc) to afford the title compound (207.4 mg, 95%) as
colorless oil. \([\alpha]_D^{22} = -68.0\) (c 1.0, CH\(_2\)Cl\(_2\)); IR (film) 3480.4 2929.34 92.5344 3 2857.02 1771.3 1471.9 1252.54 1183.11 1061.62 836.955 777.172 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta 4.64\) (dtd, \(J = 10.0, 7.3, 2.8 \text{ Hz, 1H})\), 4.00 (dq, \(J = 9.8, 3.6 \text{ Hz, 1H})\), 3.62 (dd, \(J = 11.3, 4.2 \text{ Hz, 1H})\), 3.47 (dd, \(J = 11.3, 3.5 \text{ Hz, 1H})\), 2.57 – 2.52 (m, 2H), 2.37 (dq, \(J = 13.2, 6.8 \text{ Hz, 1H})\), 1.94 – 1.85 (m, 3H), 1.76 (ddd, \(J = 14.6, 10.1, 3.2 \text{ Hz, 1H})\), 0.91 (s, 9H), 0.11 (d, \(J = 1.9 \text{ Hz, 6H})\); \(^13\)C NMR (126 MHz, Chloroform-d) \(\delta 177.16, 77.64, 69.52, 66.90, 40.59, 28.90, 28.52, 25.95, 18.16, -4.36, -4.63\); HRMS (ESI) m/z 275.1679 [(M+H)\(^+\); calcd for C\(_{13}\)H\(_{28}\)O\(_4\)Si: 275.1674].

**Aldehyde (−)-1.3**: To oxalyl chloride (0.19 ml, 2.22 mmol, 2.0 equiv.) in DCM (15 ml) at -78 °C, DMSO (0.39 ml, 5.55 mmol, 5.0 equiv.) was added dropwise. After stirred at this temperature for 30 min, alcohol (−)-1.16 (305 mg, 1.11 mmol, 1.0 equiv.) in DCM (11 ml) was added dropwise. After stirred for 20 min, triethyl amine (0.62 ml, 4.44 mmol, 4.0 equiv.) was added dropwise followed by warming up to room temperature in 1 hour. The reaction mixture was then quenched by water. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO\(_4\), and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (7:3 hexane/EtOAc) to afford the title compound (242 mg,
80%) as pale-yellow oil. \([\alpha]_D^{22} = -64.2\) (c 1.0, CH\(_2\)Cl\(_2\)); IR (film) 2929.34 2856.54 1778.53 1738.03 1471.9 1254.47 1179.74 913.12 9.9 7.1, 3.0 Hz, 1H), 4.26 (dd, \(J = 10.3, 3.0 \text{ Hz, } 1H\)), 2.56 (dd, \(J = 9.3, 6.7 \text{ Hz, } 2H\)), 2.38 (ddt, \(J = 13.5, 7.6, 6.7 \text{ Hz, } 1H\)), 2.00 (ddd, \(J = 14.3, 10.0, 3.0 \text{ Hz, } 1H\)), 1.96 – 1.86 (m, 1H), 1.77 (ddd, \(J = 14.3, 10.2, 3.1 \text{ Hz, } 1H\)), 0.92 (s, 9H), 0.10 (d, \(J = 5.7 \text{ Hz, } 6H\)); \(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta 202.91, 176.68, 76.18, 74.74, 38.39, 28.73, 28.19, 25.85, 18.25, -4.46, -4.99\); HRMS (ESI) \(m/z 273.1522\) [\((M+H)^+\)]; calcd for C\(_{13}\)H\(_{25}\)O\(_4\)Si: 273.1522].

Lactone (\(\rightarrow\)-1.27): To alcohol (\(\rightarrow\)-1.15) (100 mg, 0.4 mmol, 1.0 equiv.) at room temperature, silver oxide (140 mg, 0.6 mmol, 1.5 equiv.), molecular sieves powder (100 mg, flamed dried) and methyl iodide (2 ml, 0.2 M) was added. The reaction mixture was stirred for 24 hours in the dark before it was filtered via a pad of celite. The filtrate was concentrated in vacuo to provide the crude product as a yellow oil. This oil was then purified with silica gel flash column chromatography (3:2 hexane/EtOAc) to afford the title compound (95 mg, 90%) as pale-yellow oil. \([\alpha]_D^{22} = -63.4\) (c 1.0, CH\(_2\)Cl\(_2\)); IR (film) 3853.56 3745.56 2917.29 1772.74 1456.96 1179.26 749.692 698.105 676.41 623.377 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-d) \(\delta 7.40 – 7.26 \text{ (m, } 5H\)), 4.80 – 4.71 (m, 1H), 4.56 (d, \(J = 3.2 \text{ Hz, } 2H\)), 3.64 – 3.45 (m, 3H), 3.44 (s, 3H), 2.58 – 2.51 (m, 2H), 2.35
(dq, $J = 13.0, 6.7$ Hz, 1H), $1.94 - 1.75$ (m, 3H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ $177.30, 138.21, 128.54, 127.82, 127.75, 77.98, 73.51, 71.20, 58.19, 38.91, 29.05, 28.54$; HRMS (ESI) $m/z$ 264.1396 [$M^{+}$; calcd for C$_{15}$H$_{20}$O$_{4}$: 264.1362].

**Alcohol (−)-1.28:** To lactone (−)-1.27 (90 mg, 0.34 mmol, 1.0 equiv.) in THF/MeOH (3.3 ml/3.3 ml, 0.05 M), Palladium on carbon (18 mg, 20% weight) was added in one portion at room temperature. Then the reaction mixture was purged by hydrogen gas three times. After stirred for 1 hour, the mixture was filtered via a pad of celite and washed by EtOAc. The filtrated was concentrated in vacuo to provide the crude product as light-yellow oil. This oil was then purified with silica gel flash column chromatography (1:4 hexane/EtOAc) to afford the title compound (54 mg, 91%) as colorless oil. [$\alpha$]$_{D}^{22}$ = $−67.2$ (c 2.0, CH$_2$Cl$_2$); IR (film) 3852.11 3446.17 2941.39 1770.81 1652.7 1558.2 1456.96 1186.97 1074.64 918.915 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 4.72 (ddddd, $J = 9.8, 8.4, 6.6, 3.0$ Hz, 1H), 3.84 (dd, $J = 11.6, 3.5$ Hz, 1H), 3.54 – 3.45 (m, 2H), 3.45 (s, 3H), 2.58 – 2.53 (m, 2H), 2.37 (ddd, $J = 13.2, 12.5, 6.6$ Hz, 1H), 1.96 – 1.84 (m, 2H), 1.74 (ddd, $J = 14.7, 10.0, 3.2$ Hz, 1H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 177.26, 78.19, 78.01, 63.20, 57.98, 38.24, 29.00, 28.57; HRMS (ESI) $m/z$ 197.0798 [(M+Na)$^{+}$; calcd for C$_8$H$_{14}$O$_4$Na: 197.0790].
Aldehyde (−)-1.17: To oxalyl chloride (0.053 ml, 0.62 mmol, 2.0 equiv.) in DCM (3 ml) at -78 °C, DMSO (0.11 ml, 1.55 mmol, 5.0 equiv.) was added dropwise. After stirred at this temperature for 30 min, alcohol (−)-1.28 (54 mg, 0.31 mmol, 1.0 equiv.) in DCM (2 ml) was added dropwise. After stirred for 20 min, triethyl amine (0.17 ml, 1.24 mmol, 4.0 equiv.) was added dropwise followed by warming up to room temperature in 1 hour. The reaction mixture was then quenched by water. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (2:3 hexane/EtOAc) to afford the title compound (42.7 mg, 80%) as pale-yellow oil. ¹H NMR (500 MHz, Chloroform-d) δ 9.68 (s, 1H), 4.72 (dddd, J = 10.2, 8.7, 6.7, 3.3 Hz, 1H), 3.85 (ddd, J = 10.5, 3.0, 1.4 Hz, 1H), 3.50 (s, 3H), 2.59 – 2.53 (m, 2H), 2.38 (dq, J = 13.2, 6.8 Hz, 1H), 1.99 (ddd, J = 13.1, 9.8, 3.1 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.79 (ddd, J = 14.0, 10.5, 3.4 Hz, 1H); ¹³C NMR (126 MHz, Chloroform-d) δ 202.54, 176.75, 82.61, 76.53, 76.47, 59.16, 36.11, 28.83, 28.26.
PMB Ether (+)-1.23: To Wittig salt fragment 1.4 (130 mg, 0.12 mmol, 1.0 equiv., prepared according to literature\(^4\)) in THF (2 ml), MeLi LiBr (0.08 ml, 1.5 M in Et\(_2\)O, 0.12 mmol, 1.0 equiv.) was added at room temperature. The mixture was stirred for 5 min before it was cool to -78 °C. After stirring for 20 mins, aldehyde (--)\(-1.3\) (32.5 mg, 0.12 mmol, 1.0 equiv.) in THF (2 ml) was added dropwise. The reaction was then allowed to warm up to room temperature naturally overnight. The reaction mixture was then quenched by saturated aqueous NH\(_4\)Cl solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO\(_4\), and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (4:1 hexane/EtOAc) to afford the title compound (33 mg, 30 %) as yellow oil. \([\alpha]_D^{22} = +28.7\ (c\ 1.0,\ CH_2Cl_2);\) IR (film) 2928.86 2856.54 1782.39 1514.33 1462.26 1249.65 1042.34 835.99 774.279 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.29 (d, \(J = 8.6\ Hz, 2H\)), 6.88 (d, \(J = 8.7\ Hz, 2H\)), 6.65 – 6.54 (m, 1H), 6.02 (t, \(J = 11.0\ Hz, 1H\)), 5.58 (t, \(J = 10.5\ Hz, 1H\)), 5.27 – 5.19 (m, 3H), 5.13 (d, \(J = 10.0\ Hz, 1H\)), 4.99 (d, \(J = 10.0\ Hz, 1H\)), 4.71 (dq, \(J = 8.2, 6.7\ Hz, 1H\)), 4.65 – 4.60 (m, 1H), 4.57 (d, \(J = 10.5\ Hz, 1H\)), 4.47 (d, \(J = 10.5\ Hz, 1H\)), 3.81 (s, 3H), 3.44 (dd, \(J = 5.4, 3.4\ Hz, 1H\)), 3.26 (dd, \(J =
7.7, 3.7 Hz, 1H), 3.22 (t, J = 5.4 Hz, 1H), 3.01 (ddd, J = 10.4, 6.9, 3.6 Hz, 1H), 2.59 – 2.48 (m, 3H), 2.43 (dt, J = 10.1, 6.3 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.00 (t, J = 12.4 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.78 – 1.74 (m, 1H), 1.72 (td, J = 6.4, 5.5, 2.6 Hz, 2H), 1.64 (d, J = 12.8 Hz, 1H), 1.55 (d, J = 1.3 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 3.2 Hz, 12H), 0.92 (s, 9H), 0.89 (s, 9H), 0.87 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H), 0.11 (d, J = 4.2 Hz, 6H), 0.08 (d, J = 1.6 Hz, 6H), 0.05 (s, 3H), 0.03 (s, 3H); 13C NMR (126 MHz, Chloroform-d) δ 177.09, 159.16, 134.49, 132.94, 132.83, 132.29, 131.70, 129.30, 129.18, 117.80, 113.81, 84.71, 80.62, 77.58, 75.21, 66.04, 55.41, 44.91, 40.19, 37.83, 36.08, 35.44, 29.01, 28.44, 26.44, 26.34, 26.00, 23.10, 18.82, 18.76, 18.54, 18.27, 17.03, 15.05, 10.62, -2.99, -3.02, -3.13, -4.07, -4.17, -4.67; HRMS (ESI) m/z 977.6590 [(M+H)+]; calcd for C55H98NaO7Si3: 977.6518.

