Total Synthesis of (-)-Enigmazole A

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Total Synthesis of (-)-Enigmazole A

Abstract
The dissertation contained herein presents a total synthesis of (-)-enigmazole A utilizing a late-stage large-fragment Petasis-Ferrier union/rearrangement protocol. Chapter One details the isolation, structural elucidation and subsequent biological studies of (-)-enigmazole A. The previous synthetic studies of (-)-enigmazole A are also introduced. The chapter then outlines the Smith three-step Petasis-Ferrier union/rearrangement protocol, as well as a number of the successful total syntheses achieved over the years by the Smith group utilizing this protocol. Herein, a late-stage large-fragment Petasis-Ferrier union/rearrangement will be utilized as the synthetic cornerstone for the Smith total synthesis of (-)-enigmazole A.

Chapter Two describes the retrosynthetic strategy toward (-)-enigmazole A and subsequent total synthesis. The late-stage large-fragment Petasis-Ferrier union/rearrangement, which generates the entire carbon skeleton of (-)-enigmazole A, is described after the construction of the requisite eastern and western hemispheres. The chapter then describes the subsequent macrolactonization studies and the end game of the total synthesis. In addition to the Smith three-step Petasis-Ferrier union/rearrangement protocol, highlights of the total synthesis includes a Negishi cross-coupling, a dithiane-epoxide union, a Type I ARC multicomponent coupling, a Yamaguchi macrolactonization and chemoselective oxidation/reduction strategies the details of which are also described in Chapter Two.

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TOTAL SYNTHESIS OF (−)-ENIGMAZOLE A

Yanran Ai

A DISSERTATION

in

Chemistry

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

2015

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Dedication

to

Tingyi Wu

Hua Ai and Sujuan Tan
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ABSTRACT

TOTAL SYNTHESIS OF (−)-ENIGMAZOLE A

Yanran Ai

Amos B. Smith, III

The dissertation contained herein presents a total synthesis of (−)-enigmazole A utilizing a late-stage large-fragment Petasis-Ferrier union/rearrangement protocol. Chapter One details the isolation, structural elucidation and subsequent biological studies of (−)-enigmazole A. The previous synthetic studies of (−)-enigmazole A are also introduced. The chapter then outlines the Smith three-step Petasis-Ferrier union/rearrangement protocol, as well as a number of the successful total syntheses achieved over the years by the Smith group utilizing this protocol. Herein, a late-stage large-fragment Petasis-Ferrier union/rearrangement will be utilized as the synthetic cornerstone for the Smith total synthesis of (−)-enigmazole A.

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List of Abbreviation

Ac……………………………………………………………………………….. Acetyl
ACN……………………………………………………………………… Acetonitrile
AcOH…………………………………………………………………….. Acetic Acid
ARC……………………………………………………………………… Anion Relay Chemistry
ASG………………………………………………………………………… Anion Stabilizing Group
BAIB…………………………………………………………………… [Bis(acetoxy)iodo]benzene
Bn……………………………………………………………………………. Benzyl
Boc………………………………………………………………………… tert-Butyl Carbamates
BPS………………………………………………………………………… tert-Butyldiphenylsilyl Chloride
BuLi………………………………………………………………………… Butyllithium
Cp…………………………………………………………………………… Cyclopentadienyl
CSA…………………………………………………………………………… 10-Camphorsulfonic Acid
DCC……………………………………………………………………… N,N’-Dicyclohexylcarbodiimide
DCM………………………………………………………………………… Dichloromethane
DDQ……………………………………………………………………… 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H……………………………………………………………… Disobutylaluminum Hydride
DIPEA……………………………………………………………………… Diisopropylethylamine
DMAP……………………………………………………………………… 4-(N,N-Dimethylamino)pyridine
DMF………………………………………………………………………… Dimethylformamide
DMSO…………………………………………………………………….. Dimethyl Sulfoxide
DMPU……………………………………………………………………… 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
d.r………………………………………………………………………….. Diastereomeric Ratio
DtBMP…………………………………………………………………… 2,6-Di-tert-butyl-4-methylpyridine
EDC.HCl………………………………………………………………… 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride
EtOAc……………………………………………………………………… Ethyl Acetate
EtOH………………………………………………………………………… Ethanol
Fm…………………………………………………………………………… 9-Fluorenlymethyl
GI50………………………………………………………………………… Growth Inhibition of 50%
HMDS…………………………………………………………………….. Hexamethyldisilazane
HMPA…………………………………………………………………….. Hexamethylphosphoramide
HPLC……………………………………………………………………… High Pressure Liquid Chromatography
IC50………………………………………………………………………… Half Maximal Inhibitory Concentration
Ipc…………………………………………………………………………… Isopinocampheyl
LA…………………………………………………………………………… Lewis Acid
LG…………………………………………………………………………… Leaving Group
LDA………………………………………………………………………… Lithium Diisopropylamide
IR…………………………………………………………………………….. Infrared
mCPBA………………………………………………………………… meta-Chloroperoxybenzoic acid
MeOH……………………………………………………………………… Methanol
Megahertz
Mass Spectrometry
Methanesulfonyl
Methoxymethyl
2-Naphthylmethyl
N-Methylmorpholine N-Oxide
Nuclear Magnetic Resonance
Protecting Group
Phenyl
Triphenylphosphine
4-Methoxybenzyl
4-Methoxyphenyl
Preparative Thin Layer Chromatography
Pyridine
Room Temperature
Tris(dimethylamino)sulfonium Difluorotrimethylsilicate
Tetraethylammonium Fluoride
Tetraethylammonium Iodide
Tetrabutylammonium Difluorotriphenylsilicate
tert-Butyldiphenylsilyl
tert-Butyldimethylsilyl
2,2,6,6-Tetramethyl-1-piperidinyloxyl, Free Radical
Triisopropylsilyl
Trifluoromethyl
Trifluoromethanesulfonic Acid
Tetrahydrofuran
Thin Layer Chromatography
Trimethylsilyl
2,4,6-Triisopropylbenzylsulfonylimidazole
Ultraviolet
Chapter 1. Introduction

1.1. Isolation and Biological Activity of the Enigmazoles

The enigmazoles A (1.1), and B (1.4), as well as related congeners, constitute the first and to date only family of known phosphate-containing marine macrolides. Isolated by Gustafson and coworkers at the National Cancer Institute in 2006 from Cinachyrella enigmatica, a marine sponge endemic to Papua New Guinea,\(^1\) the extracts from Cinachyrella enigmatica displayed significant cytotoxic activity in the NCI 60-cell antitumor screen.\(^2\) Perhaps of greater interest, several of the fractions were shown to inhibit mutant c-Kit containing cells selectively, while cells containing wild-type c-Kit were relatively unaffected. This differentiation comprises a rare phenotype, thus far observed only in 32 natural product extracts out of the 134,631 extracts tested at the NIH to date.\(^3\) The mutation of c-Kit, a type-III receptor tyrosine kinase (RTK), has been implicated in a number of cancers.\(^4,5\) With the goal of developing novel cancer therapeutics, exploration of the most highly active chromatographic fractions of the Cinachyrella enigmatica sponge extract led to the identification of the enigmazoles (Figure 1.1).
In 2010, a full paper was published by Gustafson and coworkers presenting the isolation, elucidation and biological activities of the enigmazole family. Their studies revealed that enigmazole A (1.1) was the primary cytotoxic constituent of the Cinachyrella enigmatica extract. In particular, enigmazole A was found to be highly cytotoxic against IC-2 mast cells (IC$_{50}$ = 0.37μg/mL), and against the 60 human tumor cell lines with a mean activity of GI$_{50}$ of 1.7 μM in the NCI 60-cell antitumor assay. This bioactivity data illustrates the potential of enigmazole A (1.1), thus making it an important new lead compound for the treatment of multiple cancer types. However, the lack of a diagnostic pattern in the tumor panel specificity assay has made it difficult to
identify precisely the possible molecular target and/or a pathway associated with the observed bioactivity.\textsuperscript{1,7} Although the original isolated extract fraction displayed selectivity against c-Kit mutant cells, both enigmazole A (1.1) and the congeners (1.2 and 1.3) were equally cytotoxic against both wild-type and mutant c-Kit. Evidence however suggests that other compounds bearing the enigmazole core, either enigmazole B (1.4) or additional enigmazole analogues, might be responsible for the selectivity in the c-Kit assays.\textsuperscript{1,8} Due to the limited amount of enigmazole analogues available from the natural source, the synthesis of the enigmazoles and future chemical derivatization resulting in analogues would hold the promise of identifying the cellular targets and pathways involved, as well as improving both the antitumor activity and the mutation c-Kit selectivity.

In addition to the potent biological activity, the structural complexity and uniqueness of the enigmazoles provides the chemical community with an excellent platform for the further development of synthetic methods and strategies. For example, enigmazole A (1.1) is composed of an 18-member macrolide, with an embedded methylene cis-2,6-disubstituted tetrahydropyran ring, a functionalized disubstituted oxazole side-chain at C17, and a phosphate ester at C5. This type of functional group array is rare in polyketide natural products. Careful examination of the structures of enigmazole A (1.1) and B (1.4) in the Smith research group led to a synthetic plan, whereby synthetic methods recently developed in our laboratory, including of Petasis-Ferrier union/rearrangement\textsuperscript{9} and Anion Relay Chemistry (ARC)\textsuperscript{10} could be applied.
1.2. Previous Synthetic Studies of (-)-Enigmazole A

In addition to the Smith research group, the promising biological activity and complicated architecture of enigmazole A (1.1), have attracted attention from a number of organic groups, resulting in the first total synthesis of enigmazole A published by Molinski and coworkers in 2010.\textsuperscript{11}

One of the key reactions of the Molinski synthesis was a hetero-Diels-Alder (HDA) reaction leading to the construction of the embedded tetrahydropyran structure (Scheme 1.1). To this end, treatment of a mixture of aldehyde 1.7 and diene 1.8 with a catalytic amount of BF$_3$·OEt$_2$ furnished the desired product 1.9 in 81% yield with a diastereomer ratio of 4.2: 1.0: 0.25. The subsequent steps, including a Wittig olefination, led to 1.10, which was then transformed into the requisite macrolactonization precursor 1.11, after selective hydrogenation, saponification and acetonide removal. Another key reaction in the Molinski synthetic sequence was a chemoselective macrolactonization, which selectively formed the macrolactone ring at C17 hydroxyl rather than at the C15 hydroxyl. Initial screening of a variety of mactolactonization conditions, however, did not lead to desired product 1.12, but either gave the 16-member macrolide by activation of C15 hydroxyl or complex intractable mixtures.
Scheme 1.1. Molinski’s Synthesis of Enigmazole A: HDA Cycloaddition

To alter the conformation of the macrolactonization precursor to achieve lactonization, intermediate 1.10 was subjected to macrolactonization after both methyl ester hydrolysis and acetonide removal (Scheme 1.2). To Molinski’s delight, the Keck conditions then successfully furnished the desired 18-member macrolide 1.12, albeit in only 35% yield over the 3 step sequence. A further 6 steps were required to complete the natural product total synthesis. In summary, Molinski and co-workers achieved the first total synthesis of enigmazole A (1.1) in 22 steps and 0.41% yield from a known compound.
Fürstner and co-workers also published a synthetic effort toward enigamazole A in 2013. To increase the structural span/impact of their alkyne metathesis, they designed a synthesis toward a model compound related to the enigamazole A core (Scheme 1.3). Starting from alkyne 1.13, which was prepared in turn by the alkyne metathesis, DDQ oxidation and the subsequent gold-catalyzed Meyer-Schuster rearrangement furnished racemic cis-disubstituted tetrahydropyran 1.15. Acetyl deprotection then gave racemic ketone 1.16, which the authors considered to be the core of enigamazole A (1.1).

Scheme 1.3. Fürstner’s Model Study Toward the Core of Enigamazole A

In the Smith research group, enigamazole A was considered an excellent candidate both to showcase and improve the synthetic methods currently being developed. Thus, Smith and colleagues proposed a highly convergent and stereocontrolled route utilizing a novel late-stage large-fragment Petasis-Ferrier union/rearrangement tactic, as well as both anion relay chemistry (ARC) and a dithiane-epoxide coupling tactic. Their synthetic plan
shared no similarity with either the Molinski total synthesis or the Fürstner model study.

1.3. Petasis-Ferrier Union/Rearrangement – A Successful Tactic for Complex Molecule Total Synthesis

![Chemical structures and reactions]

**Scheme 1.4.** An Example of the Petasis-Ferrier Union/Rearrangement Protocol in a Complex Molecule Total Synthesis

1.3.1. Development of the Petasis-Ferrier Union/Rearrangement

The pioneering work leading to the Petasis-Ferrier union/rearrangement tactic was first published in 1962 by Ferrier and coworkers (Scheme 1.5). In this seminal publication, they suggested a process involving the formation of oxocarbonium ion 1.17 in the six-membered ring system, as well as a subsequent nucleophilic addition. This synthetic tactic, named the Ferrier rearrangement, was extended in 1979 to the Ferrier carbocyclization. The process involves the fragmentation of hemiacetal 1.19, promoted by a Lewis acid, resulting in the formation of aldehyde 1.21, which undergoes a rearrangement to β-hydroxy cyclohexanone 1.22 by an intramolecular aldol reaction. Ferrier’s pioneering work provided a perfect starting point for the design of the Petasis-Ferrier union/rearrangement, including: (i) formation and fragmentation of acetal type
substrates; (ii) formation of oxocarbonium ions or other carbonyl intermediates as electrophiles; and (iii) an intramolecular aldol-type nucleophilic addition to a carbonyl intermediate.

**Scheme 1.5. Ferrier Rearrangement and Carbocyclization**

Twenty years later, Petasis and co-workers envisioned use of the Ferrier rearrangement to construct the tetrahydropyran ring systems (Scheme 1.6).\(^\text{15}\) The starting material of the Petasis cascade, enol-acetal 1.23, comprises a variant of the Ferrier substrate (1.20 in Scheme 1.5). Triisobutylaluminum \([\text{Al}((i-\text{Bu})_3] \) promoted the rearrangement of enol-acetal 1.23 and an intramolecular Aldol-type addition to oxocarbonium ion 1.24 to furnish tetrahydropyranone 1.25. However, the reaction sequence did not yield ketone 1.25 but instead underwent a subsequent nonstereoselective Meerwein-Pondorf-Verley reduction, to give rise to tetrahydropyranol 1.26 as final product. Although this method held promise for the construction of a variety of tetrahydropyran moieties, application in the synthesis of complex natural products was hindered due to the formation of the tetrahydropyranol 1.26, often as a racemic mixture depending on the specific substrate. Further studies were required to achieve stereochemical control at the carbonyl center in unsymmetrical systems for efficient
The synthesis of complex molecules.

Scheme 1.6. Petasis’ Synthesis of Tetrahydropyranol

In the late 1990s, Smith and co-workers recognized the considerable promise of this rearrangement *vis-à-vis* the construction of architecturally complex natural products, and thus designed a three step Petasis-Ferrier union/rearrangement protocol to construct cis-2,6-disubstituted tetrahydropyran natural product fragments in a highly stereocontrolled fashion (Scheme 1.7). To this end, bis-silylation of a chiral non-racemic β-hydroxy acid (1.27) with HMDS, followed by the addition of an aldehyde (1.28) and a catalytic amount of TMSOTf, led to the union product dioxanone (1.29). Subsequent olefination utilizing either the Tebbe or Petasis protocol, resulted in the formation of an enol-acetal (1.30). Lewis acid-promoted rearrangement then furnished the desired cis-2,6-disubstituted tetrahydropyranone (1.32) via ring opening, bond rotation and ring closure. Further chemical modification of tetrahydropyranone (1.32) could then yield other nonracemic pyran analogues (i.e., tetrahydropyran, tetrahydropyranol and methylene-tetrahydropyan), which comprise important constructs in some natural product targets.
Scheme 1.7. The Smith 3 Step Protocol of Petasis-Ferrier Union/Rearrangement

The Smith three step protocol, which was designed and developed for application in natural product total synthesis, has become a commonly utilized Petasis-Ferrier union/rearrangement protocol and has proven crucial in a number of the successful total syntheses achieved over the years by the Smith group. Examples include (+)-phorboxazole A, (+)-zampanolide, (+)-dactylole, (+)-spongistatins 1 and 2, (−)-kendomycin, (−)-clavosolide A and (−)-okilactomycin (vide infra).\(^9\)

1.3.2. Application of the Petasis-Ferrier Union/Rearrangement in Natural Product Total Synthesis

The Petasis-Ferrier union/rearrangement protocol, specifically the Smith three step cascade, has gradually become an established tactic in the Smith group for natural product total synthesis.

The architecturally complex marine natural product (+)-phorboxazole A (1.33) was the first target in which the Petasis-Ferrier union/rearrangement protocol was utilized by the Smith laboratory.\(^{18,19}\) Two highly functionalized 2,6-cis-tetrahydropyran fragments
were constructed using this method. Importantly, the practicality of this synthesis established the utility of this three step tactic (Scheme 1.8).

During a model study for the synthesis of tetrahydropyranone 1.35, a screen involving a number of Lewis acids was carried out, culminating in the identification of Me₂AlCl as the most appropriate promoter. Use of Me₂AlCl led to the highest yield and importantly avoided the troublesome subsequent reduction that was incurred with the use of the originally used reagent Al(i-Bu)₃ employed by Petasis. Following the experience gained from this model study, synthetic efforts toward tetrahydropyranone 1.35 were undertaken. Unfortunately, initial attempts to carry out the rearrangement employing enol-acetal 1.39 did not result in the formation of any of the desired product 1.35, due to strong chelation between the aluminum and oxazole nitrogen. Therefore a second-generation Petasis-Ferrier rearrangement precursor enol-acetal 1.38 was constructed by exchange of the β-hydroxy acid and aldehyde coupling partners. Gratifyingly, rearrangement of new precursor 1.38 led to the desired product (1.35) in excellent yield (Scheme 1.7).
Encouraged by the first successful preparation of a natural product fragment utilizing the Petasis-Ferrier union/rearrangement protocol, focus turned to the synthesis of the cis-disubstituted tetrahydropyran fragment (1.34) of (+)-phorboxazole A (1.33) (Scheme 1.8). The challenge of this synthesis was the need to control formation of two stereocenters at C23 and C25, only one of which could be pre-installed on the union precursor. To solve this problem, an E/Z mixture of olefin 1.43 was constructed. Pleasingly, subjection of the mixture of isomers (1.43) to Me₂AlCl led to a single diastereomer (1.34) in excellent yield. This transformation was viewed as a divergent-convergent event.
During the second-generation synthetic study toward (+)-phorboxazole A (1.33), the three-step protocol underwent further development.\textsuperscript{22,23,24} In particular, by use of a more concentrated solution of the Petasis reagent and addition of ethyl pivalate, the reaction time of the Petasis olefination was significantly reduced, thus minimizing the undesired [2+2] side-reaction between the enol-acetal and excess Petasis reagent. Another undesirable reaction had also been observed during the large-scale preparation of fragment 1.35, whereby the Lewis acidity of the \(\text{Me}_2\text{AlCl}\) catalyzed the removal of the primary PMB group. This issue could be easily overcome by the addition of \(\text{Cs}_2\text{CO}_3\). These optimizations permitted the multi-gram synthesis of cis-2,6-tetrahydropyran moieties.

Construction of a common 2,6-cis-disubstituted tetrahydropyran fragment (1.46) for the natural products (+)-zampanolide (1.44) and (+)-dactylolide (1.45) comprised the Smith group’s next encounter with the Petasis-Ferrier union/rearrangement (Scheme 1.9).\textsuperscript{25,26,27} The successful union reaction between \(\beta\)-hydroxy acid 1.47 and \(\alpha,\beta\) unsaturated aldehyde 1.48 highlighted the important role of TfOH. This acid significantly improved the yield, particularly for larger scale preparation. Presumably, on small scale a trace amount of water generated TfOH in situ from TMSOTf, greatly facilitating the formation of the dioxanone. In the end, the rearrangement of enol-acetal 1.50 led to the desired product 1.46 in 59% yield, together with 12% of the trans isomer, the formation of which is likely due to the lack of steric hinderance, which destabilized the 1,3-diaxial interaction in the chair-like transition state (transition states shown in Scheme 1.9).
Scheme 1.9. Petasis-Ferrier Union/Rearrangement in the Total Synthesis of (+)-Zampanolide

The Petasis-Ferrier union/rearrangement also played an important role in the Smith total synthesis of the complex natural products spongistatin 1 and 2 (1.51 and 1.52, respectively) (Scheme 1.10). The densely substituted tetrahydropyran 1.53 was constructed via a Petasis-Ferrier union/rearrangement, followed by the diastereoselective installation of the C(42) hydroxyl group and base epimerization of C(40) methyl group. This successful sequence revealed the potential for the installation of additional stereocenters on the tetrahydropyran ring after the union/rearrangement. Equally important, the robust nature of the Petasis-Ferrier union/rearrangement reaction was exemplified by the large-scale synthesis of intermediate 1.53 (>15 g).
Scheme 1.10. Petasis-Ferrier Union/Rearrangement in the Total Synthesis of Spongistatins

One of the highlights of Smith’s next total synthesis, (−)-kendomycin (1.57), was the construction of the highly sterically encumbered tetrahydropyran fragment 1.58 utilizing a Petasis-Ferrier union/rearrangement.\textsuperscript{29,30} Although the TMSOTf promoted union of β-hydroxy acid 1.59 with the sterically encumbered aldehyde 1.60 proceeded only in modest yield (59%), the Kurihara condensation protocol,\textsuperscript{31} involving the use of TMSOTf and i-PrOTMS, resulted in the formation of the desired intermediate (1.61) in the considerably improved yield of 77%. After the union/rearrangement procedure, subsequent methylation and diastereoselective reduction furnished the fully substituted tetrahydropyranol 1.58 (Scheme 1.11).
Scheme 1.11. Petasis-Ferrier Union/Rearrangement in the Total Synthesis of (-)-Kendomycin

Smith’s synthesis of the natural product (-)-clavosolide A (1.63) next demonstrated that the Petasis-Ferrier union/rearrangement tactic could be utilized in the presence of acid-labile functional groups, such as a cyclopropylcarbinyl system (Scheme 1.12). The union of β-hydroxy acid 1.65 and cyclopropyl aldehyde 1.66 furnished dioxanone 1.67 in 94% yield. The addition of 2,6-di-tert-butyl-4-methylpyridine (DtBMP) was required to prevent decomposition of the acid sensitive product. Equally important, during the rearrangement step, the rapid addition and quenching of the Lewis acid proved crucial for construction of the tetrahydropyranone fragment 1.64.
Scheme 1.12. Petasis-Ferrier Union/Rearrangement in the total Synthesis of (−)-Clavosolide A

Smith’s total synthesis of the natural product (−)-okilactomycin (1.68) next demonstrated that acetals could also be employed as a precursor for the Petasis-Ferrier union/rearrangement (Scheme 1.13). To this end, treatment of a mixture of β-hydroxy acid 1.70 and dimethyl acetal 1.71 under the Kurihara union conditions led to the desired dioxanone 1.72. Olefination and rearrangement then furnished the desired product (1.69). This sequence also demonstrated that the union/rearrangement protocol could be carried out in the presence of a potentially labile alkyl bromide.

Scheme 1.13. Petasis-Ferrier Union/Rearrangement in the Total Synthesis of (−)-Okilactomycin
In summary, the Smith three-step Petasis-Ferrier union/rearrangement protocol has now been firmly established and well developed during numerous total synthetic ventures. The protocol has demonstrated versatility, allowing the use of acid, base and water sensitive substrates. The ability to interchange the β-hydroxy acid and aldehyde union partners has also increased the utility of this method. Moreover, construction of sterically encumbered fragments, including of fully substituted tetrahydropyrans, has further illustrated the robustness of the union/rearrangement protocol. Stereocenters have also been installed on all five positions of the tetrahydropyan ring with high stereochemical fidelity before, during and after the implementation of the union/rearrangement protocol. Several additives have also been shown to improve significantly the efficiency of the reaction. In short, this method has been demonstrated as a powerful synthetic tool for the construction of complex natural products.

1.3.3. Late-Stage Large-Fragment Petasis Ferrier Union/Rearrangements

Although the efficiency of Petasis-Ferrier union/rearrangement protocol has now been well established, the protocol has only been used for the construction of small and medium size building blocks (Figure 1.2). The construction of a late stage intermediate, such as the entire carbon skeleton of a natural product, utilizing the Petasis-Ferrier union/rearrangement tactic employing two large fragments, has not until this thesis been explored. The union and rearrangement of large fragments at the late stage of a total synthesis would not only reveal the further versatility and robustness of this synthetic method, by illustrating the tolerance of the reaction conditions to steric hinderance and multiple functional groups, but would also demonstrate a high degree of convergence,
which is essential to many successful synthetic plans. We therefore began a project exploring a late-stage large-fragment Petasis-Ferrier union/rearrangement protocol in the context of the architecturally complex natural product enigmazole A (1.1), an excellent target to showcase the extended utility of this method.

Figure 1.2. Petasis-Ferrier Union/Rearrangement Utilized in the Total Syntheses of Natural Products

For enigmazole A (1.1) (Scheme 1.14) we envisioned the required macrolactonization precursor (1.70) would possess a tetrahydropyranone core embedded in the center of a long chain. We reasoned that this intermediate could arise from a late-stage Petasis-Ferrier union/rearrangement protocol. During this process, we envisioned that excellent diastereomeric selectivity would be obtained, thus demonstrating another advantage of employing large fragments in the union/rearrangement. Previously, during the total synthesis of (+)-phorboxazole A\(^{18}\) and (+)-zampanolide\(^{25}\), the Smith group
revealed that the smaller substituents at the 2,6 positions of tetrahydropyran could
destabilize the 1,3-diaxial interaction in the chair-like rearrangement transition state, thus
leading to the undesired trans-isomer. We reasoned that two large substituents on the
tetrahydropyran ring of intermediate 1.70, derived from large fragments 1.71 and 1.72
would in contrast ensure a significant energy difference between the favored and
disfavored Petasis-Ferrier rearrangement intermediates, thus leading to satisfactory
diastereoselective control.

Scheme 1.14. Petasis-Ferrier union/rearrangement on the platform of enigmazole A

A detailed analysis of our retrosynthetic plan toward enigmazole A (1.1),
utilizing late-stage large-fragment Petasis-Ferrier rearrangement, as well as the resulting
total synthesis, will be discussed in greater detail in Chapter 2.

1.4. Anion Relay Chemistry- A Successful Tactic for Complex Molecule Total
Synthesis

In addition to the cornerstone late-stage large-fragment Petasis-Ferrier
union/rearrangement protocol, we envisioned that Anion Relay Chemistry (ARC),
another successful tactic for complex molecule total synthesis developed in the Smith
group, could be applied in the total synthesis of (−)-enigmazole A (1.1).
The concept of Anion Relay Chemistry (ARC) was initially introduced as Smith’s multicomponent dithiane linchpin coupling reaction in the 1990s (Scheme 1.15). Treatment of dithiane linchpin 1.73 with n-BuLi or t-BuLi followed by the addition of epoxide 1.74 leads to the lithium alkoxide 1.75. The [1,4]-Brook rearrangement could then be triggered in a controlled manner by altering the solvent polarity with the addition of HMPA or DMPU. Simultaneous addition of epoxide 1.76 furnishes the desired tri-component adduct 1.78 in a one-pot and stereocontrolled manner.

