FORMAL TOTAL SYNTHESIS OF PSEUDOPTEROXAZOLE.

PROGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B.

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PROGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B

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Dedicated to my daughter Caroline, my wife Jing and my parents.
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LIST OF ABBREVIATIONS

Ac: acetyl

ACN: acetonitrile

Ar: aryl (substituted aromatic ring)

BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

Boc: t-butoxycarbonyl

Bn: benzyl

dba: dibenzylideneacetone

DCM: dichloromethane

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

DIBAL: diisobutylaluminum hydride

DMAP: N,N-4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: N,N-dimethylformamide

DMSO: dimethylsulfoxide

dppf: 1,1′-bis(diphenylphosphino)ferrocene

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

DIPEA: (Hünig’s base) diisopropylethyl amine

ee: enantiomeric excess

EWG: electron-withdrawing group

IBX: o-iodoxybenzoic acid
KHMDS: potassium bis(trimethylsilyl)amide
IR: infrared spectroscopy
LAH: lithium aluminum hydride
LDA: lithium diisopropylamide
LiHMDS: lithium bis(trimethylsilyl)amide
m-CPBA: meta chloroperbenzoic acid
MOM: methoxymethyl
Ms: mesyl (methanesulfonyl)
MS: molecular sieves
NBS: N-bromosuccinimide
NCS: N-chlorosuccinimide
NMO: N-methylmorpholine oxide
NMR: nuclear magnetic resonance
PCC: pyridinium chlorochromate
PDC: pyridinium dichromate
Ph: phenyl
Py: pyridine
PMHS: polymethylhydrosiloxane
p-TsOH: p-tolyl sulfonic acid
TEA: triethylamine
TBAF: tetra-n-butylammonium fluoride
FORMAL TOTAL SYNTHESIS OF PSEUDOPTEROXAZOLE.
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ABSTRACT

In the first chapter, a formal total synthesis of pseudopteroxazole is presented, highlightening an E-selective Horner-Emmons reaction, a Buchwald-Hartwig coupling, and a diastereoselective intramolecular Michael addition.

In the second chapter, the effort toward synthesizing anti-viral natural product hamigeran B is summarized. Several routes to the core structure were shown separately, including those unexpected discoveries when pursuing those routes. Tius-Nazarov cyclization was first applied in synthesizing natural product; an efficient palladium-catalyzed oxidative intramolecular carbocyclization was realized on an α-hydroxy enone for the first time; an interrupted Nazarov cyclization of a hydrolysis intermediate of dithiane was achieved.
CHAPTER ONE

FORMAL TOTAL SYNTHESIS OF PSEUDOPTEROXAZOLE

1.1 Introduction

It has been well recognized that the synthesis of natural products has played a significant role in the development of organic chemistry and chemistry as a whole in the past century. The richness of natural products available from terrestrial plants and water-born plants, and the metabolites of microorganisms provide practically unlimited structures for organic synthetic chemists to work on. By striving to synthesize natural products, numerous new reagents, new methodologies, new strategies, and even new concepts are developed, enriching the textbook of organic chemistry. Apart from the applications of total synthesis of natural products to the discovery of medicines, the pure beauty of designing the strategy, the exquisiteness of manipulating materials at the molecular level, and the beauty of structural transformations are more than enough to attract numerous people to devote years of the best time of their lives to this field. Becoming a true synthetic organic chemist is also demanding: one should be, at first, a skilled technician, good at hands-on bench work, always driven by challenges; he should be an artist with a heart for beauty; also, he should be a scientist who puts integrity above everything, practices logic, and discover the truth.

As the knowledge about organic synthesis exploded during the last century, new concepts, such as Corey’s retrosynthetic analysis,\(^1\) the Woodward-Hoffmann rules,\(^2\) and Baldwin’s rules were formulated\(^3\); challenging natural products, such as taxol, strychnine, vitamin B\(_{12}\), and brevetoxin B were synthesized; bioactive small molecules were
discovered and developed into drugs that improved the quality of human health. With the introduction of modern combinatorial chemistry and high-throughput screening approaches to drug lead discovery, the importance of natural product guided approach for drug discovery has never be undermined.  

What needs to be resolved at the synthesis stage is the efficiency of the syntheses.

In the first part of this chapter, the background of a natural product synthesis project will be introduced, including the source of the natural product, its natural relatives, and their bioactivities; the total syntheses of this natural product to date; and a proposed chemical relationship of this family of natural products to be scrutinized.

The second part of this chapter will introduce the synthetic plan and the detailed synthetic efforts leading to the formal total synthesis of pseudopteroxazole. The key reactions are: a completely $E$-selective Horner-Wordsworth-Emmons (HWE) reaction, a Buchwald-Hartwig coupling, and a stereoselective intramolecular Michael addition.
1.1.1 Marine Natural Products from *Pseudopterogorgia Elisabethae*

To natural product chemists, finding a good source for isolating novel natural products is obviously a very important factor for their productivity. To that end, the gorgonian coral (sea whip) *Pseudopterogorgia elisabethae* did not disappoint them. In the genus of *Pseudopterogorgia* in the animal kingdom, *Pseudopterogorgia elisabethae* is typically found at a depth of 40 to 70 meters underwater. The animal samples used by the Rodriguez group to isolate pseudopteroxazole were collected in the eastern Caribbean sea.

![Figure 1](http://gorgonien.npage.de/pseudopterogorgia_elisabethae_neu_70837353.html)

1.1.2 Selected Serrulatane Diterpenoids From *Pseudopterogorgia Elisabethae*

There are many novel carbon skeletons discovered from the natural products isolated from *Pseudopterogorgia elisabethae*. An excellent review by Heckrodt and Mulzer covered this topic more comprehensively. In the following, five skeletons are shown, with the representatives for each skeleton and bioactivities of those natural products.
First, let us look at the serrulatane skeleton (Shown in Figure 2). Nine natural products possessing serrulatane carbon skeleton were discovered, four of which are shown in Figure 2. These differ in the substitution on the aromatic ring, or as for elisabethadione, the aromatic ring is oxidized. Two of the other natural products with the serrulatane skeleton are also of higher oxidation state, indicating the presence of an oxidizing environment producing these metabolites. Erogorgiaene showed 96% growth inhibition of *Mycobacterium tuberculosis*, seco-pseudopterosin glycosides showed better anti-inflammatory and analgesic activity than existing drugs in animal models.⁷

**Figure 2**

![serrulatane skeleton](image)

1 Erogorgiaene 96%
2 seco-Pseudopterosin A-D, E-G aglycone
3 seco-Pseudopteroxazole
4 Elisabethadione

Nine natural products isolated from *Pseudopteroxazole elisabethae* share the amphilectane skeleton (Figure 3). Pseudopteroxazole falls into this class of natural
products. It has shown strong inhibition effects toward tuberculosis bacteria (TB). (97% inhibition at 12.5 µg/ml) It is worth noting that some of them have different stereochemistry, such as pseudopterosin A-F aglycone, pseudopterosin K, L aglycone. The diversity of the stereochemistry is associated with the different collection sites of the *Pseudopterogorgia elisabethae* sample. The sample from which pseudopterosins G-J were isolated was collected near Bermuda Island; samples containing pseudopterosins M-O were collected from Florida Keys; pseudopterosins K and L were obtained from Bahamian samples.

Figure 3

Elisabethin A and elisabethin D share a novel tricyclic core structure called elisabethin skeleton. (Figure 4) While the relative stereochemistry was unambiguously...
determined by a single-crystal X-ray diffraction experiment, the absolute stereochemistry has not yet been determined. Though it was once thought to have been resolved by the total synthesis of elisabethin A, it was later found that the total synthesis product was not actually the natural product, but rather the epimer of elisabethin A. We expect the total synthesis of elisabethin A to come in the future since organic synthetic chemists are always ready to embark upon the formidable challenges.

Another novel diterpene skeleton is the tetracyclic elisapterane skeleton (Figure 5). Through oxidation and cyclization, a variety of secondary metabolites containing elisapterane skeleton were also produced. Elisapterosin B exhibited anti-TB activity (79% inhibition). Elisapterosin A showed anticancer activity \textit{in vitro}.  

The colombiane skeleton is represented in colombiasin A (Shown in figure 6).
1.1.3 Biosynthesis of the Common Intermediate Elisabethatriene.

The biosynthesis of this class of natural products is believed to start with geranylgeranyl phosphate, and through a serrulatane intermediate, producing a diversity of carbon skeletons and stereochemical complexities. While the sea creature *Pseudopterogorgia elisabethae* has been using this kind of diversity-oriented synthesis to generate metabolites for quite a long time with its enzymes, humans are still trying hard...
to mimic this feat in the hope to discover more bioactive molecules that could benefit people.\textsuperscript{12}

As shown in Scheme 1, the biosynthesis of pseudopterosins was determined to start with geranylgeranyl pyrophosphate.\textsuperscript{13} Elisabethatriene was found to be a product of a diterpene cyclase, based on radiolabelling experiments (Scheme 1).

\textbf{Scheme 1}

The mechanism for the generation of elisabethatriene from geranylgeranyl pyrophosphate was proposed as shown in Scheme 2. Ionization of pyrophosphate yields an allylic cation, which could be trapped by an internal double bond. A series of hydride shifts generate another allylic cation at the same position, which can then react with another double bond to form a tertiary carbocation. The elimination of the terminal proton in addition to a couple of hydride shifts affords the elisabethatriene.
1.1.4 Proposed Diversity Oriented Synthesis of Serrulatane Diterpenoids

Having discussed the biosynthesis of pseudopterosin diterpenoids, biomimetic syntheses of several of the natural products from this family were proposed as an alternative to what was proposed in Mulzer’s review. As shown in scheme 3, pseudopteroxazole 5 could be produced via selective enamine formation and condensation with orthoformate. Oxidation of 6 could lead to elithabethol 18, which could in turn generate elithabethin A 9, after an acyloin rearrangement. Further oxidation leads to elithabethin D 10, which, after allylic oxidation, phosphonation, and C15 allylation, yields elisapterosin D 13. Hydration of 13 will lead to semiketal elisapterosin A 14 and F 19. C2 allylation of 9 would generate colombiasin A 15; CAN oxidation of 9 would lead to elisapterosin B 11.
1.1.5 Total Synthesis of *Pseudopteroxazole* by the Corey Group

As early as 2001, Johnson and Corey published a total synthesis of the proposed structure of pseudopteroxazole.\(^\text{14}\) In 2003, the Corey group reported the first total synthesis of pseudopteroxazole together with three diastereomers.\(^\text{15}\) It took 19 steps to get the natural product in 7% overall yield from an abundant natural product, \((S)-(-)-\)limonene 20 (Figure 7). This total synthesis showcased the use of inexpensive chiral natural products as chiral sources to set up the stereocenters in the synthesis of natural products. An earlier application of the enantiopure \((S)-(-)-\)limonene in total synthesis came from the same laboratory in 1998, as evidenced by their paper of the total synthesis of pseudopterosins (Figure 7).\(^\text{16}\)

**Figure 7**

As is illustrated in Scheme 4, starting from the readily available \((S)-(-)-\)limonene 20, TBDPS-protected \((8R)-\)hydroxy ketone 25 (8R:8S = 99:1 from HPLC analysis of their corresponding derivatives) was obtained through hydroboration followed by oxidation, selective oxidation of secondary alcohol, diastereoselective acetylation catalyzed by Amano PS lipase, and protection with a tert-butyl-diphenylsilyl group. Next,
kinetic deprotonation with LDA followed by trapping with TMSCl led to an enol silyl ether, which underwent a Mukaiyama-type Michael addition with enone 26, giving a 61% yield of 27 as a mixture of diastereomers (about 1:1 ratio). An intramolecular aldol
reaction followed by elimination of the tertiary hydroxyl group led to the net Robinson annulation product 28 in 69% yield. Oxime formation followed by acylation gave the oxime pivalate diastereomers 29, which were aromatized under modified Wolff-Semmler conditions by heating with a stoichiometric amount of acetyl chloride in toluene in a sealed reaction vessel. Thus, the two diastereomers were converged to one aromatic compound 30. Deprotection of the benzyl group freed the phenol, which was treated with carbonyldiimidazole to form the cyclic carbamate 31. After hydrolysis of the carbamate, the TBDPS group was removed with a hydrofluoric acid-pyridine complex. Perruthenate-catalyzed oxidation led to the aldehyde, which reacted under Wittig-Vedejs $E$-selective olefination conditions to produce the diene 32, setting up the stage for the key cationic cyclization to form 33.

It is interesting to note that, in this catalytic cyclization, changing the solvent from acetic acid to dichloromethane completely reversed the diastereoselectivity. In order to explain this phenomenon, they proposed two transition states for the cationic cyclization (Scheme 5). First, the protonation of the conjugated diene 32 gave an allylic cation 32a. Then, the road diverges. One path leads to a six-membered ring transition state 32b, affording the undesired diastereomer 33b; the other is through a five-membered ring transition state 32c, leading to the other diastereomer 33a. Presumably, when dichloromethane is used as the solvent, the oxygen is a better electron donor to the aromatic ring system than the nitrogen in the cyclic carbamate, activating the para-position of the aromatic ring (C14), forming the six-membered ring transition state. Rearomatization leads to the diastereomer 33b. When acetic acid is used as the solvent, it is proposed to serve as a hydrogen bond acceptor, stabilizing the transition state in which
the nitrogen atom is a better electron donor (32c). The nitrogen atom activates the \textit{para}-position relative to the nitrogen (C1), leading to the five-member ring transition state 32c, which after rearomatization affords the other diastereomer 33a.

\textbf{Scheme 5}

In other experiments with the corresponding mesylate (34) or triflate, the diastereomer 35, generated from the oxygen-activated route was formed in a greater than 20:1 ratio, in either dichloromethane or acetic acid (Scheme 6). Keeping in mind that the methanesulfonyl group, being strongly electron withdrawing, should attenuate the electron donating ability of the oxygen atom, the acylated nitrogen atom failed in competing with the oxygen in activating the aromatic ring. Combined with the result of the cyclic carbamate 32, it proves that the planarity of the cyclic carbamate enables the nitrogen’s lone electron pair to be perpendicular with the aromatic ring, which is crucial for its ability to activate the aromatic ring.
Having discussed this cationic cyclization, another set of examples should not be overlooked. In the paper about the total synthesis of pseudopterosins from the Corey group, the diastereoselectivity was switched, by switching the mesyl group to the TBS group (Scheme 7). Considering the different electronic properties of the two functional groups, the mesyl group being strongly electron withdrawing while TBS group being electron donating, the stereoselectivity can be rationalized based on different oxygen atoms serving as the predominant activating group.17
After this biomimetic cyclization, acylation of the free NH with Boc₂O, cleavage of the cyclic carbamate, and treatment with trifluoroacetic acid and triethyl orthoformate gave the desired natural product pseudopteroxazole 5, confirming the absolute structure of this natural product at the same time.

1.1.6 Total Synthesis of Pseudopteroxazole by the Harmata Group

The second total synthesis of pseudopteroxazole came from our group in a couple of communications reported in 2004 and 2005.¹⁸ In the first communication, Harmata and Hong applied the methodology they developed and published in 2003,¹⁹ the intramolecular Michael addition of sulfoximine carbanions to α,β-unsaturated esters, to the synthesis of an intermediate for the total synthesis of pseudopteroxazole, which is essentially a benzothiazine analog of pseudopteroxazole. This endeavor proved the fidelity of the methodology in setting up the benzylic stereocenters diastereoselectively.

In this world of organometallic catalysis, organocatalysis, and enzymatic catalysis, auxiliary-controlled stereoselectivity is overlooked due to its intrinsic lack of step and atom economy. But when it comes to achieving as high stereoselectivity as nature does, (100% d.r. within detection limit) developing this unique chiral sulfoximine auxiliary-controlled intramolecular Michael addition is irresistible. What is more, the stability, the stereoregidity, the hydrophilicity, and being the bioisostere of the ester hydrolysis intermediate render the compounds containing this functional group more added values, with respect to the discovery of new medicines at least.²⁰
As shown in Scheme 8, the synthesis began with a known substituted ortho-
bromocinnamate 40, which can be made from commercially available anisole in five
steps. (R)-N-methyl-N-phenylsulfoximine 41 was coupled to the ortho-bromocinnamate
40 via a Buchwald-Hartwig coupling reaction. Treatment with two equivalents of lithium
diisopropylamide, followed by kinetic protonation, led to the Michael addition product 43
as 10:1 ratio of two diastereomers. Although there could be up to four diastereomeric
products produced from this reaction, as there are two new stereogenic centers formed,
there were only two diastereomers formed with diastereomeric ratio being ten to one, as
determined by $^1$H-NMR analysis. This application of the intramolecular Michael addition
of a sulfoximine stabilized carbanion to an unsaturated ester not only provided complete stereocontrol over the benzylic position, but also expanded the power of the reaction to the control of the stereogenic center next to the benzylic position. Although the reaction is highly stereoselective, it generated the products favoring the diastereomer with the wrong stereochemistry.

Nevertheless, Harmata and Hong pushed the mixture of products to the end of the total synthesis with great dedication and stamina. Lithium aluminum hydride reduction and Swern oxidation transformed the ethyl ester 43 to the aldehyde 44 in 67% yield. With prolonged reaction time in the presence of base, the mixture of two diastereomers underwent epimerization, giving another mixture of diastereomers favoring the one with the correct stereochemistry as the thermodynamically more stable aldehyde. To make the dienyl branch, a Wittig-Vedejs E-selective olefination was applied to this mixture of benzothiazines, generating a 52% yield of the diastereomer 46 with the required stereochemistry and a 33% yield of one with the wrong stereochemistry. These were separated by flash chromatography.

Scheme 9

![Scheme 9](image-url)
The next step was a cationic cyclization, forming the six-membered ring with complete diastereoselectivity (Scheme 9). Assuming the nitrogen is a better electron donor, the cationic cyclization was rationalized by the steric hindrance between the S-phenyl group and the allylic cation through a five-membered ring transition state (46a). It was the first report on this type of cationic cyclization of benzothiazine. The diastereoselectivity was completely reversed if the oxygen is a better electron donor and the cationic cyclization processed through a six-membered ring transition state based on Corey’s studies (Scheme 7, from 36 to 37).21

Scheme 10

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1. LiHMDS, THF
2. allylbromide, 100%

1. HONO
2. K₂CO₃, EtNH, 100%

1. Zn, rt, 1h
2. CH₂Cl₂, 65%

1. NaH, EtSH
2. DMF, 87%

HONO, 84%

1. LiHMDS, THF
2. allylbromide, 100%
The second report from our group detailed the total synthesis of pseudopteroxazole in nine steps from the tricyclic benzothiazine 47 (Scheme 10). First, the benzothiazine 47 was deprotonated by LiHMDS diastereoselectively, presumably by the direction of the oxygen on the sulfur through lithium cation. Then the carbanion was trapped by allyl bromide, giving a quantitative yield of the allylated product 48 in diastereopure form. Next, sodium amalgam cleaved the sulfur-carbon bond, producing the aniline 49 in 92% yield. The aniline 49 was efficiently transformed to the corresponding iodide 51 through a 1-aryl-3,3-diethyltriazene intermediate 50. The last ring was formed by an innovative intramolecular Heck coupling. The next step is another highlight of this total synthesis, the regioselective and diastereoselective homogeneous hydrogenation catalyzed by an iridium catalyst 53. In this case, both the catalyst and the structure of the molecule worked together to enable the high regioselectivity and stereoselectivity of this hydrogenation in a near perfect fashion. Later, it was found that the rigidity of the tricycle is crucial for the selectivity.22 After deprotection of the methoxy group by in situ generated NaSEt in refluxing DMF, nitration yielded the nitrophenol 56, which was reduced and treated with methyl orthoformate to give the natural product pseudopteroxazole 5.

1.2 Formal Total Synthesis of Pseudopteroxazole

From the review of the first generation of total synthesis of pseudopteroxazole, the innate ability to control stereoselectivity by a sulfoximine as a chiral auxiliary was clearly demonstrated in the intramolecular Michael addition, which set up two of the four stereocenters contained in pseudopteroxazole. The preference for the wrong
diastereomer, however, diminished the usefulness of that synthetic route. Through strategic design, a new approach was proposed to ameliorate the drawback of the first total synthesis of pseudopteroxazole.

1.2.1 Synthetic Plan

Bearing in mind the major pitfall of the first generation of total synthesis being the highly diastereoselective intramolecular Michael addition favoring the diastereomer with the wrong stereochemistry, the methyl group on C-3 (pseudopteroxazole numbering) was changed to an ester group as a surrogate. Though reducing an ester to an alkane has been shown to be quite facile in a similar system, a subtle change of the structure rendered this reduction process quite challenging, as will be discussed later. Another strategic change was made in the pursuit of better efficiency of the total synthesis. The diene branch was planned to be installed prior to the Buchwald-Hartwig coupling reaction. Though there are many “philosophic concepts” about the economy in total synthesis in the modern literature world, in academic environment, the value of a good total synthesis can always be appreciated by its aesthetically pleasing transformations perceived by the mind through drawings on the paper, or more and more frequently, on a screen; and by its ease to perform, and hence the satisfying feelings arising from it, by the practitioners in the laboratory. To access the starting material 58 for the key reaction (intramolecular Michael addition), a two-step sequence (Horner-Wadsworth-Emmons reaction and Buchwald- Hartwig coupling) was designed to merge three relatively simple starting materials together convergently (Scheme 11).
1.2.2 Preparation of Coupling Partners

The (R)-(−)-S-methyl-S-phenylsulfoximine 41 was prepared according to the published procedure.24 Another coupling partner, 2-bromo-3-methoxy-5-methylbenzaldehyde 60 was made following Koyama and Kamikawa’s protocol.25 The isopropyl dienolate 59 was synthesized through a modified Minami procedure in four to five steps, depending on which starting material used (Shown in Scheme 12).26
3-Methyl-2-buten-1-ol 61 could be purchased from Acros at a price of $180.6/25 mL, or it could be synthesized directly from 3-methyl-2-buten-1-ol ($55/kg) by pyridinium chlorochromate oxidation. We used 3-methyl-2-buten-1-ol as the initial starting material most of the time, for economic reasons. However, 3-methyl-2-buten-1-ol 61 is very volatile, in spite of a relatively high boiling point (132-133°C), and a significant amount of material was lost after distillation. Therefore, the aldehyde starting material 61 was used as a solution in dichloromethane in most cases. As for the Knoevenagel condensation between the allylic aldehyde 61 and the trimethyl phosphonate 62, titanium isopropoxide was chosen as the Lewis acid instead of titanium chloride used by Minami and his coworkers.26,27 The next step was a regioselective cyclopropane formation, followed by pyrolysis of the cyclopropane intermediate to the homologated isopropyl ester 59.