Alcohol (+)-1.24: To PMB ether (+)-1.23 (30 mg, 0.031 mmol, 1.0 equiv.) in DCM/H2O (0.015 M, 2 ml/0.07 ml), DDQ (10.7 mg, 0.047 mmol, 1.5 equiv.) was added at 0 °C. After stirring for 15 mins at the same temperature, the reaction was warmed up to room temperature and was stirred for another 1 hour. The reaction mixture was then quenched by saturated aqueous NaHCO3 solution. The organic layer was separated, and
the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (9:1 hexane/EtOAc) to afford the title compound (24 mg, 89%) as yellow oil. \([\alpha]_D^{22} = +45.0\ (c\ 1.0, \text{CH}_2\text{Cl}_2)\) IR (film) 2925.97 2853.65 1779.97 1558.2 1456.47 1252.06 1087.17 836.473 774.279 cm⁻¹; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 6.64 (ddddd, \(J = 16.8, 11.2, 10.2, 1.1\) Hz, 1H), 6.20 – 6.11 (m, 1H), 5.35 (t, \(J = 10.5\) Hz, 1H), 5.29 – 5.23 (m, 3H), 5.17 (d, \(J = 9.9\) Hz, 1H), 5.05 (d, \(J = 9.8\) Hz, 1H), 4.76 – 4.68 (m, 1H), 4.64 (q, \(J = 6.5\) Hz, 1H), 3.63 (dd, \(J = 5.7, 3.3\) Hz, 1H), 3.35 (dt, \(J = 7.9, 3.0\) Hz, 1H), 3.26 (t, \(J = 5.3\) Hz, 1H), 2.82 (dt, \(J = 10.0, 7.0\) Hz, 1H), 2.59 – 2.46 (m, 4H), 2.34 (ddddd, \(J = 12.8, 8.7, 6.7, 5.2\) Hz, 1H), 2.20 (t, \(J = 12.4\) Hz, 1H), 1.93 – 1.80 (m, 3H), 1.77 – 1.71 (m, 3H), 1.60 (s, 3H), 1.00 – 0.95 (m, 9H), 0.94 (s, 9H), 0.92 (s, 9H), 0.90 (d, \(J = 6.7\) Hz, 3H), 0.89 (s, 9H), 0.75 (d, \(J = 6.8\) Hz, 3H), 0.10 (d, \(J = 1.9\) Hz, 6H), 0.07 (d, \(J = 4.9\) Hz, 6H), 0.05 (d, \(J = 8.1\) Hz, 6H); \(^1^3\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 177.13, 134.79, 132.98, 132.85, 132.19, 131.86, 131.74, 131.17, 118.62, 80.65, 78.88, 77.62, 76.41, 66.11, 44.88, 38.11, 37.65, 36.41, 35.55, 34.95, 29.84, 29.01, 28.44, 26.37, 26.00, 23.31, 18.61, 18.57, 18.26, 17.31, 17.25, 16.78, 13.65, 9.61, -2.90, -3.14, -3.43, -4.07, -4.14, -4.68; \(^1^3\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 177.21, 157.24, 129.96, 118.13, 80.64, 78.92, 77.64, 76.94, 66.07, 44.86, 37.97, 37.74, 36.32, 35.56, 35.21, 34.55, 29.84, 29.01, 28.40, 26.35, 25.99, 23.06, 18.65, 18.55, 18.26, 17.62, 17.13, 17.00, 13.70, 10.25, -2.96, -3.24, -3.34, -4.08, -4.15, -4.67.
Carbamate 1.25: To alcohol (+)-1.24 (22 mg, 0.026 mmol, 1.0 equiv.) in DCM (2 ml), trichloroacetyl isocyanate (0.08 ml, 1 M in DCM, 0.08 mmol, 3.0 equiv.) was added dropwise at room temperature. After stirring for 2 hours, the mixture was loaded on a column with Al₂O₃ (pre-wash by DCM) followed by a 2 ml DCM rinse. After 4 hours, the crude was flushed by EtOAc (80 ml) and MeOH (30 ml). Concentration and purification with silica gel flash column chromatography (4:1 hexane/EtOAc) to afford the title compound (22 mg, 90%) as yellow oil. ¹H NMR (500 MHz, Chloroform-d) δ 6.65 – 6.56 (m, 2H), 6.33 – 6.2 (br, 2H), 6.04 (t, J = 11.0 Hz, 1H), 5.38 (t, J = 10.5 Hz, 1H), 5.28 – 5.21 (m, 3H), 5.17 – 5.12 (m, 1H), 5.02 (d, J = 10.3 Hz, 1H), 4.75 – 4.66 (m, 3H), 4.66 – 4.62 (m, 3H), 3.45 – 3.41 (m, 1H), 3.24 (t, J = 5.4 Hz, 1H), 3.00 (dt, J = 10.2, 6.7 Hz, 1H), 2.57 – 2.51 (m, 3H), 2.46 (dt, J = 10.0, 6.4 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.12 (t, J = 12.3 Hz, 1H), 1.94 – 1.82 (m, 4H), 1.74 – 1.65 (m, 4H), 1.26 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 1.9 Hz, 12H), 0.92 (s, 9H), 0.88 (s, 12H), 0.72 (d, J = 6.8 Hz, 3H), 0.10 (d, J = 12.0 Hz, 6H), 0.07 (d, J = 3.3 Hz, 6H), 0.04 (d, J = 9.3 Hz, 6H); ¹³C NMR (126 MHz, Chloroform-d) δ 177.21, 157.24, 129.96, 118.13, 80.64, 78.92, 77.64, 66.07, 44.86, 37.97, 37.74, 36.32, 35.56, 35.21, 34.55, 29.84,
Butyrolactone 1.2: To carbamate 1.25 (15 mg, 0.017 mmol) in MeOH (4.5 ml), 4 N HCl (1.2 ml) was added dropwise in 2 hours. White precipitation was observed. The reaction was stirred at room temperature overnight before it was quenched by saturated aqueous NaHCO₃ solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (3% MeOH/DCM to 4.5% MeOH/DCM) to afford the title compound (10 mg, 50%) as colorless oil. ¹H NMR (500 MHz, Chloroform-d) δ 6.63 (dt, J = 16.7, 10.6 Hz, 1H), 6.04 (t, J = 11.0 Hz, 1H), 5.55 – 5.44 (m, 2H), 5.38 (t, J = 10.5 Hz, 1H), 5.24 (d, J = 16.7 Hz, 1H), 5.19 – 5.11 (m, 2H), 4.82 – 4.59 (m, 5H), 3.29 (t, J = 5.3 Hz, 1H), 3.22 (dd, J = 6.6, 4.9 Hz, 1H), 3.02 (dt, J = 10.1, 6.8 Hz, 1H), 2.80 (dt, J = 9.3, 6.7 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.39 (dq, J = 13.2, 6.6 Hz, 1H), 2.06 (m, 2H), 1.98 – 1.79 (m, 6H), 1.67 (d, J =
1.3 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.03 – 0.98 (m, 6H), 0.96 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.1 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-d) δ 177.19, 157.19, 134.90, 133.81, 133.79, 132.71, 132.26, 130.03, 129.67, 118.07, 79.06, 78.88, 78.09, 75.99, 65.55, 43.35, 37.48, 36.06, 35.95, 35.33, 34.85, 33.19, 28.98, 28.63, 23.42, 18.59, 17.59, 15.69, 13.89, 9.01; HRMS (ESI) m/z 558.3387 [(M+Na)$^+$; calcd for C$_{30}$H$_{49}$NO$_7$Na: 558.3407]. The $^1$H NMR and $^{13}$C NMR of the title compound matched with the literature report.\(^5\)

3.1.3 References


3.2 Experimental Section Relevant to Chapter Two

3.2.1 Materials and Methods

Reactions were performed either in flame or oven-dried glassware under a nitrogen atmosphere unless noted otherwise. Anhydrous diethyl ether (Et₂O), tetrahydrofuran (THF), dichloromethane (CH₂Cl₂) and toluene were obtained from a solvent purification system. Triethylamine, diisopropylethylamine and pyridine were freshly distilled from calcium hydride under a nitrogen atmosphere. All chemicals were purchased from commercial vendors, unless otherwise referenced. Reactions were magnetically stirred unless stated otherwise and monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates. Silica gel chromatography was performed utilizing ACS grade solvents and silica gel. Preparatory TLC was performed using 500 μm pre-coated silica gel plates and ACS grade solvents. Medium pressure liquid chromatography was conducted by using a medium pressure pump equipped with a high pressure glass column (350 mm ÅL 35 mm or 350 mm Å~ 10 mm) packed with silica gel (Standard Grade, porosity 60 Å, particle size 32-63 μm). Infrared spectra were obtained using a FT/IR plus spectrometer. Optical rotations were obtained using a polarimeter at 589 nm. CD spectra were obtained using a circular dichroism spectrometer in a 1 mm quartz cell. ¹H NMR spectra (500 MHz field strength) and ¹³C NMR spectra (125 MHz field strength) were obtained on a 500 MHz spectrometer or a cryomagnet (500MHz/52mm) with a 5 mm dual cryoprobe. Chemical shifts are reported relative to chloroform (δ 7.26), benzene (δ 7.16) or methanol (δ 3.31) for ¹H NMR spectra and chloroform (δ 77.16), benzene (δ 128.06) or methanol (δ 49.15) for ¹³C spectra. The following abbreviations are used to describe multiplicities in ¹H NMR spectra: s (singlet), brs (broad singlet), d (doublet), dd
(doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), t (triplet), td (triplet of doublets), m (multiplet) and q (quartet), app (apparent). High-resolution mass spectra (HRMS) were measured on a LC-TOF mass spectrometer.