![Scheme 1.15. Smith’s Multicomponent Dithiane Linchpin Coupling Reaction](image)

In the following two decades, two main reaction classes of Anion Relay Chemistry, namely Type I and Type II, have been established during ongoing studies in the Smith group, thus enhancing the efficiency, versatility and applicability of the ARC tactic (Scheme 1.16). Type I ARC involves the nucleophilic addition of an anionic linchpin (1.79) to an electrophile (1.80), resulting in the formation of anion 1.81. The negative charge is then transferred back to the original nucleophilic locus of the linchpin.
via a Brook rearrangement. Subsequent nucleophilic addition to a second electrophile then furnishes the desired product 1.82. In Type II ARC the bifunctional linchpin 1.83 serves as both an electrophile and a nucleophile. The anion resulting from nucleophilic addition of the initiating nucleophile to the linchpin (1.83) can be transferred across space to the new carbon center, stabilized by an anion stabilizing group (ASG) on the linchpin. The addition of an electrophile then furnishes the desired product 1.85. Both Type I and Type II ARC has proven crucial in a number of the successful total syntheses achieved to date by the Smith group.\textsuperscript{10}

\begin{center}
\includegraphics[width=\textwidth]{scheme16.png}
\end{center}

**Scheme 1.16.** Type I and Type II Anion Relay Chemistry

Recognizing the considerable efficiency of Anion Relay Chemistry for complex molecule synthesis in a highly stereocontrolled manner, we envisioned the use of a Type I ARC would prove valuable for the construction of the eastern hemisphere of (−)-enigmazole A. The resulting synthetic study will be discussed in greater detail in Chapter 2.1 and Chapter 2.3.
1.5 References Relevant to Chapter 1


32. Smith, A. B., III; Simov, V. Org. Lett. 2006, 8, 3315


Chapter 2. Total Synthesis of (−)-Enigmazole A

2.1. Retrosynthetic Analysis of (−)-Enigmazole A

2.1.1. A First Generation Retrosynthetic Analysis and Synthetic Study

The first generation retrosynthetic plan for (−)-enigmazole A envisioned disconnection of the macroclide to reveal carboxylic acid 2.2 (Scheme 2.1). Carboxylic acid 2.2 in turn would arise from olefin 2.3 via a four-step sequence. A late-stage large-fragment Petasis-Ferrier union/rearrangement (Chapter 1.3) would then be utilized to unite the eastern and western hemispheres (2.5 and 2.4). Construction of the eastern hemisphere 2.5 was envisioned to be achieved by the union of aldehyde 2.7 and oxazole 2.6, while the western hemisphere 2.4 would in turn be constructed from commercially available (-)-Roche’s ester. Our initial strategy included functionalization of the C(16-17) double bond after formation of the tetrahydropyran core, rather than before, given that the C(17) hydroxyl group might interfere the Petasis-Ferrier union tactic by undesired interactions with the western hemisphere aldehyde in acidic conditions.
Scheme 2.1. A First Generation Retrosynthetic Analysis of (−)-Enigmazole A

Unfortunately, during the synthetic study based on the first retrosynthetic plan, Smith and colleagues observed that the C(16-17) double bond was extremely stable and very difficult to functionalize. In a model study, Dr. Mariya Kozytsaka in our research group demonstrated that olefin 2.8 would not succumb to the desired transformation under various conditions, including directed hydrosilylation, hydroboration, iodocarbonation, as well as directed epoxidation (Scheme 2.2). We believe that this lack of reactivity is due to the stability of the C(16-22) conjugation.

Scheme 2.2. Functionalization of C(16-17) double bond
2.1.2. A Second Generation Retrosynthetic Analysis and Synthetic Study

We therefore launched a second generation retrosynthetic plan, whereby the C(17) hydroxyl group would be installed before formation of the conjugated system (Scheme 2.3). Assembly of the eastern hemisphere precursor, 1,5-dihydroxydithiane 2.13, was envisioned to arise via the Type I Anion Relay Chemistry (ARC) protocol developed in our group (Chapter 1.4).²

![Scheme 2.3. A Second Generation Retrosynthetic Analysis of (-)-Enigmazole A](image)

After the construction of all three fragments, Dr. Mariya Kozytsaka explored the Type I ARC protocol (Scheme 2.4). Unfortunately, the one-pot transformation to generate dithiane 2.13 proved unsuccessful. The major product under these conditions was dithiane 2.17, which resulted from the addition of anionic TBS-dithiane 2.14 to epoxide 2.15 followed by Brook rearrangement and anion protonation. The use of a stronger base, such as t-BuLi, or treating the epoxide 2.16 with the anion of dithiane
2.17 still did not lead to the desired product. Dr. Kozytsaka next focused on identifying potential proton source that could quench the dithiane anion prior to the coupling with epoxide 2.16. Interestingly, treatment of the reaction mixture of dithiane 2.17 and n-BuLi with deuterated methanol gave only the deuterated oxazole 2.18, with no deuterium-incorporation in the dithiane species. This observation suggested that Type I ARC would be difficult to employ in the presence of an unprotected oxazole species without further optimization.

**Scheme 2.4. Anion Relay Chemistry with Oxazole Moieties**

### 2.1.3. A Third Generation Retrosynthetic Analysis

We therefore designed a third generation retrosynthetic plan, whereby construction of epoxide 2.24 would again be carried out using Type I ARC before incorporation of the oxazole species (Scheme 2.5). Petasis-Ferrier union/rearrangement would then unite the eastern hemisphere 2.22 with the western hemisphere 2.4 at a late stage to furnish the methylene tetrahydropyran 2.21, which could be used to direct the macrolactonization of advanced intermediate 2.20 in two to three steps. Western
hemisphere 2.4 in turn could be constructed from commercially available (-)-Roche’s ester, while the eastern hemisphere 2.22 would be elaborated via a process highlighting a dithiane-epoxide coupling protocol. Construction of the prerequisite oxazolyl dithiane 2.23 would employ a procedure including a Negishi union, while the epoxide 2.24 would derive via a Type I ARC protocol.

Assuming success, the late-stage large-fragment Petasis-Ferrier union/rearrangement protocol would represent the cornerstone of the synthesis, fashioning the entire carbon skeleton of (-)-enigmazole A (2.21) in a single cascade sequence.

Scheme 2.5. A Third Generation Retrosynthetic Analysis of (-)-Enigmazole A
2.2. Construction of the C(17-25) Oxazolyl Dithiane (+)-2.23 via Negishi Cross Coupling

Figure 2.1. Structure of C(17-25) Oxazoyl Dithiane (+)-2.23

We envisioned the synthesis of the C(17-25) oxazolyl dithiane (+)-2.23, a common intermediate potentially for both the enigmazole A and enigmazole B total syntheses, two synthetic projects undertaken by the Smith group, would involve a palladium-mediated Negishi cross-coupling. The synthesis of one of the coupling partners, Z-iodoalkene (+)-2.29, began with commercially available, inexpensive racemic 3-butyn-2-ol (±)-2.25 (Scheme 2.6). Although enantiopure (R)-3-butyn-2-ol (+)-2.25 was also commercially available, the enzymatic resolution of racemic TMS-alkyne (±)-2.26 was a more economically viable alternative. To this end, deprotonation of racemic 2.25 with ethylmagnesium bromide, followed by the addition of TMSCl, and an acidic workup furnished TMS-alkyne (±)-2.26. Using the less expensive Amano Lipase from Pseudomonas fluorescens and hexanes, instead of Amano Lipase AK and pentane as reported in the literature, we achieved the same yield and enatioselectivity in the
enzymatic resolution. The resulting enantiopure (+)-2.27 was then treated with potassium carbonate (K₂CO₃) in diethanolamine to furnish (R)-3-butyn-2-ol (+)-2.25.⁷ According to literature precedent, iodo alcohol (+)-2.28 was next constructed as the single Z-isomer via iodomethylation.⁸ Subsequent conversion of the alcohol to the corresponding methyl ether (+)-2.29 was achieved with sodium hydride (NaH), methyl iodide and 15-crown-5. Although a number of the intermediates (2.25, 2.27, 2.28 and 2.29) proved highly volatile in this sequence, carrying out the sequence with considerable care led to high yields in all five steps, permitting the preparation of multi-gram quantities of (+)-2.29.

Scheme 2.6. Synthesis of Z-iodoalkene (+)-2.29

The second coupling partner, oxazole 2.33, was also prepared according to literature precedent (Scheme 2.7).⁸ Condensation between urea (2.30) and ethyl bromopyruvate (2.31), followed by diazotiazation and chloride displacement generated the desired ester 2.33. We discovered that the recrystallization of oxazole 2.33 proved much more efficient than the flash column chromatography as described in the literature.
We next envisioned that a Negishi cross-coupling could be employed as the key reaction for the formation of the C(17-25) oxazolyl dithiane (+)-2.23 (Scheme 2.8). Dr. Anton Khartulyari and Dr. Alia Orbin in the Smith laboratory contributed significantly to this procedure during the enigmazole B synthesis project.\(^3\) Although Molinski and co-workers synthesized the same compound, (+)-2.34, utilizing a Negishi cross-coupling in their total synthesis of enigmazole A, we independently had designed the Negishi cross-coupling reaction with different coupling partners in 2008 before their publication.\(^9\) To this end, lithium-halogen exchange was achieved by treatment of iodide (+)-2.29 with \(t\)-BuLi; the transmetallation gave a vinylzinc species, which was then coupled with oxazolyl chloride 2.33 in the presence of a catalytic amount of tetrakis (triphenylphosphine) palladium to furnish oxazolyl ester (+)-2.34 in 80% yield. The resulting ester (+)-2.34 in turn was reduced with DIBAL-H to provide aldehyde (+)-2.35. Conversion of the aldehyde (+)-2.35 to the corresponding dithiane (+)-2.23 was then achieved with BF\(_3\).OEt\(_2\) and 1,3-propanedithiol. We found afterwards that dithiane (+)-2.23 was not stable upon storage, presumably due to the presence of residual BF\(_3\).OEt\(_2\). Washing the reaction mixture of (+)-2.23 four to five times with 3 M aqueous NaOH solution circumvented this problem.
Scheme 2.8. Construction of C(17-25) Oxazolyl Dithiane (+)-2.23

In summary, after initial development most of the synthetic procedures utilized for the synthesis of the C(17-25) oxazolyl dithiane (+)-2.23 was optimized, permitting in good yield the large scale (> 5g) and a highly economically synthesis. In the end, more than 15 g of (+)-2.23 was prepared, which was used in both the enigmazole A and B projects.

2.3. Construction of the C(9-16) Epoxide (-)-2.24

2.3.1. Construction of the C(9-16) Epoxide (-)-2.24 via Type I Anion Relay Chemistry (ARC)

Dr. Mariya Kozytsaka and I designed a route for the synthesis of the C(9-16) epoxide (-)-2.24 utilizing Type I anion relay chemistry (ARC) (Chapter 1.4). The
requisite epoxides ($-2.36$) and ($-2.41$) were constructed via either Jacobsen kinetic resolution$^{10}$ or from enantiopure commercially available starting materials (Scheme 2.9).

Scheme 2.9. Synthesis of Requisite Epoxides for Type I ARC

The three component ARC tactic was then applied, using lithiated TBS dithiane and the enantiopure epoxides ($-2.36$) and ($-2.41$) (Scheme 2.10). The desired product, dithiane ($-2.42$) was formed in high yield after careful optimization. The dithiane moiety of ($-2.42$), was in turn removed under reductive conditions to furnish alcohol ($-2.43$), and the alcohol was submitted to Raney nickel conditions to remove the PMB protecting group to furnish diol ($-2.44$) in high yield. When attempts were made to reduce directly ($-2.42$) to ($-2.44$), only a small amount of desired product ($-2.44$) was observed, presumably due to catalyst poisoning by dithiol. The large scale preparation of alcohol ($-2.43$) (>1 g scale) also proved problematic due to the same poisoning effect. In the end, epoxide ($-2.24$) was generated in one step from diol ($-2.44$) following the Fraser-Reid protocol.$^{11}$
In summary, epoxide \((-\,2.24\)) was constructed utilizing Type I ARC, affording the desired intermediate as a single diastereomer in high yield (74.1% over 4 steps). The limitation of this route, however, was the inability to carry out the reductive dithiane removal reaction on large scale.

### 2.3.2. Construction of the C(9-16) Epoxide \((-\,2.24\)) via Sharpless Dihydroxylation

Another synthetic route to the C(9-16) epoxide \((-\,2.24\)) was designed beginning with epoxide \((-\,2.41\)) (Scheme 2.11). To this end, treatment of \((-\,2.41\)) with but-3-en-1-yl magnesium bromide solution in the presence of a catalytic amount of copper(I) catalyst furnished the desired product \((+\,2.45\)). A screen of copper(I) sources led to identification of the most efficient catalyst, copper(I) iodide, which led to the formation of \((+\,2.45\)) in excellent yield. Protection of the secondary alcohol with TBSOTf then furnished \((-\,2.46\)) in 92.4% yield. Subsequent Sharpless asymmetric dihydroxylation provided diol \((-\,2.44\)) in 91% yield. Further studies, however, revealed that the diastereoselectivity of the dihydroxylation reaction was not higher than 2.5:1. Changing solvents, catalysts and temperatures, unfortunately, did not affect the selectivity. Moreover, the two diastereomers could not be separated using either normal phase silica gel flash
chromatography or reverse phase HPLC. In the end, the requisite epoxide (−)-2.24, together with the inseparable diastereomer (about 30%), was generated in one step from diol (−)-2.44 following Fraser-Reid protocol.\textsuperscript{11}

In summary, the synthetic route towards the C(9-16) epoxide (−)-2.24 utilizing a copper-assisted Grignard epoxide opening, followed by Sharpless dihydroxylation, provided the desired product in extremely high yield (78.2% over four steps) on large scale (> 4 g). However, the major shortcoming of this route was the formation of the inseparable, undesired diastereomer during the Sharpless dihydroxylation (d.r. = 2.5:1 to 2:1).

2.3.3. The Two Synthetic Tactics to Construct the C(9-16) Epoxide (−)-2.24

To construct C(9-16) Epoxide (−)-2.24, we had designed and validated two routes utilizing totally different synthetic methods. Both routes could be carried out efficiently and in high yield (ARC route: 74.1% for 4 steps; dihydroxylation route: 78.2% over 4 steps).

Besides the high yield achieved during the ARC route, the strategy permitted formation of a diastereomerically pure compound; the only limitation however was the
inability to carry out the reductive dithiane removal on large scale (> 1g).

The dihydroxylation route, which could be carried out quickly (3 days) and on large scale (>4 g), provided access to the desired product in an economic fashion, albeit as an inseparable mixture of diastereomers (2.5:1). This mixture of diastereomers could not be separated by either silica flash chromatography or reverse phase HPLC over the next 15 steps (!), until the formation of the macrolides. Nonetheless this was a very valuable material that could be used to explore the subsequent 15-step sequence. In some cases, however, there were significant difficulties with the identification and characterization of the intermediates (Figure 2.3).

![Figure 2.3. Diastereomers Derived from Sharpless Dihydroxylation](image)

Recognizing the pros and cons for both routes, another route directed toward the C(9-16) epoxide (−)-2.24 was attempted, which combined the advantages of both the ARC route and the dihydroxylation routes (Scheme 2.12). The C(15) stereocenter was pre-installed from readily available, naturally abundant malic acid, which was transformed to the Grignard reagent 2.50 in 4 steps. Unfortunately, treatment of the epoxide (−)-2.38 with Grignard reagent 2.50 did not lead to the desired product 2.51 under various conditions. This route was thus abandoned.
Scheme 2.12. Synthetic Study towards C(9-16) Epoxide Starting from L-malic Acid

In conclusion, considering the enormous burden of carrying mixtures of inseparable diastereomers over 15 steps, the ARC route (Scheme 2.9) leading to the C(9-16) epoxide (-)-2.24 was mainly used in the total synthesis of enigmazole A albeit requiring many iterations on small scale (< 1 g). The Sharpless dihydroxylation route (Scheme 2.10), on the other hand, was used as a complementary method for fast reaction development.

2.4. Construction of C(9-25) Eastern Hemisphere (+)-2.22 via Dithiane-Epoxide Union

Figure 2.4. Structure of C(9-25) Eastern Hemisphere (+)-2.22
2.4.1. A First Generation Synthesis of the Eastern Hemisphere (+)-2.22

After the construction of dithiane (+)-2.23 and epoxide (−)-2.24 (Scheme 2.8 and 2.10), we turned to the elaboration of the eastern hemisphere starting with a dithiane-epoxide union tactic. This eight step, first generation procedure was designed by Dr. Mariya Kozytsaka and I (Scheme 2.13). Deprotonation of dithiane (+)-2.23 with n-BuLi generated the nucleophile, which after the addition of epoxide (−)-2.24 in a mixture of Et₂O and HMPA furnished the desired product dithiane (+)-2.52 in fair yield (40-60%), with recovery of the excess epoxide (−)-2.24. The mercury(II)-mediated hydrolysis of the dithiane then successfully removed the dithiane moiety of (+)-2.52 to furnish β-hydroxyketone (+)-2.53, which was next exposed to the Narasaka-Prasad reduction conditions to produce diol (+)-2.54 as a single diastereomer. The diol (+)-2.54 was then protected with p-methoxybenzaldehyde dimethyl acetate in the presence of a catalytic amount of CSA to provide PMP acetal (+)-2.55 in 80% yield.
Scheme 2.13. The First Generation Synthesis of Eastern Hemisphere (+)-2.22

Previous studies carried out during the Smith total synthesis of phorboxazole A had revealed that the oxazole moiety could form a strong complex with boron and aluminum Lewis acids.$^{15}$ We therefore hypothesized that the DIBAL-H reagent could reduce chemoselectively the benzylacetal functional group of (-)-2.55 to open the acetal C-O bond proximal to the oxazole. Treatment of (+)-2.55 with a DIBAL-H solution at -78 °C furnished the desired product (+)-2.56 in excellent yield (92%) with near perfect selectivity. To the best of our knowledge there is no precedent of a similar transformation aside from the work of Smith, whereby the neighboring nitrogen atom chemoselectively directs the reduction of a benzyl acetal.

HF-pyridine was then used to remove chemoselectively the primary TBS group over the secondary TBS group of alcohol (+)-2.56 to furnish diol (+)-2.57 in 80% yield. The subsequent chemoselective oxidation proved problematic. Due to the stability of the C(17-22) conjugated system, which had been observed in our earlier endeavor with the first retrosynthetic analysis (Scheme 2.2), the hydroxyl group at C17 proved very prone to undergo oxidation. Thus the chemoselective oxidation of the primary alcohol over the C17 alcohol using TEMPO, albeit viable, in some cases provided irreproducible (10-60%) yields. Notwithstanding this problem, we were able to remove the remaining secondary TBS group with hydrochloric acid in ethanol, thus furnishing the desired eastern hemisphere (+)-2.22 in 85% yield for the final step.

In summary, eastern hemisphere (+)-2.22 was constructed, albeit with our first generation procedure employing the dithiane-epoxide protocol proceeded in only 1.1% to 6.4% yield for the eight steps. Thus reactions with fair to low yield, or with
irreproducible problems, including of dithiane-epoxide coupling and TEMPO oxidation, required revision and/or optimization.

2.4.2. Dithiane-Epoxide Union Studies

Although we had demonstrated that the dithiane anion was difficult to generate in the presence of an oxazole moiety in our earlier synthetic endeavors (e.g., dithiane 2.17 in Scheme 2.4), Dr. Alia Orbin revealed that dithiane (+)-2.23 was an exception in her studies directed toward the total synthesis of enigmazole B, the structure of which possesses the same conjugated oxazole side chain as enigmazole A. In particular, treatment of dithiane (+)-2.23 with n-BuLi provided the dithiane anion which could be readily attacked with a variety of alkyl iodides to furnish dithiane 2.58 in 40%-70% yield (Scheme 2.14). The more ready deprotonation of the dithiane (+)-2.23 could be due to a stabilizing effect of the anion via the C(17-22) conjugated system.

![Scheme 2.14. Nucleophilic Addition Utilizing Dithiane (+)-2.23](image)

We therefore utilized the dithiane (+)-2.23 in our first generation synthesis of the eastern hemisphere (+)-2.22. However, the yield of the dithiane-epoxide coupling was not satisfactory (40-60%). Analysis of the reaction by-products revealed the formation of diastereomer 2.59 and dithiane 2.60. Formation of such products, strongly suggests the generation of the dianion, whereby deprotonation had occurred at both C17 and C23 (Table 2.1)
Observing the unusually high reactivity of dithiane (++)-2.23, again presumably due to the C(17-22) conjugated system, brought into question the necessity for the polar solvent HMPA, and suggested that perhaps greater success could be achieved by altering the number of equivalents of n-BuLi and epoxide (--)2.24. As a result, a screen, using different conditions was performed to achieve higher yield (Table 2.1).

During the screen, although HMPA is commonly used in dithiane-epoxide union reactions to increase the reactivity, we found that the presence of HMPA only led to more

<table>
<thead>
<tr>
<th>entry</th>
<th>result: (++)-2.52</th>
<th>conditions</th>
<th>2.59</th>
<th>2.60</th>
<th>2.24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.5: 1.5</td>
<td>Et₂O/HMPA, -78 °C, 2 h</td>
<td>48%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.5: 1.5</td>
<td>Et₂O, -78 °C, 2 h</td>
<td>60%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.5: 1.5</td>
<td>THF, -78 °C, 2 h</td>
<td>32%</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.5: 1.5</td>
<td>Et₂O, -78 °C - 0 °C, 2 h</td>
<td>45%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>5</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 2: 2</td>
<td>Et₂O, -78 °C, 2 h</td>
<td>30%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>6</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1: 1.5</td>
<td>Et₂O, -78 °C, 2 h</td>
<td>42%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1: 1.5</td>
<td>Et₂O, -78 °C - 0 °C, 2 h</td>
<td>51%</td>
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<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.15: 1.5</td>
<td>Et₂O, -78 °C - 0 °C, 2 h</td>
<td>73%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>9</td>
<td>(+)-2.23: n-BuLi: (--)2.24 = 1: 1.15: 1.0</td>
<td>Et₂O, -78 °C - 0 °C, 2 h</td>
<td>77%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2.1. the Dithiane-Epoxide Coupling**

Observe the unusually high reactivity of dithiane (++)-2.23, again presumably due to the C(17-22) conjugated system, brought into question the necessity for the polar solvent HMPA, and suggested that perhaps greater success could be achieved by altering the number of equivalents of n-BuLi and epoxide (--)2.24. As a result, a screen, using different conditions was performed to achieve higher yield (Table 2.1).
by-products in the case of dithiane (+)-2.23, while similar side reactions were also observed when more than 1.5 equivalents of n-BuLi was used. On the other hand, the use of less than 1.15 equivalent of n-BuLi induced the formation of an inseparable mixture due to incomplete reaction. Pleasingly, we subsequently discovered that the best conditions (entry 9, Table 2.1) led to the desired product in 77% yield. Although under these conditions some complex intractable by-products with high polarity were found, by-products 2.59 and 2.60 were not observed. Thus, the conditions of entry 9 in Table 2.1 were employed to advance material to (+)-2.52.

2.4.3. Chemoselective Oxidation and Reduction Studies

In addition to the dithiane-epoxide union, optimization of the chemoselective TEMPO oxidation (Scheme 2.15) also proved to be very important. Again, due to the C(17-22) conjugated system, differentiation between the C9 primary hydroxyl and the C17 oxazolyl hydroxyl under oxidative conditions was difficult. Moreover, the similar retention on TLC of the starting material (+)-2.57 and the desired product (+)-2.61 further complicated optimization. As a result, the reaction results were inconsistent because of either over-oxidation, which led either to by-product 2.62, or to incomplete reaction.

![Scheme 2.15. Chemoselective TEMPO Oxidation](image)

Initially, a stepwise procedure was implemented, utilizing a TEMPO/BAIB (bisacetoxyiodobenzene) oxidation to furnish aldehyde 2.63, followed by a Pinnick
oxidation to the corresponding acid (Scheme 2.16). Formation of aldehyde 2.63 could be easily observed on TLC, which led to a more consistent yield. However, the efficiency of this procedure remained unsatisfactory, due both to the inclusion of an additional step and the formation of the unstable aldehyde 2.63. Thus further revision was still necessary.

Scheme 2.16. Stepwise TEMPO Oxidation

The most straightforward solution for this differentiation problem was to mask the C17 hydroxyl group. However, the inclusion of further protection/deprotection steps would lead to inefficiency. Given that the C19 hydroxyl group was just released during the PMP ring opening reaction, two steps before the problematic chemoselective oxidation, we realized that this problem could be solved by alteration of the reaction sequence. The oxidation was thus carried out prior to the PMP ring opening reaction (Scheme 2.17). After chemoselective removal of the primary TBS group of (-)-2.55, the resulting alcohol (-)-2.64 was submitted to the TEMPO oxidation. Now there was no selectivity problem for the oxidation; thus carboxylic acid (+)-2.65 was obtained in excellent yield (95%). Focus was then turned to the chemoselective PMP ring opening reaction.

Scheme 2.17. Oxidation Prior to the PMP Ring Opening

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In our first generation synthesis, we disclosed the chemoselective PMP ring opening reaction, whereby treatment of (+)-2.55 with a DIBAL-H solution furnished the desired product (+)-2.56 (Scheme 2.13). This selective reaction would become more challenging after the formation of the carboxylic acid because DIBAL-H can also potentially reduce the carboxylic acid moiety. Pleasingly however, treatment of (+)-2.65 with a DIBAL-H solution in hexanes at -78 °C furnished the desired product (+)-2.61 in surprisingly high yield (93%). This result represented completion of our optimization of the route to (+)-2.61 by altering the sequence of the oxidation and reduction steps (Scheme 2.16). In the end, deprotection of TBS group of (+)-2.61 led to the eastern hemisphere (+)-2.22.