After a cursory screening of conditions, 2-bromo-3-methoxy-5-methylbenzaldehyde 60 was coupled with the dienoate 59 under very mild conditions, barium hydroxide in THF and water at room temperature. This generated the coupled product 64 in 84% to 98% yield, with complete E-selectivity (Scheme 13).

Scheme 13
1.2.3 Buchwald-Hartwig Coupling and the Intramolecular Michael Addition

Aware of the possibility of an intramolecular Heck reaction,\textsuperscript{28} we coupled the aryl bromide 64 with (\textit{R})-\textit{(S)}-\textit{S}-methyl-\textit{S}-phenylsulfoximine 41 through a Buchwald-Hartwig reaction. Gratifyingly, the Buchwald-Hartwig coupling product 58 was produced with up to 81\% yield.\textsuperscript{29} Only trace amounts of the fluorescent Heck product 65 was formed, demonstrating the high selectivity of this catalyst system (Scheme 14).

Scheme 14

The highlight of this synthetic route would be the intramolecular Michael addition to generate chiral benzothiazine 57 with two contiguous chiral centers. At -78 °C, two equivalents of lithium hexamethyldisilamide in THF solution was added to a solution of starting material 58 in THF. After TLC analysis showed the complete consumption of starting material, the reaction mixture was quenched by slowly adding a pre-cooled HCl solution in MeOH. This reaction was clean and diastereoselective, favoring the product 57 with the right stereochemistry which was separated from 57a with flash chromatography (Scheme 15).
The stereocontrol over the benzylic position was consistent with all other related examples. The stereoselectivity could be rationalized based on the steric interactions in the transition state, or it could be conceived as an oxygen-directed kinetic deprotonation of the α-carbon next to sulfur. Though the sigma bond connecting the α-carbon and sulfur could rotate freely, the chelation between the oxygen, lithium, and nitrogen could restrict the rotation about the sigma bond, forcing the Michael accepter approaching from the bottom face to react with the carbanion (Scheme 16).
diastereoselectivity on the C-3 could be rationalized as the result of kinetic protonation from the Re face, since the Si face of the enolate was hindered by the aromatic system.

1.2.4 End Game of Formal Total Synthesis of Pseudopteroxazole

Now, what needed to be done was reduction of the isopropyl ester 57 to the 47. There are a lot of tactics to furnish this transformation in organic chemists’ arsenal. However, this seemingly simple functional group transformation proved to be quite troublesome in this circumstance. First, after a cursory screening of reductants, DIBAL gave the best yield (88%) of the alcohol 66, though in some cases, a variable amount of the aniline product 67 was isolated as byproduct (Scheme 17).

Scheme 17

A similar byproduct was identified by reducing an analogous benzothiazine with LAH. A proposed mechanism for the formation of the chiral tetrahydrofuran is shown in Scheme 18. First, the isopropyl ester 57 was reduced to alkoxide by DIBAL; hydride reduction of the benzothiazine followed by elimination of hydrogen led to sulfoxide intermediate. The sulfoxide underwent a Pummerer rearrangement; elimination of the oxygen on the sulfur atom formed a sulfonium intermediate, which was trapped intramolecularly by the alkoxide to form the tetrahydrofuran product 67.
Having acquired the alcohol 66, the last move now was to deoxygenate 66 to the 47. The first strategy coming to mind for this transformation was converting the hydroxy group to a good leaving group, followed by hydride reduction. Thus, iodination of the alcohol 66 afforded the corresponding iodide 69 in rather low yield with a major byproduct 70 (Scheme 19).

Initially, the structure of this cyclopropane was established based on NMR study (Figure 8). The chemical shifts in the high field from δ1.7 to δ0.7 and the coupling pattern were typical for cyclopropanes. It is known that for cyclopropanes, the coupling constant between the two geminal hydrogens of the cyclopropanes is 5 Hz, while the coupling constants of the vicinal hydrogens are from 4 Hz to 5 Hz for trans-cyclopropanes and 8 Hz to 9 Hz for cis-cyclopropanes.32 The chemical shifts and coupling constants for hydrogens on C10, C9, C16a, and C16b are: δ 1.64 (dddd, J = 4.5, 4.5, 8.5, 8.5 Hz, 1H), 1.04 (dddd, J = 4, 4, 9, 9 Hz, 1H), 0.85 (ddd, J = 5, 5.5, 8 Hz, 1H), 0.76 (ddd, J = 4.5, 5, 8 Hz, 1H) (Figure 9). The coupling constant between C10 and C9 is
about 5 Hz. This is in accordance with trans-cyclopropanes. This cyclopropane is stable at room temperature open to air for at least one year. And we were able to get the single crystal and thus the X-ray crystallography of 70, which confirmed the trans-cyclopropane structure (Scheme 19).

Figure 8
Next mesylation was tried with success, giving the mesylate 68 in a 79\% yield with trace amount of the same byproduct 70 as in the iodination (Scheme 20). Then, the mesylate 68 was treated with excess amount of NaI in acetone, in order to be transformed to the iodide 69. However, it led to a mixture of the iodide 69 and again the same
byproduct 70. When the crude mesylate 68 was used directly for the iodination reaction, 42% of 69 and 42% of 70 were obtained (Scheme 20).

Scheme 20

Though it was not the product we expected, the enantiopure cyclopropane compound 70 could be obtained in high yield, simply by treating the mesylate 68 with four equivalents of imidazole in refluxing acetone (Scheme 21).
A working mechanism was proposed to rationalize the high stereoselectivity of this cationic cyclopropanation reaction. An ionization mechanism was unlikely due to the high energy of primary carbocation. An intramolecular SN$_2$ reaction of the mesylate 68 generated an allylic carbocation. Elimination by imidazole led to the final product 70. The stereoselectivity was presumably the result of a strong 1,3-allylic strain between the benzothiazine group and the allylic hydrogen (Scheme 22).

Scheme 22

![Scheme 22](image)

Finally, the mesylate 68 was reduced with a combination of lithium iodide and super hydride, giving up to a 79% yield of the deoxygenated product 47. This reduction presumably involved the in situ formation of the corresponding iodide, followed by reduction by super hydride (Scheme 23).

Scheme 23

![Scheme 23](image)
1.3 Concluding Remarks and Outlook

A convergent and diastereoselective formal total synthesis of pseudopteroxazole was achieved, once again demonstrated by the fidelity of the stereocontrol of chiral sulfoximine on the benzylic position (Scheme 24). This was the third report on synthesis of anti-TB natural product pseudopteroxazole. The newly developed synthetic route corrected the diastereoselectivity issue from the first total synthesis of pseudopteroxazole reported from our group. At the same time, it is more efficient and more step economic than our first synthesis. What is noteworthy in this sequence is the completely $E$-selective HWE reaction, the Buchwald-Hartwig coupling between a triene and sulfoximine, the highly diastereoselective intramolecular Michael addition, and the super hydride reduction of mesylate influenced by lithium iodide. During the synthesis progress, a diastereoselective formation of a tetrahydrofuran and a diastereoselective cyclopropane formation were also discovered, opening up opportunity to explore more new reactivity of chiral benzothiazine.

The drawback of this methodology is the same as all the others using chiral auxiliaries to control stereochemistry, poor atom economy and step economy. However, from another point of view, it provided the opportunity to make sulfoximine-substituted analogs of the natural products, which would certainly change their pharmacological properties. This should need to be tested.
1.4 References


11. Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L., Novel Terpenoids from the West Indian Sea Whip *Pseudopterogorgia elisabethae* (Bayer). Elisapterosins A


17. The drawn product for each reaction were the major diastereomer formed: for the mesylate, the d.r. is 25:1; for the TBS protected, the d.r. is 8:1.


21. Refer to the above discussion about E. J. Corey's total synthesis of pseudopteroxazole.


24. Though the price of (R)-(S)-methyl-S-phenylsulfoximine is 217.5 USD per gram from Aldrich, multi-gram scale production of it is an entering level task in our lab.


27. The deconjugated isomer was formed before the acidic treatment, which isomerized the isomer and transesterified it to the final isopropyl ester product.


1.5 Experimental Section

General Information:

All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Reactive liquid reagents (LHMDS, etc.) were measured and transferred by gastight syringes through rubber septa. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl. Toluene was distilled from CaH₂. The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residue solvents were usually removed under reduced pressure using vacuum pump (approximately 1mm Hg).

Flash chromatographic separations were carried out on silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin layer chromatography was performed on glass–backed silica gel plates with F254 indicator. Compounds were visualized under UV light or by developing in iodine, vanillin, phosphomolybdic acid solution or with potassium permanganate solution followed by heating in a hot plate to approximately 350°C. Melting points were determined with a melting point apparatus.

¹H NMR spectra were recorded in Fourier transform mode at 250, 300 or 500 MHz, respectively, as CDCl₃ solutions with tetramethylsilane (Δ = 0 ppm) as the internal standard. ¹³C NMR spectra were recorded on the same instruments at 62.5, 75 or 125 MHz, respectively, with CDCl₃ (Δ = 77 ppm) as the internal reference. ³¹P NMR spectra were recorded on the same instruments at 101 MHz, respectively, with 85% H₃PO₄ (Δ = 0 ppm) as the external standard. Chemical shifts (Δ) were reported in parts per million (ppm). Multiplicities were reported as s (singlet), b (broad), d (doublet), t (triplet), q
(quartet), m (multiplet), and dd (doublet of doublet), etc. In $^1$H NMR spectra of
diastereomeric mixtures, the signals for individual isomers were reported when possible.
Infrared spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded
on a polarimeter with sodium D line at the temperatures as indicated in the experimental
for specific compounds. High resolution mass spectra were obtained on a magnetic sector
instrument with a resolution greater than 10,000.

(E/Z)-isopropyl 2-(dimethoxyphosphoryl)-5-methylhexa-2,4-dienoate (63): A mixture
of 3-methylbut-2-enal 61 (5 mL, 0.065 mol) and trimethyl phosphonoacetate 62 (5.26
mL, 0.033 mol) in THF (300 mL) with molecular sieves (4 Å) was placed in a 1 L round-
bottom flask under an argon atmosphere. To this solution, Ti(OiPr)$_4$ (29 mL, 0.098 mol)
was added. Then TEA (17 mL, 0.13 mol) was added over 30 min, and the mixture was
stirred at 0°C for 7 h. The reaction mixture was poured into 1 N HCl and vigorously
stirred at rt for 1 h. It was extracted by ethyl acetate (3 x 300 mL) and the extract was
washed with 300 mL saturated sodium bicarbonate solution and 300 mL brine. The
organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated,
affording the product as a mixture of E/Z (2:1) isomers (5.82 g, 92%). (Z)-isomer: IR
(neat): 2978, 2953, 2848, 1699, 1618, 1564, 1250, 1025, 829 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500
MHz) δ 8.20 (dd, 1 H, J = 12.5, 44.5 Hz), 7.22 (dd, 1 H, J = 1.0, 12.0 Hz), 5.12 (septet, 1
H, J = 6.5 Hz), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.00 (s, 3H), 1.98 (s, 3H), 1.30 (d, 6 H, J = 6.0
Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 165.9 (d, J = 15.0 Hz), 155.2 (d, J = 2.5 Hz), 152.9
(d, J = 10.0 Hz), 122.4 (d, J = 5.0 Hz), 115.6 (d, J = 186.0 Hz), 68.7, 52.6 (d, J = 5.0 Hz),
27.6, 21.7 (d, J = 10.0 Hz), 19.0; HRMS calcd for C_{12}H_{21}O_{5}PNa [M+Na]^+ 299.1019;
Found: 299.1006; ^{31}P NMR (CDCl\textsubscript{3}, 250 MHz) δ 23.4 (85% H\textsubscript{3}PO\textsubscript{4} as external standard).

\[ \text{(E)-isopropyl 2-(dimethoxyphosphoryl)-6-methylhepta-3,5-dienoate (59):} \]
To a solution of 63 (4.86 g, 0.018 mol) in ether (20 mL) in a 50 mL round-bottom flask, a 0.5 M diazomethane solution in ether (0.088 mL, 0.045 mol) at 0 °C was added dropwise.
The reaction was warmed to rt and stirred for 12 h. After the reaction was complete, the solvent was evaporated and the crude product was heated at 100 °C for 1 h. After flash chromatography with 50% ethyl acetate in hexanes, colorless oil (4.54 g, 84% for two steps) was obtained, the product 59 having only an (E) configuration. IR (neat): 2983, 2851, 1728, 1450, 1262, 1102, 1025, 796 cm\textsuperscript{-1}; \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz) δ 6.44 (ddd, 1H, J = 5.0, 11.0, 15.5 Hz), 5.85 (d, 1H, J = 11.0 Hz), 5.65 (ddd, 1H, J = 7.0, 9.5, 16.0 Hz), 5.07 (septet, 1H, J = 6.5 Hz), 3.81 (d, 3H, J = 11.0 Hz), 3.79 (d, 3H, J = 11.0 Hz), 3.75 (dd, 1H, J = 9.5, 24.0 Hz), 1.78 (s, 3H), 1.76 (s, 3H), 1.28 (d, 3H, J = 4.5 Hz), 1.26 (d, 3H, J = 4.0 Hz); \(^13\)C NMR (CDCl\textsubscript{3}, 125 MHz) δ 167.0 (d, J = 5.0 Hz), 136.9 (d, J = 5.0 Hz), 131.9 (d, J = 12.5 Hz), 124.0 (d, J = 5.0 Hz), 118.5 (d, J = 12.5 Hz), 69.2, 53.7 (d, J = 7.5 Hz), 53.4 (d, J = 7.5 Hz), 50.6, 49.6 (d, J = 130.0 Hz), 25.8, 21.5 (d, J = 10.0 Hz), 18.2; HRMS calcd for C\textsubscript{13}H\textsubscript{25}O\textsubscript{5}PNa [M+Na]^+ 313.1175; Found: 313.1171.
(2E, 3E)-Isopropyl 2-(2-bromo-3-methoxy-5-methylbenzylidene)-6-methylhepta-3,5-dienoate (64): To a solution of o-bromoaldehyde 60 (2.22 g, 10 mmol) and phosphonoacetate 59 (3.43 g, 12 mmol) in 120 mL THF and 6 mL of H₂O, Ba(OH)₂ (7.35 g, 43 mmol) was added in portions with vigorous stirring at 40 °C. After 10 min, the reaction was allowed to reach rt and was diluted with 200 mL CH₂Cl₂. It was washed with 1 x 100 mL saturated NaHCO₃ and 1 x 100 mL brine. It was dried with MgSO₄, filtered through Celite and concentrated in vacuo. After flash chromatography (1% TEA, 10% ethyl acetate in hexane), 3.2 g (84%) of the bromo ester 64 was obtained as a viscous oil. IR (neat): 2974, 2930, 1714, 1234, 1096 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.33(s, 1H), 7.16 (dd, 1H, J = 11.0, 15.6), 6.79 (s, 1H), 6.67 (s, 1H), 6.22 (d, 1H, J = 15.6 Hz), 5.82 (d, 1H, J = 11.0 Hz), 5.22 (septet, 1H, d = 6.0 Hz), 3.90 (s, 3H), 2.33 (s, 3H), 1.79 (s, 6H),1.38 (s, 3H), 1.36 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.0, 155.8, 138.3, 137.6, 137.4, 135.8, 132.2, 131.8, 126.2, 123.9, 122.2, 112.2, 110.1, 68.4, 56.2, 26.2, 21.8, 21.4, 18.6; HRMS calcd for C₂₀H₂₅O₃BrNa [M+Na]⁺ 415.0879; Found: 415.0875.
58: A 100 mL round bottom flask with condenser was charged with palladium acetate (15 mg, 0.065 mmol), rac-BINAP (60 mg, 0.1 mmol), in 35 mL toluene. The mixture was stirred for 15 min at room temperature. The bromo ester 64 510 mg (0.5 mmol) and (R)-41 220 mg (0.77 mmol) in 5 mL toluene was added, followed by addition of Cs₂CO₃ (1.17 g, 2 mmol). It was refluxed at 110°C for 12 h. Then it was diluted with 40 mL CH₂Cl₂, filtered through Celite, which was washed with 3 x 50 mL CH₂Cl₂, and concentrated in vacuo. After flash chromatography (25% ethyl acetate in hexanes), 491 mg (81%) of 58 was obtained as pale yellow semisolid. IR (film): 3064, 2974, 2925, 1703, 1560, 1454, 1336, 1270, 1233, 1094, 735 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 8.00 (dd, 2H, J = 1.5, 10.0 Hz), 7.77 (s, 1H), 7.56-7.50 (m, 3H), 7.20 (dd, 1H, J = 11.0, 15.5 Hz), 6.80 (s, 1H), 6.60 (s, 1H), 6.40 (d, 1H, J = 15.5 Hz), 5.87 (d, 1H, J = 11.0 Hz), 5.21 (m, 1H, J = 6.0 Hz), 3.59 (s, 3H), 3.10 (s, 3H), 2.28 (s, 3H), 1.81 (s, 6H), 1.36 (s, 3H), 1.34 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 167.6, 152.2, 142.4, 137.2, 136.9, 132.3, 132.0, 131.6, 130.7, 130.2, 129.8, 128.9, 127.5, 126.6, 123.4, 113.1, 67.8, 55.6, 46.0, 26.2, 22.0, 21.2, 18.6; HRMS calcd for C₂₇H₃₅NO₄SNa [M+Na]+ 490.2022; Found: 490.2016; [α]²⁵°D = 77.975 (c 0.79, CHCl₃).
The Heck coupling product 65 is a byproduct that was formed in trace amount under the Buchwald coupling condition. It was isolated as a fluorescent colorless oil: IR (neat): 2978, 2917, 1708, 1573, 1454, 1372, 1274, 1221, 1136, 1103 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 8.28 (d, 1H, \(J = 1.5\) Hz), 7.67 (s, 1H), 7.30 (s, 1H), 6.94 (s, 1H), 6.73 (d, 1H, \(J = 1.0\) Hz), 5.29 (septet, 1H, \(J = 6.0\) Hz), 3.87 (s, 3H), 1.96 (d, 3H, \(J = 1.0\) Hz), 1.71 (d, 3H, \(J = 1.5\) Hz), 1.40 (d, 6H, \(J = 6.5\) Hz); \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 166.4, 157.3, 136.1, 135.7, 135.3, 130.9, 128.5, 128.0, 127.7, 126.8, 124.9, 121.6, 110.4, 68.3, 55.9, 26.0, 22.0, 21.7, 19.1; HRMS calcd for C\(_{20}\)H\(_{24}\)O\(_3\)Na [M+Na]\(^+\) 335.1618; Found: 335.1618.

57: A 100 mL round-bottom flask was charged with bromo ester 58 (1.58 g, 3.38 mmol) in 40 mL THF. LiHMDS 6 mL (1 M in toluene, 6 mmol) was added dropwise to the solution at -78°C. After 10 min at -78°C, the reaction was quenched with 1 N HCl in methanol at -78°C. It was poured into water, extracted with 3 x 20 mL CH\(_2\)Cl\(_2\), dried with MgSO\(_4\), and concentrated in vacuo. After flash chromatography (30% ethyl acetate in hexane), 1.28 g (81%) of 57 was obtained as the major isomer. IR (film): 2970, 2921, 2868, 1720, 1462, 1245, 1102 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 8.10-8.12 (m, 2H), 7.62-7.66 (m, 1H), 7.54-7.57 (m, 2H), 6.68 (s, 1H), 6.64 (s, 1H), 6.26 (dd, 1H, \(J = 11.0, 15.0\) Hz), 5.77 (d, 1H, \(J = 11.0\) Hz), 5.49 (dd,
1H, J = 7.5, 15.0 Hz), 4.89 (septet, 1H, J = 6.0 Hz), 3.96 (t, 1H, J = 7.0 Hz), 3.88 (s, 3H), 3.60-3.64 (m, 1H), 3.52-3.56 (m, 2H), 2.3 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H), 1.15 (d, 3H, J = 6.5 Hz), 1.05 (d, 3H, J = 6.0 Hz); 13C NMR (CDCl3, 125 MHz) δ 172.3, 152.6, 139.4, 136.8, 133.8, 132.1, 131.1, 129.9, 129.5, 129.4, 124.9, 124.3, 119.4, 111.9, 68.4, 56.2, 51.1, 49.2, 38.4, 26.2, 21.8, 21.6, 18.6; HRMS calcd for C27H33NO4SNa [M+Na]⁺ 490.2022; Found: 490.2012; [α]25D = -60.48 (c 1.66, CHCl3).