3.2.2 Experimental Procedures

\[ \text{O} \quad \text{OTBS} \]

**Aldehyde 2.14**: To 2-(tert-butyldimethylsilyloxy) ethanol (8 g, 45.37 mmol) in DCM (181.5 ml, 0.25 M), KBr (540 mg, 4.5 mmol, 0.1 equiv.) in H\textsubscript{2}O (4.5 ml, 1 M) was added. The solution was then cooled to 0 °C, TEMPO (14.4 mg, 0.2 % equiv.) and saturated NaHCO\textsubscript{3} (136.45 ml) aqueous solution were added. Bleach (NaClO 8.25% wt) was then added slowly via dropping funnel. Upon completion the color of the reaction turned from light orange to colorless. Next saturated Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} aqueous solution was added via dropping funnel, and the reaction was warmed up to room temperature naturally. The organic layer was separated, and the aqueous layer was extracted with Et\textsubscript{2}O. The combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, and filtered. The filtrate was concentrated in vacuo (room temperature water bath) to provide the crude product as light-yellow oil. This oil was then purified with silica gel flash column chromatography (pentane) to afford the title compound (7.49 g, 94.9%) as colorless oil. (Caution: the compound is volatile and unstable upon long-term storage) The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR of the title compound matched with the literature report.\textsuperscript{1}
Alcohol (−)-2.15: (−)-Ipc₂BOMe was prepared in situ according to the following procedure:

To a stirring solution of (+)-α-pinene (80 ml, 503.5 mmol, 2.4 equiv.) in anhydrous THF (8 M, 62.9 ml) at room temperature, BH₃·DMS (19.9 ml, 20.98 mmol, 1.0 equiv.) was added rapidly. The reaction flask was kept in water bath to hold room temperature. Stopped stirring immediately when addition was finished. After the water bath was removed, the reaction flask was kept untouched under nitrogen overnight (>12 h). Next the reaction flask was cooled at 0 °C for 1 hour. The white crystalline solid was crushed with needle and the supernatant liquid was removed using a cannula. The solid was further washed with anhydrous pentane three times before it was dried under high vacuum for 1 hour. The resulting white crystalline solid of Ipc₂BH (~47 g, 164.16 mmol) was stirred vigorously in anhydrous Et₂O (1 M, 164 ml) at 0 °C for 1 hour to form a suspension. Then anhydrous methanol (7.97 ml, 197 mmol, 1.2 equiv., pre-cooled to 0 °C) was added dropwise to the suspension at 0 °C using syringe pump over a period of 2 to 3 hours. The mixture was stirred at 0 °C until a clear homogeneous solution was formed indicating the completion of methanolysis. Finally, the solvent and excess methanol were removed under high vacuum for 3 hours to provide (−)-Ipc₂BOMe (48 g, 72.3% for two steps) as colorless oil (white crystalline solid upon storage in -80 °C refrigerator).
To a solution of 3-methoxy-1-propene (14.92 ml, 159 mmol, 1.41 equiv.) in anhydrous THF (2.5 M, 63.58 ml) was added sec-butyllithium (106.3 ml, 1.36 M in cyclohexane, 144.51 mmol, 1.29 equiv.) dropwise at -78 °C. The reaction mixture became orange red. After 20 minutes, (–)-Ipc₂BOMe (48 g, 151.74 mmol, 1.35 equiv.) dissolved in anhydrous THF (1 M, 151 ml) was added dropwise at -78 °C. The reaction mixture decayed to colorless or pale yellow upon completion of the addition. After 1 hour, boron trifluoride etherate (24.91 ml, 201.8 mmol, 1.8 equiv.) was added dropwise at -78 °C followed the addition of aldehyde 2.14 (19.6 g, 112.4 mmol, 1.0 equiv.) in anhydrous THF (1 M, 112 ml). The mixture was stirred at -78 °C for 12 hours before the cooling bath was removed. Then the mixture was warmed up to room temperature before it was quenched with ethanolamine (10 ml, 167 mmol, 1.49 equiv.) at 0 °C. The reaction mixture became cloudy upon the addition. After stirring 2 hours at 0 °C, the reaction mixture was stirred at room temperature for 24 hours. Saturated aqueous NH₄Cl was added. The organic layer was separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as light-yellow oil. This oil was then purified with silica gel flash column chromatography (19:1 to 9:1 hexane/EtOAc) to afford the title compound (22.1 g, 80%, 95% dr, 93% ee) as colorless oil. [α]D²² = –12.6 (c 1.0, CH₂Cl₂); IR (film) 3476.06 2930.31 2857.02 1471.42 1254.47 1115.62 926.628 836.955 777.172 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 5.79 – 5.71 (m, 1H), 5.37 – 5.30 (m, 2H), 3.72 – 3.59 (m, 4H), 3.35 (s, 3H), 2.60 (d, J = 4.0 Hz, 1H), 0.92 (s, 9H), 0.09 (d, J = 2.9 Hz, 6H); ¹³C NMR (126 MHz, Chloroform-d) δ 135.05, 119.39, 83.12, 74.05, 63.53, 56.76, 26.01, 18.42, -5.27, -5.29; HRMS (ESI) m/z 247.1735 [(M+H)+]; calcd for C₁₂H₂₇O₃Si: 247.1729].
The absolute configuration at C-4 was determined by Mosher ester analysis:

(S)-MTPA Ester of (−)-2.15: To a solution of (−)-2.15 (8.5 mg, 0.034 mmol, 1.0 equiv.) in 0.4 ml DCM, DMAP (16.6 mg, 0.136 mmol, 4.0 equiv.) was added at room temperature followed by addition of (R)-MTPA-Cl (12.9 μl, 0.069 mmol, 2.0 equiv.). After stirring for 0.5 hour at room temperature, the reaction was quenched with saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as orange red oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (15.48 mg, 97%) as light-yellow oil. ¹H NMR (500 MHz, Chloroform-d) δ 7.70 – 7.60 (m, 2H), 7.41 (dd, J = 5.2, 2.0 Hz, 3H), 5.60 (ddd, J = 16.9, 10.6, 7.5 Hz, 1H), 5.35 – 5.17 (m, 3H), 3.85 (dd, J = 11.4, 3.3 Hz, 1H), 3.81 – 3.71 (m, 2H), 3.67 – 3.57 (m, 3H), 3.20 (s, 3H), 0.90 (s, 9H), 0.07 (d, J = 2.7 Hz, 6H); HRMS (ESI) m/z 463.2132 [(M+H)+]; calcd for C₂₂H₃₄F₃O₅Si: 463.2128.
(R)-MTPA Ester of (−)-2.15 was prepared followed the same procedure with (S)-MTPA acid chloride. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.71 – 7.62 (m, 2H), 7.41 (dd, $J = 5.0$, 2.0 Hz, 3H), 5.71 (ddd, $J = 17.5$, 10.3, 7.4 Hz, 1H), 5.45 – 5.34 (m, 2H), 5.17 (ddd, $J = 7.8$, 4.9, 3.3 Hz, 1H), 3.90 (t, $J = 7.4$ Hz, 1H), 3.80 – 3.66 (m, 2H), 3.61 (s, 3H), 3.31 (s, 3H), 0.86 (s, 9H), -0.01 (d, $J = 1.8$ Hz, 6H), HRMS (ESI) $m/z$ 485.1960 [(M+Na)$^+$; calcd for C$_{22}$H$_{33}$F$_3$O$_5$SiNa: 485.1947].

The benzoate derivative of the title compound and its enantiomer were made for UV detection in chiral SFC.
Table 3.1 Determination of enantiomeric excess for (--)-2.15 by chiral SFC

<table>
<thead>
<tr>
<th>Sample</th>
<th>t_R 1</th>
<th>Area 1(%)</th>
<th>t_R 2</th>
<th>Area 2(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-2.15</td>
<td>3.807</td>
<td>53.995</td>
<td>4.303</td>
<td>46.005</td>
</tr>
<tr>
<td>(--)-2.15</td>
<td>3.828</td>
<td>96.645</td>
<td>4.370</td>
<td>3.355</td>
</tr>
</tbody>
</table>
SFC condition: column: Chiralcel® OJ-H column (5 μm, 4.6 mm Å~ 250 mm); eluent: 99.8:0.2 supercritical CO2/MeOH; flow rate: 4 mL/min; pressure: 12 MPa; time: 10 min.

Alkene (−)-2.38: To a solution of alcohol (−)-2.15 (20.9 g, 84.8 mmol, 1.0 equiv.) in DCM (0.25 M, 339 ml), DMAP (1.55 g, 12.72 mmol, 0.15 equiv.) added at room temperature. Then the mixture was cooled to -78 °C followed by addition of DIPEA (44.3 ml, 254.4 mmol, 3.0 equiv.) and acryloyl chloride (13.7 ml, 169.63 mmol, 2.0 equiv.). After stirring for 10 hours, the reaction mixture was quenched with saturated aqueous NH₄Cl at -78 °C and was warmed up to room temperature. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as orange red oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (20.4 g, 80%) as light-yellow oil. [α]D²² = −13.2 (c 1.0, CH₂Cl₂); IR (film) 2930.31 1729.83 1471.42 1405.85 1258.32 1191.79 1096.33 984.48 837.919 55.656 10 777.172; ¹H NMR (500 MHz, Chloroform-d) δ 6.44 (dd, J = 17.3, 1.4 Hz, 1H), 6.18 (dd, J = 17.3, 10.4 Hz, 1H), 5.85 (dt, J = 10.4, 1.1 Hz, 1H), 5.72 (ddd, J = 17.5, 10.4, 7.2 Hz, 1H), 5.38 – 5.28 (m, 2H), 5.04 (q, J = 5.2 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.83 (dd, J = 10.7, 5.4 Hz, 1H), 3.72 (dd, J = 10.6, 5.9 Hz, 1H), 3.33 (s, 3H), 0.89 (s, 9H), 0.06 (d, J =
5.8 Hz, 6H); $^{13}$C NMR (126 MHz, Chloroform-\textit{d}) $\delta$ 165.82, 134.30, 131.05, 128.56, 119.03, 80.74, 75.74, 61.22, 57.31, 25.90, 25.77, 18.31, -5.32, -5.35; HRMS (ESI) \textit{m/z} 301.1838 [(M+H)$^+$]; calcd for C$_{15}$H$_{29}$O$_4$Si: 301.1835.