The intermediates involved in this chemoselective reduction is outlined in Scheme 2.18. The first equivalent of DIBAL-H would react with the carboxylic acid proton, while the second would complex with the oxazole nitrogen to form a reactive five-member ring intermediate together with the neighboring acetal oxygen. Due to the potential chelation between the nitrogen or oxygen in the five member ring, we reason that the reduction is directed selectively toward the neighboring C-O bond of the acetal. Presumably the low temperature of the reaction prevents further reduction of the carboxylic acid. Aqueous work-up in turn then leads to the desired product (+)-2.61. This reaction sequence revealed the strong potential of DIBAL-H as a chemoselective reagent.
2.4.4. A Second Generation Synthesis of the Eastern Hemisphere (+)-2.22

The optimizations carried out for the dithiane-epoxide union, as well as the chemoselective oxidation and reduction, provided the framework for a second generation synthesis of eastern hemisphere (+)-2.22 (Scheme 2.21). Utilizing the conditions found in the screen revealed in Chapter 2.4.2, the union of dithiane (+)-2.23 with epoxide (-)-2.24 furnished the desired product (+)-2.52 in 77% yield (Scheme 2.19). Compared with the traditional mercury(II)-mediated hydrolysis that was utilized in our first generation synthesis, a new environmentally friendly protocol disclosed in 2013, employing hydrogen peroxide catalyzed by Fe(acac)$_3$ and sodium iodide, was applied to remove the dithiane moiety leading to the ketone (+)-2.53 in higher yield (75 vs. 63%).$^{18}$ Subsequent exposure of ketone (+)-2.53 to the Narasaka-Prasad reduction then provided diol (+)-2.54 as a single diastereomer in excellent yield (95%).$^{14}$

Protection of diol (+)-2.54 with \( p \)-methoxybenzaldehyde dimethyl acetate in the presence of CSA next provided the desired PMP acetal \((-)-2.55\) in 80\% yield (Scheme 2.20). Despite the good yield, about 10\% of alcohol \((-)-2.64\), which was the desired product for the next step, was also observed. This result presented the possibility of achieving the two steps in one-pot. To this end, treatment of the mixture resulting from the PMP protection with an additional 10\% of CSA, followed by stirring a further 5 hours in the same solvent, led to the desired product \((+)-2.64\) however in only 23\% together with multiple by-products. Similar results were obtained utilizing the HF-pyridine complex. Pleasingly however, upon exposure of the mixture resulting from the PMP protection reaction to TBAF/HOAc without changing the solvent, the desired product \((-)-2.64\) was obtained now in very good yield (ca. 88\%, entry 3 in Scheme 2.19).
**Scheme 2.20.** One-pot Chemoselective TBS Group Removal

With a significantly improved route to alcohol \((-\)-2.64), oxidation employing TEMPO/NaClO/NaClO₂ resulted in the formation of carboxylic acid \((+)-2.65\) in excellent yield (Scheme 2.21). The subsequent chemoselective DIBAL-H reduction, which was discussed in detail in Chapter 2.4.3 for opening the acetonide, now furnished the desired alcohol \((+)-2.61\) in 93% yield with excellent selectivity. Finally, TBAF/AcOH cleanly removed the secondary TBS group on \((+)-2.61\) to furnish eastern hemisphere \((+)-2.22\) in 88% yield. Compared with the HCl/EtOH conditions employed previously, the neutral conditions avoided the undesired deprotection of the PMB group, thus leading to a more reproducible reaction.
In summary, the second-generation synthesis of eastern hemisphere (+)-2.22 furnished the desired product in 37.4% yield over the 7 steps. This procedure was one step shorter and proceeded in consistent yield, which was now 6 to 34 times higher than our first generation synthesis. Highlights of the second-generation synthesis include the carefully optimized dithiane-epoxide union, an efficient one-pot protection/deprotection reaction sequence, as well as an unprecedented tris-chemoselective DIBAL-H reduction reaction. Most importantly, the second generation synthesis provided (+)-2.22 on gram scale.
2.5. Construction of C(1-7, 26-27) Western Hemisphere (-)-2.4

With the eastern hemisphere (+)-2.22 now in hand, we turned to construction of the western hemisphere (-)-2.4, the synthesis of which at the outset appeared relatively straightforward (Scheme 2.22). Beginning with the commercially available (-)-R-Roche’s acid, TBDPS protection of hydroxyl group, followed by DIBAL-H reduction of the ester and iodination led to the desired iodide (-)-2.66 in 89% over 3 steps. Exposure of (-)-2.66 to the two-step Myers alkylation protocol employing pseudoephedrine as the chiral auxiliary provided alcohol (-)-2.68 as a single diastereomer in excellent yield (99% over two steps).19 Subsequent Parikh-Doering oxidation and Brown allylation then furnished olefin (-)-2.69 in excellent yield (91% over two steps), again as a single diastereomer.20,21 Having generated the requisite three stereogenic centers required for the western hemisphere (-)-2.4, the hydroxyl group in olefin (-)-2.69 was protected with TIPSOTf to furnish the requisite TIPS silyl ether (-)-2.70 in 91% yield. Finally, ozonolysis provided the western hemisphere (-)-2.4 in good yield (e.g., 77%).
Although satisfied in general with the high yields and diastereoselectivity achieved in the construction of (-)-2.4, three problems remained. First, the final product aldehyde (-)-2.4 was not stable for long periods of time, and secondly, the decomposition often occurred during large scale purification after the ozonolysis. The third problem from a preparative scale viewpoint was the presence of the pinene residue, produced during the Brown allylation, which was difficult to separate from either (-)-2.69, (-)-2.70 or (-)-2.4. Pleasingly, a minor optimization solved two of the problems. Instead of the final ozonolysis, treatment of olefin (-)-2.70 with the dihydroxylation conditions of OsO₄/NMO led to the corresponding stable diol, which was easily separated from the pinene residue. Transformation of the diol to the final product (-)-2.4 could then be carried out utilizing the inorganic reagent NaIO₄ to cleave the resultant diol in a fast and clean manner, permitting the fresh preparation of the aldehyde (-)-2.24 immediately before the key union reaction of the eastern and western hemispheres [(+)-2.22 and (-)-
2.4, respectively].

In summary, a viable construction of C(1-7, 26-27) western hemisphere (−)-2.4, designed by Dr. Anoton Khartulyari and I, had been achieved. The reaction sequence could be carried out in excellent yield (54.7% over 10 steps), and importantly permitted large scale access to the western hemisphere with perfect diastereomer selectivity.

2.6. Construction of the Entire Carbon Skeleton of (-)-Enigmazole A (+)-2.21 via a Late-Stage Large-Fragment Petasis-Ferrier Union/Rearrangement Protocol

Figure 2.6. Late-Stage Large-Fragment Petasis-Ferrier Union/Rearrangement Protocol

2.6.1. The First Union of the Eastern and Western Hemispheres, (+)-2.22 and (−)-2.4

After the syntheses of ample quantities of the eastern hemisphere β-hydroxy acid (+)-2.22 and the western hemisphere aldehyde (−)-2.4, the unprecedented late-stage large-fragment Petasis-Ferrier union/rearrangement directed toward the formation of the entire carbon skeleton of engimazole A was attempted.

Two potential challenges were envisioned for the first step of the Smith three step Petasis-Ferrier union/rearrangement protocol: (i) the potential problem of overcoming the steric effects due to the large fragments; and (ii) the difficulty associated
with the formation of the tris-silylated β-hydroxy acid. To solve these challenges, both the use of the HMDS/TMSOTf protocol and the Kurihara protocol\textsuperscript{22} were investigated (Table 2.2). By exposure of (+)-2.22 to a mixture of HMDS/THF, tris-silylated β-hydroxy acid was formed as confirmed by \textsuperscript{1}H NMR. After thorough removal of the HMDS/THF by high vacuum, treatment of the tris-silylated β-hydroxy acid with (−)-2.4 in the presence of TMSOTf at -78°C provided the desired union product (−)-2.70, albeit in very low yield (<5%). Fortunately, when employing HMDS/TMSOTf, most of the starting materials, namely the aldehyde (−)-2.4 and a mixture of silylated (+)-2.22 (mono-, bis-, or tris-) could be recovered. However in the case of Kurihara protocol, although similar amounts (< 5%) of the union product (−)-2.70 were produced, the starting materials could not be recovered. Multiple unstable by-products were observed by NMR studies, all of which revealed the lack of the C17 TMS ether. This result suggested that Kurihara protocol would be incapable of installing the TMS protecting group at low temperature. Further optimization of the Kurihara protocol using different temperatures and reaction times did not lead to a favorable result. We therefore focused our optimization studies on the HMDS/TMSOTf protocol.
At the beginning of our optimization study (Table 2.3), we reasoned that the low conversion was due to the mild conditions. As a result, we increased the temperature. Unfortunately, although the conversion increased at the higher temperature, no starting material was recovered; moreover the yield of desired product \((-\cdot)2.70\) remained unsatisfactory (5-20%). Multiple by-products, including the cis-isomer of \((-\cdot)2.70\), were observed. These results suggested that low temperatures were essential to avoid side-reactions and to obtain high diastereoselectivity. We then recalled that in the Smith total synthesis of (+)-zampanolide,23 the addition of catalytic amount of TfOH significantly improved the yield, especially on larger scale. The presumption in that case was that on small scale, trace amounts of water generated TfOH in situ from TMSOTf, greatly facilitating the formation of the dioxanone. We therefore added a catalytic amount of TfOH to our reaction mixture at low temperature. Unfortunately, the yield of desired
product (–)-2.70 was still unsatisfactory (5%-25%); moreover no starting material could be recovered. The NMR analysis of multiple major by-products suggested that although the dioxanone moiety had been generated, an undesired loss of the TMS group or both the TMS and PMB groups had also occurred. The derived alcohol or diol then underwent further reactions with aldehyde (–)-2.4 to form multiple complex by-products. This result suggested that addition of TfOH was necessary but that the substrates in hand were sensitive under the acidic conditions. A similar situation arose in the Smith synthesis of spongistatin,\textsuperscript{24} whereby the addition of the sterically hindered base DtBMP (2,6-di-tert-butyl-4-methylpyridine) to buffer the catalytic amount of TfOH led to the dioxanone. This protocol was applied to our synthesis, but did not lead to a satisfactory result.
Finally, we turned to generate TfOH in situ with TMSOTf. The addition of catalytic amount of water again resulted in a similar outcome. Surprisingly however, slow introduction of moisture via simple exposure of the -78 °C reaction mixture to room

Table 2.3. Optimization of Large-Fragmental Petasis-Ferrier Union Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>temp. (°C)</th>
<th>equiv of 2.4</th>
<th>conditions</th>
<th>recovery of 2.4</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, 3 h</td>
<td>80-90%</td>
<td>0-5</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>1.35</td>
<td>TMSOTf, 3 h</td>
<td>80-90%</td>
<td>0-5</td>
</tr>
<tr>
<td>3</td>
<td>-40</td>
<td>2.0</td>
<td>TMSOTf, 3 h</td>
<td>60-70%</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1.35</td>
<td>TMSOTf, 3 h</td>
<td>0</td>
<td>5-20</td>
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<tr>
<td>5</td>
<td>0</td>
<td>2.0</td>
<td>TMSOTf, 3 h</td>
<td>0</td>
<td>0-5</td>
</tr>
<tr>
<td>6</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, TfOH (0.3 equiv) 3 h</td>
<td>0</td>
<td>0-5</td>
</tr>
<tr>
<td>7</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, TfOH (0.1 equiv) 3 h</td>
<td>0</td>
<td>5-25</td>
</tr>
<tr>
<td>8</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, TfOH and DHBMP (0.2 equiv) 3 h</td>
<td>0</td>
<td>5-10</td>
</tr>
<tr>
<td>9</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, H2O (0.25 equiv) 3 h</td>
<td>0</td>
<td>5-10</td>
</tr>
<tr>
<td>10</td>
<td>-78</td>
<td>1.35</td>
<td>TMSOTf, moisture via needle from open air, 3 h</td>
<td>10%</td>
<td>75-90</td>
</tr>
<tr>
<td>11</td>
<td>-78</td>
<td>1.1</td>
<td>TMSOTf, moisture via needle from open air, 2 h</td>
<td>0</td>
<td>85-95</td>
</tr>
</tbody>
</table>
temperature air via the insertion of a needle (1.2 mm diameter) for 5 to 10 minutes proved successful, and remarkably led to the desired product (−)-2.70 in excellent yield (95%) as a single diastereomer, with no by-products observed!

In summary, after introducing moisture through an innovative and simple method, the Petasis-Ferrier union of western hemisphere (−)-2.4 and eastern hemisphere (+)-2.22 had been achieved in excellent yield (95%). The important role of TfOH in the Petasis union had been demonstrated yet again. The near perfect cis-selectivity (NMR) on the tetrahydropyran ring provided strong evidence that larger fragments led to better cis-selectivities. This experiment also demonstrated that acid-sensitive substrates could be utilized in this acid-facilitated Petasis-Ferrier union reaction in the absence of a base buffer.


Turning next to the olefination, the second step of the Smith 3-step of Petasis-Ferrier union/rearrangement protocol; both Petasis olefination25 and Tebbe olefination26 were initially explored (Table 2.4). Commercially available Tebbe’s reagent and freshly prepared Petasis reagent following the literature procedure27 had been employed in our laboratory. Similar to other Smith’s syntheses utilizing Petasis-Ferrier union/rearrangement as the synthetic cornerstone, the Petasis reagent led to enol acetal (−)-2.71 in better yield compared to that obtained with Tebbe’s reagent. We thus focused on the optimization of the Petasis olefination.
Table 2.4. Olefination of Dioxanone (−)-2.70

Although the Petasis olefination led to a much better yield compared with Tebbe olefination, the 40-50% yield obtained was not considered satisfactory at this stage of a total synthesis. A major by-product, which was not easy to separate from the desired reaction, was observed. We thus turned to the Smith second-generation synthetic study leading to (+)-phorboxazole A, wherein higher concentrations of the Petasis reagent, as well as the addition of ethyl pivalate, significantly decreased the reaction time of Petasis olefination and minimized the unwanted known [2+2] side reaction between the product enol-acetal and excess Petasis reagent. We therefore applied this tactic to our synthesis (Table 2.5). The experiments demonstrated that although the more concentrated Petasis reagent could lead both to a shorter reaction time (10 h) and to a slightly higher yield
(55%), further optimization was still necessary. We next turned our attention to the possibility of utilizing microwave heating, which has become a widely accepted energy source for organic synthesis. To our delight, exposure of the reaction mixture to microwave heating conditions furnished the desired enol acetal (−)-2.71 in very good yield (87%). Moreover, the microwave heating significantly decreased the reaction time and led to the clean formation of (−)-2.71. Compared to conventional heating, microwave heating has a number of special characteristics, including rapid and volumetric heating, as well as selective heating of polar substrates. All or only one of these thermal effects upon microwave heating could be responsible for the improvement of our Petasis olefination, while the shorter reaction times could disfavor formation of side products. (See the experimental section for exact details.)
Table 2.5. Optimization of Petasis Olefination

<table>
<thead>
<tr>
<th>entry</th>
<th>concentration of Petasis reagent [M]</th>
<th>additives</th>
<th>heating condition</th>
<th>temp (°C)</th>
<th>time</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>2,6-lutidine</td>
<td>conventional</td>
<td>70</td>
<td>15 h</td>
<td>40-50</td>
</tr>
<tr>
<td>2</td>
<td>0.125</td>
<td>2,6-lutidine</td>
<td>conventional</td>
<td>70</td>
<td>10 h</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>0.125</td>
<td>2,6-lutidine ethyl pivalate</td>
<td>conventional</td>
<td>70</td>
<td>10 h</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>2,6-lutidine</td>
<td>conventional</td>
<td>70</td>
<td>10 h</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>0.125</td>
<td>2,6-lutidine</td>
<td>microwave</td>
<td>90</td>
<td>4 h</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>0.125</td>
<td>2,6-lutidine</td>
<td>microwave</td>
<td>100</td>
<td>3 h</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>0.125</td>
<td>2,6-lutidine</td>
<td>microwave</td>
<td>110</td>
<td>3 h</td>
<td>78</td>
</tr>
</tbody>
</table>

In summary, by employing microwave heating, we were able to achieve the Petasis olefination, the second step of the Smith 3-step protocol, to furnish the enol acetal \((-)-2.71\) in very good yield (87%). Thus microwave augmentation of the Petasis olefination has the potential to be utilized in future natural product synthesis.

2.6.3. Petasis-Ferrier Rearrangement to the Methylene Tetrahydropyran Core of \((-)-Enigmazole A\)

Turning to the final step of the Smith three step protocol of Petasis-Ferrier union/rearrangement, \(\text{Me}_2\text{AlCl}\) is generally employed as the promoter for the catalytic rearrangement (Table 2.6). Unfortunately, during initial attempts the desired
rearrangement product (−)-2.72 was not observed under a variety of conditions (Table 2.6). The molecular weight of the major undesired product 2.73, when utilizing 1 to 2 equivalent of Me₂AlCl, was 15 amu units higher by MS than the substrate (−)-2.71, with the structure remaining unclear. On TLC the rf of the undesired product 2.73 was similar to that of the substrate (−)-2.71, which also made the reaction difficult to monitor.

When additional equivalents of Me₂AlCl (3.0 equiv to 6.0 equiv) were applied, another major undesired product 2.74 was observed, the NMR of which clearly demonstrated an α,β-unsaturated ketone structure. We reasoned that the formation of 2.74 was due to catalyst promoted intramolecular retro-Michael addition, after the

<table>
<thead>
<tr>
<th>entry</th>
<th>equiv of Me₂AlCl</th>
<th>temp. (°C)</th>
<th>time</th>
<th>% yield of 2.72</th>
<th>% yield of 2.73</th>
<th>% yield of 2.74</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0</td>
<td>5 min</td>
<td>-</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>0</td>
<td>5 min</td>
<td>-</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>r.t.</td>
<td>1 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>0</td>
<td>5 min</td>
<td>-</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>0</td>
<td>5 min</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2.6. Initial Attempts of Petasis-Ferrier rearrangement
construction of the desired tetrahydropyranone structure (Scheme 2.23). This observation suggested that utilizing a large excess of the Lewis acid might permit the formation of the desired product (−)-2.72, but unfortunately these conditions also led to further undesired over-reactions assisted by the excess Lewis acid. We therefore started to optimize the reaction by shortening the reaction time, decreasing the reaction temperature, and the screening of base additives.

![Scheme 2.23. Formation of α,β-unsaturated ketone](image)

Fortunately, by shortening the reaction time to 2 seconds at 0 °C, a 40% yield of the desired product (−)-2.72 could be isolated after careful separation by PTLC (Table 2.7). This was an exciting observation but the required 2-second reaction time led to extremely inconsistent results. Pleasingly, the reaction could be controlled by simply decreasing the reaction temperature to -78 °C. Within a reaction time range between 20 seconds and 35 seconds at -78 °C, the desired product (−)-2.72 could be isolated in 50% to 85% yield. To increase further the consistency of the reaction, additives such as Cs₂CO₃, utilized in the synthesis of spongistatin, and molecular sieves, utilized in the synthesis of clavosolide were investigated. Unfortunately, neither led to a promising result.
Table 2.7. Optimizations of Petasis-Ferrier rearrangement

During the optimization studies, we also discovered that the yield of the rearrangement reaction significantly varied depending on the applied quenching conditions. Quenching with organic bases such as trimethylamine, diisopropylethylamine or 2,6-lutidine only led to low yield. In contrast, quenching with aqueous solutions of
NaHCO₃ or NaOH at -78 °C led to a 50% to 85% isolated yields. However again the reaction results remained inconsistent. We therefore developed an unconventional quenching and further olefination tactic by using a methylene ylide solution to generate directly the methylene tetrahydropyran structure in a one-pot fashion. Surprisingly, treatment of the rearrangement mixture with a solution of freshly prepared methylene ylide in THF at -78 °C led to the desired product (−)-2.21 in 70% to 85% yield with good consistency (Scheme 2.24). We therefore had successfully achieved the entire carbon skeleton of enigmazole A utilizing a more efficient late-stage large-fragment Petasis-Ferrier union/rearrangement.

![Scheme 2.24. Direct Formation of Methylene Tetrahydropyran](image)

2.6.4. Summary of the Late-Stage Large-Fragment Petasis-Ferrier Union/Rearrangement

In summary, as outlined in Scheme 2.25 we have achieved an unprecedented late-stage large-fragment Petasis-Ferrier union/rearrangement to furnish the entire carbon skeleton of enigmazole A in high yield (70% over 3 steps) with excellent diastereoselectivity (>20:1). Contributions of this synthetic sequence included: (i)
construction of the entire carbon skeleton, including all stereocenters of the natural product; (ii) demonstration that our presumption that larger fragments in the Petasis-Ferrier union/rearrangement would proceed to furnish better cis-selectivities; (iii) development of the versatility of the Petasis-Ferrier union/rearrangement through significant optimizations, including slow introduction of moisture to the union mixture, microwave-augmentation of the olefination protocol, an unconventional ylide quenching method; and (iv) the demonstration that substrates containing free hydroxyl groups could be employed in the union/rearrangement reactions without protection.

Scheme 2.25. Late-Stage Large-fragment Petasis-Ferrier Union/Rearrangement
2.7. Construction of the Advanced Enigmazole Macrolide (+)-2.48

![Figure 2.7. Structure of Macrolide (+)-2.48](image)

2.7.1. Construction of the Macrolactonization Precursor (+)-2.20 via Chemoselective Oxidation

Attention turned next to the synthesis of macrolactonization precursor, whereby we planned to remove the primary TBDPS and secondary TMS ether together in one step. Unfortunately, neither fluoride nor acidic conditions (TBAF, HF/pyridine or CSA) led to the desired product in a good yield. We therefore attempted to utilize basic conditions. During the Smith total synthesis of phorboxazole A, potassium hydroxide (KOH) and 18-crown-6 had been used to remove selectively a primary TBDPS ether in the presence of secondary TBS and TIPS ethers.\(^\text{15}\) Pleasingly, by utilizing similar conditions in our system, the desired diol (+)-2.75 was available in 75-80\% yield, together with 15\% to 20\% of the transsilylation by-product 2.76 (Scheme 2.26).
**Scheme 2.26.** Deprotection of TBDPS and TMS group

The subsequent chemoselective oxidation to furnish the requisite macrolactonization precursor acid (+)-2.20 however proved problematic. In particular, the similar retention time on TLC of the starting material (+)-2.75 and the desired acid (+)-2.20 complicated reaction monitoring. As a result, a stepwise procedure was implemented, utilizing a TEMPO/BAIB oxidation to furnish aldehyde (+)-2.76 in 76.9% yield, followed by a Pinnick oxidation to provide the desired acid (+)-2.20 in 85.4% yield. With a TLC sample of desired acid (+)-2.20 in hand, direct oxidation from (+)-2.75 to (+)-2.48 using TEMPO/NaClO/NaClO₂ could now be carried out. Pleasingly, such conditions yielded the macrolactonization precursor (+)-2.20 in 67.3% yield, together with 20% of an over-oxidized by-product 2.77 (Scheme 2.27).
Scheme 2.27. Synthesis of Macrolactonization Precursor (+)-2.20

2.7.2. Macrolactonization: Construction of (+)-2.48

Turning to the macrolactonization, the Keck conditions, as utilized in the Molinski total synthesis of enigmazole A, led to the desired (+)-2.48 in modest yield (40%-50%).\textsuperscript{9,33} Unfortunately, macrolide (+)-2.48 proved very difficult to purify due to the large amount of urea residue derived from the macrolactonization reagent DCC. Another macrolactonization reagent, EDCI.HCl, which would have permitted for simpler purification, was also tested but only provided the desired product in low yield (10%) (Scheme 2.28).
Pleasingly however the Yamaguchi conditions, commonly used for macrolactonizations, furnished the desired (+)-2.48 in 88.5% yield without any purification problems (Scheme 2.29).\textsuperscript{34}

**Scheme 2.29.** Construction of Macrolide via Yamaguchi macrolactonization

In summary, macrolide (+)-2.48 was successfully constructed from the Petasis-Ferrier
union/rearrangement product (−)-2.21 via chemoselective silyl ether removal, chemoselective oxidation and macrolactonization.

2.8. Construction of Enigmazole A: Endgame of the Total Synthesis

![Figure 2.8. Endgame of the Total Synthesis](image)

2.8.1. Removal of the TIPS Protecting Group

Turning to the endgame of the total synthesis after the construction of macrolide (+)-2.48, the TIPS group at C5 would require removal before phosphorylation. This deprotection reaction seemed relatively straightforward at the outset of our retrosynthetic analysis given the TIPS group would be the only silyl ether protecting group remaining on our advanced intermediate, and thus there would be no differentiation issues. However, upon screening a variety of different conditions, including most of the common silyl ether removal methods such as acid, base or fluoride ion, a promising result was not obtained (Table 2.8). Mild conditions were incapable of removing the protecting group, while harsher conditions, led to either complex intractable mixtures or a single undesired product having the same molecular weight as the desired product (+)-2.78. Subsequent
NMR analysis of the undesired product suggested a δ-lactone structure (2.79), which we envisioned arising via an intramolecular transesterification after formation of desired alcohol (+)-2.78. Additional evidence for a δ-lactone was the observation of an IR absorption at 1738 cm⁻¹.

![Chemical structures](image)

Table 2.8. Initial Attempts of TIPS Deprotection

A similar transesterification had been observed in the dephosphorylation of (−)-enigmazole A during Gustafson’s structure elucidation study. More specifically, δ-lactone 2.81 was observed together with the desired dephosphorylation product 2.80 upon treatment with weak acid. Despite the undesired side reaction, the absolute configurations of C4 and C5 of enigmazole A could be assigned via the NMR studies of δ-lactone 2.81 (Scheme 2.30).³⁵
**Scheme 2.30.** Dephosphorylation of Enigmazole A, Formation of the δ-lactone

To compare the TIPS deprotection by-product (−)-2.79 with the natural product-derived δ-lactone (−)-2.81, PMB deprotection studies were carried out (Scheme 2.31). Initially, treatment of 2.79 with DDQ did not furnish the desired product (−)-2.81, but the PMP acetal 2.82. An acetonide removal from 2.82, employing TFA/H₂O, smoothly led to the desired δ-lactone (−)-2.81. Subsequent studies also demonstrated that direct exposure of PMB ether (−)-2.79 with the same TFA/H₂O conditions successfully removed the PMB protecting group to furnish δ-lactone (−)-2.81. To our delight, the deprotection product (−)-2.81 displayed NMR spectral properties in excellent agreement with those recorded in the structural elucidation paper [i.e., ¹H and ¹³C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties]. This result not only confirms the structure of the transesterification by-product (−)-2.79, but also proves the precise configurations of all eight stereogenic centers of our advanced intermediates.
Despite the promising evidence relating the stereogenic centers, the transesterification side-reaction remained problematic. Presumably in our case, formation of the six membered ring lactone and the associated conformational stability were the driving force for formation of the undesired product (+)-2.79 (Table 2.8). Importantly, the transesterification reaction proceeded extremely fast, thus making access to alcohol (+)-2.78 very challenging.

Turning to the literature, Carreira et al. had encountered a similar problem in their synthesis of (+)-zaragozic acid (Scheme 2.32). Indeed, in their attempt to remove the TBS group from advanced intermediate 2.83, a variety of commonly employed deprotection conditions were screened. The desired alcohol 2.85 however could not be isolated, given that it instantaneously underwent an intramolecular reaction with an acetyl group to yield 2.84. After extensive screening, Carreira et al. found that the desired primary alcohol 2.85 could only be obtained by employing HF-pyridine, buffered with large excess of pyridine. We therefore applied this method to our substrate (+)-2.48.
Scheme 2.32. TBS Deprotection in the Synthesis of (+)-Zaragozic Acid

Upon treatment of (+)-2.48 with HF-pyridine complex buffered with large excess of pyridine, the desired macrolide (+)-2.78 could be isolated. Although the undesired by-product 2.79 was still observed, a screen of different ratios of HF and pyridine, as well as reaction temperatures and times led to the best conditions, furnishing alcohol (+)-2.78 in 70% yield (Scheme 2.33).