(2S,3E)-6-Methyl-2-[(2R,4R)-2-oxido-2-phenyl-3,4-dihydro-2H,1-benzothiazin-4-yl]hepta-3,5-dien-1-ol (66): To a solution of the ester 57 (383mg, 0.819 mmol) in 8 mL THF, was slowly added 8.19 mL of DIBAL (1M in THF) at 0°C. After 2 h, it was carefully quenched with ethyl acetate and water. After filtration, followed by washing with 20 mL ethyl acetate, it was concentrated. After flash chromatography (50% ethyl acetate in hexanes), 0.285 g (88%) of 66 was obtained as a semisolid. IR (film): 3448, 2962, 2917, 1577, 1462, 1250, 1102, 1017 cm⁻¹; ¹H NMR (CDCl3, 500 MHz) δ 8.10-8.12 (m, 2H), 7.63-7.66 (m, 1H), 7.54-7.57 (m, 2H), 6.69 (s, 1H), 6.69 (s, 1H), 6.40 (dd, 1H, J = 11.0, 15.5 Hz), 5.82 (d, 1H, J = 10.5 Hz), 5.51 (dd, 1H, J = 9.0, 15.5 Hz), 3.89 (s, 3H, CH₃), 3.69 (ddd, 1H, J = 4.0, 7.0, 11.0 Hz), 3.46-3.55 (m, 3H), 2.98-3.13 (m, 1H), 2.32 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.35 (dd, 1H, J = 4.5, 6.5 Hz); 13C NMR (CDCl3,
125 MHz) δ  152.8, 139.2, 136.1, 133.9, 132.2, 131.0, 130.2, 129.5, 128.4, 125.1, 124.7, 119.1, 111.6, 62.7, 56.2, 50.3, 45.0, 37.5, 26.2, 21.7, 18.6; HRMS calcd for C_{24}H_{29}NO_3SNa [M+Na]^+ 434.1760; Found: 434.1751; [α]^{25}_D = -4.04 (c 3.02, CHCl_3).

(2R,4R)-4-[(1S,2E)-1-Methanesulfonyloxymethyl-5-methyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl-2-phenyl-2γ4-2,1-benzothiazine-2-oxide (68): To a solution of alcohol 66 (48 mg, 0.116 mmol) in 2 mL CH_2Cl_2 was added TEA (33 µl, 24 mg, 0.24 mmol) and mesyl chloride (14 µl, 21 mg, 0.18 mmol) at 0°C. The reaction was allowed to reach rt and was stirred for 17 h. It was quenched with 1 mL saturated NH_4Cl, extracted with 2 mL CH_2Cl_2, washed with 2 mL brine, dried with Na_2SO_4, and concentrated in vacuo. After chromatography (50% ethyl acetate in hexanes), 45 mg (79%) of 68 was obtained as a white semisolid. IR (film): 3060, 2929, 2226, 1569, 1462, 11348, 1242, 1172, 1103, 964, 833, 731, 682 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 500 MHz) δ  8.11 (d, 2H, J = 7.5 Hz), 7.66 (dd, 1H, J = 7.0, 8.0 Hz), 7.56 (dd, 2H, J = 8.0, 7.5 Hz), 6.70 (s, 1H), 6.67 (s, 1H), 6.37 (dd, 1H, J = 11.0, 15.5 Hz), 5.80 (d, 1H, J = 11.0 Hz), 5.47 (dd, 1H, J = 7.5, 15.0 Hz), 4.24 (dd, 1H, J = 4.5, 10.0 Hz), 4.05 (dd, 1H, J = 7.5, 10.0 Hz), 3.88 (s, 3H), 3.61 (dt, 1H, J = 11, 5 Hz), 3.51 (dd, 1H, J = 4.5, 13.0 Hz), 3.43 (m, 1H), 3.06 (dd, 1H, J = 11.5, 12.5 Hz), 2.90 (s, 3H), 2.33 (s, 3H), 1.77 (s, 3H), 1.72 (s, 3H); \(^{13}\)C
NMR (CDCl₃, 125 MHz) δ 152.7, 138.5, 136.6, 133.8, 131.9, 130.9, 130.2, 129.3, 129.2, 126.0, 124.2, 123.5, 118.8, 111.6, 69.0, 56.0, 49.6, 41.9, 37.3, 37.2, 25.9, 21.4, 18.3; HRMS calcd for C₂₅H₃₁NO₅S₂Na [M+Na]⁺ 512.1536; Found: 512.1526; [α]²⁵ D = -13.82 (c 0.55, CHCl₃).

69: To a stirred solution of mesylate 68 106 mg (0.22 mmol) in 2 ml CH₂Cl₂ was added 0.33 g NaI. It was stirred at rt for 3 days, diluted with 2 ml CH₂Cl₂, washed with 2 ml water, and 2 ml saturated Na₂S₂O₃, 2 ml brine, concentrated and column chromatographed using 30% ethyl acetate in hexane to get iodide 69 60 mg (50%), and cyclopropane compound 70 57 mg (50%). Iodide 69: IR: 2909, 1573, 1462, 1332, 1246, 1160, 1107, 1017 cm⁻¹; ¹H NMR (CDCl₃, 500MHz, ppm) δ 8.14-8.16 (2H, m, ArH), 7.68-7.69 (1H, m, ArH), 7.58-7.62 (2H, m, ArH), 6.72 (1H, s), 6.65 (1H, s), 6.29 (1H, dd, J=11, 15 Hz), 5.84 (1H, d, J=11 Hz), 5.4 (1H, dd, J=9, 15 Hz), 3.91 (3H, s,CH₃), 3.48-3.54 (2H, m), 3.21-3.28 (2H, m), 3.11-3.17 (1H, m), 2.78 (1H, dd, J=9, 9 Hz), 2.36 (3H, s, CH₃), 1.80 (3H, s, CH₃), 1.74 (3H, s, CH₃); ¹³C NMR (CDCl₃, 500MHz, ppm) δ 153.0, 139.2, 136.4, 134.0, 132.1, 130.8, 130.6, 129.6, 129.4, 129.1, 124.5, 124.5, 119.4, 111.9, 56.3, 49.5, 44.8, 40.8, 26.2, 21.7, 18.6, 7.8; HRMS calcd for C₂₄H₂₄INO₅SNa [M+Na]⁺ 544.077764; Found: 544.075818; [α]²⁵ D = -11.05 (c 0.60, CHCl₃).
70: IR: 3066, 2936, 2852, 1630, 1463, 1326, 1275, 1231, 1202, 1159, cm⁻¹; ¹H NMR (CDCl₃, 500MHz, ppm) δ  8.07-8.08 (2H, m, ArH), 7.63-7.66 (1H, m, ArH), 7.54-7.57 (2H, m, ArH), 6.97 (1H, s), 6.72 (1H, s), 6.41 (1H, d, J=16 Hz), 5.34 (1H, dd, J=9, 15.5 Hz), 4.94 (2H, s), 4.90 (1H, s), 3.90 (3H, s, CH₃), 3.50 (1H, dd, J=3, 11.5 Hz), 2.74-2.84 (2H, m), 2.30 (3H, s), 1.86 (3H, s, CH₃), 1.64 (1H, m), 1.04 (1H, m), 0.85 (1H, m), 0.76 (1H, m); ¹³C NMR (CDCl₃, 500MHz, ppm) δ 133.7, 132.4, 131.5, 129.3, 129.2, 119.1, 114.5, 111.3, 56.0, 51.9, 39.0, 24.4, 24.2, 21.5, 18.7, 12.4; HRMS calcd for C₂₄H₂₇NO₂SNa [M+Na]⁺ 416.165471; Found: 416.164164; [α]²⁵D = -284.00(c 1.40, CHCl₃)

(2R,4R)-4-[(1S,2E)-1,5-Dimethyl-2,4-hexadienyl]-3,4-dihydro-8-methoxy-6-methyl-2-phenyl-2γ4-2,1-Benzothiazine-2-oxide (47): To a solution of mesylate 68 (71 mg, 0.15 mmol) and LiI (201 mg, 1.5 mmol) in 7.5 mL dry THF at -30°C, was added 1.5 mL
of 1 M LiBHEt₃ in THF slowly. After it was kept at -30°C for 26 h, it was diluted with 15 mL DCM and quenched with 10 mL 10% NaOH, and 5 mL 30% H₂O₂. After it was stirred for 30 min at rt, it was washed with 10 mL saturated Na₂S₂O₃ solution, followed by 30 mL brine. After drying with Na₂SO₄, it was concentrated under vacuum. Chromatography (20% ethyl acetate in hexanes) afforded 45 mg (79%) of 47 as a colorless oil. The NMR data matched the published.³³
CHAPTER TWO
PROGRESS TOWARD TOTAL SYNTHESIS OF HAMIGERAN B

2.1 Introduction

Hamigerans are a family of natural products isolated from the poecilosclerid sponge *Hamigera tarangaensis* by Bergquist and Fremont from shallow water off the eastern coast of New Zealand.\(^1\) Hamigeran B stands out in the family, due to its impressive inhibitory activities against herpes and polio viruses and *in vitro* activity against P-388 leukemia cell line.\(^1\) The initial goal for this project was to apply a methodology that had been discovered and developed in our research group, the eight-electron cyclization reaction of cyclopentadienes to build the aromatic ring-fused [4.3.0] bicycle.\(^2\) Since its appearance in the literature, hamigeran B has attracted a significant amount of synthetic effort among organic chemists, due to its interesting bioactivity, and novel, relatively complex structure within a fairly compact architecture.\(^3\)

2.1.1 Hamigerans

Hamigeran A (1), debromohamigeran A (2), hamigeran B (3), 4-bromohamigeran B (4), hamigeran C (5), hamigeran D (6), hamigeran E (7), and debromohamigeran E (8) were isolated from poecilosclerid sponge *Hamigera tarangaensis*, which belongs to Anchinoidae family (Figure 1). Only phorboxazoles and the anchinopeptolides that have been isolated from Anchinoidae family members. Phorboxazoles attracted a lot of attention from organic chemists, leaving the anchinopeptolides almost uninvestigated.
2.1.2 Proposed Chemical Relationship of Hamigerans

Though hamigerans are obviously structurally related, there is no reported biosynthesis of hamigerans. Based on their structural relationship, a biomimetic chemical relationship was proposed for the hamigeran family members (Scheme 1). Hamigeran D may be in equilibrium with the corresponding 1,2-diketone, which can be oxidized to an acyloin. Upon acylation, it will lead to hamigeran C; upon further oxidation to triketone, a Norrish type-1 fragmentation (which is possible since the sea sponge was collected in shallow sea water, where sunlight is abundant), followed by trapping with methanol, will give hamigeran A. After hydrolysis of the ester and decarboxylation, hamigeran B would be obtained. Further oxidative cleavage of hamigeran B would produce hamigeran E.
2.1.3 Total Syntheses of Hamigeran B

A review by Clive, written in 2005, contains a collection of various total syntheses of hamigeran B.³ Since this review, several formal total syntheses of this natural product by a variety of strategies have appeared.

2.1.3.1 Total Synthesis of Hamigeran B by Nicolaou, Gray and Tae

In 2001, two back-to-back communications in Angewandte Chemie reported Nicolaou, Gray and Tae’s efforts in developing and applying the photoenolization of substituted benzaldehydes and subsequent Diels-Alder (PEDA) trapping of the hydroxyl-\-o-quinodimethanes.⁴,⁵ The full article published in 2003 provided the readers with more details (Scheme 2).⁶
Starting from benzamide 11, enantiopure alcohol 13 was obtained by a sequence of directed lithiation and regioselective epoxide ring opening. Acid-catalyzed lactone formation, followed by LAH reduction yielded the diol, which was sequentially and selectively protected with TBS group and MOM group. Wacker oxidation of the terminal double bond of 14 led to a ketone, which further produced the α,β-unsaturated ester 15 (E/Z ratio was ca. 3.5:1) through a HWE reaction. The TBS group was selectively deprotected and the exposed benzylic alcohol was oxidized to the benzaldehyde 16, which set the stage for the PEDA reaction. On irradiation, the substituted benzaldehyde 16 underwent photoenolization to give the quinone methide 17. Intramolecular Diels-Alder cyclization then proceeded with high diastereoccontrol to give ester 18 as a mixture of epimers.

The hydroxyl group on carbon 6 served as a handle to epimerize the stereocenter of carbon 5 once being oxidized. Next, it served as the electrophile to install the isopropyl group, leading to 20. After failed attempts to hydrogenate the trisubstituted double bond in 20, they found that hydroboration and oxidation led to the acetonide 21 as the major product.

Deprotection of the acetonide 21, followed by oxidation and bromination, provided hamigeran A. Hydrolysis under aerobic conditions enabled a saponification, decarboxylation, and auto-oxidation cascade sequence to give (−)-hamigeran B. (Scheme 2)
2.1.3.2 Total Synthesis of (−)-Hamigeran B by Clive and Wang

In 2003, Clive and Wang published their total synthesis of racemic hamigeran B and later, (−)-hamigeran B.\textsuperscript{7,8} Again, the stereochemistry of carbons 5 and 6 were controlled by the C9 stereogenic center. While Nicolaou’s paper showed that
hydrogenation of the cyclopentene 20 produced a mixture of products with the one with an exo-isopropyl group as the major product under a variety of hydrogenation conditions.\textsuperscript{6} Clive’s synthetic route featured a hydrogenation of cyclopentadiene 31 to get the product with endo-isopropyl group.

Scheme 3
As shown in Scheme 3, the core carbon skeleton 26 was constructed very efficiently from the iodide 23 and Meyers’ chiral lactam 24. Then, dehydrogenation by DDQ, followed by dihydroxylation, and protection with TBSOTf produced cyclopentenone 29. Moreover, it was reduced by DIBAL, and eliminated via the mesylate intermediate to give the cyclopentadiene 31. A rather mild hydrogenation of 31 with Pd/C led to 32 with the right stereochemistry. It was proposed by the authors that the bulky TBS groups were essential for controlling the stereochemical outcome.

After removing the two TBS groups with TBAF, the diol 33 was oxidized to diketone 34. Demethylation with LiCl in DMF, and mono-bromination gave hamigeran B (Scheme 3).

2.1.3.3 Total Synthesis of Hamigeran B by Trost, Pissot-Soldermann, Chen, and Schroeder

A year later, the Trost group published their total synthesis of (-)-hamigeran B, featuring their palladium-catalyzed asymmetric allylic alkylation reaction, which was used to install the quaternary stereogenic C9 center. The full article on this work was published in 2005 and included more details of the total synthesis. A noteworthy reaction in this sequence is the kinetic hydrogenation of the trisubstituted alkene 47 to 48 by iridium black under high pressure. Under similar conditions, Pd/C gave only the exo-isopropyl product, which was hypothesized to be the result of the undesired equilibration
of the semihydrogenation intermediates, leading to the thermodynamically more stable diastereomer (Scheme 4).

Scheme 4
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2.1.3.4 Total Synthesis of (±)-Hamigeran B by Piers and Lau

A different strategy, developed by Piers and Lau, for the synthesis of hamigeran B involved the installation of stereogenic centers, followed by the construction of the core structure. While most synthetic organic chemists prefer to use aromatic rings as one of the starting materials if the natural products contain them, Piers and Lau made the aromatic system instead of starting with it, in order to take advantage of the preset stereochemistry of the ketone 53.

The enone 52 was prepared following the protocol developed by Snider, Corey and Engler. Hydrogenation with Pd/C yielded 53 with ease, setting up all of the three contiguous stereogenic centers. A Reusch enone migration protocol was later applied to convert enone 55 to epoxide 60, which nicely set up the stage for a Diels-Alder reaction using an excess amount of the reactive diene 60. Under rather harsh conditions (150 °C, 4 days), the DA product was formed in satisfying yields (61-77%). Hydrolysis and
aromatization led to a known ketone 48, which upon bromination yielded racemic hamigeran B (Scheme 5).
2.1.3.5 Total Synthesis of (-)-Hamigeran B by Taber and Tian

In 2008, Taber and Tian reported their total synthesis of hamigeran B utilizing rhodium-mediated intramolecular C-H insertion, a methodology they developed.\(^{11}\) They borrowed the stereochemistry of citronellal to get the enantiomerically pure citronellol derivative \(64\) as the starting material. After extensive efforts aimed at optimizing the reaction conditions for the diazo transfer step and the Rh-mediated intramolecular C-H insertion step, three more operations led to ketone \(71\). Olefination with the non-basic Petasis reagent, in the presence of NaHCO\(_3\) to prevent isomerization of the product,
yielded an intermediate 72. To their delight, the iridium-catalyzed hydrogenation with 1100 psi hydrogen gas in the Parr reactor selectively reduced the more strained double bond after 4-8 hours, leaving the benzylic alkene untouched. Upjohn dihydroxylation, hydrogenolytic cleavage of cyclopropane together with the benzylic alcohol, followed by TBAP/NMO oxidation led to a known diketone 34. Following Clive’s procedure, (-)-hamigeran B was obtained (Scheme 6).

2.1.3.6 Formal Total Synthesis of Hamigeran B by Miesch, Welsch, Rietsch, and Miesch

The Miesch group accomplished a formal total synthesis of racemic hamigeran B, using the methodology developed in their lab, the intramolecular akynyllogous Mukiyama aldol-type reaction of cycloalkanones tethered to alkynyl esters (Scheme 7).12

**Scheme 7**
2.1.3.7 Formal Total Synthesis of (+)-Hamigeran B by Mukherjee, McDougal, Virgil, and Stoltz

Starting from the same starting material Miesch used, the Stoltz group synthesized (+)-hamigeran B, using a palladium-catalyzed decarboxylative allylic alkylation reaction.\textsuperscript{13}

Scheme 8

After the highly enantioselective (94% ee) decarboxylative allylic alkylation, catalyzed by Pd\textsubscript{2}(dba\textsubscript{3}) using the trifluoromethylated derivative of (S)-t-BuPHOX (85) as
ligand, cross-metathesis and reductive cyclization yielded 90, the core structure of hamigeran B. After dehydration of the β-hydroxyketone 90, enone 91 was obtained, which was used to prepare (+)-hamigeran B (92) following Miesch’s protocol.

2.2 Progress Toward Total Synthesis of Hamigeran B

2.2.1 The Eight-electron Cyclization Reaction

Harmata, Zheng, Schreiner and Navarro-Vázquez published a novel electrocyclization of 2-bromocyclopentenones to form aromatic ring fused [4.3.0] bicycles (Scheme 9). The theoretical study supported a cyclopentadienone intermediate 93d, which underwent an electrocyclization driven by deantiaromatization (Scheme 10).

Scheme 9

\[
\begin{align*}
\text{Scheme 9} & \\
93a & : R_1, R_2, R_3 = H & 69\% 93b \\
94a & : R_1 = H; R_2 = OMe & 61\% 94b \\
95a & : R_1 = OMe; R_2 = H; R_3 = Me & 64\% 95b \\
96a & : R_1 = H; R_2 = -OCH_2O- & 61\% 96b
\end{align*}
\]
2.2.2 Initial Synthetic Plan

Since the natural product hamigeran B has the aromatic ring fused [4.3.0] bicycle substructure, we thought this new methodology was perfect to synthesize hamigeran B. Since the Clive group had published their total synthesis of hamigeran B, using enone 26 as an intermediate, our initial efforts were focused on synthesizing 26 to realize a formal total synthesis.

Retrosynthetic analysis revealed that 26 might be derived from a 2-hydroxycyclopentenone 98 via cyclopentadienone 99 as a reactive intermediate through
the electrolyciztion reaction. Furthermore, 98 can be synthesized via a Tius-Nazarov cyclization reaction from the 1,2-diketone 97 (Scheme 11).\textsuperscript{14, 15}

2.2.3 Preparation of 2-Hydroxycyclopentenone

Based on the proposed synthetic route, making 98 would be the required for testing the electrolyciztion reaction. Tius had pioneered the use of \( \alpha \)-diketones and \( \alpha \)-alkoxydienones as starting material for the Nazarov cyclization (Scheme 12). From their studies, \( \alpha \)-ethoxydienone 99 readily underwent Nazarov cyclization in the presence of \( \text{bis(acytonitrile)}\text{dichloropalladium(II)} \) in wet acetone at room temperature. The possibility that the reaction was a Michael addition was considered unlikely, since the \( 5\)\textit{-endo-trig} cyclization was not possible due to the poor orbital overlap. They also did a control experiment to rule out \( \text{HCl} \) serving as the catalyst. Formally, treatment of 99 with \( \text{HCl} \) led to the hydrolysis product 101 quantitatively. Moreover, they discovered a Nazarov cyclization of \( \alpha \)-diketones such as 102 with the Lewis acid ytterbium(III) triflate, silica gel, or lithium tetramethylpiperidide (Scheme 11). We wanted to use this chemistry in the synthesis of 98, since it is potentially the product of Nazarov cyclization of diketone 97, \( \alpha \)-siloxydienone or \( \alpha \)-ethoxydienone (Scheme 12).

A variety of approaches to the synthesis of \( \alpha \)-diketone 97 were considered, as shown in Scheme 13 and Scheme 14. In Scheme 13, the \( \alpha \)-diketone 97 was envisioned to be assembled via an umplong approach from an electrophilic carbonyl component (acyl chloride, Weinreb’s amide, N-acyl morpholine, etc.) and a nucleophilic carbonyl equivalent (dithiane, protected cyanoxydrin, alkylvinyl ether, etc.). The vinyl group on
the aromatic ring can be installed via Pd-catalyzed coupling reaction. (Heck reaction, Suzuki coupling, Stille coupling, etc)

**Scheme 12**

*Tius’ result:*

\[ \text{MeO} \overset{\text{PdCl}_2(\text{MeCN})_2}{\text{MeO}} \overset{\text{LiTMP, LiHMDS or silica}}{\text{MeO}} \overset{\text{THF, -78 °C to rt}}{\text{MeO}} \]

**Proposed:**

\[ \text{MeO} \overset{\text{PdCl}_2(\text{MeCN})_2}{\text{MeO}} \overset{\text{LiTMP, LiHMDS or silica}}{\text{MeO}} \]

**Scheme 13**

\[ \text{MeO} \overset{\text{Umplong}}{\text{MeO}} \overset{\text{Coupling}}{\text{MeO}} \]

\[ R^1 = \text{Cl, N(OMe)Me, etc.} \]
\[ R^2 = \text{OTMS, SCH}_2\text{CH}_2^- \]
\[ R^3 = \text{CN, SCH}_2^- \]
\[ M = \text{Sn, B, Si, etc.} \]
In Scheme 14, α-siloxydienone or α-ethoxydienone was planned to be synthesized through HWE reaction, with either the aromatic part being the aldehyde coupling partner or being the phosphonate coupling partner.