![Image](image-url)

**Alkene (+)-2.39** was isolated as byproduct from above reaction (~10%). [\(\alpha\)]$_{D}^{22}$ = +22.2 (c 1.0, CH$_2$Cl$_2$); IR (film) 2930.31 2857.02 1730.8 1406.82 1255.43 1192.76 1137.8 983.518 835.99 808.992 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-\textit{d}) $\delta$ 6.41 (dt, \(J\) = 17.3, 1.6 Hz, 1H), 6.13 (ddd, \(J\) = 17.4, 10.5, 1.4 Hz, 1H), 5.83 (dt, \(J\) = 10.4, 1.6 Hz, 1H), 5.79 – 5.67 (m, 1H), 5.33 – 5.26 (m, 2H), 4.29 (dt, \(J\) = 11.2, 2.2 Hz, 1H), 4.05 (ddd, \(J\) = 11.2, 7.4, 1.4 Hz, 1H), 3.96 (tt, \(J\) = 5.6, 4.3, 1.9 Hz, 1H), 3.58 (t, \(J\) = 6.4 Hz, 1H), 3.30 (s, 3H), 0.89 (s, 9H), 0.08 (d, \(J\) = 9.0 Hz, 6H); $^{13}$C NMR (126 MHz, Chloroform-\textit{d}) $\delta$ 166.16, 134.50, 130.83, 128.53, 118.88, 84.42, 72.56, 66.26, 56.98, 25.90, 18.29, -4.49, -4.60. HRMS (ESI) \textit{m/z} 301.1838 [(M+H)$^+$]; calcd for C$_{15}$H$_{29}$O$_4$Si: 301.1835.

![Image](image-url)

**Lactone (−)-2.17:** Alkene (−)-2.38 (12 g, 39.93 mmol, 1.0 equiv.) and Hoveyda-Grubbs catalyst 2nd generation (475.49 mg, 0.7588 mmol, 1.9% equiv.) were added to a 2 L
round bottom flask. Then it was connected with a vigreux condenser. The system was backfilled with argon three times. Freshly distilled toluene (0.053 M, 750 ml) was added via cannulation to form a dark green reaction mixture. The flask was then put into a 110 °C oil bath and heated for 12 hours. The reaction mixture turned to dark brown. After cooling, the reaction mixture was concentrated *in vacuo* to provide the crude product as a black brown oil. This oil was then purified with silica gel flash column chromatography (9:1 to 4:1 hexane/EtOAc) to afford the title compound (9 g, 82%) as brown solid. $[\alpha]_D^{22} = -162.7$ (c 1.0, CH$_2$Cl$_2$); IR (film) 2929.34 2856.06 1725.01 1462.74 1383.68 1253.5 1098.26 1073.19 1006.66 836.955 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.08 (dd, $J$ = 9.8, 5.4 Hz, 1H), 6.19 (d, $J$ = 9.7 Hz, 1H), 4.41 (ddd, $J$ = 8.4, 5.5, 2.9 Hz, 1H), 4.01 (dd, $J$ = 10.0, 8.3 Hz, 1H), 3.94 (dd, $J$ = 5.4, 3.0 Hz, 1H), 3.87 (dd, $J$ = 10.0, 5.6 Hz, 1H), 3.44 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 162.72, 142.42, 124.44, 80.02, 67.48, 60.40, 57.48, 25.93, 18.34, -5.31, -5.44; HRMS (ESI) $m/z$ 273.1514 [(M+H)$^+$; calcd for C$_{13}$H$_{25}$O$_4$Si: 273.1522].

**Alcohol 2.48:** To a solution of lactone (−)-2.17 (22 g, 80.76 mmol, 1.0 equiv.) in DCM (0.22 M, 360 ml), DIBAL (74 ml, 1.2M in toluene, 88.83 mmol, 1.1 equiv.) was added dropwise at -78 °C. After 1 hour, the reaction mixture was quenched with MeOH at -78 °C. Then cooling bath was removed followed by addition of saturated aqueous NaHCO$_3$
and saturated aqueous Rochelle’s ester. Stirred vigorously overnight. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated \textit{in vacuo} to provide the crude product which was used for the next step without further purification.

The crude hemilactal from last step was dissolved in anhydrous EtOH (0.176 M, 460 ml) and PPTS (4.059 g, 0.2 equiv.) was added in one portion. The reaction was stirred at room temperature for 3 hours before quenched with NaHCO₃ solid (~5 g added portionwise) at 0 °C. After stirred for 0.5 hour at room temperature, the mixture was filtered and concentrated \textit{in vacuo} to provide the crude product which was used for the next step without further purification.

A solution of the crude lactal 2.18 from last step in anhydrous THF (0.22 M, 360 ml) was treated with TBAF (88.84 ml, 1 M in THF, 88.84 mmol, 1.1 equiv.) dropwise at room temperature. After 2 hours, the reaction mixture was quenched with saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated \textit{in vacuo} to provide the crude product as brown oil. This oil was then purified with silica gel flash column chromatography (1:1 to 3:2 hexane/EtOAc) to afford the title compound (12.46 g, diastereomeric mixture, 82% for three steps) as brown solid. IR (film) 3445.21 2975.62 2890.77 1388.5 1322.93 1188.9 1103.08 1053.91 1012.45 743.424 cm⁻¹; \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 6.15 (dddd, \(J = 55.2, 10.4, 4.4, 1.3\) Hz, 1H), 6.07 – 5.87 (m, 1H), 5.07 (dd, \(J = 26.8, 2.4\) Hz, 1H), 4.14 – 3.80 (m, 4H), 3.65 – 3.52 (m, 2H), 3.41 (d, \(J = 2.6\) Hz, 3H), 1.29 – 1.18 (m,
3H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 130.71, 130.45, 127.79, 126.04, 96.37, 94.04, 74.10, 71.56, 70.26, 70.23, 64.20, 63.87, 62.96, 62.36, 56.70, 56.57, 15.40, 15.36; HRMS (ESI) m/z 211.0927 [(M+Na)$^+$; calcd for C$_9$H$_{16}$O$_4$Na: 211.0946].

![Chemical Structure](image)

**Aldehyde 2.19**: A solution of alcohol 2.48 (4.05 g, 21.52 mmol, 1.0 equiv.) in DCM/H$_2$O (0.09 M, 240 ml, 1:1/v:v) was treated with TEMPO (3.36 g, 21.52 mmol, 1.0 equiv.) and BAIB (7.62 g, 23.67 mmol, 1.1 equiv.) portionwise at room temperature. After stirring vigorously for 2 hours, the reaction was cooled to 0 °C and was quenched with solid NaHCO$_3$ (~4.4 g) and solid Na$_2$S$_2$O$_3$ (~400 mg) carefully. Stirred vigorously for 1 hour. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO$_4$, and filtered. The filtrate was concentrated *in vacuo* to provide the crude product as orange oil. This oil was then purified with silica gel flash column chromatography (3:7 hexane/EtOAc) to afford the title compound (2.77 g, 69%) as yellow solid. IR (film) 2976.59 97.422 2 2896.56 1739.48 1321.96 1188.9 1111.76 1051.98 1014.37 892.88 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 9.81 – 9.66 (m, 1H), 6.26 – 6.12 (m, 1H), 6.11 – 5.90 (m, 1H), 5.24 – 5.13 (m, 1H), 4.47 (d, $J = 3.1$ Hz, 1H), 4.12 – 3.90 (m, 2H), 3.91 – 3.79 (m, 1H), 3.68 – 3.56 (m, 1H), 3.46 – 3.32 (m, 4H), 1.23 (tdd, $J = 7.2$, 5.1, 2.1 Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 200.28, 131.59, 130.36, 127.04, 125.27, 96.67, 94.07, 78.52,
75.59, 70.89, 69.56, 64.40, 64.19, 56.88, 15.32, 15.27; HRMS (ESI) \( m/z \) 209.0799 [(M+Na)⁺; calcd for C₉H₁₄O₄Na: 209.0790].

![Phosphonate 2.22](image)

**Phosphonate 2.22:** To P(OEt)₃ (2.94 g, 17.64 mmol, 1.0 equiv.) in two-neck flask heated to 120 °C, (E)-tert-butyl-4-bromobut-2-enoate was added dropwise via a syringe. The reaction was stirred at 130 °C for 2 hours before cooling to room temperature. The crude was then purified with silica gel flash column chromatography (EtOAc) to afford the title compound (4.13 g, 84%) as solid. IR (film) 2980.45 30.072 2 1713.44 1653.66 1367.28 1328.71 1256.88 1165.76 1026.91 965.68 845.151 cm⁻¹; \(^1\)H NMR (500 MHz, Chloroform-d) δ 6.78 (dq, \( J = 15.4, 7.7 \) Hz, 1H), 5.90 (dd, \( J = 15.6, 5.1 \) Hz, 1H), 4.13 (m, 4H), 2.73 (dd, \( J = 22.7, 7.9, 1.4 \) Hz, 2H), 1.49 (s, 9H), 1.34 (t, \( J = 7.0 \) Hz, 6H); \(^13\)C NMR (126 MHz, Chloroform-d) δ 165.03, 136.19, 136.10, 127.82, 127.71, 80.67, 62.36, 62.31, 31.11, 30.00, 28.22, 16.51.

![Ester 2.20](image)

**Ester 2.20:** To aldehyde 2.19 (590 mg, 3.17 mmol, 1.0 equiv.) in THF (32 ml, 0.1 M) at room temperature, phosphonate side chain 2.22 (1.33 g, 4.79 mmol, 1.5 equiv.) and pre-activated molecular sieves (6.1 g, 4 Å beads, flame-dried) were added followed by
addition of LiOH·H₂O (200 mg, 4.79 mmol, 1.5 equiv.) in one portion. The mixture was then heated at 70 °C with vigorous stirring. The color of the reaction mixture turned to yellow then orange and finally dark red. After 0.5 hour, the mixture was filtered via a pad of Celite and the filtrate was concentrated in vacuo to provide the crude product as orange oil. This oil was then purified with silica gel flash column chromatography (4:1 hexane/EtOAc) to afford the title compound (590 mg, 60%) as yellow oil. IR (film) 2976.59 81.6322 2 1706.69 1648.84 1618.95 1367.28 1278.57 1240 1136.83 1099.23 1043.3 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 7.23 (dd, J = 15.3, 11.0 Hz, 1H), 6.50 (dd, J = 15.4, 11.1 Hz, 1H), 6.27 – 6.13 (m, 2H), 6.01 (dd, J = 10.1, 3.0 Hz, 1H), 5.83 (d, J = 15.2 Hz, 1H), 5.09 (d, J = 2.9 Hz, 1H), 4.66 – 4.57 (m, 1H), 3.85 – 3.75 (m, 1H), 3.60 – 3.50 (m, 2H), 3.33 (s, 3H), 1.47 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H); ¹³C NMR (126 MHz, Chloroform-d) δ 166.35, 142.96, 138.06, 130.04, 128.92, 126.67, 123.72, 94.23, 94.18, 80.31, 70.95, 70.93, 70.42, 64.00, 56.74, 28.27, 15.42.