Scheme 2.33. Deprotection of TIPS Protecting Group

In summary, advanced intermediate (+)-2.78 was constructed via a carefully optimized TIPS removal protocol to avoid an undesired transesterification. Importantly, the further transformation of the transesterification by-product (+)-2.79 provided strong evidence of the precise stereogenicity of all eight centers of our advanced synthetic intermediates.
2.8.2. Phosphate Installation and Removal of the PMB Protecting Group

Focus next turned to the formation of the phosphate ester. One of the most commonly utilized methods for the formation of phosphate esters is the conversion of a P-N bond of phosphorus(III) reagent to a P-O bond by the substrate alcohol in the presence of a catalytic amount of 1H-tetrazole, followed by oxidation of the phosphorus(III) compound to the phosphorus(IV) compound with peroxides.\textsuperscript{37} We attempted to employ this method to our synthesis. Due to the possible acid-lability of the natural product enigmazole A, a base-cleavage phosphate protecting group 9-fluorenylethynylmethyl (Fm) was employed,\textsuperscript{40} which had proven efficient in the Molinski total synthesis of enigmazole A,\textsuperscript{9} as well as the Boger total synthesis of cytostatin.\textsuperscript{38} The requisite phosphate reagent, difluorenyl phosphoramidite, was freshly prepared according to a conventional procedure via phosphoramidous chloride.\textsuperscript{40,41}

However, initial attempts at the phosphorylation proved problematic (Scheme 2.34). Fewer equivalents (\(<10\) equiv) of phosphate reagent only led to incomplete reaction, whereas employing more equivalents of phosphate reagent led to reaction mixtures very difficult to purify due to the large amount of phosphate residue.

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{Scheme2.png}
\end{center}
\end{scheme}

\textit{Scheme 2.34. Initial Attempts of Phosphorylation}
Given the limited amount of advanced intermediate (+)-2.78, a model study employing the western hemisphere intermediate (−)-2.69 was carried out to screen phosphorylation conditions, as well as to practice purification methods to remove phosphate residue (Scheme 2.35). The model study demonstrated that a large excess of \( iPr_2NP(OFm)_2 \) (>15 equiv) proved necessary to achieve complete conversion. A screen of different equivalents of the phosphate reagent led to a best conditions (20 equiv of \( iPr_2NP(OFm)_2 \), 93% isolated yield of 2.87)

\[
(+)-2.78 \xrightarrow{\text{model}} \xrightarrow{\text{tetrazole, 20 equiv}} \xrightarrow{\text{Then } H_2O_2/H_2O} \xrightarrow{93\%} (-)-2.69 \xrightarrow{\text{hydrolysis}} 2.87
\]

**Scheme 2.35. Model Study of Phosphorylation**

Employing the best conditions found in the model study, phosphoric ester (+)-2.86 could be constructed in good NMR yield (Scheme 2.35). However, a small amount of phosphate residue could not be removed from the desired product 2.86 by normal phase silica gel flash chromatography. We envisioned that those impurities could be removed after the subsequent PMB deprotection of (+)-2.86. Thus the mixture was moved to the next step.

The PMB protecting group of the phosphoric ester was envisioned to be removed utilizing the commonly applied oxidative reagent DDQ. Although literature
precedents suggested conjugated systems, including of 1,3-dienes, 1,4-dienes and trienes, could not withstand the DDQ oxidative conditions,\textsuperscript{41,42} our earlier studies of PMB deprotection of \(\delta\)-lactone 2.79 demonstrated the robustness of the C(18-22) conjugated system upon DDQ oxidative conditions (Scheme 2.31). Pleasingly, treatment of PMB ether 2.86 with DDQ led not only to the desired alcohol (-)-2.67, but also permitted during purificaiton removal of phosphate impurities derived from the phosphate installation step (Scheme 2.36).

\begin{center}
\textbf{Scheme 2.36.} Phosphorylation and PMB Removal, Construction of (-)-2.87
\end{center}

In summary, alcohol (-)-2.87, the last intermediate in the total synthesis of enigmazole A, had been successfully constructed via phosphate installation followed by a PMB removal reaction; the yield was 61\% over two steps.

2.8.3. Removal of Fm Group: Total Synthesis of (-)-Enigmazole A (2.1)

Turning to the final step of the total synthesis of (-)-enigmazole A (2.1), K\textsubscript{2}CO\textsubscript{3} was used to remove the Fm protecting group on the phosphoric acid (Scheme 2.37) following the procedure outlined in the Molinski publication.\textsuperscript{9} Monitoring the reaction by LC-MS revealed complete conversion after 3 hours. NMR experiments of the reaction product were carried out after removal of Fm residue through extraction.
Scheme 2.37. Deprotection of Fm Group, Construction of Dipotassium Phosphate of Enigmazole A

Disappointingly, although our deprotection product 2.88 displayed a very similar $^1$H NMR spectrum to enigmazole A recorded in the isolation paper, two disagreements (e.g., 0.11 ppm) for H2 and H5 were observed (Table 2.9). Given that the correctness of all eight stereogenic centers of our advanced intermediates had been demonstrated in the experiments related to $\delta$-lactone 2.79 (Scheme 2.31 in Chapter 2.8.1), we initially reasoned these spectral disagreements, particularly of the protons near to the phosphoric acid and carbonyl functional groups including of H2 and H5, arose due to the presence of different counter-ions on the phosphate group based on the suggestion in the Molinski’s publication. Thus ion-exchange experiments were carried out.
Table 2.9. Comparison of $^1$H NMR Spectra of Potassium Salt of Enigmazole A 2.88 with Natural Enigmazole A

<table>
<thead>
<tr>
<th>Position No.</th>
<th>(-)-2.1</th>
<th>2.88</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>7.68 s</td>
<td>7.69 s</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>21</td>
<td>6.21 s</td>
<td>6.21 s</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>17</td>
<td>5.95 dd</td>
<td>5.93 d</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>12.8, 2.5 Hz</td>
<td>13 Hz</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>5.24 q 6.5 Hz</td>
<td>5.24 q 6.5 Hz</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>28 (2H)</td>
<td>4.69 d 1.5 Hz</td>
<td>4.68 s</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>5</td>
<td>4.42 m</td>
<td>4.31 m</td>
<td>0.11</td>
</tr>
<tr>
<td>15</td>
<td>3.62 m</td>
<td>3.63 m</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>11</td>
<td>3.29</td>
<td>covered by methanol</td>
<td></td>
</tr>
<tr>
<td>OMe (3H)</td>
<td>3.20 s</td>
<td>3.20 s</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>7</td>
<td>3.12 dd</td>
<td>3.14 m</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>2.98 m</td>
<td>3.09 m</td>
<td>0.11</td>
</tr>
<tr>
<td>16 (2H)</td>
<td>2.50, 1.77</td>
<td>2.50 (covered by impurity)</td>
<td></td>
</tr>
<tr>
<td>25 (3H)</td>
<td>1.89 s</td>
<td>1.89 s</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>24 (3H)</td>
<td>1.26 d</td>
<td>covered by grease</td>
<td></td>
</tr>
<tr>
<td>26 (3H)</td>
<td>1.10 d 6.4 Hz</td>
<td>1.10 d 6.5 Hz</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>27 (3H)</td>
<td>0.97 d 6.4 Hz</td>
<td>0.97 d 6.5 Hz</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

NMR solvent: MeOD

Ion-exchange chromatography as well as further purification studies were carried out employing similar procedures as those recorded in the Molinski total synthesis publication. By employing reverse phase HPLC, using an aqueous solution buffered with NaClO$_4$ furnished the desired enigmazole A (→)-2.1 probably as a sodium salt. Despite the limited quality of our NMR sample due to the large amount of H$_2$O co-crystallized with NaClO$_4$, our synthetic enigmazole A (→)-2.1 displayed $^1$H NMR spectral properties in excellent agreement with those recorded in the elucidation paper (Table 2.10).
Table 2.10. Initial Comparisons of $^1$H NMR Spectra of Synthetic Enigmazole A with Natural Enigmazole A

Although the $^1$H NMR spectra of our totally synthetic enigmazole A matched that of natural product, the real format of the isolated enigmazole A remained an issue. Despite utilizing exactly the same method employed in the final purification, Gustafson and Molinski came to a different conclusion related to the counter-ions of (−)-enigmazole A in their publications. Gustafson et al. reported (−)-enigmazole A as a free phosphoric acid, whereas Molinski et al. concluded that the synthetic natural product as a sodium salt. Neither group however provided further evidence to justify their solution structural assignments.

To obtain full characterization data of our final product, as well as to solve the question related the real format of the isolated natural product, further experiments were carried out. To avoid the involvement of unnecessary potassium ion and subsequent
troublesome ion-exchange experiment, Na₂CO₃ was employed in the Fm deprotection reaction instead of K₂CO₃ (Scheme 2.38). Monitoring the reaction by C18 TLC revealed complete conversion after 24 hours, with the Fm residue removed via extraction with pentane. NMR experiments of the reaction product after solvent removal were carried out. To our surprise, the ¹H NMR spectrum of the sodium salt 2.89 is exactly the same as that of the potassium salt 2.88, thus proving that the different counter ions (Na⁺ or K⁺) are not the main reason for the spectral disagreements for H2 and H5. We then reasoned these disagreements were due to the different levels of proton dissociation of the phosphoric acid.

**Scheme 2.38.** Deprotection of Fm Group and Construction of Disodium Phosphate of Enigmazole A

To prove this hypothesis, proton exchange experiments were carried out in a 5 mm-diameter glass NMR tube (Scheme 2.39). Treatment of a solution of disodium phosphate 2.89 in CD₃OD with 10 μL of TFA-d furnished the free phosphoric acid. The ¹H NMR spectrum of 2.90 changed significantly for the H2 and H5 signals compared with those of the sodium salt 2.89. However the spectrum was still not in full agreement with the
enigmazole A spectrum recorded in the original elucidation paper. We next treated phosphoric acid 2.90 with 20 mg of solid NaHCO₃ to furnish monosodium phosphate 2.91. To our surprise, the ¹H NMR spectrum of 2.91 was now in excellent agreement with enigmazole A recorded in the isolation paper.

![Scheme 2.39. Phosphoric Acid Dissociation Experiments](image)

Based on these NMR experiments, we conclude that the natural product (−)-enigmazole A was isolated as a monophosphate. The ¹H NMR spectra of the different levels of phosphoric acid dissociation however presented no neglectable disagreements, whereas the different counter ions (Na⁺ or K⁺) does not make an observable difference in the NMR spectra (Table 2.11). The product of Fm removal reaction utilizing K₂CO₃ is a dipotassium phosphate rather than the monopotassium phosphate recorded in Molinski’s publication. The disagreements of NMR spectra after the subsequent HPLC ion-exchange experiment are not due to the cation exchange, but due to the change of the proton association on the phosphate.
To synthesize all three phosphate formats of enigmazole A, we next employed acetic acid-d₄ (CD₃COOD) to quench the reaction mixture during the Fm deprotection reaction utilizing Na₂CO₃ (Scheme 2.40). After removal of the Fm residue by extraction with pentane, the reaction mixture was concentrated to give enigmazole A monophosphate (2.1) together with sodium acetate-d₃. The product was then purified and converted to phosphoric acid format 2.90 by employing reverse phase HPLC (CH₃CN/H₂O, 0.1% TFA). After obtaining ¹H and ¹³C NMR spectra of the free acid

### Table 2.11. Comparisons of ¹H NMR Spectra of Different Acid Dissociation Levels of Engimazole A

<table>
<thead>
<tr>
<th></th>
<th>synthetic dipotassium phosphate (R₁ = R₂ = K)</th>
<th>synthetic disodium phosphate (R₁ = R₂ = Na)</th>
<th>synthetic phosphoric acid (R₁ = R₂ = H)</th>
<th>synthetic monosodium phosphate (R₁ = Na, R₂ = H)</th>
<th>natural product</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2</td>
<td>3.09 ppm</td>
<td>3.09 ppm</td>
<td>2.87 ppm</td>
<td>2.98 ppm</td>
<td>2.98 ppm</td>
</tr>
<tr>
<td>H5</td>
<td>4.31 ppm</td>
<td>4.31 ppm</td>
<td>4.58 ppm</td>
<td>4.42 ppm</td>
<td>4.42 ppm</td>
</tr>
</tbody>
</table>

All other protons do not have disagreements bigger than 0.02 ppm (solvent MeOD)
format 2.90, the synthetic enigmazole A was converted to the monophosphate format through the addition of saturated NaHCO$_3$ Methanol-d$_4$ solution. The resulting synthetic monophosphate (−)-enigmazole A 2.1 displayed NMR spectral properties in excellent agreement with those recorded in the elucidation paper [i.e., $^1$H, $^{13}$C, $^{31}$P NMR (500, 125, 200 MHz, respectively), HRMS parent ion identification, and chiroptic properties]. The NMR spectra comparisons are summarized in Figure 2.9, Figure 2.10. Table 2.12 and Table 2.13. Subsequent Treatment of monophosphate 2.1 with dilute NaOH Methanol-d$_4$ solution then furnished the diphosphate format 2.91.

Scheme 2.40. Synthesis of all Three Phosphates Formats of Enigmazole A (2.1)
Figure 2.9. Comparisons of 1H NMR Spectra of Synthetic Enigmazole A with Natural Enigmazole A (Upper: Natural Enigmazole A, Lower: Synthetic Monophosphate)

Figure 2.10. Comparisons of 13C NMR Spectra of Synthetic Enigmazole A with Natural Enigmazole A (Upper: Literature Enigmazole A, Lower: Synthetic Monophosphate)
Table 2.12. Comparisons of $^1$H NMR Spectra of Synthetic Enigmazole A with Natural Enigmazole A

<table>
<thead>
<tr>
<th>Position No.</th>
<th>Natural Enigmazole A</th>
<th>Synthetic Enigmazole A</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>7.68 s</td>
<td>7.68 s</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>6.21 s</td>
<td>6.21 s</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
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**Table 2.13.** Comparisons of $^{13}$C NMR Spectra of Synthetic Enigmazole A with Natural Enigmazole A
Finally, we synthesized all three possible phosphate forms of enigmazole A. The comparisons of $^1$H NMR are summarized in Figure 2.11 and the detail full characters of all the three formats are attached in experimental information (Chapter 3). Moreover, enigmazole A could exist as a mixture of two different phosphate formats in some certain pH level. Interestingly, the $^1$H NMR spectra in that case does not demonstrate a mixture of two different compounds, but one single compound with average signals between the two formats, presumably due to the rapid proton exchange (e.g. Figure 2.12). We therefore conclude that the NMR spectra of enigmazole A vary with the different pH levels.

**Figure 2.11.** Comparisons of $^1$H NMR Spectra of Three Phosphate Formats of Enigmazole A (Upper: Diphosphate, Middle: Monophosphate, Lower: Phosphoric Acid)
2.9. Summary of the Total Synthesis Enigmazole A

In summary, we have completed the total synthesis of enigmazole A (−)-2.1 in 22 steps and 2.45% overall yield from the commercially available (+)-2.25 exploiting a highly convergent retrosynthetic analysis (Scheme 2.41). The cornerstone of the synthesis is an unprecedented late-stage large-fragment Petasis-Ferrier union/rearrangement, which generated the entire carbon skeleton of (−)-enigmazole A in a single cascade sequence, further developing the versatility and robustness of the Smith three step Petasis-Ferrier union/rearrangement protocol. Other key reactions of the synthesis include a Negishi cross-coupling, a dithiane-epoxide union, a Type I multicomponent ARC coupling and a Yamaguchi macrolactonization. Chemoselective oxidation/reduction strategies and one-pot reactions were frequently used in the synthetic sequence, thus enhancing the
efficiency. Moreover, the total synthesis had been achieved in a highly stereocontrolled manner with no undesired diastereomer observed in the process of construction of all eight stereogenic centers. Finally, all the three formats of the natural products have been synthesized.

Scheme 2.41. Summary of the Total Synthesis of Enigmazole A
2.10. References Relevant to Chapter 2


11. Hicks, D. R.; Fraser-Reid, B. Synthesis 1974, 3, 203


32. Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315


1979, 52, 1989


**Post Script: Potential Synthesis Access to the Congeners of (-)-Enigmazole A**

Although enigmazole A comprises the principle cytotoxic constituent of the *Cinachyrella enigmatica* extract, a number of related congeners including enigmazole B, 15-MeO-enigmazole A, 13-OH-15-MeO-enigmazole A, cis-enigmazole B and 14-15-dehydro-enigmazole B were also identified (Figure P.S.).\(^1,2\) While the original *Cinachyrella enigmatica* extract fraction displayed selectivity against c-Kit mutant cells, enigmazole A (3.1) upon isolation proved equally cytotoxic to both wild-type and mutant c-Kit. This observation suggests the possibility that the other congeners, either enigmazole B (3.4) or the related enigmazole analogues, might be responsible for the selectivity observed in the c-Kit assays.\(^1,3\) Due to the importance of the selectivity issue, in conjunction with the limited amounts of the enigmazole congeners available from the natural source, the synthesis of seminal congeners could prove important in improving both the antitumor activity and the c-Kit mutation selectivity. With these considerations in mind, recognizing the considerable advantages of our now complete synthesis of enigmazole A, utilizing a late-stage large-fragment Petasis-Ferrier union/rearrangement, in conjunction with anion relay chemistry (ARC) to access diverse advanced synthesis, we have the potential to access 15-MeO-enigmazole A, 13-OH-15-MeO-enigmazole A, enigmazole B and cis-enigmazole B (Figure P.S.). Such studies are planned in the Smith group.
**Figure P.S.** Structure of Enigmazole A, B and Related Congeners

Reference:


Chapter 3. Experimental Information

3.1. Material and Methods

Reactions were carried out in oven-dried glassware unless otherwise specified. Anhydrous THF, DCM, diethyl ether and toluene were obtained from the Pure Solve™ PS-400. Triethylamine, diisopropylamine, diisopropylethylamine, HMPA and DMPU were freshly distilled from calcium hydride under an nitrogen atmosphere, All chemicals were purchased from Sigma Aldrich, Acros or TCI America. Reactions were magnetically stirred unless stated otherwise and monitored by SiO₂ thin layer chromatography (TLC). Silica gel chromatography was performed utilizing ACS grade solvents and silica gel from Silicycle.

Infrared spectra were obtained using a Jasco FT/IR-480 plus spectrometer. Optical rotations were obtained using a Jasco polarimeter or Jasco P2000 polarimeter. ¹H magnetic resonance spectra and ¹³C magnetic resonance spectra were obtained on either a Bruker AMX 500 MHz or a Bruker Avance III 500 MHz spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26), benzene (δ 7.16) or methanol (δ 3.30) for ¹H NMR spectra and chloroform (δ 77.23), benzene (δ 128.39) or methanol (δ 49.00) for ¹³C NMR spectra. High resolution mass spectra were measured at the University of Pennsylvania.
3.2. Detailed Experimental Procedures Relevant to Chapter 2

\[
\text{Z-iodoalkene (+)-2.29}
\]

To a stirred suspension of NaH (23.1 g, 578 mmol, 60% in mineral oil, 5.0 equiv) in 250 mL of Et₂O at 0 °C under a nitrogen atmosphere, a solution of iodide (+)-2.28 (24.5 g, 115.5 mmol, 1.0 equiv.) in 100 mL Et₂O was added slowly. After complete addition, the temperature was increased to room temperature and the reaction mixture was allowed to stir for 20 min before it was recooled to 0 °C. Methyl iodide was added dropwise, followed by very slow addition (over 40 min) of 15-crown-5 (30.5 g, 138.7 mmol, 1.2 equiv.) at 0 °C. The resulted mixture was stirred overnight at room temperature and quenched at 0 °C by very careful addition of saturated aqueous NH₄Cl (100 mL over 1 hour). The organic layer was removed and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated, the resulting oil was purified by reduced pressure distillation (80 °C at 5 mm Hg) to give Z-iodoalkene (+)-2.29 (23.4 g, 104 mmol, 90.0%) as a colorless liquid; \([\alpha]_D^{20} = +9.45 \text{ (c 2.16, CHCl}_3\text{)}\); IR (film) 2979, 2927, 2900, 2819, 1654, 1443, 1370, 1338, 1281, 1206, 1145, 1115, 1098, 1031, 968, 866, 774, 655 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃-d) \(\delta = 6.03 \text{ (d, J = 1.0 Hz, } 1\text{H}), 4.27 \text{ (q, J = 6.5 Hz, 1H), 3.23 (s, 3H), 1.80 (d, J = 1.0 Hz, 3H), 1.20 (d, J = 6.5 Hz, 3H);} \(^1\)C NMR (125 MHz, CDCl₃) \(\delta = 147.5, 80.9, 75.7, 56.5, 18.6, 18.0; \) high resolution mass spectrum (CI) m/z 225.9852 \([M^+ \text{ calcd for C}_6\text{H}_{10}\text{IO}]\)
**Oxazolyl Chloride 2.33:** To a solution of tert-butyl nitrite (90%, 7.62 mL, 57.7 mmol, 1.5 equiv) and copper(II) chloride (7.67 g, 57.7 mmol, 1.5 equiv) in acetonitrile (200 mL) at 60 °C was added portionwise aminooxazole 2.32 (6.0 g, 38.4 mmol, 1.0 equiv) over 15 min. The resulted mixture was then heated at 80 °C for 2 hours (warning: toxic gas formation). The reaction mixture was then cooled to room temperature and quenched by the addition of large amount of hydrochloric acid (200 mL 1M in water). The mixture was diluted with dichloromethane (500 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (50 mL) twice. The combined organic layers were washed with saturated aqueous NH₄Cl and brine, dried over MgSO₄, filtered and concentrated. The crude product was then purified by recrystallization (ethyl acetate: hexanes 10:90, 0 °C) to furnish oxazolyl chloride 2.33 (4.83 g, 27.6 mmol, 72.0%) as a white solid. IR (film) 3148, 2995, 1728, 1538, 1375, 1333, 1278, 1141, 1097, 977, 945, 858, 773, 675 cm⁻¹; ¹H NMR (500 MHz, CDCl₃-d) δ = 8.16 (s, 1H), 4.35 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 160.1, 148.4, 145.5, 135.3, 61.8, 14.3; high resolution mass spectrum (ES⁺) m/z 176.0116 [(M+H)⁺ calcd for C₆H₇ClNO₃]

**Oxazolyl Easter (+)-2.34:** To a solution of Z-iodoalkene (+)-2.29 (19.0 g, 84.1 mmol, 1.0
equiv) in Et₂O (70 mL) under a nitrogen atmosphere at -78 °C was added dropwise t-BuLi (99 mL, 1M in pentane, 168.0 mmol, 2.0 equiv) over 30 min. The resulting heterogeneous mixture was stirred for 1 hour at the same temperature, then ZnCl₂ solution (100 mL, freshly prepared from solid flame-dried ZnCl₂, 1 M in THF, 100.0 mmol, 1.19 equiv) was added dropwise and the reaction mixture was allowed to warm to room temperature over a 30 min period. At this point pentane and diethyl ether were removed from the reaction under reduced pressure and nitrogen atmosphere. A solution of oxazolyl chloride 2.33 (14.9 g, 84.1 mmol, 1.0 equiv) and Pd(PPh₃)₄ (2.0 g, 1.73 mmol, 0.02 equiv) was separately prepared in THF (80 mL) and was added dropwise. The resulting mixture was vigorously stirred at reflux for 2 hours, then cooled to room temperature and quenched by the addition of a saturated aqueous NH₄Cl solution (50 mL). The mixture was diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated, the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 15:85, 20:80) to furnish oxazolyl easter (+)-2.34 (16.1 g, 67.3 mmol, 80.0%) as a colorless oil: [α]D²⁰ = +43.94 (c 0.47, CHCl₃); IR (film) 2980, 1743, 1722, 1654, 1576, 1448, 1370, 1316, 1178, 1113, 1025, 839, 770 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 8.11 (s, 1H), 6.26 (s, 1H), 5.14 (q, J = 6.5 Hz), 4.39 (q, J = 7.1 Hz, 2H), 3.23 (s, 3H), 1.93 (d, J = 1.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.32 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 161.4, 161.0, 153.2, 142.8, 134.2, 112.7, 74.8, 61.2, 56.5, 19.4, 17.9, 14.4; high resolution mass spectrum (ES+) m/z 262.1051 [(M+Na)+ calcld for C₁₂H₁₇NO₄Na]
Oxazolyl Aldehyde (+)-2.35: A solution of ester (+)-2.34 (9.00 g, 37.6 mmol, 1 equiv) in 200 mL CH₂Cl₂ was treated with DIBAL-H (1 M in hexanes, 75.2 mL, 75.2 mmol, 2.0 equiv) at -78 °C under nitrogen atmosphere, followed by stirring at that temperature for 30 min. The resulted mixture was quenched with MeOH (20 mL) at -78 °C before it was warmed to room temperature. Saturated aqueous Rochelle’s salt solution (80 mL) was then added and the mixture was stirred vigorously for 1 h. The resulting mixture was diluted with 100 mL diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (50 mL) twice. The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated, the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 15:85, 20:80) to furnish aldehyde (+)-2.35 (6.35 g, 32.7 mmol, 87.0%) as a white amorphous solid; [α]$_D^{20}$ = +25.15 (c 1.0, CHCl₃); IR (film) 2978, 2924, 1699, 1651, 1562, 1114 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl₃) δ = 9.95 (s, 1H), 8.18 (s, 1H), 6.23 (s, 1H), 5.24 (q, J = 6.5 Hz), 3.24 (s, 3H), 1.94 (d, J = 1.5 Hz), 1.33 (d, J = 6.5 Hz); $^{13}$C NMR (125 MHz, CDCl₃) δ = 184.8, 161.5, 154.8, 143.0, 141.7, 112.2, 75.0, 56.8, 19.4, 18.1; high resolution mass spectrum (ES+) m/z 196.0971 [(M+H)+ calcd for C$_{10}$H$_{14}$NO$_3$]
Oxazolyl Dithiane (+)-2.23: A solution of aldehyde (+)-2.35 (2.30 g, 11.7 mmol, 1.0 equiv) in 60 mL CH$_2$Cl$_2$ was treated with 1,3-propanedithiol (1.75 mL 17.51 mmol, 1.5 equiv.) and BF$_3$.OEt$_2$ (0.55 mL, 4.08 mmol, 0.35 equiv) respectively at 0°C under a nitrogen atmosphere, followed by stirring at that temperature for 2 h. The resulting mixture was quenched by the addition of a 2 M NaOH aqueous solution (20 mL), and diluted with 30 mL diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with the 2 M NaOH aqueous (15 mL) three times, saturated aqueous NaHCO$_3$ (20 mL), and brine (20 mL), dried over MgSO$_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 10:90, 15:85, 20:80) to furnish dithiane (+)-2.23 (3.21 g, 11.2 mmol, 96.1%) as an amorphous white solid; [α]$_D^{20}$ = +43.68 (c 4.75, CHCl$_3$); IR (film) 2977, 2931, 2819, 1654, 1542, 1446, 1422, 1368, 1273, 1204, 1149, 1112, 1095, 971.0, 875, 760 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ = 7.60 (s, 1H), 6.21 (t, $J$ = 1.5 Hz, 1H), 5.16 (q, $J$ = 6.5 Hz), 5.13 (s, 1H), 3.23 (s, 3H), 3.06 – 2.95 (m, 4H), 2.17 (m, 1H), 2.01 (m, 1H), 1.89 (d, $J$ = 1.5 Hz, 3H) 1.31 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ = 160.2, 151.1, 140.6, 134.4, 113.2, 74.7, 56.4, 41.3, 30.3, 25.3, 19.2, 17.6; high resolution mass spectrum (ES+) m/z 286.0940 [(M+H)$^+$ calcd for C$_{13}$H$_{20}$NO$_2$S$_2$]
Dithiane (−)-2.42: A solution of tert-butyl(1,3-dithian-2-yl)dimethylsilane (4.12 g, 17.6 mmol, 1.2 equiv) in diethyl ether (30 mL) was treated dropwise with n-BuLi (7.70 mL, 19.3 mmol, 2.5 M in hexanes, 1.3 equiv) at 0 °C under a nitrogen atmosphere. The mixture was kept at 0 °C for 15 min, warmed to ambient temperature and then stirred for 18 min before it was cooled to -78 °C. Epoxide (−)-2.41 (4.00 g, 19.8 mmol, 1.35 equiv.) in 40 mL of diethyl ether was added to the reaction mixture dropwise via a syringe followed by warming to -30 °C and stirring at that temperature for 2 hours. The reaction mixture was cooled back to -78 °C, and the epoxide (−)-2.36 (2.85 g, 14.7 mmol, 1.0 equiv.) in 25 mL of diethyl ether and 5 mL of DMPU was added dropwise via a syringe. The reaction mixture was kept at -78 °C for 30 min and then slowly warmed to ambient temperature overnight without removing the bath. The resulting mixture was quenched with the addition of saturated aqueous NH₄Cl (20 mL) and diluted with diethyl ether (30 mL). The organic layer was removed, and the aqueous layer extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10: 90, 15: 85, 20: 80) to furnish dithiane (−)-2.42 (8.30 g, 13.2 mmol, 89.8%) as a light yellow oil. [α]D²⁰ = -3.80 (c 4.0, CHCl₃); IR (film) 3466, 2954, 2928, 2856, 1613, 1514, 1471, 1250, 1097, 1038, 836, 775, 664 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.50 (s, 2H),
4.28 – 4.20 (m, 2H), 3.80 (s, 3H), 3.75 – 3.67 (m, 2H), 3.43 (dd, J = 4.5 Hz, 9.0 Hz, 1H), 3.39 (dd, J = 6.5 Hz, 9.0 Hz, 1H), 3.15 (s, 1H), 2.97 – 2.91 (m, 1H), 2.89 – 2.75 (m, 3H), 2.31 (m, 2H), 2.10 (m, 2H), 1.98 (m, 2H), 1.92 (m, 1H), 1.76 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ = 159.4, 130.4, 129.5, 112.9, 74.4, 73.0, 68.0, 67.6, 59.8, 55.4, 51.6, 47.1, 43.1, 42.2, 26.7, 26.3, 26.2, 26.1, 24.9, 18.3, 18.2, -3.6, -4.0, -5.1, -5.14; high resolution Mass-spectrum (ES+) m/z 653.3168 [(M+Na)+ calcd for C\(_{31}\)H\(_{58}\)O\(_5\)S\(_2\)Si\(_2\)Na]