Scheme 14

With many possible ways making the key intermediates 97 and its related derivatives, we identified the ortho-vinylbenzaldehyde being a versatile and important intermediate that can lead to many of the other possible starting materials. An efficient way of making large quantities of 102 would be crucial for the success of this project.

2.2.4 Preparation of Important Intermediate 102

Aldehyde 102 can be disassembled in at least two ways, as shown in Scheme 15. The vinyl group can be installed on the known o-bromobenzaldehyde via Stille coupling reaction with vinylstannanes or via Suzuki coupling reaction with vinylboronates. The alternative approach would be to form the vinyl group through Wittig reaction of a lactol intermediate generated from the known lactone 106.
2.2.4.1 Palladium-Catalyzed Coupling Reactions to 102

As shown in Table 1, (2-bromo-3-methoxy-5-methylphenyl)methanol reacted with tributylvinylstannane under standard Stille coupling condition to yield 105 in 23% yield, with 46% recovered starting material. (2-Iodo-3-methoxy-5-methylphenyl)methanol reacted with potassium vinyltrifluoroborionate under standard Suzuki coupling condition to generate 105 in 91% yield.

<table>
<thead>
<tr>
<th>M</th>
<th>X</th>
<th>Yield</th>
<th>Conditions</th>
<th>Recovered SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SnBu₃, Br</td>
<td></td>
<td>23%</td>
<td>1 mol% Pd(Ph₃P)₂Cl₂, 4 mol% Ph₃P, 1.5 equiv CsF, Toluene (0.12 M), 100°C, 18 h,</td>
<td>46%</td>
</tr>
<tr>
<td>BF₃K, I</td>
<td></td>
<td>91%</td>
<td>2 mol% Pd(OAc)₂, 6 mol% Ph₃P, 3 equiv Cs₂CO₃, THF/H₂O = 9:1(0.2 M), 90°C, 16.5 h,</td>
<td></td>
</tr>
</tbody>
</table>
Starting with the known 2-bromo-3-methoxy-5-methylbenzaldehyde, Stille coupling yielded the vinylated product 102 in 82% yield; Suzuki reaction gave 102 in 51% yield. Using 2-iodo-3-methoxy-5-methyl-benzaldehyde as starting material, Stille reaction provided 102 in higher yield (74%, 78%) than Suzuki reaction (69%) (Table 2).

### Table 2

| M = SnBu₃, X = Br: 1.1 equiv, | 1 mol% Pd(Ph₃P)₂Cl₂, 4 mol% Ph₃P, 1.5 equiv CsF, Toluene (0.25 M), 100°C, 6 h, | 82% |
| M = SnBu₃, X = I: 1.1 equiv, | 1 mol% Pd(Ph₃P)₂Cl₂, 4 mol% Ph₃P, 1.5 equiv CsF, Toluene (0.25 M), 90°C, 16 h, | 78% |
| 1 equiv, | 0.2 mol% Pd(Ph₃P)₂Cl₂, 0.8 mol% Ph₃P, 1.5 equiv CsF, Toluene (0.25 M), 90°C, 10 h, | 74% |
| M = BF₃K, X = Br: 1.5 equiv, | 2 mol% Pd(OAc)₂, 6 mol% Ph₃P, 3 equiv Cs₂CO₃, THF/H₂O = 9:1, microwave, 45°C, 30 min; 75°C, 60 min, SM:P = 2:1 |
| 2 equiv, | 2 mol% Pd(OAc)₂, 6 mol% Ph₃P, 3 equiv Cs₂CO₃, THF/H₂O = 9:1, seal tube, 85°C, 21 h, | 51% |
| M = BF₃K, X = I: 1 equiv, | 2 mol% Pd(OAc)₂, 6 mol% Ph₃P, 3 equiv Cs₂CO₃, THF/H₂O = 9:1(0.2 M), 90°C, 11 h, | 69% |

#### 2.2.4.2 The Wittig Route to 102

The isobenzofuranone 106 was synthesized from 4-methylsalicylic acid 107 following Snider’s protocol. Double methylation of 107 and basic hydrolysis yielded acid 108 almost quantitatively. Amide 109 was obtained from acid 108 via the corresponding acyl chloride in almost quantitative yield. Directed lithiation by amide group generated an α-lithium benzamide that was trapped with N,N-dimethylformamide.
to yield 120. Reduction by sodium borohydride and acid-catalyzed lactonization led to 106 in 70% yield. Next, the isobenzofuranone 106 was reduced partially with diisobutyl aluminium hydride at -78 °C to the lactol. Treating the reaction mixture with Wittig reagent in the same pot generated the alcohol 105 in 22% yield (Scheme 16).

**Scheme 16**

![Chemical diagram](attachment:image.png)

2.2.5 Preparation of Phosphonates for Olefination Reaction

As shown in Scheme 14, the HWE reaction requires the synthesis of phosphonate to react with the aldehyde 102. Scheme 17 summarizes three routes to synthesize three different phosphonates from ethyl oxalate. In the first step, reacting the diethyl oxalate with isobutyl magnesium chloride at -78 °C generated the ketoester 111. The second step of route A involved trapping the enol with a TBS group, giving only the Z-silyl enol ether 112; the second step of route B consists of converting the carbonyl group to dithiane 115, with BF₃ as Lewis acid catalyst; route C protected the carbonyl group as methyl vinyl
ether 117. The last step was to install the phosphonate by an acylation reaction (Scheme 17).

**Scheme 17**

**A:**

```
\[ \text{EtO} \text{O} \text{O} \text{Et} \quad \text{\( \rightarrow \)} \quad \text{\( \text{BuMgCl} \)}} \quad \text{Et}_2\text{O}, -78^\circ\text{C} \quad 98\% \\
\text{Me} \quad \text{P}(\text{OEt})_2 \quad 113 \quad \text{\( \rightarrow \)} \quad \text{\( nBuLi, \text{THF}, -78^\circ\text{C} \)}} \quad 64\% \\
\text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Me} \text{P}(\text{OEt})_2 \text{O} \text{Me} \text{P}(\text{OEt})_2 \quad \text{\( \rightarrow \)} \quad \text{\( \text{BuLi, \text{THF}, -78^\circ\text{C} \)}} \quad 92\% \\
```

**B:**

```
\[ \text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Et} \quad \text{\( \rightarrow \)} \quad \text{\( \text{BuS}_2\text{O} \quad \text{BF}_3\text{Et}_2\text{O} \)}} \quad \text{DCM, 83\%} \quad \text{111} \quad \text{\( \rightarrow \)} \quad \text{\( \text{Me} \quad \text{P}(\text{OEt})_2 \quad 113 \)}} \quad \text{\( nBuLi, \text{THF}, -78^\circ\text{C} \)}} \quad 96\% \\
\text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Et} \quad \text{\( \rightarrow \)} \quad \text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Me} \text{P}(\text{OEt})_2 \}} \quad \text{\( \rightarrow \)} \quad \text{\( \text{BuLi, \text{THF}, -78^\circ\text{C} \)}} \quad 92\% \\
```

**C:**

```
\[ \text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Et} \quad \text{\( \rightarrow \)} \quad \text{\( \text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Et} \quad \text{\( \rightarrow \)} \quad \text{\( \text{\( \text{Bu} \text{O}\text{Et} \quad \text{O} \text{O} \text{Me} \text{P}(\text{OEt})_2 \text{O} \text{Me} \text{P}(\text{OEt})_2 \quad \text{\( \rightarrow \)} \quad \text{\( \text{BuLi, \text{THF}, -78^\circ\text{C} \)}} \quad 92\%} \\
```

### 2.2.6 Preparation of Methylphosphonate 103

Bromination of alcohol 105 with tetrabromomethane and triphenylphosphine yielded benzyl bromide 119 in 81% yield. Methylphosphonate 103 was synthesized from 108 via a nucleophilic substitution with trimethyl phosphite (Scheme 18).
The other coupling partner ketone 104 was prepared from (E)-5-methylhex-3-en-2-one 120 by dihydroxylation with osmium oxide and N-methyl morpholine N-oxide, and ketal formation with 2,2-dimethoxy propane in 85% yield. (E)-5-Methylhex-3-en-2-one 120 was made following Ragoussis’ procedure for regioselective aldol condensation between methyl 3-oxobutanoate and isovaleraldehyde (Scheme 19). 15

Next, the proposed olefination reaction was carried out. The solution of phosphonate 103 in THF was added with 1 equivalent of KHMDS (0.5 M in toluene) slowly. After 30 min at -78 °C, about two equivalents of the ketone 104 was added. The reaction mixture was allowed to rise to rt and quenched with water. However, the desired olefination product was not observed from the crude 1H-NMR (Scheme 20). (E)-Stilbene 121 was formed cleanly from the analysis of crude 1H-NMR. The structure of 121 was unambiguously confirmed by X-ray crystallography. It was repeated to get 45% of
stilbene with 17.6% of recovered phosphonate starting material. \((E)\)-Stilbene 121 was formed exclusively when phosphonate 103 was treated with potassium hexamethyldisilazide at -78 °C for 20 minutes. Though the crude \(^1\)H-NMR for this reaction was very clean, the isolated yield of stilbene 121 was 40% in this case. This is a rare example of stilbene formation from a phosphonate. If the reaction is general, it could provide an alternative for generation of stilbenes otherwise difficult to make. We proposed a possible mechanism for this transformation (Scheme 21). After the deprotonation of phosphonate 103 with KHMDS, the carbanion attacked another phosphonate fast enough to generate a new phosphonate. After elimination under basic conditions, the \((E)\)-stilbene 121 was formed.

**Scheme 20**
2.2.7 Heck Coupling Route to 97

Starting from orcinol, salicylic acid 124 was prepared according to Bräse’s protocol. The salicylic acid 124 was treated with triflic anhydride and triethylamine to yield the triflate 125 (Scheme 22). Ketone 104 was reacted with Wittig reagent to produce the disubstituted alkene 126 in low yield, a result caused by the volatility of this compound (Scheme 23).

Scheme 22
The Heck coupling reaction between triflate 125 and alkene 126 was tried but no coupling product was formed. Due to the low yield of alkene 126, methyl methacrylate was used as the coupling partner for the Heck reaction. While, Pd(OAc)$_2$ with triphenylphosphine as ligand in triethylamine resulted in no conversion under microwave conditions.

**Scheme 23**

![Scheme 23 diagram](image_url)

**Scheme 24**

![Scheme 24 diagram](image_url)
conditions, switching to dppb as ligand generated the detriflated benzaldehyde only from
the analysis of crude proton NMR. The triflate 125 did react with methyl methacrylate to
yield a mixture of two isomeric products in 48% and 33% yield (Scheme 24). However,
this reaction failed when it was scaled up to 4.3 grams scale, due to the polymerization of
methacrylate under the conditions.

2.2.8 Preparation of α-Hydroxyl Cyclopentenone

Finally, vinylation of o-bromo-α-methyl cinnamaldehyde was explored, generating excellent yields of the vinylated product. This working protocol was one of the earliest to be explored, since 129 was also the starting material used for the total synthesis of pseudopteroxazole. HWE reaction with triethyl 2-phosphonopropionate yielded the o-bromo-α-methylcinnamate 130 cleanly with complete (E)-selectivity. Reduction with DIBAL and allylic oxidation with manganese(IV) oxide led to the o-bromo-α-methylcinnamaldehyde 131 in very good yield. Very gratifyingly, both of the Suzuki and Stille coupling produced the vinylated α-methylcinnamaldehyde 132 in good yield (Scheme 25).

Scheme 25

\[\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{OMe} \\
\end{align*}\]

1. DIBAL, THF, 2.5 h
2. MnO₂

\[\begin{align*}
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{OMe} \\
\text{Me} & \quad \text{CHO} \\
\end{align*}\]

A: Pd(Ph₃P)₂Cl₂, Ph₃P, CsF, PhMe, 90°C, 17 h, 94%
B: Pd(OAc)₂, Ph₃P, Na₂CO₃, PrOH/H₂O = 2:1, 90°C, 7 h, 92%
Having the aldehyde 132 in hand, it was added to a solution of lithiated dithiane solution that was generated from 2-isobutyl-1,3-dithiane with n-butyl lithium at -20 °C. The crude mixture was hydrolyzed with mercury oxide and boron trifluoride-etherate to yield the hydroxyketone 134, which was oxidized with IBX to generate α-diketone 97 in 83% yield (Scheme 26). α-Diketone 97 was treated with strong non-nucleophilic bases, lithium hexamethyldisilazide, lithium tetramethylpiperidide, and potassium hexamethyldisilazide (Table 3). Up to 71% yield of the desired product was obtained under optimized conditions. It also seemed that the acidification step during workup may contribute to the higher yield, since the 1H-NMR of the crude product was consistently clean.

Scheme 26

![Scheme 26 Diagram]
Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 equiv LiTMP, THF, -78°C to rt, 28 h, 59%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.1 equiv LiHMDS, THF, -78°C to rt, 21 h, 42%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.2 equiv LiHMDS (0.24M in THF), THF, -78°C to rt, 18 h, 44%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.5 equiv LiHMDS (0.8M in THF), THF, -78°C slowly to rt, 2 days, 71%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.4 equiv LiHMDS (0.9M in THF), THF(0.1 M), -78°C slowly to rt, 1 days, 64%</td>
<td></td>
</tr>
</tbody>
</table>

2.2.9 The Dead End and the Detour

At this stage of synthesis, we were ready to try the key electrocyclization reaction on this α-hydroxycyclopentenone 98.

2.2.9.1 The Key Reaction Did Not Go

Trapping the Tius-Nazarov cyclization product with triflic anhydride produced the triflate 136 in an 8% yield. Next, the triflate 136 was dissolved in acetonitrile and treated with Hünig’s base, producing no desired product 135. The crude 1H-NMR showed only a mess. Treating α-hydroxycyclopentenone 98 with PhN(Tf)2 and triethylamine in dichloromethane yielded a mess from the crude NMR too. The negative results were not
too surprising, since a β-substituted α-bromocyclopentenone (137) failed to undergo the electrocyclization too, yielding only the elimination product 138.\textsuperscript{16}

**Scheme 27**

Based on the above results, we decided to abandon the use of the electrocyclization method to construct the six-membered ring. Instead, we used this opportunity to invent new tactics, since there was no reported literature about this specific type of transformation. This also presents a common occurrence in the total synthesis, which requires discovery and development of new methodologies.

**2.2.9.2 Wacker-type Oxidative Carbocyclization**

Based on the above results, we decided to abandon the use of the electrocyclization method to construct the six-membered ring. Instead, we used this opportunity to invent new tactics, since there was no reported literature about this specific type of transformation. This also presents a common occurrence in the total synthesis, which requires discovery and development of new methodologies.
2.2.9.2.1 Wacker and Wacker-type Oxidations

Using oxygen as an oxidant, nature evolved oxidase and oxygenase enzymes such as cytochrome P450 for oxidizing small organic molecules. In the world of organic synthesis, the Wacker oxidation uses oxygen as the ultimate oxidant too (Scheme 28). Though there was a review published after we overcame this obstacle, covering all kinds of “addition of metal enolate derivatives to unactivated carbon carbon multi-bonds”, we were specifically interested in a Wacker-type oxidative process for two reasons: the efficiency of Wacker oxidation has been proved for long time, though the mechanism is still under debate, and the process is relatively green and biomimetic, using molecular oxygen as oxidant rather than stoichiometric amount of metals or organic oxidants.

The mechanism of Wacker oxidation generally is considered to include the activation of the alkene by the Lewis acidic palladium(II). A water molecule then attacks the activated alkene, followed by a facile β-hydride elimination. The palladium catalyst is regenerated by the copper salt, which is oxidized by oxygen ultimately (Scheme 29).
More recently, Wacker-type reactions using palladium(II) as a Lewis acid to activate alkenes and nucleophiles to form Pd-\(\pi\)-allyl complex or Pd-\(\pi\)-benzyl complex were developed (Scheme 30).\textsuperscript{21}

The work of Widenhoefer concerning nucleophilic addition of \(\beta\)-diketones to "unactivated" double bonds was found to be most similar to the Wacker-type oxidative
alkylation of an α-hydroxyenone with an adjacent vinyl group. It provided us a strong reason to try their conditions, based on the similar mechanisms of the two processes.\textsuperscript{22, 23} Yang’s work on β-ketoamides was also inspiring (Scheme 31).\textsuperscript{24}

\textbf{Scheme 31}

\textit{Widenhoefer’s intramolecular oxidative alkylation:}

\begin{center}
\begin{tikzpicture}
\node[draw, rounded corners] (a) at (0,0) {\ce{\text{Et} - \text{O} - \text{O}}};
\node[draw, rounded corners] (b) at (1,0) {\ce{\text{Et} - \text{O} - \text{O}}};
\node[draw, rounded corners] (c) at (0,-1) {\ce{\text{PdCl\_2(MeCN)\_2 \ 5 \ mol \ % \ CuCl\_2 (2.5 \ equiv) \ \text{DCE, \ rt, \ 97\%}}}};
\node[draw, rounded corners] (d) at (1,-1) {\ce{\text{Me - O - O}}};
\node[draw, rounded corners] (e) at (2,-1) {\ce{\text{Me - O - O}}};
\node[draw, rounded corners] (f) at (2,-2) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (g) at (0,-2) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (h) at (1,-2) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (i) at (0,-3) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (j) at (1,-3) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (k) at (2,-3) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (l) at (2,-4) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (m) at (0,-4) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (n) at (1,-4) {\ce{\text{Me\_2N - Me\_2N}}};
\node[draw, rounded corners] (o) at (2,-4) {\ce{\text{Me\_2N - Me\_2N}}}.
\end{tikzpicture}
\end{center}

\textit{Yang’s aerobic oxidative cyclization:}

\begin{center}
\begin{tikzpicture}
\node[draw, rounded corners] (a) at (0,0) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (b) at (1,0) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (c) at (0,-1) {\ce{\text{PdCl\_2(MeCN)\_2 \ 10 \ mol \ % \ Yb(OTf)\_3 \ 1 \ equiv \ \text{O\_2 1 \ atm \ THF, \ rt, \ 98\%}}}};
\node[draw, rounded corners] (d) at (1,-1) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (e) at (2,-1) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (f) at (2,-2) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (g) at (0,-2) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (h) at (1,-2) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (i) at (2,-2) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (j) at (0,-3) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (k) at (1,-3) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (l) at (2,-3) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (m) at (0,-4) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (n) at (1,-4) {\ce{\text{Me\_2N - O - O}}};
\node[draw, rounded corners] (o) at (2,-4) {\ce{\text{Me\_2N - O - O}}}.
\end{tikzpicture}
\end{center}

\textbf{2.2.9.2.2 Pd(II) Catalyzed Oxidative 6-endo-trig Carbocyclization}

We were really excited by the preliminary results on this reaction. With 0.3 equivalent of PdCl\(_2\)(MeCN)\(_2\), the product to starting material ratio was 0.6 to 1 from the crude proton NMR (Table 4, entry 1). Using THF as solvent enabled the reaction to happen at room temperature (Table 4, entry 2). Further optimization indicated that oxygen gas is superior to air as the oxidant, and prolonged reaction time led quantitative yield of the enol ketone 144 after tautomerization with catalytic amount of silica and TEA (Table 4, entry 6).
We proposed a simplified mechanism for this reaction (Scheme 32). The Lewis acidic palladium(II) coordinates and activates the vinyl group. Then the adjacent nucleophilic enol attacks the electrophilic vinyl palladium complex. This is followed by β-hydride elimination, leading to the product 143, which could be tautomized to the more stable enol ketone 144. The catalyst was regenerated with oxidation of Cu(II), which in turn was regenerated by oxygen.
2.2.10 Attempts for Tandem Reactions

Having a working reaction for the carbocyclization available, we envisioned making this synthetic sequence more efficient and attractive by designing tandem reactions for the key cyclization steps. As shown in Scheme 33, treating the lithiated TBS cyanohydrin 145 with ketene 146 would generate the dienone 147. Based on Tius’ results on Nazarov cyclization and our result on Wacker-type oxidative carbocyclization, the benzene-fused [4.3.0] bicyclic compound 144 would be produced by the same catalyst: PdCl₂(MeCN)₂.

Scheme 33

(proposed tandem 1,2-addition and Nazarov cyclization):
To try this idea out, the preparation of the TMS-protected cyanohydrin was attempted first, generating 92% of the crude 148a. However, the product 148a was too labile and decomposed back to the starting material on silica and alumina columns. After passing the crude material through a short pack of silica gel, 148a was deprotonated with LiHMDS in THF at low temperature and trapped with isovaleraldehyde and the corresponding amide, leading to a complex mixture (Scheme 34).

Then, the TBS-protected cyanohydrin 148 was prepared directly from the vinylated cinnamaldehyde 132 with KCN, TBSCl and catalytic amount of ZnI$_2$ in 91% yield (Scheme 35). The dimerization of ketene 146 was too facile. And the attempted reactions for making it yielded only the dimer. Treating the deprotonated TBS-protected cyanohydrin 148 with isovaleraldehyde led to ketone 149 (Scheme 35). Oxidation of ketone 149 to dienone 150 would produce the same starting material for trying the palladium-catalyzed tandem reaction (Scheme 36). However, Saegusa oxidation and IBX oxidation did not yield the desired dienone.

Scheme 34

![Scheme 34 Diagram](image_url)
Scheme 35

Finally, the ketone 149 was deprotected with TBAF to generate the α-hydroxyketone 150, which then was oxidized with pyridinium dichlorochromate or Dess-Martin periodinane to yield the α-diketone 97 in good yields (Scheme 37).
2.2.11 An Interrupted Nazarov Cyclization

The Nazarov cyclization has been developed for decades. It has been applied in the total synthesis of natural products beautifully. Also known is the interrupted Nazarov cyclization, the trapping of the oxocarbenium intermediate with nucleophiles, such as aromatic rings, alkenes, or dienes.