**Lactone (−)-2.12:** To ester 2.20 (510 mg, 1.64 mmol, 1.0 equiv.) in DCM (17 ml, 0.1 M) at room temperature, pre-activated molecular sieves (1.5 g, 4 Å powder, flame-dried) was added. Then the mixture was cooled to -20 °C, m-CPBA (340 mg, 1.97 mmol, 1.2 equiv., purified via literature procedure²) was added in one portion followed by dropwise addition of BF₃·Et₂O. The reaction was stirred at the same temperature for 1 hour before it was quenched with saturated aqueous NaHCO₃ and saturated aqueous Na₂S₂O₃ at -20
The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated \textit{in vacuo} to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (4:1 to 1:1 hexane/EtOAc) to afford the title compound (417 mg, 90.5%) as yellow oil. $[\alpha]_D^{22} = -119.3$ ($c$ 0.96, CH₂Cl₂); IR (film) 2976.59 81.6322 2 1706.69 67.4641 3 1648.84 1618.95 1367.28 1278.57 1240 1136.83 1099.23 1043.3 cm⁻¹; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.21 (dd, $J$ = 15.4, 11.0 Hz, 1H), 6.95 (dd, $J$ = 9.9, 4.5 Hz, 1H), 6.55 (dd, $J$ = 15.5, 11.1 Hz, 1H), 6.24 – 6.14 (m, 2H), 5.90 (d, $J$ = 15.3 Hz, 1H), 5.10 – 5.03 (m, 1H), 4.05 (t, $J$ = 4.3 Hz, 1H), 3.42 (s, 3H), 1.50 (s, 9H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 166.04, 162.33, 143.00, 141.70, 133.22, 131.63, 125.54, 123.40, 80.73, 79.03, 71.08, 71.03, 57.42, 28.27; HRMS (ESI) $m/z$ 303.1200 [(M+Na)$^+$]; calcd for C₁₅H₂₀O₅Na: 303.1208.

\[ \text{Acid (−)-2.21: A solution of lactone (−)-2.21 (608 mg, 2.17 mmol, 1.0 equiv.) in DCM (0.29 M, 7.5 ml) was treated with TFA (2.5 ml) dropwise at 0 °C. The reaction mixture turned to brown. The mixture was stirred for 4 hours at the same temperature before careful removal of the solvent and excess reagent under high vacuum at 0 °C. The residue was further dried under vacuum for 2 hours to provide the crude product as brown solid which was used for the next step without further purification. IR (film) 2923.07 1722.12} \]
1620.39 1381.26 1250.13 1101.64 1056.8 1002.8 826.83 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-\textit{d}) $\delta$ 9.48 (s, 1H), 7.42 (dd, $J$ = 15.4, 11.1 Hz, 1H), 6.98 (dd, $J$ = 9.9, 4.4 Hz, 1H), 6.67 – 6.57 (m, 1H), 6.30 (dd, $J$ = 15.4, 5.4 Hz, 1H), 6.20 (d, $J$ = 9.9 Hz, 1H), 5.99 (d, $J$ = 15.3 Hz, 1H), 5.11 (t, $J$ = 4.9 Hz, 1H), 4.09 (t, $J$ = 4.2 Hz, 1H), 3.43 (s, 3H); $^{13}$C NMR (126 MHz, Chloroform-\textit{d}) $\delta$ 171.85, 162.50, 145.42, 143.13, 135.42, 131.09, 123.39, 122.29, 78.86, 70.90, 57.38.

\[ \text{Aldehyde (-)-2.3: To a solution of the crude acid (-)-2.21 from last step in DCM (0.2 M, 10.8 ml) at 0 \degree C, Ghosez's reagent chloroenamine (0.86 ml, 6.51 mmol, 3.0 equiv.) was added dropwise. The cloudy brown mixture became clear. Then the reaction mixture was warmed up to room temperature and stirred for 1 hour at the same temperature. DCM was removed under high vacuum at 0 \degree C. The residue was further dried under vacuum for 2 hours to provide the crude product as brown oil which was used for the next step without further purification.} \]

To a solution of the crude acid chloride from above in anhydrous THF (0.1 M, 21 ml) at -78 \degree C, LiAl(O\text{tBu})$_3$H (2.37 ml, 1.1 M in THF, 2.6 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for 0.5 hour before it was quenched with saturated aqueous NaHCO$_3$ and saturated aqueous Rochelle’s ester at -78 \degree C. After stirring vigorously for 1 hour at room temperature, the organic layer was separated and
the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (3:2 to 2:3 hexane/EtOAc) to afford the title compound (265 mg, 59% for two steps) as bright yellow solid. \([\alpha]_{D}^{22} = -130.3 \text{ (c 0.71, CH}_2\text{Cl}_2); IR \text{ (film) } 2928.38 \text{ 1725.98 1680.66 1647.87 1380.78 1250.61\ 1101.15 1056.8 990.268 826.348 cm}^{-1}; \text{ } ^1\text{H NMR (500 MHz, Chloroform-d) } \delta 9.62 (d, J = 7.9 \text{ Hz, 1H}), 7.15 (dd, J = 15.4, 10.9 \text{ Hz, 1H}), 6.98 (dd, J = 9.9, 4.4 \text{ Hz, 1H}), 6.72 (ddd, J = 15.6, 10.8, 1.6 \text{ Hz, 1H}), 6.38 (dd, J = 15.5, 5.5 \text{ Hz, 1H}), 6.24 (dd, J = 15.6, 8.0 \text{ Hz, 1H}), 6.20 (dd, J = 9.9, 0.8 \text{ Hz, 1H}), 5.13 (t, J = 5.1 \text{ Hz, 1H}), 4.12 (t, J = 4.2 \text{ Hz, 1H}), 3.44 (s, 3H); \text{ } ^{13}\text{C NMR (126 MHz, Chloroform-d) } \delta 193.54, 161.98, 149.85, 142.92, 136.18, 133.27, 131.29, 123.49, 78.75, 70.90, 57.32, 29.82; \text{ HRMS: a mass spectrometric analysis was not possible since only polymer was detected. }

**Alcohol 2.24:** To a solution of methyl propargyl ether (4.15 g, 59.2 mmol, 1.05 equiv.) in anhydrous THF (1.4 M, 40 ml) at -78 °C, n-butyllithium (34.36 ml, 53.6 mmol, 1.56 M in hexane, 1.0 equiv.) was added dropwise. After 1 hour, a solution of propionaldehyde (4.07 ml, 53.6 mmol, 1.0 equiv.) in anhydrous THF (1.4 M, 40 ml) was added via cannula at the same temperature. The reaction mixture was stirred for 3 hours at -78 °C before it was quenched by saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with
brine, dried over MgSO$_4$, and filtered. The filtrate was concentrated in vacuo (25 °C water bath) to provide the crude product (5.84 g, 85%) as yellow oil. IR (film) 3399.89 2934.16 1453.1 1358.6 1187.94 1140.69 1101.15 1037.52 966.16 910.23 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-d) δ 4.39 (tt, $J = 6.4$, 1.7 Hz, 1H), 4.15 (d, $J = 1.7$ Hz, 2H), 3.40 (s, 3H), 1.82 – 1.70 (m, 2H), 1.03 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (126 MHz, Chloroform-d) δ 87.57, 80.71, 63.83, 60.02, 57.70, 30.95, 9.53; HRMS (ESI) m/z 128.0833 [M$^+$; calcd for C$_7$H$_{12}$O$_2$: 128.0837].

Alcohol 2.25: To a solution of propargyl alcohol 2.24 (5.92 g, 46.2 mmol, 1.0 equiv.) in methanol (0.58 M, 80 ml), Lindlar Catalyst (592 ml, 10% w/w) was added at room temperature. The reaction flask was backfilled with H$_2$ for three times. The reaction was carefully monitored via TLC analysis until no starting material left. After about 2 hours, the reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo (25 °C water bath) and methanol was further removed via a vigreux column. The resulting crude (orange oil) was used for the next step without further purification. IR (film) 3398.92 2963.09 2929.34 2877.27 1455.99 1190.83 1096.33 1007.62 961.34 911.20 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-d) δ 5.68 (dt, $J = 11.7$, 6.2 Hz, 1H), 5.61 (dd, $J = 11.3$, 8.1 Hz, 1H), 4.33 (q, $J = 7.0$ Hz, 1H), 4.08 (ddd, $J = 12.3$, 6.6, 1.4 Hz, 1H), 3.97 (ddd, $J = 12.4$, 5.8, 1.2 Hz, 1H), 3.36 (s, 3H), 2.11 (s, 1H), 1.63 (dp, $J = 14.4$, 7.3 Hz, 1H), 1.50 (dp, $J = 14.4$, 7.3 Hz, 1H), 0.92 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (126 MHz,
Chloroform-d) δ 136.33, 127.64, 69.15, 69.12, 68.38, 58.21, 30.21, 9.70; HRMS (CI) m/z 113.0968 [(M-OH)+; calcd for C7H13O: 113.0961].

Alkene 2.26: To a solution of alcohol 2.25 crude from last step in anhydrous THF (0.53 M, 80 ml), NaH (2.15 g, 85 mmol, 95% in mineral oil, 2.0 equiv.) was added portionwise at 0 °C. The reaction mixture was stirred for 1 hour at the same temperature. Then MeI (5.3 ml, 85 mmol, 2.0 equiv.) was added dropwise at 0 °C. Then the mixture was warmed up to room temperature. After 12 hours, the mixture became pale white slurry. The reaction was then quenched carefully with saturate aqueous NH4Cl at 0 °C. The organic layer was separated and the aqueous layer was extracted with Et2O. The combined organic layers were washed with brine, dried over MgSO4, and filtered. The filtrate was concentrated in vacuo (25 °C water bath) to provide the crude product as orange oil. This oil was then purified with silica gel flash column chromatography (4:1 pentane/Et2O) to afford the title compound (5.2 g, 84.8% for two steps) as colorless oil. IR (film) 2962.13 2927.41 1715.37 1456.96 1375.96 1260.25 1194.69 1094.4 804.17 cm⁻¹; 1H NMR (500 MHz, Chloroform-d) δ 5.77 (dddd, J = 11.4, 6.9, 5.8, 1.1 Hz, 1H), 5.42 (ddt, J = 10.9, 9.0, 1.6 Hz, 1H), 4.07 (ddd, J = 12.4, 7.0, 1.5 Hz, 1H), 3.98 (ddd, J = 12.4, 5.8, 1.7 Hz, 1H), 3.87 – 3.81 (m, 1H), 3.35 (s, 3H), 3.27 (s, 3H), 1.71 – 1.58 (m, 1H), 1.45 (dp, J = 14.4, 7.3 Hz, 1H), 0.89 (t, J = 7.5 Hz, 3H); 13C NMR (126 MHz, Chloroform-d) δ 133.75, 129.87, 78.17, 68.46, 58.21, 56.20, 28.43, 9.67; HRMS (ESI) m/z 115.0743 [(M-Et)+; calcd for C6H11O2: 115.0759].
Dienyl Ether 2.4: To a solution of alkene 2.26 (2 g, 13.87 mmol, 1.0 equiv.) in anhydrous Et₂O (0.45 M, 30.8 ml) was added n-butyllithium (8.32 ml, 20.8 mmol, 2.5 M in hexane, 1.5 equiv.) at -20 °C. The clear solution became pale yellow suspension as n-butyllithium was added. The reaction mixture was stirred at -20 °C for 40 minutes before it was quenched by water. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The solvent was then removed via a vigreux column to provide a light-yellow oil. This oil was then purified quickly with silica gel flash column chromatography with pentane to afford the title compound (1.43 g, 92%) as colorless oil. (Caution: the product is rather volatile.) IR (film) 3733.51 3445.21 2968.87 1731.76 1693.19 1456.96 1114.65 975.804 668.214 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.35 (dd, J = 15.5, 11.0 Hz, 1H), 5.82 (d, J = 6.0 Hz, 1H), 5.63 (dt, J = 14.0, 6.5 Hz, 1H), 5.06 (dd, J = 10.8, 6.1 Hz, 1H), 3.66 (d, J = 0.8 Hz, 3H), 2.11 (p, J = 7.2 Hz, 2H), 1.01 (t, J = 7.5 Hz, 3H); ¹³C NMR (126 MHz, Chloroform-d) δ 145.67, 133.18, 121.77, 107.14, 60.05, 26.01, 13.83; HRMS (ESI) m/z 112.0880 [M⁺; calcd for C₇H₁₂O: 112.0888].