Alcohol (--)\(-2.43\): Commercially available Raney nickel (19.0 g with water, Grade: Raney \(\text{®} 2800\) nickel from Aldrich) as a slurry in water was weighed out into the 200 mL round-bottomed flask and washed with anhydrous ethanol (20 mL) three times under a nitrogen atmosphere. Dithane (--)\(-2.42\) (1.59 mmol, 1.0 equiv) in 35 mL ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through for 20 min. The mixture was heated to 80 °C and kept at that temperature for 2.5 hours with stirring under a hydrogen atmosphere before it was brought to room temperature. Then the liquid phase was carefully transferred using a pipet to separate the desired product from residual flammable Raney nickel and washed with ethanol (15 mL) 4 times. The combined liquid was concentrated and purified by column chromatography (SiO\(_2\), ethyl acetate: hexanes 10: 90, 15: 85, 20: 80) to furnish alcohol (--)\(-2.43\) (0.79 g, 1.50 mmol, 94.5 %) as a colorless oil. [\(\alpha\)\(_D\)]\(^{20}\) = -4.1 (c 5.0, CHCl\(_3\)); IR: 3466, 2953, 2929, 2857, 1613, 1514, 1463, 1388, 1361, 1302, 1251, 1093, 1039, 836, 775, 664 cm\(^{-1}\); \(^1\)H NMR (500
MHz, CDCl$_3$) $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 4.48 (s, 2H), 3.80 (s, 3H), 3.80 – 3.75 (m, 2H), 3.64 (m, 2H), 3.47 (dd, $J = 9.8$ Hz, 2.8 Hz, 1H), 3.28 (t, $J = 8.8$ Hz, 1H), 2.31 (brs, 1H), 1.63 (q, $J = 6.5$ Hz, 2H) 1.55 – 1.30 (m, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 9H), 0.03(s, 3H); IR (film) 3466, 2954, 2929, 2857, 1613, 1514, 1463, 1388, 1360, 1302, 1251, 1094, 1039, 836, 775, 664 cm$^{-1}$; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 159.4$, 130.2, 129.4, 113.9, 74.4, 73.0, 70.3, 69.2, 60.0, 55.2, 40.1, 37.5, 33.4, 26.1, 26.0, 21.2, 18.3, 18.2, -4.3, -4.5, -5.2; high resolution mass-spectrum (ES+) m/z 549.3394 [(M+Na)$^+$ calcd for C$_{28}$H$_{54}$O$_5$Si$_2$Na]

Diol (−)-2.44 (Synthesis via Raney nickel reduction, route 1): Commercially available Raney nickel (9.0 g with water, Grade: Raney® 2800 nickel from Aldrich) as a slurry in water was weighed out into the 100 mL round-bottomed flask and washed with anhydrous ethanol (10 mL) three times under a nitrogen atmosphere. Alcohol (−)-2.43 (0.50 g, 0.95 mmol, 1.0 equiv) in 25 mL ethanol was added via syringe to the slurry mixture before hydrogen gas was bubbled through over 20 min. The mixture was heated to 80 °C and kept at that temperature for 15 hours with stirring under a hydrogen atmosphere before it was allowed to attain room temperature. The liquid phase was transferred carefully using a pipet to separate it from residual flammable Raney nickel and washed with ethanol (8 mL) 4 times. The combined liquid was concentrated and purified by column chromatography (SiO$_2$, ethyl acetate: hexanes, 20: 80, 30:70, 40:60) to furnish diol (−)-2.44 (337 mg, 0.830 mmol, 87.3 %) as a colorless oil.
\[ \alpha \]_D^{20} = -7.54 (c 5.0, CHCl₃); IR (film) 3379, 2953, 2929, 2857, 1472, 1361, 1255, 1094, 938, 836, 774, 664 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 3.81 (m, 1H), 3.71 (m, 1H), 3.70 – 3.63 (m, 3H), 3.43 (dd, \( J = 8.0 \) Hz, 11.0 Hz, 1H), 1.95 – 1.75 (brr, 2H), 1.65 (ddd, \( J = 2.3 \) Hz, 6.5 Hz, 11Hz, 2H), 1.58 – 1.42 (m, 5H), 1.42 – 1.35 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H), 0.04(s, 6H); ¹³C NMR (125 MHz, CDCl₃-d) δ = 72.4, 69.3, 66.9, 60.2, 40.2, 37.5, 33.5, 26.2 (3C), 26.1 (3C), 21.3, 18.5, 18.3, -4.2, -4.4, -5.1; high resolution mass-spectrum (ES+) m/z 429.2844 [(M+Na)+ calcd for C₂₀H₄₆O₄Si₂Na ]

**Diol (−)-2.41 (Synthesis via Sharpless dihydroxylation, route 2):** To a solution of olefin (−)-2.46 (4.70 g, 12.62 mmol, 1.0 equiv) in 80 mL t-BuOH and 80 mL water, a mixture of (DHQ)₂PHAL (500 mg, 0.642 mmol, 5 mol %), K₂CO₃ (5.23 g, 37.86 mmol, 3.0 equiv), K₃Fe(CN)₆ (12.50 g, 37.86 mmol, 3.0 equiv) and potassium osmate(VI) dehydrate (100 mg, 0.271 mmol, 2 mol %) was added at 0 °C. The reaction mixture was stirred for 10 hours at 0 °C before it was diluted with ethyl acetate (200 mL). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (50 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 20:90, 30:70) to furnish diol (−)-2.41 with its diastereomer (4.66 g, 11.5 mmol, 91.0%) as a colorless oil.

![TBSO](image)

**Epoxide (−)-2.24:** To a solution of diol (−)-2.44 (1.57 g, 3.87 mmol, 1.0 equiv.) in 40 mL THF 223 mg of NaH (95 weight-%, 8.83 mmol, 2.28 equiv) was added at 0 °C in nitrogen atmosphere, followed by stirring at room temperature for 20 min. The reaction
mixture was then cooled to 0 °C and solid TrisIm (1.54 g, 4.62 mmol, 1.2 equiv) was added in one portion. The resulting mixture was stirred for 1 h before it was quenched with the addition of 10 mL saturated aqueous NH₄Cl and diluted with diethyl ether. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (15 mL) twice. The combined organic layers were washed with the saturated aqueous NaHCO₃ (10 mL) and brine (10 mL) subsequently, dried over MgSO₄, filtered and concentrate. The resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 5:95, 10:90) to furnish epoxide (−)-2.24 (1.50 g, 3.86 mmol, quantitative) as a colorless oil. [α]D²⁰ = -10.33 (c 4.4, CHCl₃); IR (film) 2954, 2929, 2857, 1472, 1388, 1361, 1255, 1095, 1006, 938, 836, 774, 664 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 3.83 (m, 1H), 3.71 (td, J = 6 Hz, 3.5 Hz, 2H), 2.90 (m, 1H), 2.75 (t, J = 4.5 Hz, 1H), 2.46 (dd, J = 5.2 Hz, 2.8 Hz, 1H), 1.65 (ddd, J = 2.3 Hz, 6.5 Hz, 11Hz, 2H), 1.58 – 1.42 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ = 69.1, 59.9, 52.3, 47.0, 40.1, 37.3, 32.8, 26.1, 26.0, 21.7, 18.4, 18.2, -4.3, -4.4, -5.2; high resolution mass-spectrum (ES+) m/z 411.2729 [(M+Na)+ calcd for C₂⁰H₄₄O₃Si₂Na]

**Alcohol (+)-2.45:** To a solution of epoxide (−)-2.38 (1.80 g, 8.90 mmol, 1.0 equiv) and copper(I) iodide (0.70 g, 3.67 mmol, 0.41 equiv) in 30 mL Et₂O at -78 °C under a nitrogen atmosphere, a solution of but-3-en-1-ylmagnesium bromide (1 M in Et₂O, 26.7 mL, 26.7 mmol, 3.0 equiv) was added dropwise. After complete addition, the temperature was increased to room temperature, and the reaction mixture was continued to stir for 4
hours before it was recooled to 0 °C. The resulting mixture was quenched at 0 °C by addition of saturated aqueous NH₄Cl (20 mL). The organic layer was removed and the aqueous layer was extracted with diethyl ether (30 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 15:85, 20:80) to furnish alcohol (+)-2.45 (2.14 g, 8.28 mmol, 93.0%) as a colorless oil. [α]D²⁰ = +14.40 (c 1.40, CHCl₃); IR (film) 3443, 3077, 2928, 2858, 1641, 1472, 1463, 1256, 1090, 1005, 910, 837, 777 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 5.77 (m, 1H), 4.97 (d, J = 17.0 Hz, 1H), 4.91 (d, J = 10.0 Hz, 1H), 3.86 (m, 1H), 3.78 (m, 2H), 3.44 (s, 1H), 2.04 (m, 2H), 1.61 (m, 2H), 1.48 – 1.60 (m, 2H), 1.39 – 1.48 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ = 139.0, 114.6, 72.1, 63.0, 38.5, 37.1, 33.9, 26.0, 25.0, 18.3, -5.39, -5.41; high resolution mass spectrum (ES) m/z 259.2088 [(M+H)+ calcd for C₁₄H₃₁O₂Si]

Olefin (-)-2.46: To a solution of alcohol (+)-2.45 (3.70 g, 14.3 mmol, 1.0 equiv) in 80 mL dichloromethane at 0 °C under a nitrogen atmosphere, 2,6-lutidine (3.5 mL, 30.1 mmol, 2.1 equiv) was added followed by TBSOTf (4.0 g, 15.15 mmol, 1.06 equiv). The reaction mixture was stirred for 2 hours at 0 °C before it was quenched by addition of saturated aqueous NaHCO₃ (20 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated, and the
resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 2:98, 5:95, 10:90) to furnish olefin (-)-2.46 (4.93 g, 13.2 mmol, 92.4%) as a colorless oil. 

\[ \alpha \]D = -9.45 (c 3.00, CHCl₃); IR (film) 2956, 2928, 2858, 1472, 1256, 1094, 839, 833, 775 cm⁻¹, ¹H NMR (500 MHz, CDCl₃) δ = 5.80 (m, 1H), 5.00 (d, J = 17.0 Hz, 1H), 4.94 (d, J = 10.5 Hz, 1H), 3.81 (brs, 1H), 3.66 (m, 2H), 2.04 (d, J = 6.5 Hz, 2H), 1.65 (q, J = 6.0 Hz, 2H), 1.48 – 1.52 (m, 4H), 0.89 (s, 18H), 0.04 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ = 139.1, 114.6, 69.4, 60.2, 40.3, 37.1, 34.1, 26.18, 26.15, 24.7, 18.5, 18.3 -4.2, -4.4, -5.1; high resolution mass spectrum (ES) m/z 373.2955 [(M+H)+ calcd for C₂₀H₄₅O₂Si₂]

**Dithiane (+)-2.52 (the second generation synthesis):** To a solution of dithiane (+)-2.23 (3.30 g, 11.6 mmol, 1.0 equiv.) in 40 mL of Et₂O at -78 °C under a nitrogen atmosphere, a solution of n-BuLi (2.30 M in hexanes, 5.79 mL, 13.3 mmol, 1.15 equiv) was allowed to add in 5 minutes. After complete addition, the reaction mixture was stirred for 20 minutes at -78 °C. Epoxide (-)-2.24 (4.50 g, 11.57 mmol, 1.0 equiv.) in 20 mL of E₂O was added to reaction mixture dropwise at the same temperature over 5 minutes. The resulting mixture was gradually allowed to come to 0 °C over 2 hours before it was quenched by addition of saturated aqueous NH₄Cl (20 mL). The organic layer was removed, and the aqueous layer was extracted with Et₂O (30 mL) twice. The combined
organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered, and concentrated, and the resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 15:85, 20:80, 30:70) to furnish dithiane (+)-2.52 (6.01 g, 8.92 mmol, 77.0%) as a colorless oil. [$\alpha$]$^\text{D}_{20}$ = +16.00 (c 1.68, CHCl$_3$); IR (film) 2928, 2856, 1468, 1255, 1096, 836, 774 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.71 (s, 1H), 6.21 (s, 1H), 5.11 (q, $J$ = 6.5 Hz, 1H), 3.89 (brs, 1H), 3.78 (m, 1H), 3.64, (dd, $J$ = 10.5 Hz, 6.5 Hz, 2H), 3.49 (s, 1H), 3.23 (s, 3H), 2.78 – 2.92 (m, 4H), 2.22 – 2.35, (m, 2H), 2.01 (m, 2H), 1.90 (s, 3H), 1.45 (m, 2H), 1.47 – 1.52 (m, 6H), 1.31 (d, $J$ = 6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 160.9, 152.1, 143.9, 136.5, 113.3, 75.1, 69.4, 68.5, 60.2, 56.8, 49.5, 40.2, 37.9, 37.7, 27.8, 27.6, 26.2, 26.1, 25.0, 21.4, 19.4, 18.5, 18.3, 17.9, -4.2, -4.4, -5.09, -5.10; high resolution mass spectrum (ES) m/z 674.3765 [(M+H)$^+$ calcld for C$_{33}$H$_{64}$NO$_5$S$_2$Si$_2$]

**Ketone (+)-2.53 (synthesis via mercury(II)-mediated hydrolysis, the first generation synthesis):** To a solution of dithiane (+)-2.52 (900 mg, 1.33 mmol, 1.0 equiv) and CaCO$_3$ (280 mg, 2.80 mmol, 2.10 equiv) in 20 mL of THF/H$_2$O (3:1) at 0 °C under air atmosphere, HgClO$_4$.6H$_2$O (1120 mg, 2.80 mmol, 2.1 equiv.) was added as a solid in one portion. The reaction mixture was stirred for 30 minutes at 0 °C before it was diluted by dichloromethane (30 mL). After filtering through a plug of Celite (5 g), the resulting mixture was washed with saturated aqueous Na$_2$S$_2$O$_3$ (20 mL). The organic layer was
removed, and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered, and concentrated, and the resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 15:85, 20:80, 30:70) to furnish dithiane (+)-2.52 (489 mg, 0.837 mmol, 62.9%) as a colorless oil.

**Ketone** (+)-2.53 (synthesis utilizing hydrogen peroxide catalyzed by Fe(acac)$_3$ and sodium iodide, the second generation synthesis): To a solution of dithiane (+)-2.52 (2.55 g, 3.77 mmol, 1.0 equiv) in ethyl acetate (40 mL) and water (40 mL), Fe(acac)$_3$ (271 mg, 0.757 mmol, 0.2 equiv), sodium iodide (848 mg, 5.66 mmol, 1.5 equiv) and 30% hydrogen peroxide (1.3 mL aqueous solution, 11.31 mmol, 3.0 equiv) were added sequentially at 0 °C under an aerobic atmosphere. The reaction mixture was stirred for 30 minutes at the same temperature before it was quenched by the addition of saturated aqueous Na$_2$S$_2$O$_3$. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 ml) three times. The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 15:85, 20:80, 30:70) to furnish dithiane (+)-2.52 (1.65 g, 2.83 mmol, 75.0%) as a colorless oil.

$[\alpha]_D^{25} = +24.60$ (c 1.40, CHCl$_3$); IR (film) 3465, 2928, 2856, 1686, 1562, 1463, 1255, 1096, 968, 836, 774, 664 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.15$ (d, $J = 1.5$ Hz, 1H), 6.24 (s, 1H), 5.19 (q, $J = 6.5$ Hz, 1H), 4.19 (brs, 1H), 3.83 (brs, 1H), 3.67 (brs, 2H), 3.25 (s, 3H), 3.13 (d, $J = 17.5$ Hz, 2H), 3.01 (d, $J = 17.5$ Hz, 9.0 Hz, 1H), 1.95 (s, 3H), 1.66 (q, $J = 6.0$ Hz, 2H), 1.35 – 1.68 (m, 6H), 1.34 (dd, $J = 6.5$ Hz, 1.0 Hz, 3H), 0.891 (s, 9H), 0.887 (s, 9H), 0.05 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 196.1$,
160.7, 154.2, 141.4, 141.2, 112.4, 75.1, 67.9, 60.2, 56.8, 46.9, 40.2, 37.5, 37.2, 26.2, 26.1, 21.3, 19.4, 18.5, 18.3, 18.1, -4.2, -4.4, -5.1; high resolution mass spectrum (ES) m/z 584.3802 [(M+H)+ calcd for C$_{30}$H$_{58}$NO$_6$Si$_2$]

Diol (+)-2.54 (the second generation synthesis): To a solution of ketone (+)-2.52 (1.70 g, 2.91 mmol, 1.0 equiv) in 30 mL of THF/MeOH (4:1), a solution of Et$_2$BOMe (1M in THF, 6.11 mL, 6.11 mmol, 2.1 equiv) was added dropwise at -78 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 15 minutes at the same temperature, NaBH$_4$ (250 mg, 6.58 mmol, 2.25 equiv.) was added in one portion. The resulting mixture was stirred for 2 hours before it was diluted by MeOH (20 mL). The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle’s salt solution (30 mL). The resulting mixture was stirred at room temperature for 30 minutes before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) three times. The combined organic layers were washed with 2 M NaOH aqueous solution (20 mL * 3), saturated aqueous NH$_4$Cl (20 mL), and brine (20 mL), then dried over MgSO$_4$, filtered and concentrated. The resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 20:80, 30:70, 50:50) to furnish diol (+)-2.54 (1.62 g, 2.76 mmol, 95.0%) as a colorless oil. [α]$_D^{20}$ = +12.75 (c 1.00, CHCl$_3$); IR (film) 3388, 2929, 2857, 1655, 1472, 1363, 1255, 1095, 836, 775 cm$^{-1}$; $^1$H NMR (500
MHz, CDCl$_3$) $\delta = 7.48$ (s, 1H), 6.18 (s, 1H), 5.13 (q, $J = 6.5$ Hz, 1H), 4.93 (d, $J = 7.0$ Hz, 1H), 3.95 (brs, 1H), 3.81 (brs, 2H), 3.66 (brs, 2H), 3.21 (s, 3H), 3.13 (brs, 1H), 1.98 (d, $J = 14.5$ Hz, 1H), 1.88 (s, 3H), 1.86 (m, 1H), 1.64 (q, $J = 6.0$ Hz, 2H), 1.32 – 1.58 (m, 6H), 1.29 (dd, $J = 6.5$ Hz, 3H), 0.874 (s, 9H), 0.868 (s, 9H), 0.03 (s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 160.7, 151.1, 144.7, 133.1, 113.5, 75.0, 72.4, 69.4, 68.5, 60.2, 56.7, 43.0, 40.2, 38.5, 37.5, 26.2, 26.1, 21.0, 19.5, 18.5, 18.3, 17.9, -4.2, -4.4, -5.1; high resolution mass spectrum (ES) m/z 586.3953 [(M+H)$^+$ calcd for C$_{30}$H$_{60}$NO$_6$Si$_2$]

**PMP-acetal (–)-2.55 (the first generation synthesis):** To a solution of diol (+)-2.54 (610 mg, 1.04 mmol, 1.0 equiv) in 20 mL of dichloromethane, CSA (20 mg, 0.086 mmol, 0.083 equiv) was added as one portion followed by addition of $p$-methoxybezaaldehyde dimethyl acetate (304 mg, 1.67 mmol, 1.60 equiv.) at 0 °C under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before it was quenched by saturated aqueous NaHCO$_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (10 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and
concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 5:95, 10:90, 20:80) to furnish PMP acetal (−)-2.55 (585 mg, 0.83 mmol, 80.0%) as a colorless oil. [α]D²⁰ = -1.62 (c 0.77, CHCl₃); IR (film) 2929, 2856, 1616, 1518, 1463, 1362, 1251, 1097, 1037, 835, 774 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.54 (s, 1H), 7.46 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 6.21 (s, 1H), 5.65 (s, 1H), 5.17 (q, J = 6.5 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 3.93 (brs, 1H), 3.81 (brs, 1H), 3.80 (s, 3H), 3.66 (d, J = 3.5 Hz, 2H), 3.23 (s, 3H), 2.00 (d, J = 12.5 Hz, 1H), 1.89 (s, 3H), 1.73 (m, 2H), 1.65 (q, J = 6.0 Hz, 2H), 1.39 – 1.61 (m, 5H), 1.31 (d, J = 6.5 Hz, 3H), 0.89 (s, 18H), 0.04 (s, 12H); ¹³C NMR (125 MHz, CDCl₃) δ = 160.5, 160.1, 150.7, 142.5, 134.0, 131.4, 127.7, 113.8, 113.7, 101.1, 75.0, 73.1, 69.4, 60.2, 56.7, 55.5, 40.3, 37.6, 36.6, 36.3, 26.2, 26.1, 20.9, 19.5, 18.5, 18.3, 17.8, -4.2, -4.3, -5.1; high resolution mass spectrum (ES) m/z 704.4380 [(M+H)+ calcd for C₃₈H₆₆NO₇Si₂]

PMP-acetal (−)-2.64 (one pot reaction from diol (+)-2.54, the second generation synthesis): To a solution of diol (+)-2.54 (790 mg, 1.35 mmol, 1.0 equiv) in 20 mL of dichloromethane, CSA (30 mg, 0.13 mmol, 0.096 equiv) was added in one portion followed by addition of p-methoxybenzaldehyde dimethyl acetate (345 mg, 1.89 mmol,
1.4 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before subsequent addition of TBAF (1.0 M in THF, 10.80 mL, 10.80 mmol, 8.0 equiv) and acetic acid (473 mg, 6.75 mmol, 5.0 equiv). The resulting mixture was allowed to increase to room temperature and was allowed to stir for 16 hours before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 5:95, 10:90, 20:80) to furnish PMP acetal (−)-2.64 (700 mg, 1.19 mmol, 88.0%) as a colorless oil. [α]D²₀ = -3.39 (c 1.60, CHCl₃); IR (film) 3435, 2929, 2856, 1615, 1518, 1463, 1368, 1336, 1250, 1171, 1112, 1035, 835, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.54 (s, 1H), 7.45 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 6.20 (s, 1H), 5.64 (s, 1H), 5.17 (q, J = 6.5 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 3.93 (brs, 2H), 3.81 (brs, 1H), 3.80 (s, 3H), 3.72 (brs, 1H), 3.22 (d, J = 1.0 Hz, 3H), 2.34 (brs, 1H), 2.00 (d, J = 12.8 Hz, 1H), 1.89 (s, 3H), 1.81 (m, 1H), 1.75 (m, 1H), 1.68 (m, 2H), 1.58 (m, 4H), 1.42 (m, 1H), 1.30 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 160.5, 160.1, 150.6, 142.4, 133.9, 131.2, 127.6, 113.7, 113.6, 101.1, 76.8, 74.8, 72.9, 71.6, 60.3, 56.6, 55.4, 38.0, 36.9, 36.5, 36.1, 26.0, 21.0, 19.4, 18.1, 17.7, -4.3, -4.5; high resolution mass spectrum (ES) m/z 590.3506 [(M+H)⁺ calcd for C₃₂H₅₂NO₇Si]
Alcohol (+)-2.56 (the first generation synthesis): To a solution of PMP acetal (−)-2.55 (250 mg, 0.355 mmol, 1.0 equiv) in 10 mL of dichloromethane, a DIBAL-H solution (1 M in hexanes, 1.24 mL, 1.24 mmol, 3.5 equiv) was added dropwise at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 100 minutes at the same temperature before it was quenched with MeOH at -78 °C. The temperature was then allowed to increase to 0 °C, at which point a saturated aqueous Rochelle’s salt solution (10 mL) was added. The resulting mixture was stirred at room temperature for 30 minutes before it was diluted by ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 30:70) to furnish acid (+)-2.56 (230 mg, 0.327 mmol, 92.0%) as a colorless oil. 