During our study of making the α-diketone 97, we discovered a rare stable hydrolysis intermediate of a dithiane, which upon treating with Lewis acids or Brønsted acids, underwent an interesting interrupted Nazarov cyclization.

It is well known that Weinreb’s amide gives ketones when reacted with organolithium or Grignard’s reagents. α-Diketone 97 could theoretically be synthesized from a Weinreb’s amide 152 through a dithiane intermediate 151 (Scheme 38).

Scheme 38

*the retrosynthesis of diketone from Weinreb's amide:*

Starting from the o-bromo-α-methacinnamate 130, Stille coupling yielded the ethyl ester 153 in 92% yield. The ester was converted to Weinreb’s amide 154 with N,O-dimethyl-N-hydroxyl amine hydrochloride and isopropyl magnesium chloride in 88% yield. The lithiated dithiane added to the amide to yield the dithiane 155 in 80% yield (Scheme 39).
Many hydrolysis conditions known for converting dithianes to ketones were tried to hydrolyze the dithiane 155. However, either no reaction happened or it gave a mess due to the decomposition of the α-diketone (Scheme 40, entry 1 to 4). From TLC, a significant new spot was detected only five minutes after adding NCS (Scheme 40, entry 5). It was estimated to be an intermediate of the hydrolysis of dithiane, based on the analysis of \(^1\)H-NMR and \(^{13}\)C-NMR. Changing the solvent to methanol and the base to 2,6-lutidine, the methyl sulfinate 156 was isolated in 86% yield (Scheme 40, entry 6). The structure of 156 was derived from \(^1\)H-NMR, \(^{13}\)C-NMR, DEPT135, COSY, high resolution mass spectrum and IR analysis. From HRMS, the observed mass 459.1636u (MNa\(^+\)) was consistent with a formula of C\(_{23}\)H\(_{32}\)O\(_4\)S\(_2\). The IR showed a strong absorbent peak at 1642 cm\(^{-1}\), indicating a conjugated carbonyl group. \(^{13}\)C-NMR and DEPT135 showed one ketone’s carbonyl group, six quaternary sp\(^2\) hybridized carbons, five sp\(^2\)
hybridized CH, one sp² hybridized CH₂, five CH₃, three aliphatic CH₂, and one aliphatic CH (Figure 2 and 3). From ¹H-NMR, the diastereotopic hydrogens on the carbon next to sulfinate (p2 in Figure 4) were obviously observed based on the splitting pattern common to the diastereotopic hydrogens. Further, COSY showed the coupling between proton b and i1 (Figure 5); v1, v2, and v3 were from the vinyl group (Figure 6); p1, p2, and p3 from the propylene group (not shown here).

Figure 2. ¹³C-NMR of 156
Figure 3. DEPT135 of 156.

13C DEPT135, CH and CH3 up, CH2 down

Figure 4. 1H-NMR of 156.
Figure 5. COSY showing b and i1.

Figure 6. COSY showing the vinilic protons v1, v2, and v3.
It was a very rare example of hydrolysis intermediate of dithianes, once again supporting the oxidative hydrolysis mechanism for NCS-mediated deprotection of dithianes. Looking at the structure of the methyl sulfinate, it is likely that this α-heteroatom dienone could be a perfect starting material for an interrupted Nazarov cyclization. It would also be catalyzed by milder Lewis acids, since the oxygen of the sulfinate functional group could coordinate with the metal, forcing the dienone in the cis-configuration to facilitate the electrocyclization. And the adjacent vinyl group, being a nucleophile, could attach the thiocarbenium intermediate to generate the benzene fused [4.3.0] bicycle.

The initial results were quite promising, giving the desired product in up to 53% yield (Scheme 41 and Experimental Section). And we proposed a mechanism for this transformation as shown in Scheme 42.
We then tried to optimize this interrupted Nazarov cyclization process. Numerous Lewis acids and Brønsted acids were screened. However, the yields were consistently low, being around 20% typically (See the Experimental Section for details). One of the byproducts isolated was determined to be the dithiane 162, a reduced product of the sulfoxide intermediate 161. This indicated there should be some auto-redox reaction happening. Being curious to see if this byproduct 162 could be transformed to a useful intermediate for the synthesis of natural product hamigeran B, a short sequence of
deoxygenation was executed on 162. Reduction by LAH led to the secondary alcohol 163 with complete diastereoselectivity, with hydride coming from the convex face. Mesylation of the secondary alcohol 163, however, led to an unexpected product 164 by that time (Scheme 43). A literature research gave us another example of this type of reaction.\textsuperscript{26} It is possible that the configuration of 164, having the hydrogen, sulfur and mesyl group aligned antiparallel to each other, made the elimination of the mesyl group and the concomitant migration of sulfur a rather facile process.

### Scheme 43

\begin{align*}
\text{OMe} & \quad \text{Me} & \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} & \quad \text{S} & \quad \text{S} & \quad \text{OMe} & \quad \text{Me} & \quad \text{H} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{S} & \quad \text{S} & \quad \text{MsCl}, \text{TEA} & \quad \text{DCM}, \text{74}\% \\
162 & \quad \text{LAH, Et}_2\text{O} & \quad 80\% & \quad 163 & \quad \text{MsCl, TEA} & \quad \text{DCM}, \text{74}\% & \quad 164
\end{align*}

2.2.12 The Dead Ends

Starting from commercially available 3,3-dimethylaniline, the diketone 143 and its tautomer 144 with the core carbon structure of hamigeran B, were obtained in twelve to fourteen steps depending on which route was used. Now, it is the stage for the end game of the total synthesis, converting the diketone to the natural product through functional group manipulations. Obviously, the two carbonyl group needs to be reduced;
the benzylic double bond needs to be oxidized into a diketone. The stereochemistry of C6, the carbon bearing the isopropyl group, need to be inverted.

Taking advantage of the lability of the α-hydrogen of ketones, the stereochemistry of C6 was destroyed by epimerizing the diketone 143 to enone ketone 144 with silica and amine base. Treatment with triflic anhydride and triethylamine yielded the triflate 165 in 83% yield. Reduction with formic acid by palladium(0) catalysis led to the enone 166 in 86% yield (Scheme 44).

With enone in hand 166, it was very tempting to do a conjugate reduction to set the C6 stereochemistry by kinetic control with hydride attacking from the less sterically hindered convex face. However, Wilkinson’s catalyst and copper hydride reduction yielded only the thermodynamic product with the exo-isopropyl group 167 (Table 5).
Given the difficulty of setting up the correct stereochemistry of C6 by conjugate reduction, we turned our attention to making Tius’ TBS-protected cyclopentadiene 31 for a formal total synthesis purpose. To that end, the enone 166 needs to be oxidized to diol 171, protected with TBS group to 170, reduced to allylic alcohol 169, mesylated and eliminated to the cyclopentadiene 31 (Scheme 45).

Scheme 45
The dihydroxylation with osmium(IV) oxide and NMO generated the diol 171 chemoselectively.\(^{27}\) The protection of the diol 171 turned out to be rather tricky. Using TBSCI as silylation reagent under different conditions resulted in no conversion. Applying TBSOTf as the silylation reagent with 2,6-lutidine yielded TBS-protected hemiketal 172 as the only product, because of the proximity of the benzylic hydroxyl group and the carbonyl group (Scheme 46). The structure of 172 was identified from analysis of H-NMR, 13C-NMR, DEPT135, HMQC and COSY. Efforts to protect the diol 171 with other protecting groups, such as acetal, dimethylsilyl group did not produce satisfying result.

Scheme 46

L-selectride reduces simple enones in a 1,4-manner, and reduces sterically hindered enones in a 1,2-manner. L-selectride reduced the enone 166 cleanly to generate the allylic alcohol 173, the relative stereochemistry of which was determined through 2-D NMR analysis of the corresponding acetate (176) (Scheme 48). From the NOESY spectrum, the hydrogen on C15 (\(\delta 5.64\)) showed correlation with hydrogens on C16 (\(\delta\)
indicating the cis-relationship between them (Figure 2). Both of the two possible
diastereomers of the allylic alcohol could be utilized for the setting up of C6 stereogenic
center. Many allylic formats can be reduced by palladium(0) to alkene via S_N2-type
fashion with inversion of stereochemistry. The other allylic alcohol diastereomer could
be reduced via OH-directed hydrogenation conditions for the construction of C6
stereochemistry.

For the formate formation, acetic formic anhydride was used to generate the
formate 174 in 87% yield. However, the palladium(0) mediated reduction did not do
anything to the starting material 174. Interestingly, palladium on carbon led to the
oxidized product 166 in 67% yield (Scheme 47).

Scheme 47
Scheme 48

173 + es. Ac₂O, DMAP → 176
DCM, rt, 11 h
3.5 mg scale

Figure 7
2.3 Concluding Remarks

In summary, the core structure of hamigeran B was constructed efficiently, using Tius-Nazarov cyclization and Wacker-type oxidative carbocyclization or an interrupted Nazarov cyclization. Instead of converting to the known intermediates for synthesis of hamigeran B through long sequence, we explored any efficient way of setting the stereochemistry of C6.
2.4 References


12. Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M., Intramolecular Alkynylologous Mukaiyama Aldol Reaction Starting from Bicyclic Alkanones Tethered to Alkynyl


25. PCC oxidation led to an unidentified product other than the desired diketone.

27. The relative stereochemistry of the diol was determined unambiguously through X-ray crystallography.
2.5 Experimental Section

General Information:

All air and moisture sensitive reactions were carried out in flame-dried glassware under an argon or nitrogen atmosphere. Reactive liquid reagents (LHMDS, etc.) were measured and transferred by gastight syringes through rubber septa. Tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl. Toluene was distilled from CaH₂. The reaction mixture was concentrated by using a rotary evaporator attached to a water aspirator. Residue solvents were usually removed under reduced pressure using vacuum pump (approximately 1mm Hg).

Flash chromatographic separations were carried out on silica gel (230-400 mesh) with ACS reagent grade solvents. Analytical thin layer chromatography was performed on glass–backed silica gel plates with F254 indicator. Compounds were visualized under UV light or by developing in iodine, vanillin, phosphomolybdic acid solution or with potassium permanganate solution followed by heating in a hot plate to approximately 350°C. Melting points were determined with a melting point apparatus.

¹H NMR spectra were recorded in Fourier transform mode at 250, 300 or 500 MHz, respectively, as CDCl₃ solutions with tetramethylsilane (δ = 0 ppm) as the internal standard. ¹³C NMR spectra were recorded on the same instruments at 62.5, 75 or 125 MHz, respectively, with CDCl₃ (δ = 77 ppm) as the internal reference. ³¹P NMR spectra were recorded on the same instruments at 101 MHz, respectively, with 85% H₃PO₄ (δ = 0 ppm) as the external standard. Chemical shifts (δ) were reported in parts per million (ppm). Multiplicities were reported as s (singlet), b (broad), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublet), etc. In ¹H NMR spectra of
diastereomeric mixtures, the signals for individual isomers were reported when possible. Infrared spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a polarimeter with sodium D line at the temperatures as indicated in the experimental for specific compounds. High resolution mass spectra were obtained on a magnetic sector instrument with a resolution greater than 10,000.

**112**: To a solution of **111** (1.38 g, 8.7 mmol) in DCM (17 mL, 0.5 M) was added TBSCl (1.57 g, 10.4 mmol), DMAP (0.1 g, 0.9 mmol), and TEA (1.76 g, 17.4 mmol) at rt sequentially. After 13 hours at rt, it was quenched with 10 mL water, washed with 10 mL brine, dried with Na$_2$SO$_4$, concentrated under reduced pressure at rt, and purified by FCC with 2-5% EA/Hex on silica gel to get **112** (1.28 g, 54%) as a colorless oil. IR (neat): 3428, 2962, 2956, 1720, 1642, 1250 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 5.84 (d, 1 H, J = 10 Hz), 4.19 (q, 2 H, J = 7.5 Hz), 2.87-2.80 (m, 1 H), 1.31 (t, 3 H, J = 7.5 Hz), 1.01 (d, 6 H, J = 7 Hz), 0.96 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 165.2, 138.9, 129.7, 60.8, 25.8, 25.1, 22.2, 18.6, 14.2, -4.4; HRMS calcd for C$_{14}$H$_{28}$O$_3$SiNa [M+Na]$^+$ 295.1700; Found: 295.1697.
**114:** To a solution of **113** (446 mg, 2.69 mmol) in THF (8 mL, 0.34 M) was added *n*BuLi (1.4 mL, 1.9 M in THF, 2.69 mmol) at -78 °C slowly. After 1 hour, **112** (245 mg, 0.896 mmol) was added slowly. It was quenched after stirring at -78 °C for 10 hours with 10 mL sat. NH₄Cl, extracted with 3 x 10 mL EA, washed with 10 mL brine, dried with Na₂SO₄, concentrated under reduced pressure to get 495 mg crude yellow oil. Then it was purified by FCC with 50% EA/Hex to get **114** (151 mg, 43%) as colorless oil. IR (neat): 3469, 2958, 1675, 1622, 1250, 1025 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.80 (d, 1 H, J = 9 Hz), 4.16-4.07 (m, 4 H), 3.76 (dq, 1 H, J = 22.5, 7 Hz), 2.95 (m, 1 H), 1.41 (dd, 3 H, J = 7, 18 Hz), 1.31 (dt, 6 H, J = 7, 6.5 Hz), 1.05 (dd, 6 H, J = 6.5, 9.5 Hz), 0.95 (d, 9 H, J = 0.5 Hz), 0.18 (s, 3 H), 0.14 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 193.2 (d, J = 5 Hz), 146.9 (d, J = 2.5 Hz), 133.3, 62.6 (d, J = 7.5 Hz), 62.4 (d, J = 6 Hz), 40.2, 39.2, 25.9, 25.6, 22.1 (d, J = 2.5 Hz), 18.8, 16.4 (d, J = 3.8 Hz), 16.36 (d, J = 5 Hz), 12.5 (d, J = 6.2 Hz), -4.0, -4.2; HRMS calcd for C₁₈H₃₇O₅P₂SiNa [M+Na]⁺ 415.2040; Found: 415.2040.

\[
\begin{align*}
\begin{array}{c}
\text{i-Bu} \quad \text{O} \quad \text{Et}
\end{array} \\
\begin{array}{c}
\text{O} \quad \text{Et}
\end{array}
\end{align*}
\]

**115:** To a solution of **111** (309 mg, 1.95 mmol) and propane-1,3-dithiol (211 mg, 1.95 mmol) in DCM (10 mL, 0.2 M) was added trifluoroborane etherate (80 µL, 48%, 0.3 mmol) at 0 °C. It was stirred at rt for 5 hours. Then, it was quenched with sat. NaHCO₃, extracted with DCM, dried with MgSO₄, concentrated under reduced pressure, and purified by FCC with 5% EA/Hex to get **115** as a colorless oil (402 mg, 83%). IR (neat): 2958, 2925, 1716, 1209, 1119, 1025 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.24 (q, 2 H, J = 7 Hz), 3.26 (m, 2 H), 2.65 (m, 2 H), 2.16-2.11 (m, 1 H), 2.00 (d, 2 H, J = 1.5 Hz), 1.86
(m, 2 H), 1.33 (t, 3 H, J = 7.5 Hz), 0.94 (d, 6 H, J = 6 Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 171.2, 61.7, 53.0, 16.9, 27.9, 25.1, 24.7, 23.6, 14.0; HRMS calcd for C\(_{11}\)H\(_{20}\)O\(_2\)S\(_2\)Na [M+Na]\(^+\) 271.0797; Found: 271.0791.

\[ \text{116: To a solution of 113 (287 mg, 1.73 mmol) in THF (2 mL, 0.86 M) was added } n\text{BuLi (0.95 mL, 1.9 M in THF, 1.8 mmol) at -78 }^\circ\text{C slowly. After 1 hour, 115 (140 mg, 0.564 mmol) was added slowly. It was quenched after stirring at -78 }^\circ\text{C for 2 hours with 2 mL sat. NH}_4\text{Cl, extracted with 3 x 2 mL EA, washed with 4 mL brine, dried with Na}_2\text{SO}_4, concentrated under reduced pressure. Then it was purified by FCC with 50% EA/Hex to get 116 (200 mg, 96 %) as colorless oil. IR (neat): 2954, 1704, 1254, 1021 cm\(^{-1}\); } \]  
\[ \text{\(^1\)H NMR (CDCl}_3, 500 MHz) \(\delta\) 4.28-4.11 (m, 4 H), 3.95 (dq, 1 H, J = 25, 7 Hz), 3.36 (dt, 1 H, J = 3, 14 Hz), 2.79 (dt, 1 H, J = 2.5, 14 Hz), 2.61 (tt, 2 H, J = 3, 15.5 Hz), 2.16 (heptet, 1 H, J = 6 Hz), 2.06-2.01 (m, 1 H), 1.91 (dd, 3 H, J = 7, 18 Hz), 1.34 (dt, 6 H, J = 5, 7 Hz), 1.05 (d, 6 H, J = 6.5 Hz); } \]  
\[ \text{\(^{13}\)C NMR (CDCl}_3, 125 MHz) \(\delta\) 199.6 (d, J = 3.75 Hz), 63.7 (d, J = 5 Hz), 62.9 (d, J = 7.5 Hz), 62.1 (d, J = 7.5 Hz), 44.8, 40.5, 39.5, 27.8 (d, J = 3.8 Hz), 25.3, 25.2, 25.1, 24.1, 16.4 (d, J = 6.2 Hz), 16.3 (d, J = 5 Hz), 16.0 (d, J = 6.2 Hz); } \]  
\[ \text{HRMS calcd for C}_{15}\text{H}_{29}\text{O}_4\text{PS}_2\text{Na [M+Na]}^+ 391.1137; } \]  
\[ \text{Found: 391.1127.} \]
To a solution of lactone 106 (422 mg, 2.37 mmol) in DCM (10 mL, 0.2 M) was added DIBAL (4.74 mL, 1 M in Toluene, 4.74 mmol) at -78 °C. After 9 hours, it was quenched with ethyl acetate. Then it was poured to a solution of Wittig reagent (4.74 mmol) in THF at 0 °C. The reaction mixture was stirred at rt overnight, quenched with 50 mL water, and washed with sat. NH4Cl. Then it was purified by FCC with 25% EA/Hex after concentration under reduced pressure to get 105 (94 mg, 22%) as colorless wax with melting point of 58-60 °C. IR (neat): 3293, 3011, 2913, 1605, 1458, 1405, 1295, 1033, 907, 837 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.89 (s, 1 H), 6.81 (dd, 1 H, J = 12, 18 Hz), 6.68 (s, 1 H), 5.64 (dd, 1 H, J = 2, 18 Hz), 5.50 (dd, 1 H, J = 2, 11.5 Hz), 4.71 (s, 2 H), 3.83 (d, 3 H, J = 2 Hz), 2.35 (s, 3 H), 1.73 (s, 1 H); ¹³C NMR (CDCl₃, 125 MHz) δ 157, 139, 138, 130, 123, 121, 119, 111, 63, 56, 22; HRMS calcd for C₁₁H₁₄O₂Na [M+Na]⁺ 379.1880; Found: 379.1881.

To a solution of (2-iodo-3-methoxy-5-methylphenyl)methanol (530 mg, 1.92 mmol) in THF/H₂O (9: 1) (10 mL, 0.2 M) was added Pd(OAc)₂ (8 mg, 0.038 mmol, 2 mol %), triphenylphosphine (26 mg, 0.115 mmol, 6 mol %), potassium vinyl fluoroborate (260 mg, 1.92 mmol), and Cs₂CO₃ (1.88 g, 5.76 mmol) at rt. After stirring at 90 °C for 16.5
hours, the top yellow organic layer was separated. The bottom aqueous layer with white solid was extracted with ethyl ether. Together, it was washed with brine, concentrated under reduced pressure, and purified by FCC with 25% EA/Hex to get 105 (310 mg, 91%).

119: To a solution of 105 (92 mg, 0.516 mmol) in DCM (10 mL, 0.05 M) was added CBr4 (205 mg, 0.619 mmol) and triphenylphosphine (162 mg, 0.619 mmol) at rt. The colorless solution was stirred for 1 hour at rt and turned to coffee color solution. Then it was concentrated under reduced pressure, and purified directly by FCC with 25% EA/Hex to get 119 (100 mg, 81%) as white solid which melted at 73-74 °C. IR (neat): 2933, 2835, 1630, 1462, 1328, 1278, 927, 845 cm⁻¹; ¹H NMR (CDCl3, 500 MHz) δ 6.84 (s, 1 H), 6.81 (dd, 1 H, J = 12, 18 Hz), 6.66 (s, 1 H), 5.79 (dd, 1 H, J = 2, 18 Hz), 5.58 (dd, 1 H, J = 2, 12 Hz), 4.57 (s, 2 H), 3.82 (s, 3 H), 2.33 (s, 3 H); ¹³C NMR (CDCl3, 125 MHz) δ 158, 138, 136, 130, 124, 123.6, 120, 112, 56, 33, 21; HRMS calcd for C₁₁H₁₃BrONa [M+Na]⁺ 263.0042; Found: 263.0044.

103: To a solution of 119 (56 mg, 0.23 mmol) was added trimethylphosphite (1 mL, 1.05 g, 8.47 mmol) and refluxed at 115 °C overnight. Then it was concentrated under reduced pressure and purified by FCC with EA to get 103 (57 mg, 90%) as colorless oil. IR
(neat): 3007, 2953, 2852, 1605, 1462, 1405, 1250, 1054 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.83 (s, 1 H), 6.72 (dd, 1 H, $J = 12, 18$ Hz), 6.61 (s, 1 H), 5.62 (dd, 1 H, $J = 2.5, 18$ Hz), 5.54 (dd, 1 H, $J = 2, 11.5$ Hz), 3.80 (s, 3 H), 3.68 (d, 3 H, $J = 0.5$ Hz), 3.65 (d, 3 H, $J = 0.5$ Hz), 3.29 (d, 2 H, $J = 22$ Hz), 2.33 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 157.5 (d, $J = 3.8$ Hz), 137.7 (d, $J = 3.8$ Hz), 131.1 (d, $J = 12.5$ Hz), 129.8 (d, $J = 8.8$ Hz), 124.6 (d, $J = 7.5$ Hz), 123.6 (d, $J = 5$ Hz), 119.9, 110.3 (d, $J = 1.2$ Hz), 55.4, 52.7 (d, $J = 6.2$ Hz), 30.4, 29.3, 21.5; HRMS calcd for C$_{13}$H$_{19}$O$_4$PNa [M+Na]$^+$ 321.1226; Found: 321.1231.