Iodide 2.30: To a solution of dienyl ether 2.3 (500 mg, 4.46 mmol, 1.0 equiv.) in anhydrous THF (0.45 M, 9.9 ml) at room temperature was added potassium tert-butoxide solid (750 mg, 6.69 mmol, 1.5 equiv.). The reaction mixture was stirred until all the solid
was dissolved to form a yellow suspension. This suspension was then cooled to -78 °C followed by the addition of n-butyllithium (5 ml, 7.35 mmol, 1.48 M in hexane, 1.65 equiv.) dropwise. The reaction mixture turned to orange then red and finally deep dark red. After 0.5 hour, the solution of iodide (1.87 g, 7.35 mmol, 1.65 equiv., precooled to -78 °C) in anhydrous Et₂O (0.35 M, 21 ml) was cannulated to above reaction mixture at -78 °C. The red color decayed to form an orange-red turbid mixture. The reaction mixture was stirred for 1 hour before it was quenched with saturated aqueous NaHCO₃ and saturated aqueous Na₂S₂O₃ at -78 °C. Then the mixture was warmed up to room temperature and was stirred vigorously. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo (25 °C water bath) to provide the crude product as orange yellow oil. This oil was then purified quickly with silica gel flash column chromatography (1.5% NEt₃ buffered) with pentane to afford the title compound (795 mg, 75%) as bright yellow oil. (Caution: the product is sensitive to light and oxygen, store under nitrogen with copper wire at low temperature.) IR (film) 2963.09 34.0646 2 2930.31 39.9214 3 1599.66 1454.55 1343.18 1186.01 1065.48 968.09 927.593 711.604 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.25 (dd, J = 15.5, 10.7 Hz, 1H), 5.95 (d, J = 10.6 Hz, 1H), 5.63 (dt, J = 15.3, 6.7 Hz, 1H), 3.50 (s, 3H), 2.08 (p, J = 7.7, 7.2 Hz, 2H), 1.01 (t, J = 7.4 Hz, 4H); ¹³C NMR (126 MHz, Chloroform-d) δ 135.45, 127.01, 122.98, 62.04, 25.75, 13.54; HRMS (ESI) m/z 112.0882 [(M-I)+; calcd for C₇H₁₂O: 112.0888].
Stannane 2.29: To a solution of dienyl ether 2.4 (300 mg, 2.67 mmol, 1.0 equiv.) in anhydrous THF (0.45 M, 5.9 ml) at room temperature was added potassium tert-butoxide solid (330 mg, 2.94 mmol, 1.1 equiv.). The reaction mixture was stirred until all the solid was dissolved to form a yellow suspension. This suspension was then cooled to -78 °C followed by the addition of n-butyllithium (1.3 ml, 3.23 mmol, 2.5 M in hexane, 1.21 equiv.) dropwise. The reaction mixture turned to orange then red and finally deep dark red. After 0.5 hour, the precooled (-78 °C) solution of iodide (1 g, 3.23 mmol, 1.21 equiv.) was cannulated to above reaction mixture at -78 °C. The red color decayed to form a golden yellow solution. The reaction mixture was stirred for 20min hour before it was warmed up naturally to room temperature. After 0.5 h, the reaction was quenched with saturated aqueous NaHCO₃. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (1.5% NEt₃ buffered) with pentane to afford the title compound (537 mg, 50%) as bright yellow oil. IR (film) 2926.45 1568.81 1458.89 1376.93 1298.34 1195.17 1115.62 971.947 874.078 667.732 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.52 (dd, J = 15.4, 10.4 Hz, 1H), 5.61 (dt, J = 15.5, 6.6 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 3.63 (s, 3H), 2.16 – 2.08 (m, 2H), 1.59 – 1.50 (m, 6H), 1.36 (h, J = 7.3 Hz, 7H), 1.04 – 0.98 (m, 9H), 0.92 (t, J = 7.3 Hz, 9H);¹³C NMR (126 MHz, Chloroform-d) δ 165.59, 132.71, 122.23, 122.01, 60.18, 29.12, 27.43, 26.02, 13.88, 13.75, 11.24; HRMS (ESI) m/z 402.1942 [M⁺; calcd for C₁₉H₃₈OSn: 402.1945].
**TMS Ether (+)-2.28**: To vinyl iodide 2.30 (31 mg, 0.13 mmol, 2.0 equiv.) in THF (0.7 ml, 0.18 M) at -78 °C, t-BuLi (0.15 ml, 1.63 M in pentane, 3.7 equiv.) was added dropwise. After stirring for 0.5 hour at the same temperature, linchpin aldehyde (−)-2.5 (22 mg, 0.088 mmol, 1.0 equiv., precooled to -78 °C) in THF (0.6 ml, 0.14 M) was cannulated to the above mixture resulting bright yellow mixture. After stirring for 0.5 hour at -78 °C, the reaction was quenched with saturated aqueous NaHCO₃ solution followed by warming up to room temperature. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (270 mg, 89%) as light-yellow oil. [α]D²² = + 5.5 (c 1.0, CH₂Cl₂); IR (film) 3446.17 2929.34 1662.34 1457.92 1250.61 1103.08 1032.69 972.912 889.023 840.812 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.35 (dd, J = 14.6, 11.7 Hz, 1H), 5.67 (dt, J = 15.0, 6.6 Hz, 1H), 5.60 (d, J = 10.9 Hz, 1H), 4.55 (d, J = 4.6 Hz, 1H), 3.97 (d, J = 7.6 Hz, 1H), 3.71 (s, 3H), 2.84 (ddt, J = 24.5, 14.0, 7.6 Hz, 4H), 2.20 – 2.06 (m, 4H), 1.89 (td, J = 6.5, 5.9, 3.4 Hz, 1H), 1.08 – 1.00 (m, 6H), 0.16 (s, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 155.09, 134.51, 122.68, 113.36, 72.26, 60.05, 51.71, 41.04, 30.59, 30.27, 26.37, 26.09, 13.75, 11.69, 0.39; HRMS (ESI) m/z 383.1511 [(M+Na)+; calcd for C₁₇H₃₂O₂S₂SiNa: 383.1510].
Alcohol (+)-2.27: To vinyl iodide 2.30 (400 mg, 1.68 mmol, 2.0 equiv.) in Et₂O (11.2 ml, 0.15 M) at -78 °C, t-BuLi (1.95 ml, 1.59 M in pentane, 3.7 equiv.) was added dropwise. After stirring for 0.5 hour at the same temperature, linchpin aldehyde (-)-2.5 (209 mg, 0.84 mmol, 1.0 equiv.), precooled to -78 °C in Et₂O (7 ml, 0.12 M) was cannulated to the above mixture resulting bright yellow mixture. After stirring for 0.5 hour at -78 °C, the reaction was quenched with saturated aqueous NaHCO₃ solution followed by warming up to room temperature. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (24 mg, 75%) as light-yellow oil. [α]D₂₂ = +46.8 (c 1.0, CH₂Cl₂); IR (film) 3468.35 2959.23 1661.37 1456.96 1245.79 1128.15 1093.44 1027.87 972.912 842.74 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.38 (dd, J = 15.4, 11.1 Hz, 1H), 5.77 – 5.70 (m, 2H), 4.97 (d, J = 5.0 Hz, 1H), 3.73 (s, 3H), 3.11 (ddd, J = 15.0, 12.3, 3.2 Hz, 1H), 2.92 (ddd, J = 14.5, 11.7, 3.1 Hz, 1H), 2.72 (q, J = 7.2 Hz, 1H), 2.50 (dq, J = 13.6, 4.4 Hz, 2H), 2.15 (m, 3H), 2.06 (dd, J = 11.8, 5.7 Hz, 1H), 1.92 (tdd, J = 12.8, 8.7, 4.0 Hz, 1H), 1.15 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.30 (s, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 157.05, 134.88, 122.43, 111.57, 69.78, 59.82, 43.15, 42.83, 26.10, 24.40, 24.28, 24.12, 13.76, 10.93, -0.62; HRMS (ESI) m/z 383.1503 [(M+Na)+]; calcd for C₁₇H₃₂O₂S₂SiNa: 383.1510.
The absolute configuration of C-3 was determined by Mosher ester analysis:

(S)-MTPA Ester of (+)-2.27 was prepared followed the procedure of synthesis of (S)-MTPA Ester of (−)-2.15. $^1$H NMR (500 MHz, Chloroform-$d$) δ 7.72 – 7.54 (m, 2H), 7.45 – 7.36 (m, 3H), 6.30 (dd, $J = 28.0$, 15.4 Hz, 1H), 5.62 (dt, $J = 14.7$, 6.5 Hz, 1H), 5.47 (d, $J = 10.5$ Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.01 – 2.92 (m, 1H), 2.85 (t, $J = 12.4$ Hz, 1H), 2.75 (q, $J = 6.9$ Hz, 1H), 2.64 (q, $J = 6.9$ Hz, 1H), 2.56 – 2.47 (m, 1H), 2.45 – 2.39 (m, 1H), 2.13 (dt, $J = 16.3$, 7.6 Hz, 2H), 1.98 (d, $J = 13.6$ Hz, 1H), 1.89 (t, $J = 12.6$ Hz, 1H), 1.31 (d, $J = 7.4$ Hz, 3H), 1.07 – 1.02 (m, 3H), 0.21 – 0.17 (m, 6H).