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\alpha_{D}^{20} = +27.72 \ (c \ 1.00, \ CHCl₃); \ H\ NMR \ (500 MHz, \ CDCl₃) \ \delta = 7.44 \ (d, \ J = 1.0 \ Hz, \ 1H), \\
7.27 \ (d, \ J = 8.6 \ Hz, \ 2H), \ 6.88 \ (d, \ J = 8.6 \ Hz, \ 2H), \ 6.19 \ (s, \ 1H), \ 5.16 \ (q, \ J = 6.5 \ Hz, \ 1H), \\
4.84 \ (d, \ J = 9.5 \ Hz, \ 1H), \ 4.61 \ (d, \ J = 11.0 \ Hz, \ 1H), \ 4.39 \ (s, \ 1H), \ 3.85-3.74 \ (m, \ 2H), \ 3.82 \ (s, \ 3H), \ 3.67 \ (m, \ 2H), \ 3.22 \ (s, \ 3H), \ 2.07 \ (dt, \ J = 11.0 \ Hz, \ 3.5 \ Hz, \ 1H), \ 1.93-1.89 \ (m, \ 1H), \\
1.89 \ (s, \ 3H), \ 1.65 \ (m, \ 4H), \ 1.51-1.37 \ (m, \ 4H), \ 1.30 \ (d, \ J = 6.5 \ Hz, \ 3H), \ 0.90 \ (s, \ 9H), \ 0.89 \ (s, \ 9H) \ 0.054 \ (s, \ 3H), \ 0.047 \ (s, \ 3H); \ ^{13}C\ NMR \ (125 MHz, \ CDCl₃) \ \delta = 160.5, \ 159.6, \\
150.3, \ 144.9, \ 133.3, \ 130.2, \ 129.8, \ 114.2, \ 113.7, \ 79.5, \ 74.9, \ 70.6, \ 69.3, \ 68.3, \ 60.1, \ 56.6,
55.4, 41.1, 40.2, 37.9, 33.9, 26.11, 26.07, 20.3, 19.4, 18.4, 18.3 17.7, -4.2, -4.4, -5.1; high resolution mass spectrum (ES) m/z 706.4501 [(M+H)^+ calcd for C_{38}H_{68}NO_{7}Si_{2}]

Acid (+)-2.65 (the second generation synthesis): To a solution of PMP acetal (-)-2.64 (184 mg, 0.312 mmol, 1.0 equiv) in 2.5 mL of t-BuOH and 0.25 mL of pH 7 buffer solution, TEMPO solution (0.025 M in CH_{3}CN, 5 mL, 0.125 mmol, 0.4 equiv) was added at room temperature under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before the subsequent addition of NaClO_{2} (1 M in water, 0.624 mL, 0.624 mmol, 2.0 equiv) and NaClO (0.025 M in water, 12.5 mL, 0.312 mmol, 1.0 equiv) solution. The reaction was stirred at room temperature for 3 hours before it was quenched by saturated aqueous Na_{2}SO_{3} (10 mL). After dilution with ethyl acetate (20 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO_{4}, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO_{2}, ethyl acetate: hexanes 5:95, 10:90, 20:80, 30:70) to furnish acid (+)-2.65 (184 mg, 0.296 mmol, 95.0%) as a colorless oil. [\alpha]^{20}_{D} = +4.84 (c 1.00, CHCl_{3}); IR (film) 2930, 1711, 1518, 1250, 1114, 834, 776 cm^{-1}; ^{1}H NMR (500 MHz, CDCl_{3}) \delta =
7.55 (s, 1H), 7.45 (d, \(J = 8.8\) Hz, 2H), 6.88 (d, \(J = 8.8\) Hz, 2H), 6.23 (s, 1H), 5.64 (s, 1H), 5.15 (q, \(J = 6.5\) Hz, 1H), 4.93 (d, \(J = 10.5\) Hz, 1H), 4.14 (t, \(J = 5.4\) Hz, 1H), 3.93 (brs, 1H), 3.80 (s, 3H), 3.23 (s, 3H), 2.50 (d, \(J = 6.1\) Hz, 2H), 2.00 (d, \(J = 12.8\) Hz, 1H), 1.89 (d, \(J = 1.5\) Hz, 3H), 1.72 (m, 1H), 1.70 (m, 1H), 1.59 (m, 4H), 1.45 (brs, 1H), 1.30 (d, \(J = 6.7\) Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 176.4, 160.5, 160.0, 150.8, 142.3, 134.0, 131.2, 127.6, 113.7, 113.6, 101.1, 76.7, 75.0, 72.8, 69.4, 56.6, 55.4, 42.1, 37.4, 36.4, 36.0, 25.9, 20.8, 19.4, 18.1, 17.7, -4.4, -4.7; high resolution mass spectrum (ES) m/z 626.3118 [(M+Na)+ calcd for C\(_{32}\)H\(_{49}\)NO\(_8\)SiNa]

**Diol (+)-2.57 (the first generation synthesis):** To a solution of alcohol (+)-2.56 (227 mg, 0.322 mmol, 1.0 equiv) in 5 mL of THF in a 50 mL plastic container, 4.7 mL of the mixture of HF-pyridine complex/pyridine/THF (1:1.5:2.5) was added dropwise at 0 °C. The reaction mixture was allowed to stir at the same temperature for 45 minutes before it was slowly quenched by saturated aqueous NaHCO\(_3\). After dilution with ethyl acetate (20 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO\(_4\), filtered and concentrated. The resulting oil was purified by column chromatography (SiO\(_2\) ethyl acetate: hexanes 20:80, 30:70, 40:60) to furnish diol (+)-2.57 (152 mg, 0.258 mmol, 80.0%) as a colorless oil. \([\alpha]_{D}^{20} = +21.11 (c 1.33, \text{CHCl}_3)\); IR
(film) 3407, 2929, 2856, 1613, 1514, 1250, 1095, 1036, 856, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.44 (s, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.19 (s, 1H), 5.16 (q, J = 6.5 Hz, 1H), 4.83 (dd, J = 8.9 Hz, 2.9 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 11.0 Hz, 1H), 4.02-3.92 (m, 2H), 3.79 (s, 3H), 3.78 (m, 2H), 3.72 (m, 1H), 3.21 (s, 3H), 2.07 (dt, J = 11.0 Hz, 3.5 Hz, 1H), 1.92 (m, 1H), 1.88 (s, 3H), 1.77 (m, 1H), 1.55 (m, 2H), 1.63 (m, 3H), 1.38 (m, 2H), 1.29 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 160.5, 159.6, 150.4, 144.8, 133.3, 130.2, 129.7, 114.2, 113.7, 79.0, 74.9, 71.5, 70.6, 67.9, 60.2, 56.6, 55.4, 41.0, 38.1, 37.3, 33.8, 26.0, 20.5, 19.4, 18.1, 17.7, -4.2, -4.5; high resolution mass spectrum (ES) m/z 592.3612 [(M+H)⁺ calcd for C₃₂H₅₄NO₈Si]

Acid (+)-2.61 (synthesis via chemoselective oxidation, the first generation synthesis)

To a solution of diol (+)-2.57 (58 mg, 0.098 mmol, 1.0 equiv) in 0.775 mL of t-BuOH and 0.5 mL of pH 7 buffer solution, a TEMPO solution (0.025 M in CH₃CN, 1.18 mL, 0.029 mmol, 0.3 equiv) was added at room temperature. The resulting mixture was stirred for 20 minutes at the same temperature before the subsequent addition of NaClO₂ (1 M in water, 0.196 mL, 0.196 mmol, 2.0 equiv) and NaClO (0.025 M in water, 4.0 mL, 0.1 mmol, 1.0 equiv). The reaction was stirred at room temperature for 3 hours before it was quenched with saturated aqueous Na₂SO₃ solution (5 mL). After dilution with ethyl
acetate (10 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 20:80, 30:70, 50:50, 80:20) to furnish acid (+)-2.61 (36 mg, 0.059 mmol, 60.0%) as a colorless oil.

**Acid (+)-2.61 (synthesis via chemoselective reduction, the second generation synthesis):** To a solution of PMP acetal (+)-2.55 (1.25 g, 2.07 mmol, 1.0 equiv) in 50 mL of dichloromethane, a DIBAL-H solution (1 M in hexanes, 9.93 mL, 9.93 mmol, 4.8 equiv) was added dropwise at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 100 minutes at the same temperature before it was quenched with MeOH at -78 °C. The temperature was then allowed to increase to 0 °C followed by the addition of saturated aqueous Rochelle’s salt (30 mL). The resulting mixture was stirred at room temperature for 30 minutes before it was diluted by ethyl acetate (50 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) six times. The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated. The resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 20:80, 30:70, 50:50, 80:20) to furnish acid (+)-2.61 (1.17 g, 1.93 mmol, 93.0%) as a colorless oil. [α]²⁰_D = +32.42 (c 1.00, CHCl₃); IR (film) 2930, 1712, 1514, 1245, 1096, 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.43 (s, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.19 (s, 1H), 5.11 (q, J = 6.5 Hz, 1H), 4.83 (dd, J = 9.5 Hz, 2.9 Hz, 1H), 4.57 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.0 Hz, 1H), 4.12 (m, 1H), 3.79 (s, 3H), 3.75 (m, 1H), 3.21 (s, 3H), 2.28 (d, J = 6.1 Hz, 2H), 2.05 (dt, J = 11.0 Hz, 3.5 Hz, 1H), 1.95 (m, 1H), 1.88 (s, 3H), 1.73 (m, 2H), 1.67 (m, 2H), 1.42 (m, 2H),
1.29 (d, \( J = 6.5 \) Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta = 175.9, 160.7, 159.6, 150.8, 144.6, 133.5, 130.2, 129.8, 114.2, 113.6, 78.8, 75.0, 70.7, 69.4, 67.6, 56.6, 55.5, 42.2, 40.8, 37.7, 33.6, 26.0, 20.3, 19.5, 18.2, 17.8, -4.3, -4.6; high resolution mass spectrum (ES) m/z 606.3466 [(M+H\(^+\)] calcld for C\(_{32}\)H\(_{52}\)NO\(_8\)Si]

\[\text{\textbeta-\text{acido\textit{}} Acido} \text{ (+)-2.22 (synthesis utilizing HCl/EtOH, the first generation synthesis):} \]

To a solution of (+)-2.61 (55 mg, 0.091 mmol, 1.0 equiv) in 1.5 mL of EtOH, 0.6 mL of HCl solution (0.54 M in EtOH, prepared by addition of 0.2 mL of trichloroacetyl chloride to 5 mL of ethanol) was added at room temperature. The reaction mixture was stirred for 3 hours before it was quenched by the addition of pyridine (0.05 mL). The resulting mixture was then concentrated under reduced pressure followed by azeotropic evaporation with toluene (5 mL) to remove excess pyridine. The resulting oil was purified by column chromatography (SiO\(_2\), ethyl acetate: hexanes 50:50, 80:20 then ethyl acetate: acetic acid 99:1) to furnish \( \text{\textbeta\text{-\textit{acido\textit{}}} Acido} \text{ (+)-2.22} \) (38 mg, 0.0774 mmol, 85.0%) as a colorless oil.

\textbf{\( \text{\textbeta\text{-\textit{acido\textit{}}} Acido} \text{ (+)-2.22 (synthesis utilizing TBAF/HOAc, the second generation synthesis):}} \]

To a solution of (+)-2.61 (800 mg, 1.32 mmol, 1.0 equiv) in 30 mL of THF, TBAF (1.0 M in THF, 9.24 mL, 9.24 mmol, 7.0 equiv) was added dropwise followed by acetic acid (400 mg, 6.60 mmol, 5.0 equiv) at room temperature. The resulting mixture
was stirred for 8 hours before it was quenched with brine. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) six times. The combined organic layers were dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 50:50, 80:20 then ethyl acetate: acetic acid 99:1) to furnish β-hydroxy acid (+)-2.22 (569 mg, 1.16 mmol, 87.7%) as a colorless oil. \([\alpha]^{20}_D = +56.17 (c 1.47, \text{CHCl}_3)\); IR (film) 3421, 2934, 1719, 1612, 1514, 1443, 1249, 1177, 1094, 1035, 822 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) \(\delta = 7.46 (s, 1H), 7.26 (d, J = 8.6 \text{ Hz}, 2H), 6.87 (d, J = 8.6 \text{ Hz}, 2H), 6.21 (s, 1H), 5.03 (q, J = 6.5 Hz, 1H), 4.86 (dd, J = 9.3 Hz, 2.6 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.0 Hz, 1H), 4.04 (brs, 1H), 3.80 (s, 3H), 3.75 (brs, 1H), 3.21 (s, 3H), 2.50 (m, 2H), 2.13 (d, J = 14.3Hz, 1H), 1.89 (m, 1H), 1.89 (s, 3H), 1.72 (m, 1H), 1.63 (m, 1H), 1.38 – 1.58 (m, 4H), 1.29 (d, J = 6.5 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) \(\delta = 176.1, 160.9, 159.5, 151.5, 144.2, 133.8, 130.2, 129.7, 114.1, 113.2, 79.1, 75.1, 70.5, 68.0, 67.4, 56.6, 55.4, 41.4, 40.7, 36.8, 33.3, 21.0, 19.5, 17.8); high resolution mass spectrum (ES) \(m/z 490.2440 [(M-H) \text{ calcd for C}_{26}\text{H}_{36}\text{NO}_8]\)

Alcohol (–)-2.68: To a solution of diisopropylamine (10.6 mL, 75.4 mmol, 4.2 equiv) in 60 mL THF, an \(n\)-BuLi solution (2.33 M in hexanes, 30 mL, 70.04 mmol, 3.9 equiv) was added dropwise over 10 minutes at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 15 minutes at the same temperature before the addition of
ammonium-borane solid (2.22 g, 71.84 mmol, 4.0 equiv) in one portion at 0 °C. The temperature was increased to room temperature, and the reaction mixture was stirred for 30 minutes before it was recooled to 0 °C. A solution of alcohol (-)-2.67 (9.55 g, 17.96 mmol, 1.0 equiv) in 90 mL of THF was then added dropwise, and the temperature was allowed to increase to room temperature after the addition. The resulting mixture was stirred at the same temperature for 2 hours before it was slowly quenched with 100 mL of 3 N HCl aqueous solution over 20 minutes at 0 °C. The resulting mixture was stirred at 0°C for a further 30 minutes before the dilution with Et₂O (200 mL). The organic layer was separated, and the aqueous phase was extracted with Et₂O (50 mL) twice. The combined organic layers were washed with saturated aqueous NaHCO₃ (50 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 50:50, 80:20) to furnish alcohol (-)-2.68 (6.60 g, 17.81 mmol, 99.2%) as a colorless oil. [α]²⁰ D = -15.66 (c 3.20, CHCl₃); IR (film) 3342, 2929, 2857, 1417, 1427, 1389, 1112, 1036, 824, 740, 701, 613.3 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.72-7.65 (m, 4 H), 7.45-7.35 (m, 6H), 3.52-3.47 (m, 3H), 3.40 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.22 (ddd, J = 13.5 Hz, 9.0 Hz, 4. Hz), 1.14 (ddd, J = 13.5 Hz, 9.0 Hz, 4.5 Hz), 1.08 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 135.8, 134.3, 134.2, 129.7, 127.8, 68.8, 69.2, 37.0, 33.31, 33.26, 27.1, 19.5, 16.8, 16.6; high resolution mass spectrum (ES) m/z 371.2390 [(M+H) calcd for C₂₃H₃₅O₂Si]
Olefin (-)-2.69: To a solution of alcohol (-)-2.68 (6.50 g, 17.5 mmol, 1.0 equiv) in 70 mL dichloromethane, diisopropylethylamine (9.15 mL, 52.5 mmol, 3.0 equiv) and DMSO (6.21 mL, 87.5 mmol, 5.0 equiv) were added followed by portionwise addition of SO$_3$.pyridine (8.36 g, 52.5 mmol, 3.0 equiv) at 0 °C under an air atmosphere. The resulting mixture was stirred for 1 hour at the same temperature before it was quenched by 2 M NaHSO$_4$ aqueous solution (30 mL). The organic layer was separated, and the aqueous phase was extracted with Et$_2$O (50 mL) twice. The combined organic layers were washed with saturated aqueous NaHCO$_3$ (50 mL) and brine (30 mL), dried over MgSO$_4$, filtered and concentrated, and the resulting corresponding aldehyde was moved to the next step as a colorless oil without further purification.

To a solution of (--)-B-methoxydiisopinocampheylborane (9.41 g, 29.8 mmol, 1.7 equiv) in 50 mL Et$_2$O, allylmagnesium bromide solution (1.0 M in Et$_2$O, 21.87 mL, 21.87 mmol, 1.25 equiv) was added dropwise over 20 minutes at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 hour at the same temperature. The temperature was allowed to increase to room temperature, and the reaction mixture was stirred for 1 hour before it was recooled to -78 °C. A solution of aldehyde (-)-2.68 (17.50 mmol, 1.0 equiv, crude) in 35 mL of Et$_2$O was then added dropwise to the reaction mixture at -78 °C over 20 minutes. The resulting mixture was stirred at the same temperature for 1 hour before the temperature was allowed to increase to 0 °C. A pH7 buffer solution (30 mL) was then added followed by the careful addition of 30% H$_2$O$_2$ (7 mL) over 20 minutes at
The resulting mixture was then stirred at room temperature overnight before it was diluted by Et₂O. The organic layer was separated, and the aqueous phase was extracted with Et₂O (60 mL) twice. The combined organic layers were washed with saturated aqueous NaS₂O₃ (30 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 20:80, 30:70) to furnish olefin (−)-2.69 (6.53 g, 15.93 mmol, 91.0% over 2 steps) as a colorless oil. [α]D²⁰ = -13.42 (c 2.86, CHCl₃); IR (film) 3325, 3071, 2959, 2858, 1709, 1640, 1589, 1471, 1428, 1389, 1112, 914, 824, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.68-7.62 (m, 4 H), 7.41-7.31 (m, 6H), 5.81 (dddd, J = 17.5 Hz, 9.7 Hz, 7.2 Hz, 6.5 Hz, 1H), 5.18-5.08 (m, 2H), 3.53-3.48 (m, 3H), 2.31-2.25 (m, 1H), 2.15 (m, 1H), 1.76 (brs, 1H), 1.62 (brs, 1H), 1.35-1.25 (m, 1H), 1.21-1.11 (m, 1H), 1.07 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 135.9, 135.7, 134.29, 134.27, 129.7, 127.8, 118.0, 74.7, 69.8, 39.2, 36.8, 35.3, 33.4, 27.1, 19.5, 16.7, 14.1; high resolution mass spectrum (ES) m/z 411.2717 [(M+H) calcd for C₂₆H₃₉O₂Si]

![Structure](image)

**Olefin (−)-2.70:** To a solution of olefin (−)-2.69 (1.03 g, 2.51 mmol, 1.0 equiv) in 20 mL of dichloromethane at 0 °C under a nitrogen atmosphere, 2,6-lutidine (0.7 mL, 6.02 mmol, 2.4 equiv) was added, followed by the dropwise addition of TIPSOTf (0.8 g, 3.01
mmol, 1.2 equiv). The reaction mixture was stirred for 2 hours at 0 °C before it was quenched by addition of saturated aqueous NaHCO₃ (10 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated, the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 2:98, 5:95, 10:90) to furnish olefin (–)-2.70 (1.29 g, 2.28 mmol, 90.7%) as a colorless oil. [α]²⁰D = -9.99 (c 2.22, CHCl₃); IR (film) 3072, 2942, 2865, 1463, 1428, 1388, 1112, 882, 824, 784, 701, 678, 613 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.71-7.68 (m, 4 H), 7.43-7.36 (m, 6H), 5.78 (dddd, J = 17.2 Hz, 9.8 Hz, 7.2 Hz, 6.5 Hz, 1H), 5.04 (dd, J = 17.2 Hz, 1.8 Hz, 1H), 4.99 (dt, J = 9.8 Hz, 1.0 Hz, 1H), 3.79 (m, 1H), 3.49 (m, 2H), 2.28 (m, 2H), 1.80-1.68 (m, 2H), 1.41 (td, J = 9.8 Hz, 4.0 Hz, 1H), 1.37 (td, J = 9.8 Hz, 4.0 Hz, 1H), 1.12-1.02 (m, 30 H), 0.89 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 136.1 135.87, 135.86, 134.39, 134.37, 129.7, 127.8, 116.6, 76.7, 70.0, 39.3, 36.4, 34.9, 33.5, 27.1, 19.5, 18.6, 18.5, 16.6, 13.9, 13.2; high resolution mass spectrum (ES) m/z 589.3871 [(M+Na)+ calcd for C₃₅H₅₈O₂Si₂Na]

Aldehyde (–)-2.4: To a solution of olefin (–)-2.70 (570 mg, 1.01 mmol, 1.0 equiv) in 35 mL of acetone/tert-butanol/water (3:3:1), NMO (357 mg, 3.0 mmol, 3.0 equiv) was added as one portion followed by potassium osmate(VI) dehydrate (30 mg, 0.08 mmol, 0.08
equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature before it was quenched with 10 g of solid Na₂S₂O₃. The resulting heterogeneous mixture was stirred for a further 30 minutes before it was diluted by ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (30 mL) three times. The combined organic layers were washed with saturated aqueous NH₄Cl (10 mL) and brine (5 mL), dried over MgSO₄, filtered and concentrated. The resulting corresponding diol was moved to the next step as a black oil without further purification.

To a solution of the corresponding diol of (−)-2.70 (1.01 mmol, crude) in 25 mL of acetone/water (4:1), NaIO₄ (750 mg, 3.50 mmol, 3.50 equiv.) was added as one portion at room temperature under air atmosphere. The resulting mixture was stirred at the same temperature for three hours before it was diluted with ethyl acetate (30 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated, the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 2:98, 5:95, 10:90) to furnish aldehyde (−)-2.4 (436 mg, 0.75 mmol, 75.0% over 2 steps) as a colorless oil. [α]¹⁰₀ = -21.74 (c 1.75, CHCl₃); IR (film) 2943, 2865, 1727, 1463, 1427, 1389, 1112, 882, 824, 740, 702, 667 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 9.87 (t, J = 2.2 Hz, 1H), 7.71-7.68 (m, 4 H), 7.46-7.39 (m, 6H), 4.34 (m, 1H), 3.51 (d, J = 6.0 Hz, 2H), 2.54 (m, 2H), 1.82 (m, 1H), 1.73 (m, 1H), 1.39 (td, J = 13.0 Hz, 2.5 Hz, 1H), 1.27 (m, 1H), 1.09 (s, 30 H), 0.91 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ = 202.4, 135.8, 134.17, 134.15, 129.7, 127.3, 72.6,
70.0, 47.7, 36.8, 34.4, 33.3, 27.0, 19.4, 18.4, 18.3, 16.1, 15.2, 12.9; high resolution mass (ES) m/z 591.3664 [(M+Na)+ calcd for C_{34}H_{56}O_{3}Si_{2}Na]

Dioxanone (−)-2.70: To a solution of β–hydroxy acid (+)-2.22 (58.0 mg, 0.118 mmol, 1.0 equiv.) in 0.9 mL of THF, 0.6 mL of HMDS was added as one portion at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 22 hours at 40 to 45 °C before the HMDS/THF was removed under high vacuum (pressure < 5 Torr). The mixture was then azeotropically purified with toluene to remove the residual amount of HMDS, applying high vacuum with no access of air followed by stirring overnight at 40 to 45 °C under the same high vacuum conditions. The resulting tris-silylated ester was dissolved in 2 mL of dichloromethane before the addition of aldehyde (−)-2.4 (80.0 mg, 0.138 mmol, 1.17 equiv) solution in 2 mL of dichloromethane at -78 °C under nitrogen atmosphere. TMSOTf (50.0 mg, 0.225 mmol, 1.90 equiv of a newly opened bottle purchased from Sigma-Aldrich®) was then added to the reaction mixture at 78 °C. The resulting mixture was stirred for 1 hour at -78 °C under a nitrogen atmosphere before allowing access to air via insertion a needle at -78 °C for 10 minutes to introduce small amount of moisture. The reaction mixture was then stirred at -78 °C under a
nitrogen atmosphere for 50 minutes before it was slowly diluted by 5 mL of dichloromethane at the same temperature. The resulting mixture was then quenched with 100 mg of 2,6-lutidine and moved to the high vacuum condition to remove solvent at 5 to 10 °C. The resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes, 10:90, 20:80) to furnish dioxanone (--)-2.70 (125 mg, 0.112 mmol, 95.1%) as a colorless oil. \([\alpha]_{D}^{20} = -3.25\) (c 1.15, CHCl₃); IR (film) 2930, 2864, 1752, 1513, 1463, 1428, 1388, 1250, 1112, 883, 824, 740, 702 cm⁻¹; \(^1\)H NMR (500 MHz, C₆D₆) \(\delta = 7.81-7.79\) (m, 4 H), 7.30 (d, \(J = 8.6\) Hz, 2H), 7.27-7.24 (m, 7H), 6.85 (d, \(J = 8.6\) Hz, 2H), 6.16 (s, 1H), 5.58 (q, \(J = 6.5\) Hz, 1H), 5.29 (q, \(J = 6.8\) Hz, 1H), 5.08 (t, \(J = 6.4\) Hz, 1H), 4.53 (d, \(J = 11.3\) Hz, 1H), 4.42 (d, \(J = 11.3\) Hz, 1H), 4.13 (m, 1H), 3.67 (m, 1H), 3.63-3.53 (m, 2H), 3.34 (s, 3H), 3.30-3.25 (m, 1H), 3.12 (s, 3H), 2.40-2.33 (m, 1H), 2.20-2.10 (m, 2H), 2.06-1.96 (m, 2H), 1.87-1.81 (m, 1H), 1.74 (d, \(J = 1.1\) Hz, 3H), 1.48-1.25 (m, 6H), 1.39 (d, \(J = 6.5\) Hz, 3H), 1.19 (s, 9H), 1.13-1.17 (m, 21 H), 1.12-1.05 (m, 3H), 1.01 (d, \(J = 6.7\) Hz, 3H), 0.92-0.89 (s, 1H), 0.83 (d, \(J = 6.7\) Hz, 3H), 0.14 (s, 9H); \(^1\)C NMR (125 MHz, C₆D₆) \(\delta = 166.7, 161.3, 160.4, 152.3, 146.9, 136.7, 135.0, 134.3, 132.3, 130.6, 130.1, 129.2, 114.7, 113.9, 102.0, 76.0, 75.7, 75.1, 73.7, 71.4, 70.9, 66.9, 56.9, 55.4, 43.3, 40.1, 37.1, 36.9, 36.6, 35.22, 35.18, 34.3, 27.8, 21.4, 20.2, 20.0, 19.21, 19.15, 18.2, 16.9, 15.4, 13.0, 0.9; high resolution mass (ES) m/z 1114.6652 [(M+H)+ calcd for C₆₃H₁₀₀NO₁₀Si₃]
**Enol Acetal (−)-2.71:** To a solution of dioxanone (−)-2.70 (200 mg, 0.180 mmol, 1.0 equiv) in 2.3 mL of THF in a glass microwave vial (2-5 mL), 0.08 mL of 2,6-lutidine was added followed by 2.4 mL of Petasis reagent (0.25 M in THF/toluene, freshly prepared, 0.60 mmol, 3.35 equiv) at room temperature under an air atmosphere. The resulting mixture was sealed and stirred for 3 hours at 100 °C in microwave at the “high” level of absorption setting before it was cooled down. The resulting mixture was diluted by 20 mL of hexanes and stirred for 10 minutes before it was filtered and concentrated. The resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes, 5:95, 10:90) to furnish enol acetal (−)-2.71 (174 mg, 0.157 mmol, 87.2%) as a colorless oil.

\[[\alpha]_D^{20} = -0.90 \text{ (c 1.43, CHCl}_3\text{)}\]; IR (film) 2930, 2864, 1512, 1462, 1428, 1388, 1249, 1112, 883, 738, 702, 666 cm⁻¹; \(^1\)H NMR (500 MHz, C₆D₆) \(\delta = 7.81-7.77 \text{ (m, 4 H)}\), 7.31 (d, \(J = 8.6 \text{ Hz, 2H}\)), 7.26-7.22 (m, 7H), 6.83 (d, \(J = 8.6 \text{ Hz, 2H}\)), 6.15 (s, 1H), 5.59 (q, \(J = 6.5 \text{ Hz, 1H}\)), 5.08 (q, \(J = 5.4 \text{ Hz, 1H}\)), 4.93 (t, \(J = 5.9 \text{ Hz, 1H}\)), 4.64 (s, 1H), 4.53-4.43 (m, 2H), 4.24 (brs, 1H), 4.10 (s, 1H), 3.72-3.67 (m, 1H), 3.61-3.53 (m, 2H), 3.48-3.44 (m, 1H), 3.31 (s, 3H), 3.12 (s, 3H), 2.40-2.33 (m, 1H), 2.17-2.06 (m, 3H), 1.91-1.85 (m, 2H),
1.74 (s, 3H), 1.64-1.46 (m, 6H), 1.39 (d, \( J = 6.5 \) Hz, 3H), 1.21-1.12 (m, 33H), 1.01 (d, \( J = 6.9 \) Hz, 3H), 0.98-0.94 (m, 1H), 0.89 (d, \( J = 6.7 \) Hz, 3H), 0.14 (s, 9H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) \( \delta = 161.2, 160.3, 158.0, 152.1, 146.9, 136.7, 135.0, 134.2, 132.4, 130.5, 130.0, 129.1, 114.6, 113.9, 101.7, 93.6, 77.3, 76.2, 75.7, 74.0, 71.3, 70.8, 66.9, 56.8, 55.3, 43.3, 40.2, 37.1, 36.8, 35.87, 35.83, 35.3, 34.3, 27.8, 21.6, 20.2, 20.0, 19.24, 19.19, 18.2, 17.1, 15.2, 14.0, 0.9; high resolution mass (ES) m/z 1112.6841 [(M+H)+ calcld for C\(_{64}\)H\(_{102}\)NO\(_9\)Si\(_3\)]

![Chemical Structure](image)

**Methylene Tetrahydropyran (−)-2.21:** To a solution of methyltriphenylphosphonium bromide (475 mg, 1.33 mmol) in 8 mL of THF, 2 mL of KO\(_t\)Bu solution (1.0 M solution in THF, 2.0 mmol) was added dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 minutes at the same temperature to give the ylide solution (0.133 M in THF, 10 mL).