$^{148a}$: To a solution of $^{132}$ (2.61 g, 12.1 mmol) in dichloromethane (24 ml, 0.5 M) was added TMSCN (1.20 g, 12.1 mmol) and ZnI$_2$ (1 mg, cat.). The reaction mixture was stirred at rt for 18 hours. Then another 0.6 g of TMSCN was added to the reaction mixture. After total reaction time of three days, the mixture was filtered through a well packed silic plug, and rinsed with DCM till the eluent became colorless. Then it was concentrated under reduced pressure to get yellow oil (3.49 g, 92% yield based on crude mass). Then it was purified on aluminum oxide (activated, basic, Brockmann I, standard grade, ~150 mesh, 58Å), it decomposed back to the starting material $^{132}$. It was passed through another silic plug quickly for further reactions. IR (neat): 2958, 1603, 1459, 1255, 1159, 1023, 845 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.72 (dd, 1 H, $J = 12, 18$ Hz), 6.70 (s, 1 H), 6.65 (s, 1 H), 6.62 (s, 1 H), 5.56 (dd, 1 H, $J = 2, 18$ Hz), 5.43 (dd, 1 H, $J = 2,$
11 Hz), 4.95 (s, 1 H), 3.83 (s, 3 H), 2.34 (s, 3 H), 1.85 (s, 3 H), 0.25 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 157.5, 137.6, 135.5, 132.2, 130.6, 129.5, 123.1, 122.6, 119.5, 118.6, 110.7, 67.0, 55.4, 21.5, 13.4, -0.3, -0.5.

148: To a solution of 132 (1.84 g, 8.52 mmol) in acetonitrile (43 ml, 0.2 M) was added TBSCl (1.92 g, 12.8 mmol), NaCN (3.34 g, 68.2 mmol), and ZnI$_2$ (27 mg, 0.08 mmol). The yellow suspension was stirred at rt for 1 day, and quenched with 40 mL water, extracted with 3x40 mL EA, washed with 40 mL brine, dried with anhydrous MgSO$_4$. Then, it was concentrated under reduced pressure. Flash chromatography purification with 0-5% EA/Hexane yielded the product 148 (2.77 g, 91%). The pink band was collected, with the following yellow band discarded. IR (neat): 2955, 2858, 1603, 1462, 1255, 1100, 840, 781 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.72 (dd, 1 H, J = 12, 18 Hz), 6.70 (s, 1 H), 6.66 (s, 1 H), 6.62 (s, 1 H), 5.55 (dd, 1 H, J = 2, 17.5 Hz), 5.42 (dd, 1 H, J = 2, 12 Hz), 4.95 (s, 1 H), 3.84 (s, 3 H), 2.35 (s, 3 H), 1.85 (d, 3 H, J = 1 Hz), 0.95 (s, 9 H), 0.23 (s, 3 H), 0.18 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 157.5, 137.6, 135.6, 132.3, 130.6, 129.3, 123.2, 122.6, 119.6, 118.7, 110.8, 67.3, 55.5, 25.5, 21.6, 18.2, 13.5, -5.2, -5.22.

110
149: To a solution of 148 (1.2 g, 3.35 mmol) in THF (16.8 mL, 0.2 M) was added LiHMDS (4.47 mL, 0.9 M in THF, 4.02 mmol) slowly at -78 °C. The color turned red upon the addition of LiHMDS. After 10 min at -78 °C, isovaleraldehyde (0.346 g, 4.02 mmol) was added neat. The color of the solution turned yellow upon finishing adding isovaleraldehyde at -78 °C. Immediately, it was quenched with saturated NH₄Cl and raised to rt. It was then extracted with ethyl ether, washed with brine, dried with MgSO₄, concentrated under reduced pressure, and purified by FCC (5-10% EA/Hex) to yield 149 (1.2 g, 89%). IR (neat): 2954, 2860, 1683, 1601, 1458, 1258, 1099, 1046, 833, 776 cm⁻¹; $^1$H NMR (CDCl₃, 500 MHz) δ 7.65 (s, 1 H), 6.81(dd, 1 H, J = 11.5, 17.5 Hz), 6.70 (d, 1 H, J = 3.5 Hz), 5.49 (dd, 1 H, J = 2, 11.5 Hz), 5.43 (dd, 1 H, J = 2, 18 Hz), 4.90 (dd, 1 H, J = 3.5, 10 Hz), 3.86 (s, 3 H), 2.37 (s, 3 H), 1.93 (s, 3 H), 1.89-1.84 (m, 1 H), 1.66 (m, 1 H), 1.48 (m, 1 H), 0.95 (d, 3 H, J = 2.5 Hz), 0.94 (d, 3 H, J = 3 Hz), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). $^{13}$C NMR (CDCl₃, 125 MHz) δ 203.2, 157.4, 140.3, 137.8, 135.3, 131.0, 123.8, 122.4, 120.5, 111.3, 74.1, 55.6, 44.8, 25.8, 24.4, 23.6, 21.7, 21.4, 18.3, 13.7, -4.5, -5.2.

150: To a solution of 149 (150 mg, 0.36 mmol) in THF (1 mL, 0.36 M) was added TBAF (0.43 mL 1 M solution in THF, 0.43 mmol) at 0 °C. After 20 min, it was quenched with sat. NaHCO₃, extracted with EA, washed with brine, dried with MgSO₄, concentrated under reduced pressure, and purified by FCC with 5% EA/Hex to get 150 (100 mg, 92%).

150
IR (neat): 3471, 2954, 2920, 1661, 1601, 1563, 1464, 1049 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.48 (s, 1 H), 6.82 (dd, 1 H, J = 11.5, 18 Hz), 6.74 (s, 1 H), 6.72 (s, 1 H), 5.52 (dd, 1 H, J = 1.5, 11.5 Hz), 5.38 (dd, 1 H, J = 2, 17.5 Hz), 4.95 (ddd, 1 H, J = 2, 7, 9.5 Hz), 3.86 (s, 3 H), 3.56 (d, 1 H, J = 7 Hz), 2.38 (s, 3 H), 2.01 (s, 3 H), 1.61-1.56 (m, 1 H), 1.41-1.35 (m, 1 H), 1.02 (d, 3 H, J = 7 Hz), 0.95 (d, 3 H, J = 6.5 Hz). ¹³C NMR (CDCl₃, 125 MHz) δ 2.41, 157.4, 141.7, 138.0, 134.4, 133.8, 130.9, 124.3, 122.4, 121.0, 111.7, 70.9, 55.6, 45.4, 25.0, 23.7, 21.7, 21.3, 13.5.

172: To a solution of diol (29 mg, 0.09 mmol) in dichloromethane (2 mL, 0.045 M), was added 2, 6-lutidine (52 µL, 0.45 mmol) and TBSOTf (63 µL, 0.27 mmol) consecutively at 0 °C. After TLC showed complete consumption of starting material, it was quenched with saturated ammonium chloride aqueous solution and extracted with dichloromethane. Then it was washed with brine, dried with MgSO₄, concentrated under reduced pressure, and purified by flash chromatography (1: 20 ethyl acetate in hexane) to get the silyl ether as a colorless oil (36 mg, 73%) ¹H NMR (CDCl₃, 500 MHz) δ 6.49 (s, 1 H), 6.41 (s, 1 H), 5.34 (s, 1 H), 5.33 (d, 1 H, J = 1.5 Hz), 3.82 (s, 1 H), 3.76 (s, 3 H), 3.30 (s, 1 H), 2.31 (heptet, 1 H, J = 6.5 Hz), 2.28 (s, 3 H), 1.16 (s, 3 H), 1.14 (d, 3 H, J = 7 Hz), 1.01 (d, 3 H, J = 6.5 Hz), 0.91 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.3, 154.4, 140.2, 138.4, 126.8, 124.2, 120.1,
115.6, 109.5, 81.2, 77.9, 57.4, 56.2, 55.4, 26.3, 26.0, 25.9, 21.8, 20.8, 20.3, 18.6, 17.9, 15.5, -2.5, -3.4, -4.7, -4.8.

4,5-dihydroxy-6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[a]naphthalen-3-one (171): To a solution of enone (20 mg, 0.07 mmol) in 1 M acetone/water (4: 1), was added 2.5% OsO₄ in 2-methylpropanol (44 µL, 0.0035 mmol) and 60% NMO in water (35 µL, 0.33 mmol) at rt. After 24 hours, 1 mL water was added, followed by 1 mL saturated sodium thiolsulfate. The mixture was extracted with dichloromethane (3 x 3 mL), washed with 2 mL brine, and dried with Na₂SO₄. After purification by flash chromatography (25% to 50% ethyl acetate in hexane), 12 mg (54%) white solid was obtained: mp 155-156 °C; IR (neat): 3420, 2962, 2929, 1675, 1609, 1462, 1090 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.70 (s, 1 H), 6.63 (s, 1 H), 5.90 (s, 1 H), 5.17 (d, 1 H, J = 11.5 Hz), 5.166 (s, 1 H), 3.81 (s, 3 H), 3.76 (s, 1 H), 3.68 (dd, 1 H, J = 2.5, 13.5 Hz), 2.61 (heptet, 1 H, J = 7 Hz), 2.07 (d, 1 H, J = 2.5 Hz), 1.44 (s, 3 H), 1.28 (d, 3H, J = 7 Hz), 1.00 (d, 3 H, J = 7 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 215.7, 188.2, 157.7, 139.7, 136.1, 124.8, 129.0, 121.7, 110.3, 79.2, 65.6, 56.9, 55.6, 45.2, 28.7, 24.9, 22.0, 21.9, 20.8; HRMS calcd for C₁₉H₂₅O₄Na [M+Na]⁺ 339.1567; Found: 339.1568.
6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3H-
cyclopenta[a]naphthalen-3-one (166): To a solution of enol triflate (132 mg, 0.307 mmol) in 3 mL DMF (0.1 M), was added palladium (II) acetate (7 mg, 0.03 mmol), triphenylphosphine (16 mg, 0.06 mmol), triethylamine (0.17 mL), and formic acid (56 µL, 1.5 mmol) at rt. The reaction was stirred at 70°C for 12 hours, and quenched with 20 mL water and 20 mL diethyl ether at rt. Then the mixture was extracted with diethyl ether (3 x 20 mL), washed with 50 mL saturated ammonium chloride aqueous solution, 50 mL saturated sodium bicarbonate aqueous solution and 50 mL water. After drying with sodium sulfate and concentrated under reduced pressure, it was purified by flash chromatography (10% ethyl acetate in hexane) to get a white solid (75 mg, 86%). mp 116 - 118°C; IR (neat): 2966, 1704, 1687, 1605, 1458, 1381 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.73 (d, 1 H, J = 10 Hz), 6.72 (s, 1 H), 6.62 (s, 1 H), 5.99 (d, 1 H, J = 2 Hz), 5.50 (d, 1 H, J = 10 Hz), 3.82 (s, 3 H), 3.78 (d, 1 H, J = 1.5 Hz), 2.48 (heptet, 1 H, J = 7 Hz), 1.23 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 0.83 (d, 3 H, J = 7 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 210.7, 185.6, 155.4, 138.1, 132.0, 129.9, 124.4, 122.8, 119.0, 118.4, 110.7, 55.5, 53.7, 52.3, 28.7, 22.4, 21.9, 21.3, 20.4; HRMS calcd for C₁₉H₂₂O₂Na [M+Na]⁺ 305.1512; Found: 305.1508.
**173**: To a solution of **166** (42 mg, 0.149 mmol) in THF (1.5 mL, 0.1 M) was added L-selectride (0.179 mL, 1 M in THF, 0.179 mmol) at 0 °C slowly. It was quenched with 4 N NaOH and 30% H$_2$O$_2$ after 30 min at 0 °C. Then it was extracted with DCM, washed with brine, dried with MgSO$_4$, concentrated and purified by FCC with 25% EA/Hex to get the allylic alcohol **173** (40 mg, 95%). IR (neat): 3346, 2954, 2917, 2860, 1605, 1569, 1454, 1324, 1127, 1017, 821 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.81 (d, 1 H, J = 10.5 Hz), 6.62 (s, 1 H), 6.58 (s, 1 H), 5.85 (d, 1 H, J = 10.5 Hz), 5.43 (d, 1 H, J = 1.5 Hz), 4.65 (d, 1 H, J = 6.5 Hz), 3.81 (s, 3 H), 3.44 (s, 1 H), 2.35 (s, 3 H), 1.92 (heptet, 1 H, J = 7 Hz), 1.57 (s, 1 H), 1.00 (d, 3 H, J = 7 Hz), 0.73 (d, 3 H, J = 7 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 155, 152, 137, 133, 129, 124, 123, 119, 110, 86, 55.4, 55, 50, 27, 23, 22, 21.8, 21; HRMS calcd for C$_{19}$H$_{24}$O$_2$Na [M+Na]$^+$ 307.1668; Found: 307.1683.

**174**: To a solution of **173** (18 mg, 0.063 mmol) in DCM (1 mL, 0.06 M) was added DMAP (15 mg, 0.123 mmol), formic acetic anhydride (11 mg, 0.125 mmol). It was concentrated under reduced pressure after 19 hours at rt, and purified by FCC with 10%
EA/Hex to get $174$ (17.5 mg, 87%). IR (neat): 2959, 2922, 1725, 1463, 1174 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.24 (d, 1 H, J = 1 Hz), 6.78 (d, 1 H, J = 10 Hz), 6.63 (s, 1 H), 6.59 (s, 1 H), 5.85 (d, 1 H, J = 10 Hz), 5.76 (s, 1 H), 3.82 (s, 3 H), 3.48 (s, 1 H), 2.35 (s, 3 H), 5.45 (m, 1 H), 1.94 (heptet, 1 H, J = 6.5 Hz), 1.17 (s, 3 H), 1.01 (d, 3 H, J = 7 Hz), 0.74 (d, 3 H, J = 6.5 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 161.2, 154.9, 153.6, 137.4, 132.7, 128.8, 122.9, 120.8, 118.94, 118.9, 110.4, 86.6, 55.4, 54.7, 49.2, 27.2, 22.4, 22.2, 21.8, 21.1.

$176$: To a solution of $173$ (3.5 mg, 0.012 mmol) in DCM was added Ac$_2$O (10.8 mg, 1.06 mmol) and DMAP (3 mg, 0.025 mmol) at rt. It was concentrated under reduced pressure after 11 hours at rt, and purified by FCC with 10% EA/Hex to get the acetate $176$. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 6.77 (d, 1 H, J = 10.5 Hz), 6.63 (s, 1 H), 6.59 (s, 1 H), 5.86 (d, 1 H, J = 10 Hz), 5.64 (s, 1 H), 5.44 (dd, 1 H, J = 1, 1.5 Hz), 3.82 (s, 3 H), 3.50-3.46 (m, 1 H), 2.35 (s, 3 H), 2.16 (s, 3 H), 1.92 (heptet, 1 H, J = 7 Hz), 1.15 (s, 3 H), 1.00 (d, 3 H, J = 7 Hz), 0.73 (d, 3 H, J = 7 Hz); DEPT135 (CDCl$_3$, 125 MHz) (CH, CH$_3$) $\delta$ 129.2, 123.0, 121.3, 118.8, 110.4, 86.8, 63.4, 55.5, 54.7, 27.2, 22.4, 22.2, 21.8, 21.3, 21.2.
(3a,9b)-6-methoxy-3a,8-dimethyl-3-oxo-1-(propan-2-yl)-3a,9b-dihydro-3H-
cyclopenta[a]naphthalen-2-yl trifluoromethanesulfonate (165): 2-hydroxy-6-
methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3H-cyclopenta[a]naphthalen-3-
one (114 mg, 0.382 mmol) in 4 mL dichloromethane (0.1 M) was cooled to 0°C by
ice/water bath. To the solution was added triethylamine (106 µL, 0.764 mmol) at 0°C.
Then triflic anhydride (77 µL, 0.458 mmol) was added dropwisely at 0°C, during which
time the solution turned dark. The reaction mixture was allowed to warm up to rt by
removing the cooling bath after stirring for 10 minutes at 0°C. After 1.5 hours, the
reaction mixture was concentrated under aspirator vacuum to get dark slow flow oil,
which was directly purified by flash chromatography (10% ethyl acetate in hexane,
between yellow band and red band) to get a colorless wax (136 mg, 83%): IR (neat):
2974, 2938, 1732, 1417, 1209, 1139, 992 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.82 (d, 1
H, J = 9.5 Hz), 6.71 (s, 1 H), 6.67 (s, 1 H), 3.78 (s, 3 H), 5.43 (d, 1 H, J = 9.5 Hz), 3.83 (s,
3 H), 3.76 (s, 3 H), 2.75 (heptet, 1 H, J = 7.0 Hz), 2.40 (s, 3 H), 1.24 (s, 3 H), 1.15 (d, 3
H, J = 7.0 Hz), 0.96 (d, 3H, J = 7.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 119.9, 168.1,
156.6, 142.5, 138.9, 129.8, 128.2, 123.4, 119.9, 119.1, 118.5 (q, J = 319 Hz), 111.6, 55.5,
50.23, 50.15, 28.4, 21.9, 19.92, 19.89, 19.0; HRMS calcd for C₂₀H₂₁F₃O₅SNa [M+Na]⁺
453.0954; Found: 453.0956.
2-hydroxy-6-methoxy-3a,8-dimethyl-1-(propan-2-yl)-3a,9b-dihydro-3H-cyclopenta[a]naphthalen-3-one (144): 4-(2-ethenyl-3-methoxy-5-methylphenyl)-2-hydroxy-3-methyl-5-(propan-2-yl)cyclopent-2-en-1-one (134 mg, 0.440 mmol) in 10 mL THF was added bis(acetonitrile)palladium(II) chloride (1 mg, 0.004 mmol, 1 mol%), cuprous iodide (2 mg, 0.0105 mmol, 2 mol%) sequentially at rt. Then, nitrogen balloon was changed to oxygen balloon. After stirring for 10 minutes at rt, yellow solution turned red. After 36 hours at rt, the reaction mixture was filtered through a Celite plug, and rinsed with dichloromethane (2x10 mL). After removing the solvent under reduced pressure on rotvapor, 146 mg of red semisolid was obtained. H-NMR showed that it was a mixture of the diketone and its enol tautomer in three to one ratio. It was further purified by flash chromatography with 10% ethyl acetate in hexane to get a red solid powder (124 mg, 93%). The pure enol tautomer was obtained quantitatively by treating the red solution of mixture of the two isomers in THF with catalytic amount of TEA and silica gel, and stirring for 5 to 7 hours. The disappearance of the red color is a sign of completion of this tautomerization process. mp 195-198°C; IR (neat): 3322, 2970, 2921, 1691, 1646, 1458, 1401, 1311, 1029 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.74 (d, 1 H, J = 10 Hz), 6.68 (s, 1 H), 6.62 (s, 1 H), 5.43 (d, 1 H, J = 10 Hz), 5.36 (s, 1 H), 3.81 (s, 3 H), 3.58 (s, 1 H), 2.54 (heptet, 1 H, J = 7 Hz), 2.39 (s, 3 H), 1.26 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 0.90 (d, 3 H, J = 7 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 204.9, 155.4, 148.9, 146.4,
138.1, 132.6, 129.1, 123.4, 118.8, 118.6, 110.7, 55.5, 49.5, 48.8, 27.5, 21.9, 20.2, 20.0, 19.9; HRMS calcd for C_{19}H_{22}O_3Na [M+Na]^+ 321.1461; Found: 321.1459.