(R)-MTPA Ester of (+)-2.27 was prepared followed the procedure of synthesis of (R)-MTPA Ester of (−)-2.15; $^1$H NMR (500 MHz, Chloroform-$d$) δ 7.63 – 7.54 (m, 2H), 7.42 (d, $J = 7.7$ Hz, 3H), 6.26 (dd, $J = 15.5$, 10.7 Hz, 1H), 6.09 (s, 1H), 5.50 – 5.41 (m, 1H), 5.28 (d, $J = 10.7$ Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 2.98 (t, $J = 12.6$ Hz, 1H), 2.89 – 2.82 (m, 1H), 2.71 (q, $J = 7.2$ Hz, 1H), 2.64 (q, $J = 7.1$ Hz, 1H), 2.53 – 2.47 (m, 1H), 2.46 (s,
1H), 2.11 (p, \( J = 7.4 \) Hz, 2H), 2.02 (d, \( J = 16.2 \) Hz, 1H), 1.95 – 1.87 (m, 1H), 1.30 (s, 3H), 1.04 (d, \( J = 7.5 \) Hz, 3H), 0.25 (s, 6H).

**Alkene (+)-2.31:** To vinyl iodide 2.30 (30 mg, 0.13 mmol, 1.5 equiv.) in THF (0.8 ml, 0.18 M) at -78 °C, \( t \)-BuLi (0.16 ml, 1.53 M in pentane, 2.85 equiv.) was added dropwise. After stirring for 0.5 hour at the same temperature, linchpin aldehyde (-)-2.5 (20.9 mg, 0.08 mmol, 1.0 equiv., precooled to -78 °C) in THF (0.7 ml, 0.12 M) was cannulated to the above mixture resulting light yellow mixture. Allylbromide (0.3 ml, 0.24 mmol, 4.0 equiv.) was then added dropwise to the reaction mixture before removing the cooling bath. After stirring for 0.5 hour at room temperature, the reaction was quenched with saturated aqueous NaHCO₃ solution. The organic layer was separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (19:1 hexane/EtOAc) to afford the title compound (28 mg, 83%) as light-yellow oil. \([\alpha]_D^{22} = + 33.9 \; (c 1.0, \text{CH}_2\text{Cl}_2); \) IR (film) 2959.23 1662.34 1423.21 1250.61 1101.15 1029.8 972.912 908.308 869.739 838.883 cm\(^{-1}\); \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \( \delta \) 6.38 – 6.29 (m, 1H), 6.07 (ddt, \( J = 17.2, 10.5, 7.1 \) Hz, 1H), 5.68 (dt, \( J = 24.8, 8.8 \) Hz, 2H), 5.16 – 5.05 (m, 3H), 3.69 (s, 3H), 2.99 (ddd, \( J = 14.1, 10.7, 3.0 \) Hz, 1H), 2.89 (ddd, \( J = 14.3, 10.6, 3.3 \) Hz, 1H), 2.69 (dd, \( J = 15.3, 7.2 \) Hz, 3H), 2.55 (dd, \( J = 192 \).
15.5, 6.9 Hz, 1H), 2.42 (q, \(J = 7.1\) Hz, 1H), 2.14 (p, \(J = 7.2\) Hz, 2H), 2.02 – 1.93 (m, 1H), 1.87 (tq, \(J = 10.1, 3.3\) Hz, 1H), 1.04 (t, \(J = 7.3\) Hz, 6H), 0.18 (s, 6H); \(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 157.23, 134.44, 134.30, 122.34, 117.54, 113.11, 70.03, 59.51, 58.00, 40.97, 40.05, 26.08, 26.00, 25.44, 24.79, 13.73, 7.85, 1.38, 1.01; HRMS (ESI) \(m/z\) 401.2010 [(M+H)+]; calcd for C\(_{20}\)H\(_{37}\)O\(_2\)S\(_2\)Si: 401.2009.

Alcohol (++)-2.2: To vinyl iodide \(2.30\) (118 mg, 0.5 mmol, 1.5 equiv.) in THF (2.8 ml, 0.18 M) at -78 °C, \(t\)-BuLi (0.6 ml, 1.6 M in pentane, 2.85 equiv.) was added dropwise. After stirring for 0.5 hour at the same temperature, linchpin aldehyde (--)\(-2.5\) (82.6 mg, 0.33 mmol, 1.0 equiv., precooled to -78 °C) in THF (2.2 ml, 0.15 M) was cannulated to the above mixture resulting bright yellow mixture. The mixture was stirred for 0.5 hour before it was cannulated to aldehyde (--)\(-2.3\) (48.5 mg, 0.23 mmol, 0.7 equiv., precool to -78 °C) in THF (2.2 ml, 0.1 M). The reaction was stirred at the same temperature for 0.5 hour before it was quenched with saturated aqueous NaHCO\(_3\) solution followed by warming up to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO\(_4\), and filtered. The filtrate was concentrated \textit{in vacuo} to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (3:2 hexane/EtOAc) to afford the diastereomeric mixture of 33.4 mg (++)-2.2 and 22.24 mg (--)\(-2.40\) (55.6 mg in total, 42%, 52% brsm) as yellow foam. [\(\alpha\)]\(_D\)^{22}
= + 8.0 (c 1.0, CH2Cl2); IR (film) 3428.81 2927.89 1729.83 1683.55 1457.92 1379.34 1250.13 1099.23 842.258 752.584 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 6.93 (ddd, J = 10.0, 4.5, 1.7 Hz, 1H), 6.51 (p, J = 10.6 Hz, 2H), 6.32 (t, J = 12.8 Hz, 2H), 6.16 (dd, J = 9.8, 1.7 Hz, 1H), 5.92 (dd, J = 13.9, 7.2 Hz, 1H), 5.70 (dt, J = 14.3, 6.8 Hz, 1H), 5.61 (d, J = 10.8 Hz, 1H), 5.08 (s, 1H), 4.99 (t, J = 5.6 Hz, 1H), 4.49 (d, J = 5.9 Hz, 1H), 4.16 (s, 1H), 4.02 (d, J = 4.8 Hz, 1H), 3.69 (s, 3H), 3.43 (s, 3H), 2.79 (dd, J = 13.7, 6.8 Hz, 4H), 2.43 (d, J = 7.5 Hz, 1H), 2.16 (p, J = 7.2 Hz, 2H), 1.97 (d, J = 6.0 Hz, 2H), 1.18 (dd, J = 7.1, 1.7 Hz, 3H), 1.05 (td, J = 7.4, 1.8 Hz, 3H), 0.22 (d, J = 1.8 Hz, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 162.81, 155.97, 143.12, 135.06, 134.79, 134.12, 131.48, 125.43, 123.40, 122.08, 113.88, 80.13, 73.47, 71.50, 71.33, 63.07, 60.00, 57.41, 42.88, 29.83, 26.22, 26.09, 25.49, 24.93, 13.71, 8.36, 1.21, 0.88; HRMS (ESI) m/z 591.2246 [(M+Na)⁺]; calcld for C_{28}H_{44}O_{6}S_{2}SiNa: 591.2251.

The absolute configuration at C-10 was determined by Mosher ester analysis:

(S)-MTPA Ester of (+)-2.2 was prepared followed the procedure of synthesis of (S)-MTPA Ester of (−)-2.15. The product decomposed during the purification therefore the crude NMR was used. ¹H NMR (500 MHz, Chloroform-d) δ 7.61 (t, J = 4.6 Hz, 2H), 7.47 – 7.35 (m, 3H), 6.97 (dd, J = 10.0, 4.4 Hz, 1H), 6.53 (dd, J = 15.0, 10.5 Hz, 1H), 6.44 (dd, J = 15.0, 10.7 Hz, 1H), 6.30 (dd, J = 15.3, 11.1 Hz, 1H), 6.20 – 6.04 (m, 3H),
5.65 (dt, J = 14.6, 6.6 Hz, 1H), 5.59 (d, J = 11.0 Hz, 1H), 5.05 (s, 1H), 4.99 (d, J = 5.3 Hz, 1H), 4.03 (t, J = 4.2 Hz, 1H), 3.63 (d, J = 12.4 Hz, 6H), 3.44 (s, 3H), 2.56 (d, J = 14.2 Hz, 1H), 2.16 – 2.04 (m, 4H), 1.91 (d, J = 7.4 Hz, 1H), 1.77 (s, 1H), 1.68 (d, J = 15.3 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.19 (s, 9H).

(R)-MTPA Ester of (+)-2.2 was prepared followed the procedure of synthesis of (R)-MTPA Ester of (–)-2.15. The product decomposed during the purification therefore the crude NMR was used. \(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 7.62 – 7.52 (m, 2H), 7.41 (dt, J = 19.6, 4.4 Hz, 3H), 6.96 (dd, J = 9.9, 4.4 Hz, 1H), 6.38 (dd, J = 15.3, 10.3 Hz, 1H), 6.30 (dd, J = 15.5, 11.1 Hz, 1H), 6.17 (d, J = 10.0 Hz, 3H), 6.07 (dd, J = 15.1, 7.1 Hz, 1H), 5.80 (dd, J = 15.4, 6.5 Hz, 1H), 5.66 (dt, J = 14.5, 6.5 Hz, 1H), 5.60 (d, J = 10.8 Hz, 1H), 5.05 (s, 1H), 4.97 (d, J = 5.4 Hz, 1H), 4.02 (t, J = 4.2 Hz, 1H), 3.69 (s, 3H), 3.61 (s, 3H), 3.44 (s, 3H), 2.91 (t, J = 12.4 Hz, 2H), 2.69 – 2.51 (m, 2H), 2.17 – 2.08 (m, 3H), 1.99 (s, 1H), 1.85 (d, J = 12.3 Hz, 1H), 1.02 (d, J = 7.5 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.22 (s, 9H).
**Alcohol (−)-2.40:** The title compound was isolated as one of the diastereomers in the key union reaction. $[\alpha]_D^{22} = -14.6 \, (c \, 0.74, \text{CH}_2\text{Cl}_2)$; IR (film) 3456.78 2928.86 1729.35 1380.3 1249.65 1098.26 1053.43 841.294 752.102 cm$^{-1}$; $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.96 (dd, $J = 9.9, 4.5$ Hz, 1H), 6.56 – 6.48 (m, 2H), 6.33 (ddt, $J = 14.3$, 10.9, 1.6 Hz, 1H), 6.29 – 6.24 (m, 1H), 6.17 (d, $J = 9.9$ Hz, 1H), 5.94 – 5.89 (m, 1H), 5.70 (dt, $J = 15.4, 6.6$ Hz, 1H), 5.64 (d, $J = 11.0$ Hz, 1H), 5.13 (s, 1H), 4.97 (dd, $J = 7.0$, 3.8 Hz, 1H), 4.60 (d, $J = 4.0$ Hz, 1H), 4.00 (t, $J = 4.2$ Hz, 1H), 3.70 (s, 3H), 3.54 (d, $J = 2.9$ Hz, 1H), 3.44 (s, 3H), 2.85 (dtd, $J = 29.8, 7.2, 6.8, 4.0$ Hz, 3H), 2.71 (ddd, $J = 14.5$, 7.6, 3.6 Hz, 1H), 2.28 (q, $J = 7.2$ Hz, 1H), 2.18 – 2.11 (m, 2H), 1.99 (dq, $J = 7.6, 3.9$ Hz, 2H), 1.14 (d, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.5$ Hz, 3H), 0.24 (s, 6H); $^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 162.97, 155.78, 143.25, 135.04, 134.90, 133.46, 130.44, 125.26, 123.50, 122.19, 113.66, 80.42, 71.46, 70.04, 62.56, 59.33, 57.61, 42.73, 29.92, 26.33, 26.17, 25.68, 25.02, 13.78, 9.75, 1.24, 1.08; HRMS (ESI) $m/z$ 591.2246 [(M+Na)$^+$; calcd for C$_{28}$H$_{44}$O$_6$S$_2$SiNa: 591.2251].
Aldehyde 2.41: The title compound was isolated as a byproduct in the key union reaction. IR (film) 3441.35 2931.27 1727.42 1610.75 1532.17 1251.09 1103.08 990.75 825.384 cm⁻¹; ¹H NMR (500 MHz, Chloroform-d) δ 9.67 (d, J = 7.7 Hz, 1H), 7.36 (dd, J = 9.4, 6.6 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.19 (dd, J = 15.1, 11.3 Hz, 1H), 6.53 (d, J = 15.0 Hz, 1H), 6.38 (dd, J = 15.2, 7.7 Hz, 1H), 6.33 (d, J = 9.4 Hz, 1H), 6.27 (d, J = 6.6 Hz, 1H); ¹³C NMR (126 MHz, Chloroform-d) δ 193.08, 160.87, 157.73, 148.50, 143.01, 135.12, 131.91, 130.45, 116.90, 107.96.