To a solution of enol acetal (−)-2.71 (70 mg, 0.0629 mmol, 1.0 equiv) in 7 mL of THF, 0.31 mL of dimethylaluminum chloride solution (1.0 M in hexanes, newly opened, 0.31 mmol, 4.9 equiv) was added over 3 seconds at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 seconds at -78 °C before the addition of freshly
prepared ylide solution (0.133 M in THF, 4.2 mL, 0.559 mmol, 8.9 equiv) at the same temperature. The resulting mixture was stirred for a further 10 minutes at -78 °C before it was quenched by 10 mL of saturated aqueous NH₄Cl solution. The resulting mixture was diluted by 20 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 2:98, 5:95, 10:90) to furnish methylene tetrahydropyran (−)-2.21 (59 mg, 0.0531 mmol, 84.4%) as a colorless oil. [α]°D = -4.12 (c 0.83, CHCl3); IR (film) 2929.8, 2864.3, 1589.5, 1512.8, 1462.3, 1428.0, 1388.0, 1249.2, 1112.2, 882.8, 739.6, 701.5 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ = 7.83 -7.80 (m, 4 H), 7.35 (d, J = 8.5 Hz, 2H), 7.28-7.23 (m, 7H), 6.86 (d, J = 8.5 Hz, 2H), 6.16 (s, 1H), 5.63 (q, J = 6.5 Hz, 1H), 5.14 (t, J = 6.2 Hz, 1H), 4.76 (d, J = 4.3 Hz, 2H), 4.53 (d, J = 5.9 Hz, 2H), 4.28-4.25 (m, 1H), 3.80-3.73 (m, 1H), 3.66-3.56 (m, 3H), 3.32 (s, 3H), 3.32-3.29 (m, 1H), 3.13 (s, 3H), 2.44-2.37 (m, 1H), 2.25-2.19 (m, 1H), 2.14 (d, J = 13.1Hz, 2H) 2.01 (d, J = 11.7 Hz, 1H), 1.92 (t, J = 11.7 Hz, 2H), 1.82 -1.70 (m, 3H), 1.75 (d, J = 1.2 Hz, 3H), 1.72-1.62 (m, 2H), 1.60-1.53 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H), 1.25-1.12 (m, 33H), 1.03 (d, J = 6.6 Hz, 3H), 0.95-0.91 (m, 1H), 0.91 (d, J = 7.3 Hz, 3H), 0.17 (s, 9H); ¹³C NMR (125 MHz, C₆D₆) δ = 160.6, 159.7, 151.5, 146.5, 145.6, 136.1, 134.6, 133.7, 132.0, 130.0, 129.5, 128.6, 114.0, 113.4, 108.4, 78.6, 75.8, 75.5, 75.2, 74.5, 70.8, 70.6, 66.4, 56.3, 54.8, 42.9, 42.2, 41.3, 40.4, 37.3 36.8, 35.0, 34.1, 33.8, 27.2, 21.8, 19.6, 19.5, 18.8, 18.7, 17.7, 16.3, 15.5, 13.6, 0.4; high resolution mass (ES) m/z 1110.7103 [(M+H)+ calcd for C₆₅H₁₀₅NO₈Si₃]
**Diol (+)-2.75**: To a solution of methylene tetrahydropyran (250 mg, 0.225 mmol, 1.0 equiv) in 46 mL of THF/H$_2$O (45:1), 18-crown-6 (1.2 g, 4.54 mmol, 20.0 equiv) was added followed by KOH (1.5 g, 26.26 mmol, 116.8 equiv) at room temperature. The resulting mixture was stirred for 3 hours at the same temperature before it was quenched by the addition of saturated aqueous NH$_4$Cl solution (30 mL). The resulting mixture was diluted by 50 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes 30:70, 40:60, 50:50) to furnish diol (-)-2.76 (145 mg, 0.181 mmol, 80.6%) as a colorless oil.

$[\alpha]_{D}^{20} = 3.13$ (c = 1.50, CHCl$_3$); IR (film) 2932, 2864, 1727, 1514, 1463, 1249, 1092 cm$^{-1}$;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.44 (s, 1H), 7.26 (d, $J$ = 8.1 Hz, 2H), 6.87 (d, $J$ = 8.1 Hz, 2H), 6.18 (s, 1H), 5.12 (q, $J$ = 6.5 Hz, 1H), 4.83 (d, $J$ = 8.7 Hz, 1H), 4.68 (s, 2H), 4.60 (d, $J$ = 10.9 Hz, 1H), 4.39 (d, $J$ = 10.9 Hz, 1H), 3.98 (brs, 1H), 3.79 (s, 3H), 3.79-3.77 (brs, 1H), 3.52-3.47 (m, 1H), 3.42-3.39 (m, 1H), 3.34 (t, $J$ = 10.1 Hz, 1H), 3.20 (s, 3H), 3.20-3.17 (m, 1H), 2.18 (d, $J$ = 12.6 Hz, 1H), 2.15-2.03 (m, 2H), 1.99-1.87 (m, 3H),
1.87 (s, 3H), 1.80-1.73 (brs, 1H), 1.70-1.59 (m, 4H), 1.59-1.50 (m, 2H), 1.49-1.40 (m, 3H), 1.32-1.25 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H), 1.20 (m, 1H), 1.11-0.99 (m, 21H), 0.87 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 160.6, 159.6, 150.4, 145.2, 144.8, 133.4, 130.2, 129.8, 114.2, 113.8, 108.4, 79.3, 78.3, 75.6, 75.0, 74.1, 70.5, 69.4, 68.3, 56.6, 55.5, 41.9, 41.0, 40.3, 36.9, 36.2, 34.3, 33.7, 33.4, 20.9, 19.5, 18.6, 18.51, 18.48, 17.8, 16.2, 15.0, 13.3; high resolution mass (ES) m/z 800.5486 [(M+H)+ calcd for C$_{46}$H$_{78}$NO$_8$Si]

![Aldehyde structure](image)

**Aldehyde (+)-2.76:** To a solution of diol (+)-2.75 (30 mg, 0.0375 mmol, 1.0 equiv) in 2 mL of dichloromethane, a solution of TEMPO (5 mg/mL in dichloromethane, 5 mg, 0.032 mmol, 0.85 equiv) was added followed by iodobenzene diacetate (24 mg, 0.075 mmol, 2.0 equiv) at room temperature in an air atmosphere. The resulting mixture was stirred for 1.5 hours at the same temperature before it was quenched with saturated aqueous Na$_2$S$_2$O$_3$ solution (5 mL). The resulting mixture was stirred for 5 minutes before it was diluted by 10 mL of ethyl acetate. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (10 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO$_4$, filtered and concentrated, and
the resulting oil was purified by column chromatography (SiO₂, ethyl acetate: hexanes 10:90, 20:80, 30:70) to furnish aldehyde (+)-2.76 (23 mg, 0.0288 mmol, 76.9%) as a colorless oil. \([\alpha]_{D}^{20} = 2.45 (c 0.42, \text{CHCl}_3)\); IR (film) 2927, 2864, 1726, 1624, 1514, 1463, 1381, 1248, 1097, 883 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) \(\delta = 9.61 (s, 1H), 7.44 (s, 1H), 7.28 (d, \(J = 8.1 \text{ Hz}, 2H\)), 6.88 (d, \(J = 8.1 \text{ Hz}, 2H\)), 6.18 (s, 1H), 5.13 (q, \(J = 6.5 \text{ Hz}, 1H\)), 4.84 (d, \(J = 8.6 \text{ Hz}, 1H\)), 4.70 (d, \(J = 6.0 \text{ Hz}, 2H\)), 4.60 (d, \(J = 11.2 \text{ Hz}, 1H\)), 4.40 (dd, \(J = 11.2 \text{ Hz}, 5.2 \text{ Hz}, 1H\)), 4.20 (brs, 1H), 3.80 (s, 3H), 3.80-3.77 (brs, 1H), 3.35 (t, \(J = 10.1 \text{ Hz}, 1H\)), 3.21 (s, 3H), 3.21-3.17 (m, 1H), 2.45 (q, \(J = 5.45 \text{ Hz}, 1H\)), 2.19 (d, \(J = 13.6 \text{ Hz}, 1H\)), 2.12 (d, \(J = 12.8 \text{ Hz}, 1H\)), 2.06 (d, \(J = 12.8 \text{ Hz}, 1H\)), 1.95-1.88 (m, 2H), 1.88 (s, 3H), 1.80-1.73 (brs, 1H), 1.70-1.60 (m, 6H), 1.60-1.52 (m, 3H), 1.42-1.44 (m, 2H), 1.29 (d, \(J = 6.5 \text{ Hz}, 3H\)), 1.25 (s, 3H), 1.11-0.99 (m, 18H), 0.95-0.85 (m, 3H), 0.82 (d, \(J = 6.9 \text{ Hz}, 3H\)); \(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta = 205.6, 160.5, 159.5, 150.3, 145.0, 144.8, 133.3, 130.1, 129.7, 114.1, 113.7, 108.5, 79.3, 78.2, 75.3, 74.9, 73.4, 70.5, 68.3, 56.6, 55.4, 44.6, 41.7, 40.9, 40.8, 40.0, 36.8, 36.6, 33.6, 31.5, 29.8, 20.7, 19.4, 18.5, 18.4, 17.7, 14.9, 13.2; high resolution mass (ES) m/z 820.5123 [(M+Na)+ calcd for C₄₆H₇₅NO₈SiNa]
Carboxylic Acid (+)-2.20 (route 1, from aldehyde (+)-2.76): To a solution of aldehyde (+)-2.76 (15 mg, 0.019 mmol, 1.0 equiv) in 3.5 mL of tBuOH/H2O (2.5:1), 2-methyl-2-butene (0.5 mL), NaH2PO3 (15 mg, 0.13 mmol, 6.7 equiv) and NaClO2 (12 mg, 90%, 0.12 mmol, 6.4 equiv) were added subsequently at room temperature in an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before it was diluted by saturated pH7 aqueous buffer solution (5 mL) and then ethyl acetate (10 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (2 mL), dried over MgSO4, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO2, ethyl acetate: hexanes 10:90, 20:80, 30:70) to furnish aldehyde (+)-2.76 (13.1 mg, 0.0161 mmol, 85.4%) as a colorless oil.

Carboxylic Acid (+)-2.20 (route 2, from diol (+)-2.75): To a solution of diol (+)-2.75 (18.0 mg, 0.0226 mmol, 1.0 equiv) in 0.5 mL of t-BuOH and 0.2 mL of pH 7 buffer solution, TEMPO solution (0.025 M in CH3CN, 0.025 mL, 0.025 mmol, 1.11 equiv.) was added at room temperature under an air atmosphere. The resulting mixture was stirred for 20 minutes at the same temperature before the subsequent addition of NaClO2 (1 M in water, 0.075 mL, 0.075 mmol, 3.32 equiv) and NaClO (0.025 M in water, 0.67 mL, 0.038 mmol, 1.66 equiv) solution. The reaction was stirred at room temperature for 3 hours before it was quenched by saturated aqueous Na2S2O3 solution (3 mL). After dilution with ethyl acetate (5 mL), the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (2 mL), dried over MgSO4, filtered and concentrated, and the resulting oil was purified by column chromatography (SiO2, ethyl acetate: hexanes 20:80, 30:70, 50:50,
80:20) to furnish acid (+)-2.61 (12.4 mg, 0.0152 mmol, 67.3%) as a colorless oil

$[\alpha]_D^{20} = 3.07$ (c 0.30, CHCl$_3$); IR (film) 2926, 2865, 1735, 1707, 1514, 1463, 1381, 1248, 883, 821, 666 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.46$ (s, 1H), $7.27$ (d, $J = 8.1$ Hz, 2H), $6.87$ (d, $J = 8.1$ Hz, 2H), $6.22$ (s, 1H), $5.03$ (q, $J = 6.5$ Hz, 1H), $4.89$ (d, $J = 8.8$ Hz, 1H), $4.68$ (d, $J = 6.0$ Hz, 2H), $4.61$ (d, $J = 11.2$ Hz, 1H), $4.40$ (d, $J = 11.2$ Hz, 1H), $3.98$ (t, $J = 6.5$ Hz, 1H), $3.80$ (s, 3H), $3.80$-3.77 (brs, 1H), $3.27$-3.20 (m, 1H), $3.21$ (s, 3H), $3.20$-3.13 (m, 1H), $2.48$ (m, 1H), $2.21$-2.10 (m, 3H), $2.01$-1.97 (m, 1H), $1.89$ (s, 3H), $1.89$-1.87 (m, 1H), $1.78$-1.65 (m, 5H), $1.61$-1.50 (m, 5H), $1.48$-1.35 (m, 2H), $1.29$ (d, $J = 6.5$ Hz, 3H), $1.30$-1.25 (m, 1H), $1.20$-1.14 (m, 4H), $1.11$-1.03 (m, 19H), $1.02$-0.93 (m, 1H), $0.87$ (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 180.4$, 160.9, 159.5, 151.1, 145.0, 144.5, 133.7, 130.1, 129.7, 114.1, 113.4, 108.4, 79.7, 78.6, 75.9, 75.0, 73.3, 70.5, 68.0, 56.6, 55.4, 42.0, 41.2, 41.0, 40.8, 37.9, 36.8, 36.6, 36.3, 33.7, 21.6, 19.5, 18.5, 18.4, 18.0, 17.8, 14.6, 13.3; high resolution mass (ES) m/z 814.5298 [(M+H)$^+$ calcd for C$_{46}$H$_{76}$NO$_9$Si]

![Macrolide](image)

**Macrolide (+)-2.48:** To a solution of carboxylic acid (+)-2.20 (24 mg, 0.030 mmol, 1.0 equiv.) in 0.75 mL of THF, Hunig’s base (0.06 mL) was added followed by 2,4,6-
trichlorobenzoyl chloride (54 mg, 0.22 mmol, 7.5 equiv) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 3 hours at the same temperature before it was diluted by toluene (3 mL). This activated macrolide precursor solution was stored at room temperature for further transformation.

To a solution of DMAP (120 mg, 0.982 mmol, 33.2 equiv) in 30 mL of toluene, the activated macrolide precursor solution was slowly added using a syringe pump over 5 hours at reflux temperature under a nitrogen atmosphere. The resulting mixture was stirred for a further 12 hours at the same temperature before it was cooled to room temperature. The resulting mixture was filtered and concentrated, the resulting mixture was purified by column chromatography (SiO₂, ethyl acetate: hexanes 5:95, 10:90, 20:80) to give the crude macrolide, which was then purified by PTLC (SiO₂, ethyl acetate: hexanes 10:90) to furnish macrolide (+)-2.48 (20.8 mg, 0.0261 mmol, 88.5%) as a colorless oil.

$[\alpha]_D^{20} = 10.31$ (c = 0.33, CHCl₃); IR (film) 2927, 2856, 1750, 1653, 1613, 1577, 1548, 1513, 1464, 1378, 1248, 1160, 1097, 883, 820, 666 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.44 (s, 1H), 7.30 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.20 (s, 1H), 5.96 (dd, $J = 12.6$ Hz, 2.6 Hz, 1H), 5.20 (q, $J = 6.5$ Hz, 1H), 4.70 (s, 2H), 4.64 (d, $J = 10.9$ Hz, 1H), 4.43 (d, $J = 10.9$ Hz, 1H), 4.12 (dd, $J = 11.1$ Hz, 4.1 Hz, 1H), 3.81 (s, 3H), 3.42 (t, $J = 10.0$ Hz, 1H), 3.30 (t, $J = 11.1$ Hz, 1H), 3.21 (s, 3H), 3.10 (t, $J = 9.2$ Hz, 1H), 2.73 (td, $J = 13.3$ Hz, 3.5 Hz, 1H), 2.69-2.63 (m, 1H), 2.13-2.03 (m, 3H), 1.99-1.93 (m, 1H), 1.91 (d, $J = 1.3$ Hz, 3H), 1.89-1.85 (m, 1H), 1.83-1.70 (m, 4H), 1.66-1.58 (m, 4H), 1.50-1.55 (m, 1H), 1.48-1.35 (m, 2H), 1.31 (d, $J = 6.6$ Hz, 3H), 1.30-1.25 (m, 2H), 1.14 (d, $J = 6.8$ Hz, 3H) 1.12-1.05 (m, 19H), 0.95-0.90 (m, 1H), 0.85 (d, $J = 6.5$ Hz, 3H); ¹³C NMR (125
MHz, CDCl$_3$) $\delta = 175.0$, 160.7, 159.5, 151.4, 145.0, 141.3, 134.0, 130.9, 129.7, 114.1, 113.4, 108.7, 76.1, 75.9, 75.0, 74.5, 71.8, 71.3, 65.0, 56.7, 55.5, 42.5, 41.8, 41.5, 39.2, 38.6, 37.6, 35.2, 34.5, 31.6, 20.8, 19.4, 18.6, 18.5, 18.1, 17.9, 14.3, 13.4; high resolution mass (ES) m/z 796.5194 [(M+H)$^+$ calcd for C$_{46}$H$_{74}$NO$_5$Si]

**Alcohol (+)-2.78:** To a solution of TIPS ether (+)-2.48 (9.0 mg, 0.0113 mmol, 1.0 equiv) in 3.5 mL of THF in a plastic container, pyridine (3.9 mL) was added followed by HF/pyridine complex (1.0 mL) at room temperature in an air atmosphere. The resulting mixture was stirred for 48 hours at 45 °C before it was quenched slowly with saturated aqueous NaHCO$_3$ (12.0 mL) at room temperature. The resulting mixture was diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (8 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO$_4$, filtered and concentrated, the resulting mixture was purified by column chromatography (SiO$_2$, ethyl acetate: hexanes, 30:70, 40:60, 50:50) to furnish alcohol (+)-2.78 (5.1 mg, 0.0080 mmol, 70.5%) as a colorless oil.

$[\alpha]_{D}^{20} = 4.93$ (c 0.42, CHCl$_3$); IR (film) 2917.8, 2849.3, 1708.1, 1552.4, 1513.4, 1463.2, 1378.4, 1149.9, 1096.8, 807.1, 720.3 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.49$ (s, 1H), 139
7.27 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 6.20 (s, 1H), 5.84 (dd, J = 12.6 Hz, 2.6 Hz, 1H), 5.16 (q, J = 6.5 Hz, 1H), 4.68 (s, 2H), 4.60 (d, J = 10.9 Hz, 1H), 4.41 (d, J = 10.9 Hz, 1H), 3.80 (s, 4H), 3.47 (t, J = 10.4 Hz, 1H), 3.30 (q, J = 10.4 Hz, 2H), 3.23 (s, 3H), 2.75 (td, J = 12.6 Hz, 3.2 Hz, 1H), 2.70-2.64 (m, 1H), 2.13 (d, J = 13.5 Hz, 2H), 2.04-1.95 (m, 2H), 1.90 (s, 3H), 1.86-1.76 (m, 3H), 1.76-1.60 (m, 5H), 1.48-1.33 (m, 4H), 1.30 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ = 175.9, 160.6, 159.4, 151.2, 145.0, 140.6, 134.7, 130.7, 129.7, 114.0, 113.4, 108.5, 76.1, 75.7, 75.03, 74.95, 71.0, 68.9, 65.8, 56.7, 55.4, 41.9, 41.7, 41.5, 38.0, 37.0, 36.5, 35.4, 33.8, 31.6, 21.1, 19.4, 17.8, 16.7, 13.1; high resolution mass (ES) m/z 640.3849 [(M+H)+ calcd for C37H54NO8]

δ-Lactone (−)-2.79: δ-lactone (−)-2.79 was isolated as a by-product of TIPS removal reaction of macrolide (+)-2.48

[α]_D^20 = -3.51 (c 0.7, CHCl3); IR (film) 2923, 2852, 1738, 1553, 1514, 1463, 1379, 1249, 1174, 1099, 1036, 804 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ = 7.45 (s, 1H), 7.27 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.18 (s, 1H), 5.13 (q, J = 6.5 Hz, 1H), 4.83 (d, J = 9.0 Hz, 1H), 4.71 (s, 2H), 4.62 (d, J = 5.5 Hz, 1H), 4.60 (d, J = 10.9 Hz, 1H), 4.41 (d, J =
10.9 Hz, 1H), 3.98 (s, 1H), 3.80 (s, 4H), 3.57 (t, J = 10.4 Hz, 1H), 3.30-3.24 (m, 1H), 3.21 (s, 3H), 2.63-2.57 (m, 1H), 2.22-2.18 (m, 2H), 2.07 (d, J = 14.3 Hz, 1H), 2.06-1.98 (m, 1H), 1.98-1.82 (m, 3H), 1.90 (s, 3H), 1.75-1.52 (m, 5H), 1.51-1.42 (m, 4H), 1.32 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 174.8, 160.6, 159.6, 150.5, 144.9, 144.3, 133.4, 130.2, 129.8, 114.2, 113.8, 109.1, 80.3, 79.2, 78.2, 75.0, 74.2, 70.5, 68.2, 56.7, 55.5, 41.5, 41.02, 40.98, 40.0, 36.7, 36.0, 33.5, 31.5, 30.6, 20.7, 19.5, 18.1, 17.8, 11.9; high resolution mass (ES) m/z 640.3859 [(M+H)$^+$ calcd for C$_{37}$H$_{54}$NO$_8$]

$\delta$-Lactone (-)-2.81: To a solution of PMB ether (-)-2.79 (4.0 mg, 0.0063 mmol, 1.0 equiv.) in 1.5 mL of dichloromethane, a mixture of TFA/H$_2$O (0.4 mL, TFA:H$_2$O 1:1) was added dropwise at room temperature. The resulting mixture was stirred for 1 hour at the same temperature before it was quenched with saturated aqueous NaHCO$_3$ (5.0 mL) at room temperature. The resulting mixture was diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (5 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO$_4$, filtered and concentrated, and the resulting mixture was purified by column
chromatography (SiO$_2$, ethyl acetate: hexanes, 40:60, 50:50, 70:30) to furnish δ-lactone (-)-2.81 (2.2 mg, 0.00419 mmol, 67.0%) as a colorless oil.

$[\alpha]_D^{20} = -12.58$ (c 0.20, CHCl$_3$); IR (film) 2920, 1727, 1649, 1551, 1449, 1379, 1323, 1204, 1097 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$OD) δ = 7.69 (s, 1H), 6.23 (s, 1H), 5.23 (q, $J =$ 6.4 Hz, 1H), 4.82 (m, 1H), 4.73 (d, $J =$ 1.5 Hz, 2H), 4.68 (ddd, $J =$ 9.5, 2.5, 2.5 Hz, 1H), 3.68 (m, 1H), 3.46 (t, $J =$ 10.5 Hz, 1H), 3.24 (m, 1H), 3.21 (s, 1H), 2.64 (m, 1H), 2.24 (s, 1H), 2.22 (s, 1H), 2.10-2.00 (m, 2H), 1.95-1.85 (m, 4H), 1.89 (s, 3H), 1.78-1.72 (m, 2H), 1.65 (m, 1H), 1.60 (m, 1H), 1.52-1.42 (m, 3H), 1.28 (d, $J =$ 6.5 Hz, 3H), 1.24 (d, $J =$ 7.3 Hz, 3H), 1.01 (d, $J =$ 6.9 Hz, 3H) $^{13}$C NMR (125 MHz, CD$_3$OD) δ = 177.0, 161.5, 151.7, 145.7, 145.6, 135.3, 114.1, 108.8, 81.8, 79.4, 75.9, 75.5, 70.5, 66.2, 56.5, 44.1, 42.0, 41.6, 40.2, 38.3, 37.0, 36.2, 32.3, 31.4, 22.3, 19.3, 17.9, 17.3, 11.8; high resolution mass (ES) m/z 520.3254 [(M+H)$^+$ calcd for C$_{29}$H$_{46}$NO$_7$]

**Phosphoric Ester (-)-2.87**: To a solution of alcohol (+)-2.78 (3.5 mg, 0.0055 mmol, 1.0 equiv) in 0.2 mL of acetonitrile, 1$H$-tetrazole solution (0.45 M in acetonitrile, 0.195 mL, 0.088 mmol, 16.0 equiv) was added followed by $i$-Pr$_2$NP(OFm)$_2$ solution (57.5 mg in 0.2
mL dichloromethane, 0.110 mmol, 20.0 equiv) at room temperature in an argon atmosphere. The resulting mixture was stirred for 50 minutes at the same temperature before it was cooled to 0 °C. 0.2 mL of H₂O₂ solution (50% in water) was added to the reaction mixture at 0 °C, allowing the resulting mixture to be stirred at the same temperature for 30 minutes. The resulting mixture was quenched by saturated aqueous NaHCO₃ (3.0 mL) at room temperature. The resulting mixture was diluted by ethyl acetate (5 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 mL) twice. The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO₂, ethyl acetate: hexanes, 40:60, 50:50, 60:40) to furnish phosphorus ester 2.86 together with inseparable phosphate impurity as a colorless oil.