4-(2-ethenyl-3-methoxy-5-methylphenyl)-2-hydroxy-3-methyl-5-(propan-2-yl)cyclopent-2-en-1-one (98): (1E)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-2,6-dimethylhept-1-ene-3,4-dione (224 mg, 0.746 mmol) in 10 mL THF was dropwise added LiHMDS (1 mL 0.9 M in THF, 0.9 mmol) at -78°C. During the addition of LiHMDS, the yellow solution turned golden color gradually. The cooling bath was removed after 10 minutes. The reaction was quenched by adding 10 mL saturated aqueous ammonium chloride solution at 0 °C after stirring for 12 hours at rt. It was extracted with ethyl acetate (3x10 mL), washed with 20 mL brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. After purification by flash chromatography (25% ethyl acetate in hexane), a colorless oil was obtained. (130 mg, 58%) IR (neat): 3326, 2954, 1699, 1650, 1462, 1401, 1115 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.78 (dd, 1 H, J = 12.5, 16.5 Hz), 6.57 (s, 1 H), 6.38 (s, 1 H), 5.61 (d, 1 H, J = 11 Hz), 5.46 (dd, 1 H, J = 2, 18 Hz), 4.12 (s, 1 H), 3.82 (s, 3 H), 2.32 (s, 1 H), 2.28 (s, 3 H), 2.22 - 2.15 (m, 1 H), 1.77 (s, 3 H), 0.89 (d, 3 H, J = 6 Hz), 0.88 (d, 3 H, J = 6.5 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 204.9, 157.1, 149.1, 146.5, 140.8, 138.5, 131.6, 125.0, 120.4, 119.2, 109.5, 60.1, 55.5, 43.0, 29.4, 21.6, 19.7, 18.5, 12.6; HRMS calcd for C$_{19}$H$_{24}$O$_3$Na [M+Na]$^+$ 323.1618; Found: 323.1614.
(1E)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-2,6-dimethylhept-1-ene-3,4-dione

(97): (1E)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-3-hydroxy-2,6-dimethylhept-1-en-4-one (1.25 g, 4.13 mmol) in 25 mL anhydrous ethyl acetate was added IBX (5.78 g, 20.6 mmol) at rt at once. It was refluxed at 90°C for 3 hours and cooled to rt, when the colorless solution turned yellow. Then, it was filtered through a packed Celite plug, and rinsed with 100 mL ethyl acetate. After concentration under reduced pressure and purification by flash chromatography (5% ethyl acetate in hexane, collect the yellow band), a yellow oil was obtained. (1.03 g, 83%) IR (neat): 2962, 2929, 1708, 1654, 1458 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (s, 1 H), 6.81 (dd, 1 H, J = 11.5, 18 Hz), 6.77 (s, 1 H), 6.72 (s, 1 H), 5.53 (dd, 1 H, J = 1.5, 11.5 Hz), 5.38 (dd, 1 H, J = 1.5, 17.5 Hz), 3.85 (s, 3 H), 2.67 (d, 2 H, J = 6.5 Hz), 2.37 (s, 3 H), 2.34 – 2.20 (m, 1 H), 2.01 (d, 3 H, J = 1 Hz), 0.99 (d, 6 H, J = 6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 204.9, 197.1, 157.4, 147.7, 137.9, 134.0, 132.6, 130.5, 124.5, 122.3, 121.4, 112.0, 55.6, 48.2, 23.8, 22.6, 21.7, 12.3; HRMS calcd for C₁₉H₂₄O₃Na [M+Na]^⁺ 323.1618; Found: 323.1628.
(1E)-1-(2-ethenyl-3-methoxy-5-methylphenyl)-3-hydroxy-2,6-dimethylhept-1-en-4-one (134): To a vigorously stirred suspension of HgO (5 g, 23 mmol) and BF₃·Et₂O (3.5 mL, 28 mmol) in 15% THF in water (120 mL) at rt, was added crude dithiane in 20 mL THF slowly. After stirring for 20 minutes at rt (only trace amount of red HgO left and a voluminous amount of white suspension formed), 100 mL diethyl ether and 50 mL brine was added. Then it was filtered though a well packed Celite, rinsed with 500 mL diethyl ether, separated and washed with saturated sodium bicarbonate (2x100 mL), brine (100 mL). after drying with sodium sulfate, and concentrated under reduced pressure, it was purified by flash chromatography (10% ethyl acetate in hexane) to get viscous oil (1.25 g, 56%): IR (neat): 3465, 2958, 2868, 1708, 1597, 1560, 1454, 1095 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.80 (dd, 1 H, J = 12, 18 Hz), 6.74 (s, 1 H), 6.69 (s, 1 H), 6.67 (s, 1 H), 5.68 (dd, 1 H, J = 2.5, 18 Hz), 5.48 (dd, 1 H, J = 2, 11.5 Hz), 4.69 (d, 1 H, J = 4.5 Hz), 4.05 (d, 1 H, J = 4.5 Hz), 3.87 (s, 3 H), 2.51 - 2.42 (m, 2 H), 2.37 (s, 3 H), 2.26 (heptet, 1 H, J = 7 Hz), 1.58 (d, 3 H, J = 1 Hz), 0.99 (d, 3 H, J = 6.5 Hz), 0.97 (d, 3 H, J = 6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 210.3, 157.6, 137.6, 136.4, 134.6, 132.0, 131.0, 123.0, 122.6, 119.4, 110.6, 83.6, 55.4, 46.5, 24.5, 22.6, 22.5, 21.6, 12.3; HRMS calcd for C₁₉H₂₆O₃Na [M+Na]⁺ 325.1774; Found: 325.1770.
(E)-1-(2-isobutyl-1,3-dithian-2-yl)-3-(3-methoxy-5-methyl-2-vinylphenyl)-2-methylprop-2-en-1-ol (133): To a solution of dithiane (1.56 g, 8.9 mmol) in 20 mL THF, was added 2.4 M nBuLi at −20°C slowly. After it was stirred at −20°C for 3 hours, the aldehyde (1.6 g, 7.41 mmol) in 5 mL THF was added dropwisely, during which time the colorless solution turned dark. After 1 hour at −20°C, it was raised to rt and quenched with 20 mL saturated ammonium chloride solution. Then it was washed with 10 mL brine, dried with Na₂SO₄, and concentrated under reduced pressure to get viscous oil which went to the next step as crude: IR (neat): 3436, 2949, 1601, 1560, 1454, 1270, 907, 833, 731 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.80 (dd, 1 H, J = 11.5, 18 Hz), 6.68 (s, 1 H), 6.65 (s, 1 H), 5.76 (dd, 1 H, J = 2, 17.5 Hz), 5.40 (dd, 1 H, J = 2.5, 12 Hz), 4.68 (s, 1 H), 3.84 (s, 3 H), 3.14 (d, 1 H, J = 1 Hz), 3.16 – 3.05 (m, 2 H), 2.68 – 2.62 (m, 2 H), 2.34 (s, 3 H), 2.16 – 2.09 (m, 2 H), 1.87 (s, 3 H), 1.94 – 1.83 (m, 2 H), 1.52 (dd, 1 H, J = 5, 15 Hz), 1.04 (d, 3 H, J = 6.5 Hz), 1.01 (d, 3 H, J = 6 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 157.7, 137.8, 137.2, 134.6, 131.2, 130.4, 123.0, 122.7, 119.0, 110.2, 75.4, 60.4, 55.4, 43.2, 26.6, 25.6, 25.5, 24.9, 24.2, 21.6, 17.5; HRMS calcd for C₂₂H₃₂O₂S₂Na [M+Na]⁺ 415.1736; Found: 415.1733.
(E)-1-(2-isobutyl-1,3-dithian-2-yl)-3-(3-methoxy-5-methyl-2-vinylphenyl)-2-methylprop-2-en-1-one (155): To a solution of dithiane (2.68 g, 15.2 mmol) in THF (30 mL, 0.5 M), was added n-buyl lithium (6 mL, 2.5 M in THF, 15 mmol) slowly over 10 minutes. After stirring for 3.5 hours at −20 °C, Weinreb’s amide (4.19 g, 15.2 mmol) in 30 mL THF was added slowly, at which time the colorless solution turned to dark. After stirring at −20 °C for 30 minutes (gradually turned to orange color), it was quenched with saturated ammonium chloride aqueous solution at −20 °C. Then it was raised to rt and stirred for 10 minutes. 40 mL brine and 40 mL diethyl ether was added. It was then extracted with diethyl ether (3 x 50 mL), washed with brine (100 mL), and dried with Na₂SO₄. After removing the solvents under reduced pressure, it was purified by flash chromatography (5% to 10% ethyl acetate in hexane) to get pale yellow oil (5.31 g, 89%).

IR (neat): 2958, 2921, 1658, 1597, 1560, 1458, 1201 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.98 (s, 1 H), 6.78 (dd, 1 H, J = 11.5, 17.5 Hz), 6.68 (s, 1 H), 6.64 (s, 1 H), 5.57 (dd, 1 H, J = 2, 17.5 Hz), 5.45 (dd, 1 H, J = 2, 12 Hz), 3.84 (s, 3 H), 3.14 (dd, 1 H, J = 2.5, 12 Hz), 3.12 (dd, 1 H, J = 2.5, 11.5 Hz), 2.74 (dd, 1 H, J = 3.5, 5 Hz), 2.71 (dd, 1 H, J = 3.5, 5 Hz), 2.36 (s, 3 H), 2.28 (d, 2 H, J = 6.5 Hz), 2.09 – 2.02 (m, 2 H), 1.99 (d, 3 H, J = 1 Hz), 1.93 – 1.84 (m, 1 H), 0.96 (d, 6 H, J = 6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 199.9, 157.4, 138.9, 137.6, 135.7, 135.1, 130.7, 123.3, 122.1, 120.1, 110.9, 61.0, 55.4, 47.9,
28.0, 25.3, 24.6, 23.8, 21.6, 16.4; HRMS calcd for $\text{C}_{22}\text{H}_{30}\text{O}_2\text{S}_2\text{Na} [\text{M+Na}]^+$ 413.1579; Found: 413.1578.

156: To a solution of 155 (5.31 g, 13.6 mmol) in methanol (35 mL, 0.4 M) was added 2,6-lutidine (9.38 g, 68 mmol) and NCS (3.6 g, 2.69 mmol) at 0 °C. After 7 min, the milky solution turned a yellow homogeneous solution. Then it was quenched with sat. Na$_2$S$_2$O$_3$, brine, and extracted with Et$_2$O 3 x 35 mL. After washing with 1N HCl, washing with brine, and drying with MgSO$_4$, it was concentrated under reduced pressure. FCC with 25% EA/Hex yielded 156 (5.1 g, 86%). IR (neat): 2962, 1642, 1454, 1234, 1127, 992 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.45 (s, 1 H), 6.78 (dd, 1 H, J = 11, 17.5 Hz), 6.73 (s, 1 H), 6.70 (s, 1 H), 6.15 (d, 1 H, J = 9.5 Hz), 5.45-5.40 (m, 2 H), 3.85 (s, 3 H), 3.74 (s, 3 H), 3.05 (m, 1 H), 2.91-2.79 (m, 2 H), 2.76 (t, 2 H, J = 7 Hz), 2.01 (d, 3 H, J = 1.5 Hz), 1.96 (t, 2 H, J = 7 Hz), 1.01 (d, 6 H, J = 5.5 Hz); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 196.5, 157.4, 149.8, 143.2, 137.9, 136.6, 135.1, 131.7, 130.8, 123.9, 122.3, 120.6, 111.5, 55.6, 55.2, 54.5, 31.3, 29.4, 22.0, 21.7, 21.6, 13.8; HRMS calcd for $\text{C}_{23}\text{H}_{32}\text{O}_4\text{S}_2\text{Na} [\text{M+Na}]^+$ 459.1634; Found: 459.1636.
(2E)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-enal (132):

**Stille coupling:** CsF (1.8 g, 12 mmol) was added in one portion into a solution of bromoaldehyde (2.17 g, 8.05 mmol), vinyltributyltin (2.81 g, 8.86 mmol), bistriphenylphosphine palladium (II) chloride (56 mg, 0.08 mmol) and triphenyl phosphine (73 mg, 0.32 mmol) in toluene (50 mL, 0.16 M). Then the mixture was stirred at 90°C for 17 hours, during which time the yellow solution turned dark. It was cooled down to rt and filtered through a well packed Celite and rinsed with 100 mL ethyl acetate to get rid of the black solids. After concentrated under reduced pressure, it was purified by flashed chromatography (pure hexane, then 2% to 5% ethyl acetate in hexane) to get the yellow oil (1.63 g, 94%). IR (neat): 3003, 2958, 2831, 2709, 1683, 1622, 1597, 1458, 1201, 1017 cm⁻¹;¹ H NMR (CDCl₃, 500 MHz) δ 9.63 (s, 1 H), 7.48 (s, 1 H), 6.83 (dd, 1 H, J = 11.5, 17.5 Hz), 6.79 (s, 1 H), 6.74 (s, 1 H), 5.52 (dd, 1 H, J = 2, 11.5 Hz), 5.41 (dd, 1 H, J = 2, 17.5 Hz), 3.86 (s, 3 H), 2.38 (s, 3 H), 1.95 (d, 3 H, J = 1.5 Hz);¹³C NMR (CDCl₃, 125 MHz) δ 195.7, 157.4, 150.4, 138.5, 137.8, 134.1, 130.4, 124.2, 122.1, 121.1, 112.0, 55.6, 21.6, 10.8; HRMS calcd for C₁₄H₁₆O₂Na [M+Na]+ 239.1042; Found: 239.1045.

**Suzuki coupling to make 132:**

To a solution of bromoaldehyde (1.04 g, 3.87 mmol) in 20 mL propanol was added vinyl pinacol borate (0.90 g, 5.8 mmol) and purged with N₂ for 10 minutes at rt. The solution
was treated with palladium (II) acetate (8.7 mg, 0.039 mmol), triphenylphosphine (30 mg, 0.11 mmol), sodium carbonate (8 mL, 0.725 M, 5.8 mmol), and purged with N₂ for 10 minutes. Then the mixture was raised to 85°C, and stirred under N₂ for 7 hours. TCL showed complete consumption of bromoaldehyde. Then, it was cooled to rt, diluted with ethyl acetate (20 mL), filtered through 2.5 g Florisil on top of a Celite plug (1 cm depth), and rinsed with ethyl acetate (2x30 mL). The two layers were separated. The aqueous layer was extracted with ethyl acetate (30 mL), washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), concentrated under reduced pressure, and purified by flash chromatography (10% ethyl acetate in hexane) to get a yellow oil (769 mg, 92%).

**Oxidation by MnO₂ to make 132:**

To a solution of the alcohol (470 mg, 2.15 mmol) in DCM (10 mL, 0.2 M) was added MnO₂ (1.87 g, 21.5 mmol) at rt in one portion. It was stirred at rt for 12 hour and filtered through Celite. After concentration under reduced pressure, it was purified by flash chromatography (5% ethyl acetate in hexane) to get the aldehyde (414 mg, 89%).

![Chemical Structure](image)

**3-methoxy-5-methyl-2-vinylbenzaldehyde (102):** It was synthesized from 2-iodo-3-methoxy-5-methylbenzaldehyde, or 2-bromo-3-methoxy-5-methylbenzaldehyde through Stille or Suzuki coupling similar to the above procedures in yields from 51% to 82% (Table 2) as a white wax. IR (neat): 3019, 2860, 1679, 1597, 1278, 1193, 1136, 1078, 996
cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 10.2 (s, 1 H), 7.34 (s, 1 H), 7.00 (dd, 1 H, J = 11, 18 Hz), 6.90 (s, 1 H), 5.71 (dd, 1 H, J = 1.5, 11 Hz), 5.31 (dd, 1 H, J = 1.8, 18 Hz), 3.87 (s, 3 H), 2.40 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 193, 157, 139, 135, 129, 128, 124, 120, 116, 56, 22; HRMS calcd for C₁₁H₁₂O₂Na [M+Na]⁺ 199.0730; Found: 199.1727.

(2E)-3-(2-bromo-3-methoxy-5-methylphenyl)-2-methylprop-2-enal (131): To a solution of alcohol (470 mg, 2.15 mmol) in DCM (10 mL, 0.2 M) was added manganese oxide (1.87 g, 21.5 mmol) at rt. The mixture was stirred for 2 days at rt, filtered through Celite to get rid of solid, and purified by flash chromatography (10% ethyl acetate in hexane) to get colorless crystal (414 mg, 89%). mp 101 - 102°C; IR (neat): 2917, 2848, 1679, 1569, 1311, 1197, 1017, 727 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 7.45 (s, 1 H), 7.26 (s, 1 H), 6.82 (s, 1 H), 6.74 (s, 1 H), 3.92 (s, 3 H), 2.37 (s, 3 H), 1.93 (d, 3 H, J = 1 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 195.4, 155.5, 138.7, 137.2, 124.4, 123.4, 110.9, 110.0, 68.0, 56.1, 21.3, 15.0 HRMS calcd for C₁₂H₁₃BrO₂Na [M+Na]⁺ 290.9991; Found: 290.9989.

Me
OMe
Br
Me
Br
Me
OH

Me
OMe
Br
Me
O
(2E)-3-(2-bromo-3-methoxy-5-methylphenyl)-2-methylprop-2-en-1-ol (131a): To a solution of the bromoester (5.64 g, 18 mol) in THF (200 mL, 0.09 M), was added DIBAL (54 mL, 1 M in toluene, 54 mmol) slowly at –30 °C. After stirring for 2.5 hours at –30 °C, it was raised to 0 °C and added 2.16 mL water slowly, 0.2 mL 4 N sodium hydroxide aqueous solution, 5.4 mL water sequentially at 0 °C. Then it was raised to rt and stirred for 15 minutes at rt, added 10 g anhydrous magnesium sulfate, stirred for 15 minutes, and filtered through Celite. After concentration under reduced pressure, it was purified by flash chromatography (25% ethyl acetate in hexane) to get the yellow oil (4.69 g, 96%). IR (neat): 3379, 2938, 2856, 1569, 1315, 1242, 1090, 1168, 911, 829, 731 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.69 (s, 1 H), 6.60 (s, 1 H), 6.50 (s, 1 H), 4.21 (d, 2 H, J = 4.5 Hz), 3.86 (s, 3 H), 2.49 (t, 1 H, J = 4.5 Hz), 2.30 (s, 3 H), 1.78 (s, 3 H); ¹³C NMR (CDCl₃, 125 MHz) δ 155.5, 138.7, 137.2, 124.4, 123.4, 110.9, 110.0, 68.0, 56.1, 21.3, 15.0; HRMS calcd for C₁₂H₁₅BrO₂Na [M+Na]⁺ 293.0148; Found: 293.0163.

Ethyl (2E)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-enoate (153): To a solution of bromo ester (5.06 g, 16.2 mmol), vinyltributyltin (7.71 g, 24.3 mmol), bistrriphenyl phosphine palladium (II) chloride (171 mg, 0.16 mmol) and triphenyl phosphine (145 mg, 0.64 mmol) in toluene (80 mL, 0.2 M), was added CsF (3.70 g, 24.3 mmol). Then the mixture was stirred at 110 °C for 20 hours, during which time the
yellow solution turned to a grayish suspension. It was cooled down to rt and filtered through a short silica plug and rinsed with 200 mL diethyl ether. After concentrated under reduced pressure, it was purified by flashed chromatography (5% to 10% ethyl acetate in hexane) to get the yellow oil (3.86 g, 92%).

IR (neat): 3085, 2979, 2958, 1704, 1597, 1560, 1454, 1242, 1115 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.73 (s, 1 H), 6.79 (dd, 1 H, \(J = 11.5, 17.5\) Hz), 6.68 (s, 1 H), 6.67 (s, 1 H), 5.52 (dd, 1 H, \(J = 1.5, 18\) Hz), 5.46 (dd, 1 H, \(J = 1.5, 11.5\) Hz), 4.26 (q, 2 H, \(J = 7\) Hz), 3.85 (s, 3 H), 2.35 (s, 3 H), 1.96 (s, 3 H), 1.34 (t, 3 H, \(J = 7.5\) Hz); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 168.5, 157.5, 139.7, 137.6, 135.6, 130.5, 128.6, 123.5, 122.3, 120.1, 111.2, 60.7, 55.5, 21.6, 14.3, 14.0; HRMS calcd for C\(_{16}\)H\(_{20}\)O\(_3\)Na [M+Na]\(^+\) 283.1305; Found: 283.1305.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

(2\textit{E})-3-(2-ethenyl-3-methoxy-5-methylphenyl)-\textit{N}-methoxy-\textit{N},2-dimethylprop-2-enamide (154): To a well mixed suspension of ethyl ester (7.18 g, 27.6 mmol) and \textit{N}-methoxymethanamine hydrochloride (5.40 g, 55.1 mmol) in THF (55 mL, 0.5 M) was added isopropyl magnesium chloride (55.2 mL, 2 M in diethyl ether) over 1 hour at −20 °C by the aid of slow addition pump, resulting a yellow solution with white solid floating at the bottom. The temperature was allowed to rise to −5 °C slowly over 2 hours, and quenched with saturated ammonium chloride aqueous solution at −5 °C, forming voluminous amount of white salt. After stirring at rt for 30 minutes, it was extracted with
diethyl ether (3 x 100 mL), washed with brine (200 mL), dried with Na₂SO₄, and concentrated under reduced pressure. After purification by flash chromatography (50% ethyl acetate in hexane), the Weinreb’s amide was obtained as a colorless viscous oil (6.75 g, 80%): IR (neat): 2962, 2938, 1650, 1560, 1454, 1368, 1291, 1201, 1103, 996, 911 cm⁻¹, ¹H NMR (CDCl₃, 300 MHz) δ 6.86 (s, 1 H), 6.77 (dd, 1 H, J = 12, 18 Hz), 6.70 (s, 1 H), 6.67 (s, 1 H), 5.65 (dd, 1 H, J = 3.5, 18 Hz), 5.45 (dd, 1 H, J = 3.5, 12 Hz), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.29 (s, 3 H), 2.35 (s, 3 H), 1.97 (d, 3 H, J = 2.5 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 172.5, 157.6, 137.5, 135.6, 132.2, 132.16, 130.6, 123.2, 122.5, 119.8, 110.8, 61.2, 55.5, 33.6, 21.6, 15.5; HRMS calcd for C₁₆H₂₁NO₃Na [M+Na]⁺ 298.1414; Found: 298.1413.

(2E)-3-(2-ethenyl-3-methoxy-5-methylphenyl)-2-methylprop-2-en-1-ol:

To a solution of the ester (540 mg, 2.07 mmol) in DCM (6 mL, 0.3 M), was added DIBAL (6.22 mL, 1 M in toluene, 6.22 mmol) slowly at 0 °C. After stirring for 1 hour at 0 °C, it was quenched with MgSO₄·7H₂O till no bubble was released. Then it was filtered through Celite, rinsed with 50 mL ethyl acetate, and concentrated under reduced pressure. After purification by flash chromatography (25% ethyl acetate in hexane), the alcohol was obtained (448 mg, 99%). IR (neat): 3354, 3015, 2913, 2852, 1605, 1564, 1454, 1303, 1156, 1095, 1005 cm⁻¹, ¹H NMR (CDCl₃, 500 MHz) δ 6.75 (dd, 1 H, J = 12, 18 Hz), 6.63
(s, 2 H), 6.52 (s, 1 H), 5.68 (dd, 1 H, J = 2.5, 18 Hz), 5.39 (dd, 1 H, J = 2, 11.5 Hz), 4.18 (d, 2 H, J = 5.5 Hz), 3.83 (s, 3 H), 2.33 (s, 3 H), 1.73 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 157.6, 137.4, 137.3, 137.2, 131.0, 125.2, 123.0, 122.6, 118.9, 110.2, 68.5, 55.4, 21.6, 15.1; HRMS calcd for C$_{14}$H$_{18}$O$_2$Na [M+Na]$^+$ 241.1199; Found: 241.1198.