Methyl Ether (−)-2.37: To alcohol (+)-2.2 (10 mg, 0.018 mmol, 1.0 equiv.) was treated with pre-activated molecular sieves (300 mg, 4 Å powder, flame-dried), silver oxide (204 mg, 0.88 mmo, 50 equiv.) and MeI (1.2 ml, 0.015 M) at room temperature. The reaction was stirred for overnight before it was filtered via a pad of Celite. The filtrate was concentrated in vacuo to provide the crude product as yellow oil. This oil was then purified with silica gel flash column chromatography (7:3 hexane/EtOAc) to afford the title compound (6.7 mg, 65%) as light-yellow oil. [α]D²² = −39.5 (c 0.21, CH₂Cl₂); IR (film) 2925 1729.35 1463.22 1379.82 1248.68 1097.78 1055.84 872.631 840.812 cm⁻¹; ¹H
NMR (500 MHz, Chloroform-d) δ 6.97 (dd, J = 9.9, 4.5 Hz, 1H), 6.46 (dd, J = 15.5, 10.2 Hz, 1H), 6.36 – 6.25 (m, 2H), 6.18 (d, J = 9.9 Hz, 1H), 5.97 (ddd, J = 31.7, 15.3, 7.7 Hz, 2H), 5.72 – 5.59 (m, 2H), 5.13 (s, 1H), 4.97 (dd, J = 7.3, 3.9 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 4.02 (t, J = 4.3 Hz, 1H), 3.69 (s, 3H), 3.45 (s, 3H), 3.32 (s, 3H), 2.72 – 2.64 (m, 1H), 2.59 (d, J = 11.5 Hz, 2H), 2.11 (hept, J = 7.2 Hz, 4H), 1.94 – 1.85 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.22 (s, 9H); ¹³C NMR (126 MHz, Chloroform-d) δ 162.70, 157.31, 143.15, 134.90, 134.26, 132.95, 132.85, 126.04, 123.53, 122.50, 113.02, 80.27, 71.25, 69.81, 59.57, 57.37, 56.58, 43.51, 29.83, 27.99, 27.72, 26.08, 25.13, 13.73, 8.10, 1.23, 0.55; HRMS (ESI) m/z 605.2404 [(M+Na)⁺; calcd for C₂₀H₄₆O₆S₂SiNa: 605.2403].

3.2.3 References


APPENDIX: INFRARED AND NMR SPECTRA
$^1$H NMR (500 MHz) Spectrum of Compound 1.12 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 1.12 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound (−)-1.13 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (−)-**1.13** in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound (-)-1.14 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (-1,14) in CDCl₃
The Infrared Spectrum of Compound (−)-1.14
$^1$H NMR (500 MHz) Spectrum of Compound (-)-1.15 in CDCl$_3$
The Infrared Spectrum of Compound (−)-1.15
$^1$H NMR (500 MHz) Spectrum of Compound (−)-1.26 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (-)-1.26 in CDCl$_3$
The Infrared Spectrum of Compound (−)-1.26
$^1$H NMR (500 MHz) Spectrum of Compound (−)-1.16 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (-)-1,16 in CDCl$_3$
The Infrared Spectrum of Compound $(-)-1.16$
$^1$H NMR (500 MHz) Spectrum of Compound (-)-1.3 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (−)-1.3 in CDCl$_3$
The Infrared Spectrum of Compound (−)-1.3
$^1$H NMR (500 MHz) Spectrum of Compound \((-\)-1.27 in CDCl$_3$)
The Infrared Spectrum of Compound (-)-1,27
^1H NMR (500 MHz) Spectrum of Compound (→)-1.28 in CDCl₃
$^{13}$C NMR (125 MHz) Spectrum of Compound (−)-1.28 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound (−)-1.17 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (−)-1.17 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (+)-1.23 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound (+)-1.24 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (+)-1,24 in CDCl$_3$
The Infrared Spectrum of Compound (+)-1.24
$^{13}$C NMR (125 MHz) Spectrum of Compound 1.25 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound 1.2 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound 2.11 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.11 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound (−)-2.15 in CDCl$_3$
The Infrared Spectrum of Compound (-)-2.15
$^1$H NMR (500 MHz) Spectrum of (S)-MTPA Ester of (−)-2.15 in CDCl$_3$
1H NMR (500 MHz) Spectrum of (R)-MTPA Ester of (−)-2,15 in CDCl₃
COSY Spectrum of (R)-MTPA Ester of (-)-2.15 in CDCl$_3$
HSQC Spectrum of (R)-MTPA Ester of (-)-2.15 in CDCl₃
$^1$H NMR (500 MHz) Spectrum of Compound (−)-2.38 in CDCl$_3$
The Infrared Spectrum of Compound (-2,38)
$^{13}$C NMR (125 MHz) Spectrum of Compound (+)-2,29 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound (−)-2,17 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.48 in CDCl$_3$
The Infrared Spectrum of Compound 2.48
The Infrared Spectrum of Compound 2.19
$^1$H NMR (500 MHz) Spectrum of Compound 2.20 in CDCl$_3$
The Infrared Spectrum of Compound 2.20
$^1$H NMR (500 MHz) Spectrum of Compound (−)-2.12 in CDCl$_3$
13C NMR (125 MHz) Spectrum of Compound (−)-2.12 in CDCl₃
The Infrared Spectrum of Compound (−)-2.12
$^1$H NMR (500 MHz) Spectrum of Compound (−)-2.21 in CDCl$_3$
The Infrared Spectrum of Compound (-)-2.21
$^1$H NMR (500 MHz) Spectrum of Compound (→)-2.3 in CDCl$_3$
$^{13}$C NMR (500 MHz) Spectrum of Compound (−)-2.3 in CDCl$_3$
The Infrared Spectrum of Compound (-)-2.3
$^1\text{H NMR (500 MHz) Spectrum of Compound 2.24 in CDCl}_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.24 in CDCl$_3$
$^{1}H$ NMR (500 MHz) Spectrum of Compound 2.26 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.26 in CDCl$_3$
The Infrared Spectrum of Compound 2.26
$^1$H NMR (500 MHz) Spectrum of Compound 2.4 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.4 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound 2.29 in CDCl$_3$
$^1$H NMR (500 MHz) Spectrum of Compound 2.30 in CDCl$_3$
$^{13}$C NMR (125 MHz) Spectrum of Compound 2.30 in CDCl$_3$
The Infrared Spectrum of Compound 2.30
$^{13}$C NMR (500 MHz) Spectrum of Compound $2.41$ in CDCl$_3$
The Infrared Spectrum of Compound 2.41
$^1$H NMR (500 MHz) Spectrum of Compound (+)-2.28 in CDCl$_3$
\[ \text{\(^{13}\)C NMR (500 MHz) Spectrum of Compound (+)-2.28 in CDCl\textsubscript{3}} \]
The Infrared Spectrum of Compound (+)-2.28
\(^1\)H NMR (500 MHz) Spectrum of Compound (+)-2.27 in CDCl\(_3\)
The Infrared Spectrum of Compound (+)-227
$^1$H NMR (500 MHz) Spectrum of (R)-MTPA Ester of (+)-2.27 in CDCl$_3$
COSY Spectrum of (R)-MTPA Ester of (+)-2,27 in CDCl₃
$^1H$ NMR (500 MHz) Spectrum of (S)-MTPA Ester of (+)-2.27 in CDCl$_3$
COSY Spectrum of (S)-MTPA Ester of (+)-2,27 in CDCl₃
$^{13}$C NMR (500 MHz) Spectrum of Compound (+)-2.31 in CDCl$_3$
COSY Spectrum of Compound (+)-2.31 in CDCl₃
$^1$H NMR (500 MHz) Spectrum of Compound (+)-2,2 in CDCl$_3$
$^{13}C$ NMR (500 MHz) Spectrum of Compound (+)-2.2 in CDCl$_3$
The Infrared Spectrum of Compound (+)-2.2
$^1$H NMR (500 MHz) Spectrum of (S)-MTPA Ester of (+)-2.2 in CDCl$_3$
COSY Spectrum of (S)-MTPA Ester of (+)-2.2 in CDCl₃
$^1$H NMR (500 MHz) Spectrum of (R)-MTPA Ester of (+)-2.2 in CDCl$_3$
COSY Spectrum of (R)-MTPA Ester of (-)-2,2 in CDCl₃
$^1$H NMR (500 MHz) Spectrum of Compound (−)-2.40 in CDCl$_3$
COSY Spectrum of Compound (-)-2.40 in CDCl₃
HSQC Spectrum of Compound \((-\)-2.40) in CDCl$_3$
HMBC Spectrum of Compound (−)-2.40 in CDCl₃
The Infrared Spectrum of Compound (→2,40)
$^1$H NMR (500 MHz) Spectrum of Compound (-)-237 in CDCl$_3$
$^{13}$C NMR (500 MHz) Spectrum of Compound (-)-2.37 in CDCl$_3$
The Infrared Spectrum of Compound (→) 2.37