To a solution of the resulting mixture, including phosphoric ester 2.86 in DCM/pH7 aqueous buffer solution (4.4 mL, 10:1), DDQ (8.0 mg) was added in one portion at room temperature. The resulting mixture was stirred for 30 minutes at the same temperature before it was diluted by diethyl ether (10 mL). The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 mL) twice. The combined organic layers were washed with brine (1 mL), dried over MgSO₄, filtered and concentrated, and the resulting mixture was purified by column chromatography (SiO₂, ethyl acetate: hexanes, 50:50, 60:40, 80:20) to furnish phosphoric ester (→)-2.87 (3.2 mg, 0.00334 mmol, 61.0% over two steps) as a colorless oil.

[α]D²⁰ = -4.00 (c 0.6, CHCl₃); IR (film) 2925, 2853, 1729, 1555, 1451, 1381, 1252, 1076, 1012, 741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 7.76-7.68 (m, 4H), 7.56-7.49 (m, 3H), 7.46 (d, J = 7.5 Hz, 1H), 7.41-7.31 (m, 4H), 7.39 (s, 1H), 7.30-7.20 (m, 4H), 6.16 (s, 1H), 143
5.98 (dd, $J = 11.8$, 3.1 Hz, 1H), 5.18 (q, $J = 6.5$ Hz, 1H), 4.72 (d, $J = 3.1$ Hz, 2H), 4.60 (m, 1H), 4.30-4.23 (m, 2H), 4.23-4.15 (m, 2H), 4.15-4.10 (m, 2H), 3.63 (brt, $J = 9.2$ Hz, 1H), 3.30 (t, $J = 10.7$ Hz, 1H), 3.22 (s, 1H), 3.07 (t, $J = 9.1$ Hz, 1H), 2.71 (m, 1H), 2.49 (m, 1H), 2.10 (d, $J = 13.5$ Hz, 1H), 2.03 (d, $J = 13.5$ Hz, 1H), 1.94-1.82 (m, 2H), 1.89 (s, 3H), 1.75 (dd, $J = 13.5$, 4.4 Hz, 2H), 1.72-1.60 (m, 4H), 1.86-1.76 (m, 3H), 1.47-1.39 (m, 2H), 1.39-1.30 (m, 2H), 1.28 (d, $J = 6.4$ Hz, 3H), 1.09 (m, 1H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 174.4$, 160.7, 151.6, 144.6, 143.38, 143.35, 143.32, 143.29, 141.5, 141.2, 133.9, 128.13, 128.11, 128.09, 127.38, 127.36, 127.31, 125.4, 125.3, 125.24, 125.22, 120.32, 120.27, 120.25, 113.2, 108.9, 78.81, 78.75, 75.1, 75.0, 74.6, 69.55, 69.48, 69.43, 69.21, 69.17, 64.9, 56.7, 48.23, 48.21, 48.18, 48.14, 42.0, 41.5, 41.4, 39.0, 38.4, 38.2, 35.2, 33.8, 33.7, 33.1, 20.9, 19.4, 17.9, 17.8, 14.3; $^{31}$P NMR (200 MHz, CDCl$_3$) $\delta = -1.53$; high resolution mass (ES) m/z 956.4521 [(M+H)+ calcd for C$_{57}$H$_{67}$NO$_{10}$P]

**Enigmazole A (Phosphoric Acid Format) 2.90:** To a solution of phosphorus ester (-)-2.87 (2.0 mg, 0.0021 mmol, 1.0 equiv) in 0.4 ml of MeOH/H$_2$O (2:1), 6 mg of Na$_2$CO$_3$ was added at room temperature. The resulting mixture was stirred for 24 hours at the
same temperature before the addition of CD$_3$COOD (15 mg). The resulting mixture then stirred at the same temperature for 10 minutes before it was extracted with pentane (0.5 mL) three times. The solvent and CD$_3$COOD was removed under high vacuum from the mixture to furnish enigmazole A (−)-2.1 together with CD$_3$COONa. The further purification was achieved by RP HPLC (Vydac$^{\text{TM}}$ 5 μm C18, 250*10 mm, 5% MeCN/95% H$_2$O with 0.1% TFA to 40% MeCN/60% H$_2$O with 0.1% TFA linear gradient over 15 min, then 40% MeCN/60% H$_2$O with 0.1% TFA for 15 min, 10 mL/min, λ = 254 nm) to give enigmazole A free acid format (1.4 mg, 0.0020 mmol, 95.0%) as a colorless oil. $^1$H NMR (500 MHz, CD$_3$OD) δ = 7.70 (s, 1H), 6.21 (s, 1H), 5.97 (dd, $J$ = 12.8, 2.2 Hz, 1H), 5.24 (q, $J$ = 6.5 Hz, 1H), 4.72 (s, 2H), 4.58 (m, 1H), 3.58 (td, $J$ = 10.1 Hz, 3.0 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 2.87 (m, 1H), 2.51 (td, $J$ = 13.7 Hz, 3.8 Hz, 1H), 2.20-2.13 (m, 2H), 2.01-1.94 (m, 3H), 1.89 (d, $J$ = 1.2 Hz, 3H), 1.86-1.83 (m, 1H), 1.78-1.70 (m, 4H), 1.69-1.60 (m, 2H), 1.48 (q, $J$ = 12.4 Hz, 1H), 1.44-1.37 (m, 1H), 1.37-1.30 (m, 1H), 1.26 (d, $J$ = 6.6 Hz, 3H), 1.11 (d, $J$ = 6.7 Hz, 3H), 1.05-1.01 (m, 1H), 0.98 (d, $J$ = 5.9 Hz, 1H) $^{13}$C NMR (125MHz, CD$_3$OD) δ = 176.2, 161.9, 152.8, 146.2, 142.2, 136.0, 114.0, 109.0, 77.8 (d, $J$ = 5.8 Hz), 76.9, 76.2, 75.9, 69.8, 65.9, 56.8, 43.0, 42.6, 42.4, 40.1, 39.6, 39.2, 36.1, 34.6 (d, $J$ = 5.2 Hz), 33.6, 21.9, 19.5, 18.1, 17.7, 15.6.
**Enigmazole A (Monophosphate Format) (−)-2.1:** To the neat phosphoric acid 2.90 (1.4 mg) in a 3 mm glass NMR tube, 0.2 mL of saturated NaHCO3 CD3OD solution was added to furnish monophosphate (−)-2.1 in CD3OD solution

\[ \alpha \]°D = -1.05 (c = 0.12, CHCl3), ¹H NMR (500 MHz, CD3OD) \( \delta = 7.68 \) (s, 1H), 6.21 (s, 1H), 5.95 (dd, \( J = 12.8, 2.5 \) Hz, 1H), 5.24 (q, \( J = 6.5 \) Hz, 1H), 4.70 (d, \( J = 1.5 \) Hz, 1H), 4.69 (d, \( J = 1.5 \) Hz, 1H), 4.42 (m, 1H), 3.62 (td, \( J = 10.1, 2.9 \) Hz, 1H), 3.20 (s, 3H), 3.12 (dd, \( J = 10.2, 8.9 \) Hz, 1H), 2.98 (m, 1H), 2.50 (td, \( J = 13.4, 3.9 \) Hz, 1H), 2.21 (d, \( J = 12.8 \) Hz, 1H), 2.13 (d, \( J = 12.8 \) Hz, 1H), 2.10 (m, 1H), 1.97 (t, \( J = 12.2 \) Hz, 1H), 1.89 (s, 3H), 1.88-1.83 (m, 3H), 1.80-1.72 (m, 3H), 1.66-1.60 (m, 2H), 1.54 (q, \( J = 12.4 \) Hz, 1H), 1.39 (t, \( J = 11.3 \) Hz, 1H), 1.37 (t, \( J = 11.1 \) Hz, 1H), 1.26 (d, \( J = 6.4 \) Hz, 3H), 1.10 (d, \( J = 6.6 \) Hz, 3H), 1.02 (td, \( J = 12.0, 2.6 \) Hz, 1H), 0.97 (d, \( J = 6.6 \) Hz, 1H) ¹³C NMR (125MHz, CD3OD) \( \delta = 176.5, 161.9, 152.7, 146.6, 142.4, 136.0, 113.9, 108.6, 77.6, 76.2, 75.7, 75.2 (d, \( J = 6.4 \) Hz), 69.8, 65.7, 56.8, 43.0, 42.6, 42.5, 40.1, 39.6, 39.3, 36.2, 34.7 (d, \( J = 6.6 \) Hz), 33.6, 21.8, 19.4, 18.3, 17.7, 15.0; ³¹P (200 MHz, CD3OD) \( \delta = 1.45 \); high resolution mass (ES) m/z 598.2759 [(M-H)⁻ calcd for C₂₉H₄₅NO₁₀P]
Enigmazole A (Diphosphate Format) 2.91: To a solution of enigmazole A (Monophosphate Format) (−)-2.1 (1.4 mg) in 0.2 mL of saturated NaHCO$_3$ CD$_3$OD solution in 3mm glass NMR tube, 0.02 mL of 1 M NaOH CD$_3$OD solution was added to furnish enigmazole A (diphosphate format) 2.91 in CD$_3$OD solution. $^1$H NMR (500 MHz, CD$_3$OD) $\delta = 7.68$ (s, 1H), 6.21 (s, 1H), 5.93 (dd, $J = 13.1$, 2.9 Hz, 1H), 5.23 (q, $J = 6.5$ Hz, 1H), 4.67 (s, 2H), 4.31 (m, 1H), 3.64 (td, $J = 10.8$ Hz, 2.8 Hz, 1H), 3.20 (s, 3H), 3.14 (m, 1H), 3.09 (m, 1H), 2.50 (td, $J = 12.3$ Hz, 3.1 Hz, 1H), 2.29-2.20 (m, 2H), 2.14-2.09 (m, 1H), 2.06-1.95 (m, 2H), 1.88 (d, $J = 1.2$ Hz, 3H), 1.87-1.78 (m, 2H), 1.78-1.70 (m, 2H), 1.78-1.67 (m, 2H), 1.63-1.51 (m, 3H), 1.48 (q, $J = 12.4$ Hz, 1H), 1.40-1.47 (m, 3H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.06-0.99 (m, 1H), 0.97 (d, $J = 6.7$ Hz, 1H) $^{13}$C NMR (125MHz, CD$_3$OD) $\delta = 177.4$, 161.9, 152.6, 147.0, 142.5, 135.9, 114.0, 108.3, 78.0, 76.3, 75.7, 73.6, 69.8, 65.7, 56.8, 43.2, 42.7, 42.6, 40.3, 39.8, 39.5, 36.3, 34.9 (d, $J = 6.8$ Hz), 33.7, 21.8, 19.5, 18.6, 17.7, 15.4 (Na$_2$CO$_3$ peak was shown in 161.5)
Appendix. Spectral Data for Compounds in Chapter 2
Figure A1.1: The 500 MHz $^1$H-NMR Spectrum of Iodide (+)-2.29 in CDCl$_3$. 
Figure A1.2 the 125 MHz $^{13}$C-NMR Spectrum of Iodide (+)-2.29 in CDCl$_3$
Figure A1.3 The Infrared Spectrum of Iodide (+)-2.29
Figure A1.4 the 500 MHz $^1$H-NMR Spectrum of chloride 2.33 in CDCl$_3$
Figure A1.5 the 125 MHz $^{13}$C-NMR Spectrum of chloride 2.33 in CDCl$_3$
Figure A1.6 the Infrared Spectrum of chloride 2.33
Figure A1.8 the 125 MHz $^{13}$C-NMR Spectrum of ester (+)-2.34 in CDCl$_3$
Figure A1.9 the Infrared Spectrum of ester (+)-2.34 in CDCl₃
Figure A1.10 the 500 MHz $^1$H-NMR Spectrum of Aldehyde (+)-2.35 in CDCl$_3$
Figure A1.11 the 125 MHz $^{13}$C-NMR Spectrum of Aldehyde (+)-2.35 in CDCl$_3$
Figure A1.12 The Infrared Spectrum of Aldehyde (+)-2.35
Figure A1.13 the 500 MHz $^1$H-NMR Spectrum of Dithiane (+)-2.23 in CDCl$_3$
Figure A1.14 the 125 MHz $^{13}$C-NMR Spectrum of Dithiane (+)-2.23 in CDCl$_3$
Figure A1.15 The Infrared Spectrum of Dithiane (+)-2.23
Figure A1.16 the 500 MHz $^1$H-NMR Spectrum of Dithiane (−)-2.42 in CDCl$_3$
Figure A1.17 the 150 MHz $^{13}$C-NMR Spectrum of Dithiane (-)-2.42 in CDCl$_3$
Figure A1.18 The Infrared Spectrum of Dithiane (-)-2.42
Figure A1.19 the 500 MHz $^1$H-NMR Spectrum of Alcohol (−)-2.43 in CDCl$_3$
Figure A1.20 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (-)-2.43 in CDCl$_3$
Figure A1.21: The Infrared Spectrum of Alcohol (\(-\)2.43)
Figure A1.22 the 500 MHz $^1$H-NMR Spectrum of Diol (-)-2.44 in CDCl$_3$
Figure A1.23 the 125 MHz $^{13}$C-NMR Spectrum of Diol (-)-2.44 in CDCl$_3$
Figure A1.21: The Infrared Spectrum of Diol (-)-2,44
Figure A1.25 the 500 MHz $^1$H-NMR Spectrum of Epoxide (-)-2.24 in CDCl$_3$
Figure A1.26 the 125 MHz $^{13}$C-NMR Spectrum of Epoxide (-)-2.24 in CDCl$_3$
Figure A1.27: Infrared Spectrum of Epoxide (-)-2,24
Figure A1.28 the 500 MHz $^1$H-NMR Spectrum of Alcohol (+)-2.45 in CDCl$_3$
Figure A1.29 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (+)-2,45 in CDCl$_3$
Figure A1.30 the Infrared Spectrum of Alcohol (+)-2.45
Figure A1.31 the 500 MHz $^1$H-NMR Spectrum of Olefin (-)-2.46 in CDCl$_3$
Figure A1.32 the 125 MHz $^{13}$C-NMR Spectrum of Olefin (-)-2.46 in CDCl$_3$
Figure A1.33 the Infrared Spectrum of Olefin (-)-2.46
Figure A1.34: The 500 MHz $^1$H-NMR Spectrum of Dithiane (+)-2,52 in CDCl$_3$
Figure A1.35 the 125 MHz $^{13}$C-NMR Spectrum of Dithiane (+)-2.52 in CDCl$_3$
Figure A1.36 the Infrared Spectrum of Dithiane (+)-2.52
Figure A1.37 the 500 MHz $^1$H-NMR Spectrum of Ketone (+)-2.53 in CDCl$_3$
Figure A1.38 the 125 MHz $^1$H-NMR Spectrum of Ketone (+)-2.53 in CDCl$_3$
Figure A1.39: The Infrared Spectrum of Ketone (+) 2.53
Figure A1.40 the 500 MHz $^1$H-NMR Spectrum of Diol (+)-2.54 in CDCl$_3$
Figure A1.41 the 125 MHz $^{13}$C-NMR Spectrum of Diol (+)-2.54 in CDCl$_3$
Figure A1.42: The Infrared Spectrum of Diol (+)-2,54
Figure A1.3: The 500 MHz $^1$H-NMR Spectrum of Acetal $(-)-2.55$ in CDCl$_3$
Figure A1.44: The 125 MHz $^1$H-NMR Spectrum of Acetal (-)-2.55 in CDCl$_3$
Figure A1.45: The Infrared Spectrum of Acetal (-2.55)
Figure A1.46 the 500 MHz $^1$H-NMR Spectrum of Alcohol (+)-2.56 in CDCl$_3$
Figure A1.47 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (+)-2.56 in CDCl$_3$
Figure A1.48: The 500 MHz $^1$H-NMR Spectrum of Diol (+)-2.57 in CDCl$_3$. 
Figure A1.49 the 125 MHz $^{13}$C-NMR Spectrum of Diol (+)-2.57 in CDCl$_3$
Figure A1.50: The Infrared Spectrum of Diol (+)-2,57
Figure A1.51 the 500 MHz $^1$H-NMR Spectrum of Alcohol (−)-2.64 in CDCl$_3$
Figure A1.52 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (-)-2.64 in CDCl$_3$
Figure A1.53 the Infrared Spectrum of Alcohol (-) 2.64
Figure A1.54 the 500 MHz $^1$H-NMR Spectrum of Acid (+)-2,65 in CDCl$_3$
Figure A1.55 the 125 MHz $^{13}$C-NMR Spectrum of Acid (+)-2.65 in CDCl$_3$
Figure A1.56: The Infrared Spectrum of Acid (+)-2.65
Figure A1.57 the 500 MHz $^1$H-NMR Spectrum of Acid (+)-2.61 in CDCl$_3$
Figure A1.58 the 125 MHz $^{13}$C-NMR Spectrum of Acid (+)-2.61 in CDCl$_3$
Figure A1.59: the Infrared Spectrum of Acid (+)-2,6,1 in CDCl₃
Figure A1.60 the 500 MHz $^1$H-NMR Spectrum of Eastern Hemisphere (+)-2.22 in CDCl$_3$
Figure A1.61 the 125 MHz $^{13}$C-NMR Spectrum of Eastern Hemisphere (+)-2.22 in CDCl$_3$
Figure A.62: The Infrared Spectrum of Eastern Hemisphere (+) and (-)
Figure A1.63: The 500 MHz $^1$H-NMR Spectrum of Alcohol (+)-2.68 in CDCl$_3$
Figure A1.64 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (−)-2.68 in CDCl$_3$
Figure A.65: The Infrared Spectrum of Alcohol (\(\Delta\varepsilon = 2.68\))
Figure A1.66 the 500 MHz $^1$H-NMR Spectrum of Olefin (-)-2.69 in CDCl$_3$
Figure A1.67 the 125 MHz $^{13}$C-NMR Spectrum of Olefin (-)-2.69 in CDCl$_3$
Figure A1.68 the Infrared Spectrum of Olefin (-)-2.69 in CDCl₃
Figure A1.69: the 500 MHz $^1$H-NMR Spectrum of Olefin (−)-2.70 in CDCl$_3$. 
Figure A1.70 the 125 MHz $^{13}$C-NMR Spectrum of Olefin (−)-2.70 in CDCl$_3$
Figure A1.71: Infrared Spectrum of Olefin (-2.70) in CDCl₃
Figure A1.72. The 500 MHz $^1$H-NMR Spectrum of Western Hemisphere (-)-2,4 in CDCl$_3$.
Figure A1.73 the 125 MHz $^{13}$C-NMR Spectrum of Western Hemisphere (−)-2.4 in CDCl$_3$
Figure A1.74: The Infrared of Western Hemisphere (h) - 2.4
Figure A1.75 the 500 MHz $^1$H-NMR Spectrum of Dioxanone(-)-2.70 in C$_6$D$_6$
Figure A1.76 the 125 MHz $^{13}$C-NMR Spectrum of Dioxanone(-)-2.70 in C$_6$D$_6$
Figure A1.77 the Infrared Spectrum of Dioxanone(-)-2.70 in C₆D₆
Figure A1.78: The 500 MHz $^1$H-NMR Spectrum of Enol Acetal (−)-271 in C$_6$D$_6$. 

The spectrum shows various peaks indicating the presence of different chemical shifts. The molecular structure on the left corresponds to the compound under investigation.
Figure A1.79 the 125 MHz $^{13}$C-NMR Spectrum of Enol Acetal (−)-2.71 in C$_6$D$_6$
Figure A1.80: The Infrared Spectrum of Enol Acetal (-2.71)
Figure A1.81 the 500 MHz $^1$H-NMR Spectrum of Olefin (-)-2.21 in C$_6$D$_6$
Figure 4.12: The 125 MHz $^{13}$C-NMR Spectrum of Olefin (-)-2,21 in $C_6D_6$. 

![NMR Spectrum](image-url)
Figure A1.83: the Infrared Spectrum of Olefin \((\cdot)\)-2,21
Figure A1.84 the 500 MHz 1H-NMR Spectrum of Diol (+)-2,75 in CDCl₃
Figure A1.85 the 125 MHz $^{13}$C-NMR Spectrum of Diol (+)-2.75 in CDCl$_3$
Figure A1.86 the Infrared Spectrum of Diol (+)-2.75
Figure A1.87 the 500 MHz 1H-NMR Spectrum of Aldehyde (+)-2.76 in CDCl₃.
Figure A1.88 the 125 MHz $^{13}$C-NMR Spectrum of Aldehyde (+)-2.76 in CDCl$_3$
Figure A1.89: The Infrared Spectrum of Aldehyde (+)-2,76
Figure A1.90 the 500 MHz $^1$H-NMR Spectrum of Acid (+)-2.20 in CDCl$_3$
Figure A1.91 the 125 MHz $^{13}$C-NMR Spectrum of Acid (+)-2.20 in CDCl$_3$
Figure A1.92: The Infrared Spectrum of Acid (+)-2,20
Figure A1.93: The 500 MHz $^1$H-NMR Spectrum of Macrolide (+)-2,48 in CDCl$_3$. 

The spectrum shows the chemical shifts and signals of the molecular structure, indicating the positions of the protons in the molecule. 

The structure labeled TIPS, OMe, and other functional groups are evident, suggesting the complexity of the macrolide's chemical makeup.
Figure A1.94 the 125 MHz $^{13}$C-NMR Spectrum of Macrolide (+)-2.48 in CDCl$_3$
Figure A1.95: The Infrared Spectrum of Macrolide (+)-2.48
**Figure A1.96** the 500 MHz $^1$H-NMR Spectrum of Alcohol (+)-2.78 in CDCl$_3$
Figure A1.97 the 125 MHz $^{13}$C-NMR Spectrum of Alcohol (+)-2.78 in CDCl$_3$
Figure A198: The Infrared Spectrum of Alcohol (+) 2.78
Figure A1.99 the 500 MHz $^1$H-NMR Spectrum of $\delta$-lactone (-)-2.79 in CDCl$_3$
Figure A1.100 the 125 MHz $^{13}$C-NMR Spectrum of $\delta$-lactone (-)-2.79 in CDCl$_3$
Figure A1.101: The Infrared Spectrum of δ-lactone (-)-2,79
Figure A1.102 the 500 MHz $^1$H-NMR Spectrum of δ-lactone (-)-2.81 in MeOD
Figure A1.103. the 125 MHz $^{13}$C-NMR Spectrum of $\delta$-lactone (-) 2.81 in MeOD
Figure A1.104: The Infrared Spectrum of δ-lactone (+)-2.81
Figure A1.105 the 500 MHz $^1$H-NMR Spectrum of Ester (-)-2.87 in CDCl$_3$
Figure A1.106: The 125 MHz $^{13}$C-NMR Spectrum of Ester (–)-2.87 in CDCl$_3$. 
Figure A1.107 the 200 MHz $^{31}$P-NMR Spectrum of Ester (-)-2.87 in CDCl$_3$
Figure A1.108: The Infrared Spectrum of Ester (\(\cdot\))-2.87
Figure A1.109  the 500 MHz $^1$H-NMR Spectrum of Enigmazole A Phosphoric Acid 2.90 in CD$_3$OD
Figure A1.110 the 125 MHz $^{13}$C-NMR Spectrum of Enigmazole A Phosphoric Acid 2.90 in CD$_3$OD
Figure A1.111 the 500 MHz $^1$H-NMR Spectrum of Enigmazole A Monophosphate (−)-2.1 in CD$_3$OD
Figure A1.112 the 125 MHz $^{13}$C-NMR Spectrum of Enigmazole A Monophosphate (−)-2.1 in CD$_3$OD
Figure A1.113 the 200 MHz $^{31}$P-NMR Spectrum of Enigmazole A Monophosphate (−)-2.1 in CD$_3$OD
Figure A1.114 the 500 MHz $^1\text{H}$-NMR Spectrum of Enigmazole A Diphosphate 2.91 in CD$_3$OD
Figure A1.115 the 125 MHz $^{13}$C-NMR Spectrum of Enigmazole A Diphosphate 2.91 in CD$_3$OD
Yanran Ai was born in Shenyang, China on Oct. 12th, 1985 as the only child to Hua Ai and Sujuan Tan. As two accomplished physicians and professors specializing in Chinese traditional medicine, Hua Ai and Sujuan Tan have successfully relieved many suffering people using traditional, natural products. They believe, however, that it would be unprofessional to continue to prescribe these products without knowing the science behind them. They named their only child “Yanran”, translated this literally means “to research the natural science”. Their wish is for Yanran to continue down their path in discovery. Raised by such a family, Yanran Ai, however, did not become conscious early of his interest for natural science, but demonstrated strong interests on history, culture, Chinese classic literature and social science.

In 1998, Yanran was selected to attend Northeast Yucai School, the best high school in the city and top ten in China. He was enrolled in “Japanese class” and went to Japan with his classmates in 2004. Yanran enrolled at Tokyo Institute of Technology in 2005 and majored in applied chemistry. In Tokyo Tech, he finally started becoming conscious of his strong interest and natural gift for natural science. His GPA ranked 2nd over 106 students in the department. It was an outstanding academic performance record even in the history of the institute as an international student. In college, Yanran received a number of honors and scholarships including fully tuition remission from Tokyo Institute of Technology, Honor Scholarship from Japan Student Supporting Organization and Monbukagakushuo Scholarship from Japan’s government. Before he received Monbukagakusho scholarship which could cover all his living expenses, he worked part-time in a restaurant and then trained as a skillful cook specialized in Japanese cuisine.
As a senior in college, Yanran entered the research group led by Prof. Takashi Takahashi. In the Takahashi group, he had the chance to familiarize himself and broaden his horizons with several efficient techniques. He took part in the project of combinatorial synthesis of antibiotics bottromycin A2, collaborating with the Kitasato Institute. In his 15 months experiences in the research laboratory, he recognized that hard-working is the most essential factor to a successful scientist.

Yanran started graduate studies at the University of Pennsylvania, United States of America, in 2009 and had the honor of joining the research group of Professor Amos B. Smith, III. In the Smith group, he was gradually brought up to a skillful organic chemist and achieved his major project, total synthesis of enigmazole A utilizing a novel late-stage large-fragment Petasis-Ferrier union/rearrangement protocol. With his hardworking, he also synthesized multiple fragments for the synthetic projects of enigmazole B and neopeltolide in gram scale as well as more than 60 compounds utilized in the HIV-entry inhibitor project.

During his graduate studies, Yanran met Tingyi Wu again, his classmate and best friend in the kindergarten, and they were married in 2012. Yanran felt very fortunate to hold Tingyi’s hand again after 23 years since the kindergarten.

Upon completion of his doctorate, Yanran will be continuing his career in “to research the natural science” at Harvard University as a post-doctoral researcher in the research group of Professor Yoshito Kishi.