Table 6

<table>
<thead>
<tr>
<th>Catalyst/additive</th>
<th>Solvent/concentration</th>
<th>Temperature/time</th>
<th>yield (A to B ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>MeOH</td>
<td>rt</td>
<td>SM</td>
</tr>
<tr>
<td>Pd[(CN)$_2$Cl$_2$</td>
<td>Acetone/H$_2$O</td>
<td>rt</td>
<td>decomposed</td>
</tr>
<tr>
<td>HCl</td>
<td>Acetone/H$_2$O</td>
<td>rt</td>
<td>decomposed</td>
</tr>
<tr>
<td>Cu(OTf)$_2$ benzene, LiClO$_4$</td>
<td>DCM</td>
<td>rt, 2 h;</td>
<td>decomposed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reflux, 4.5 h</td>
<td>(quick test) 5:7</td>
</tr>
<tr>
<td>2 mol% Cu(OTf)$_2$ benzene</td>
<td>DCE(0.05 M)</td>
<td>rt, 45 min;</td>
<td>SM gone;</td>
</tr>
<tr>
<td>2 equiv. LiClO$_4$</td>
<td></td>
<td>42°C, 45 min;</td>
<td>3 new compounds;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55°C, 7 hours</td>
<td>53% (1:3.8)</td>
</tr>
<tr>
<td>7 mol% Cu(OTf)$_2$ benzene, LiClO$_4$</td>
<td>DCE(0.1 M)</td>
<td>rt, 1 day;</td>
<td>trace amount of P;</td>
</tr>
<tr>
<td>1 equiv. LiClO$_4$</td>
<td></td>
<td>35°C, 14 h</td>
<td>35% (1:5)</td>
</tr>
<tr>
<td>12 mol% Sc(OTf)$_3$, 2 equiv. LiClO$_4$</td>
<td>DCE(0.025 M)</td>
<td>rt, 15 min;</td>
<td>SM gone after 15 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50°C, 0.5 h</td>
<td>7%</td>
</tr>
<tr>
<td>10 mol% Sc(OTf)$_3$</td>
<td>DCE(0.1 M)</td>
<td>rt, 1 h</td>
<td>no SM</td>
</tr>
<tr>
<td>10 mol% Sc(OTf)$_3$, 1 equiv. LiClO$_4$</td>
<td>DCE(0.1 M)</td>
<td>rt, 24h;</td>
<td>24% (1:1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spot to spot to spot</td>
<td>SM gone after 15 min</td>
</tr>
<tr>
<td>Reaction Conditions</td>
<td>Solvent</td>
<td>Temperature</td>
<td>Time</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>10 mol% Cu(OTf)$_2$, 1 equiv. LiClO$_4$, 20 mol% 2,6-lutidine</td>
<td>DCM (0.1 M)</td>
<td>reflux</td>
<td>unknown</td>
</tr>
<tr>
<td>10 mol% Cu(OTf)$_2$, 2 equiv. LiClO$_4$</td>
<td>DCM (0.05 M)</td>
<td>rt, 1.5 days</td>
<td>10 %</td>
</tr>
<tr>
<td>2 mol% Cu(OTf)$_2$, benzene, 2 equiv. LiClO$_4$</td>
<td>DCE (0.05 M)</td>
<td>rt to 55°C, 19 hours; rt, 5 days</td>
<td>No rxn; 10 %</td>
</tr>
<tr>
<td>10 mol% Cu(OTf)$_2$, DCE (0.05 M)</td>
<td>40 °C, 20 hours</td>
<td>25 %</td>
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</tr>
<tr>
<td>10 mol% Cu(OTf)$_2$, DCE (0.05 M)</td>
<td>40 °C, 6 hours</td>
<td>28 %</td>
<td></td>
</tr>
<tr>
<td>10 mol% Pd(ACN)$_2$Cl$_2$, 1 equiv. TEA</td>
<td>DCE</td>
<td>70 °C, 2 days</td>
<td>No rxn</td>
</tr>
<tr>
<td>10 mol% Ag$_5$BF$_6$, DCM</td>
<td>rt, 2 days</td>
<td>No rxn</td>
<td></td>
</tr>
<tr>
<td>10 mol% Dichloro(pentamethylcyclopentadienyl)iridium(III) dimer in DCM</td>
<td>Reflux, 7 hours</td>
<td>No rxn</td>
<td></td>
</tr>
<tr>
<td>1 equiv. Ti(OiPr)$_4$, DCM (0.2 M)</td>
<td>-78 °C to 45 °C</td>
<td>No rxn</td>
<td></td>
</tr>
<tr>
<td>4 equiv. BF$_3$·Et$_2$O, DCM (0.2 M)</td>
<td>-70 °C, 4 days</td>
<td>16 % (1:0.3)</td>
<td></td>
</tr>
<tr>
<td>4 equiv. BF$_3$·Et$_2$O, DCM (0.2 M)</td>
<td>-50 °C, 11 hours</td>
<td>22 %</td>
<td></td>
</tr>
<tr>
<td>10 mol% Hg(CO$_2$CF$_2$)$_2$, DCM (0.2 M)</td>
<td>-20 °C, 12 hours</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Cu(ClO$_4$)$_2$·6H$_2$O, DCM</td>
<td>Reflux, 30 h</td>
<td>No rxn</td>
<td></td>
</tr>
<tr>
<td>Cu(ClO$_4$)$_2$·6H$_2$O, DCM</td>
<td>Reflux, 30 h</td>
<td>No rxn</td>
<td></td>
</tr>
<tr>
<td>Added 2 mol% Cu(OTf)$_2$, benzene and 2 equiv. LiClO$_4$</td>
<td>DCE (0.05 M)</td>
<td>40 °C, 3 h</td>
<td>No rxn</td>
</tr>
<tr>
<td></td>
<td>48 °C, 23 h</td>
<td>22 %</td>
<td></td>
</tr>
</tbody>
</table>

**162:** To a solution of 156 (3.6 g, 8.24 mmol) in DCM (55 mL, 0.15 M) at -35 °C was added trifluoroborane etherate (3.5 g, 24.7 mmol) dropwise. The solution turned red.

After stirring at -35 °C for 5 min, it was raised to rt and stirred for 1 hour. Then, it was
cooled to 0 °C and quenched with 50 mL sat. NaHCO₃. The mixture was stirred for 30 min at rt. Then, it was washed with 2 x 50 mL brine, dried with MgSO₄, and concentrated under reduced pressure to get reddish oil. The crude H-NMR showed the ratio of 143/144/162 to be 1: 0.28: 0.25. After purification by FCC with 10% EA/Hex, 23% of 143 and 144 were isolated together with 4% of less polar 162. IR (neat): 2958, 2933, 1720, 1605, 1278, 1086 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.87 (d, 1 H, J = 9.5 Hz), 6.75 (s, 1 H), 6.60 (s, 1 H), 5.44 (d, 1 H, J = 9.5 Hz), 4.02 (dt, 1 H, J = 2.5, 13.5 Hz), 3.82 (s, 3 H), 3.31 (d, 1 H, J = 12 Hz), 3.24 (dt, 1 H, J = 2.5 14 Hz), 2.56 (dt, 1 H, J = 14, 3 Hz), 2.48 (dt, 1 H, J = 13.5, 3.5 Hz), 2.34 (s, 3 H), 2.22-2.16 (m, 1 H), 2.15 (s, 1 H), 2.15-2.11 (m, 1 H), 1.88 (m, 1 H), 1.24 (d, 3 H, J = 7 Hz), 1.17 (s, 3 H), 0.81 (d, 3 H, J = 7.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 210.5, 155.3, 138.0, 134.7, 127.5, 123.6, 120.4, 117.6, 110.4, 55.4, 54.3, 52.6, 45.6, 27.1, 26.7, 25.5, 25.1, 23.2, 21.9, 21.8, 21.3; HRMS calcld for C₂₂H₂₈O₂S₂Na [M+Na]⁺ 411.1427; Found: 411.1419.

163: To a solution of 162 (30 mg, 0.077 mmol) in Et₂O was added LAH (10 mg, 0.26 mmol) at 0 °C. After 10 min, it was filtered through a silica plug, rinsed with Et₂O, concentrated under reduced pressure to get the crude white solid product. It was purified by FCC with 25% EA/Hex to get analytically pure 163 (24 mg, 80%) as a white solid. Melting point is 143-146 °C. IR (neat): 3461, 2917, 1462, 1274 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 6.77 (d, 1 H, J = 10 Hz), 6.67 (s, 1 H), 6.56 (s, 1 H), 5.85 (dd, 1 H, J = 10, 1 Hz), 4.46 (d, 1 H, J = 12 Hz), 3.80 (s, 3 H), 3.44 (dt, 1 H, J = 3.5, 13 Hz), 3.08 (ddd, 1 H, 133
J = 2.5, 11.5, 14 Hz), 2.91 (d, 1 H, J = 12 Hz), 2.84 (dd, 1 H, J = 1.5, 12 Hz), 2.70 (dt, 1 H, J = 14, 4 Hz), 2.56 (dt, 1 H, J = 13.5, 3.5 Hz), 2.32 (s, 1 H), 2.19-2.11 (m, 1 H), 2.10-2.04 (m, 2 H), 1.91-1.82 (m, 1 H), 1.25 (d, 3 H, J = 7 Hz), 0.65 (d, 3 H, J = 7 Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ 155.1, 137.3, 136.2, 127.9, 123.5, 119.2, 118.5, 110.2, 94.4, 62.6, 58.7, 55.4, 47.2, 46.9, 29.3, 27.7, 25.6, 24.2, 23.3, 23.0, 21.8, 20.4; HRMS calcd for \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ 155.1, 137.3, 136.2, 127.9, 123.5, 119.2, 118.5, 110.2, 94.4, 62.6, 58.7, 55.4, 47.2, 46.9, 29.3, 27.7, 25.6, 24.2, 23.3, 23.0, 21.8, 20.4; HRMS calcd for C\textsubscript{22}H\textsubscript{30}O\textsubscript{2}S\textsubscript{2}Na [M+Na]\textsuperscript{+} 413.1579; Found: 413.1577.

\textbf{164}: To a solution of \textbf{163} (24 mg, 0.062 mmol) in DCM (1 mL, 0.06 M) was added TEA (12.4 mg, 0.123 mmol) and mesyl chloride (10 mg, 0.092 mmol) at 0 °C. Then it was stirred at rt for 1 hour and quenched with 2 mL sat. NH\textsubscript{4}Cl, extracted with 2x2 Ml DCM, washed with brine, dried with Na\textsubscript{2}SO\textsubscript{4}, concentrated to get a white solid crude product. It was purified by FCC to get pure \textbf{164} (17 mg, 74%) with a melting point of 168-170 °C; IR (neat): 2950, 1601, 1471, 1274, 1086 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) δ 6.64 (d, 1 H, J = 10 Hz), 6.62 (s, 1 H), 6.57 (s, 1 H), 5.52 (d, 1 H, J = 9.5 Hz), 4.19 (s, 1 H), 3.79 (s, 3 H), 3.73 (s, 1 H), 3.30 (ddd, 1 H, J = 4.5, 11.5, 15.5 Hz), 3.09 (ddd, 1 H, J = 4.5, 11, 15 Hz), 2.76 (ddd, 1 H, J = 3.5, 5, 15 Hz), 2.64 (dt, 1 H, J = 15, 4 Hz), 2.49 (heptet, 1 H, J = 7.5 Hz), 2.34 (s, 3 H), 2.19-2.04 (m, 2 H), 1.53 (s, 3 H), 1.12 (s, 3 H), 0.91 (d, 3 H, J = 7 Hz), 0.81 (d, 3 H, J = 7 Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ 154.7, 142.0, 137.2, 136.6, 133.7, 129.9, 124.4, 119.4, 118.4, 110.5, 61.5, 55.6, 55.5, 48.5, 34.5, 30.7, 28.9, 28.6, 21.8, 20.3, 18.9, 18.6; HRMS calcd for C\textsubscript{22}H\textsubscript{28}O\textsubscript{2}S\textsubscript{2}Na [M+Na]\textsuperscript{+} 395.1474; Found: 395.1472.
APPENDIX

Selected $^1$H and $^{13}$C NMR Spectra
Me
Me
P(OMe)₂
O
CO
OiPr
CAI-bromcaldehyde-colorless crystal-1H NMR

Current Data Parameters
MAKES  CAI-2II-data of brom
SHINO  1
PROCED  1

P2 - Acquisition Parameters
Data  2015420
Time  21.15
JUNGEN  DB250
PROBE  5 mm CFFC: 14-
PU-WDC  XBI
TD  45535
SO2/2577  CDOL3
MS  8
DS  2
SNR  1073.578 Hz
DFOIS  (-137502 Hz
AQ  3.1778923 sec
BG  :B
DM  41.432 usec
DS  6.20 usec
CZ  100.0 X
D1  1.00000000 sec
REFRES  0.00000000 sec
B2-Var  0.00000000 sec

======== CHANNEL f: ========
BFC1: 1H
P1: 3.00 usec
PP: 4.30 dB
SP51: 500.12315099 Hz

P2 - Processing parameters
SI  32768
SP  500.1231512 Hz
WDM  2M
SGB  1.0
LB  3.00 Hz
SC  0.0
13C NMR

Current Data Parameters
NAME   C41-III-150-1
SF     2
PROCNO 1

F1 - Acquisition Parameters
Date   100008022
Time   17.41
INSTRUM DRR500C
PROCED 5 rel CPMG 28-
FPL/PROG gnn3N
TO     71424
SOLVENT CDCl3
DS     162
DG     4
SMR   35212.270 Hz
FIDRES 0.452945 Hz
AQ    1.0163760 sec
LG    4096
DW    14.200 usec
DE    35.600 usec
TD    100.0 K
DI    2.00000000 sec
g1l   0.30000000 sec
DELTA   1.39999988 sec
NCHRM  0.00000000 sec
NCHRM  0.01500000 sec

====== CHANNEL F3 ======
SNR: 13C
R1    12.600 usec
40.60 dB
SFOC   257776234 MHz

====== CHANNEL F2 ======
CP/PSI2   val=16
NRC1  1K
PCPS2  50.00 usec
PL21  5.00 dB
PL32  22.00 dB
PL12  27.50 dB
SFO2   5031500000 MHz

F2 - Processing parameters
SC    52316
SF     257777825 Hz
WDM   0
SSB   0
LB    1.00 Hz
CB    0
PC    1.00
CAI-IV-22-4-Colorless oil-H NMR

Current Data Parameters
NAME CAI-IV-22-4
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030921
Time 23:45
INSTRUM EZX500
PRMSED 5 mm CPDCI 1H-
PULPROG zg30
TL 55536
SCLV3NT CDCl3
NS 8
DS 2
SWH 10330.578 Hz
FIDR8S 0.157632 Hz
AC 3.171923 ssc
PG 14.3
DW 48.400 usec
DE 6.00 usec
TE 500.0 K
D1 0.00000000 ssc
MRREST 0.00000000 ssc
MCWRX 0.04500000 ssc

======== CHANNEL f1 ========
NLC1 1H
f1 8.00 usec
PL1 4.30 dB
SF01 500.1315509 MHz

F2 - Processing parameters
SI 32768
SF 500.1310131 MHz
NEW EM
SSB 0
LB 0.30 Hz
GB 0
FC 1.00
CAI-IV-35-white solid-1H NMR

Current Data Parameters
NAME: CAI-IV-35
EXPTD: 1
EXPCNO: 1

F1 - Acquisition Parameters
Date: 2010-08-03
Time: 10:41
INSTRUMENT: FX500
PROCED: 5 mm [D2O] 6H-
PULPROG: 291
TD: 65535
SOLVENT: D2O
IS: 3
500.133 MHz.5 Hz
F1F15 1.887642 Hz
AQ: 8.1751923 scc
R0: 5.46 Hz
DM: 48.40 us
DE: 6.00 us
TE: 100.2 K
L1: 1.3050(0000) sec
M0RES: 0.3350(0000) sec
M0RES: 0.3350(0000) sec

-------- CHANGE F1 --------
M15: 1.7
P1: 8.02 us
P1: 4.35 us
S7: 500.133500 MHz

F2 - Processing parameters
ST: 90°/90°
SF: 500.133500 MHz
CW: 15°
SB: 0
LS: 0 Hz
GA: 0
PC: 0.60
CAI-IV-38-2-White solid-1H NMR.

Current Data Parameters
DEGS 60
DPCD 1
PRINC 1

FS - Acquisition Parameters
Date 2/9/03
Time 12:32
INSTP FM 25/000
PRIMPX 5 CM CS 641 IH-
PULLPGL 2000
TD 605.0K
SOLVENT CDCl3
NS 8
DS 2
SQX 16K 8.97 K
FIDRES 1.578 1.5 K
PQ 1.719 1 K
Fq 11.1
DJ 48.4 1000
DET 6.0 1000
TR 300.0 K
DR 1.00 300.0 1000
DRES 0.00 300.0 1000
DPMX 0.00 300.0 1000

W2 - Processing Parameters
SI 12761
SP 501.133 133 MHz
SSW SN
LBS 0.3 Hz
GS 1.0 Hz
CAI-VI-150-1H NMR

Current Data Parameters
NAME CAI-VI-150-1H
ZEXP 1
PICKT 1

P2 - Acquisition Parameters
Date 20041208
Time 21:40
INSTRUM DRX300
POWER 5 W

PULPROG zg10pad
TD 32768
SOLVENT CD2Cl
NS 16
DS 2

DN 6272.839 Hz
NQ 0.3838 Hz
AQ 2.6542580 sec
N2 256

dw 81.300 usec
d1 5.00 usec
tk 350.0 K
D1 1.00000000 sec
D3L 0.00000000 sec

********** CHANNEL f1 ********

JJ/1 7.05 usec
P1 0.00 dB
STPC 300.133534 MHz

P2 - PROCESSING parameters
GR 32768
SP 300.133052 MHz
WEN BK
GB 0
LB 3.30 Hz
PB 1.30

ppm

11 10 9 8 7 6 5 4 3 2 1 0

1.00 1.02 1.01 1.10 1.06 1.05 3.09 3.08 3.11 3.03 3.02 3.01
CAI-V-Recoved aldehyde-white wax-1H NMR
13C NMR

[Image of a 13C NMR spectrum with chemical shifts and peaks]

Current Data Parameters
NAME  CA-IT-13C-C
DEXPO  2
PROCON -

F2 - Acquisition Parameters
Data_  1D FID
Time  1.51
RARE  0.05
THETA  60
PULPROG  1H,MZ,SQ
PULSISS  SQP
TD  71244
SOLVENT  CDCl3
NS  154
DG  -
SN  33211.57 Hz
T1RES  2.425289 Hz
AQ  1.013708 sec
BG  0.999
EW  10.200 usec
ER  35.00 usec
ET  300 0 x
ET  2.000000 sec
OL  0.33333333 sec
DELTA  1.89555555 sec
DEPCST  0.000000 sec
DCONST  0.0100000 sec

******** CHANNEL 11 ********
YUT2  13C
pi  12.00 usec
PG1  0.30 dB
SP02  125.7516234 MHz

********* CHANNEL 15 *********
C7EPDG2  we756
YUT2  100
PE202  0.00000000 usec
PG2  22.00 dB
PG12  22.00 dB
PG13  22.00 dB
PG20  520.12500000 MHz

** - Processing parameters
SI  85.567
SF  125.7579336 MHz
TM  300
INT  2
RB  1200 Hz
G1  3
G2  1.15
CAI-VII-148-1 - Colorless crystal - 1H NMR

Current Data Parameters
- MODE: CAI-VII-148-1-a
- ZPWDD: 1
- PIOPEN: 1

**$E2$ - Acquisition Parameters**
- Date: 20130525
- Time: 14.44
- INSTRUM: D2550
- ZPRAW: 5 mm CP250 1H-
- PULPROG: p930
- TD: 255376
- SOLTENT: 2H2D2
- NS: 8
- ET: 2
- SW: 10332.578 Hz
- F1RES: 0.157632 Hz
- AQ: 3.170563 s/mc
- SG: 1C.1
- EW: 48.400 us/mc
- E: 6.000 us/mc
- T: 300.0 K
- T1: 1.000D000 usec
- W1: 0.0000 usec
- MCX: 0.0000 usec
- MCXK: 0.0000 usec

$****** CHANNEL E1 $******
- NUCL: 1H
- FL: 0.000 us/mc
- EFFL: 4.300 dB
- SFFL: 50.133509 MHz

$E2$ - Processing parameters
- $E2$: 2.768
- SP: 50.133509 MHz
- MWD: EM
- SKX: 0
- LS: 0.00 Hz
- SC: 1.00

Frequency range: 0 - 11 ppm
CAI-VII-27-White solid-1H NMR

Current Data Parameters

Date: 20100311
Time: 11.22

Acquisition Parameters

T1: 8.10 ussec
T2: 4.70 ussec
SFO1: 500.13MHz

Processing parameters

ST: 32768
SR: 500.13MHz
WDM: 0
SBB: 0
LB: 0.20 Hz
PC: 1.40
CAI-VIII-30-1-white needles
VITA

Zhengxin Cai was born at Huabei Oilfield, Hejian city, Hebei province in China in the winter of 1982. He went to Tianjin University in 2001, and got his B.S. degree from School of Pharmaceutical Science and Technology, Tianjin University in 2005.

He went to University of Missouri at Columbia in 2005. After a trip to New York City, he joined the Harmata group to study the art of total synthesis in 2006. In 2010, he decided to expand his passion in total synthesis to the field of molecular imaging. In 2011, after he got his Ph.D. degree, he moved to Pittsburgh to join Carolyn Anderson’s group as a postdoctoral associate.