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Nickel Catalyzed Homoallylation Reactions and Synthesis of Potent Inhibitors of YopH

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And

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Abstract

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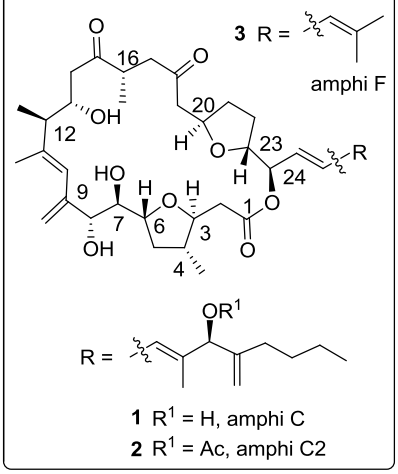
Prof. Christopher D. Spilling, Advisor

This work has been divided into two different projects; a) the development of diastereoselective homoallylation reaction and its application in the synthesis of cytotoxic natural products called amphidinolides C, C2 and F and b) a library synthesis of potent and specific inhibitors of the YopH of *Yersinia pestis*.

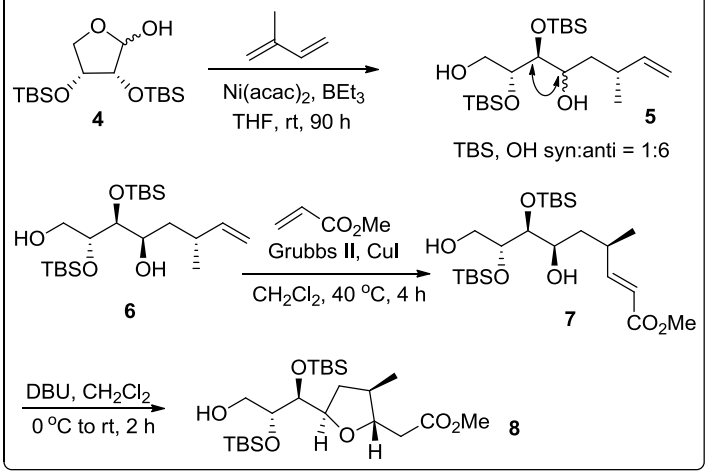
Homoallylation and its application in total synthesis: *Bis*-homoallylic alcohols are important synthetic intermediates in a number of chemical transformations. The nickel-catalyzed reductive coupling of carbonyl compounds with dienes (homoallylation) is one of the important methods for the synthesis of *bis*-homoallylic alcohols. The homoallylation reaction of diene with novel substrates, hemiacetals and epoxyaldehydes, gave good diastereoselectivity. Cross metathesis of *bis*-homoallylic alcohols with acrylates using Grubbs catalyst produced ε-hydroxy-α,β-unsaturated esters. The ε-hydroxy-α,β-unsaturated esters undergo base catalyzed cyclization to yield the 2,3,5-trisubstituted tetrahydrofuran moiety. This protocol was efficiently applied in the

synthesis of C1-C9 fragment of the anti-tumor compounds known as amphidinolides C, C2 and F.

Figure 1. Amphidinolides C, C2 and F

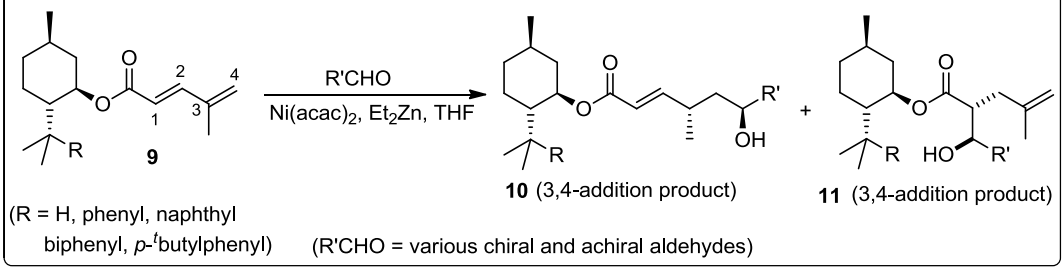


Scheme 1. Synthesis of C1-C9 Fragment of Amphidinolide C, C2, F



During the course of this synthesis, the homoallylation reaction was investigated and an efficient method of controlling the π-facial selectivity using chiral dienes was found. The scope of this method was explored using various chiral dienes along with a variety of aldehydes. A matched combination of chiral diene and aldehyde gave more than 5:1 diastereoselectivity of *bis*-homoallylic alcohols **10** and more than 99:1 regioselectivity.

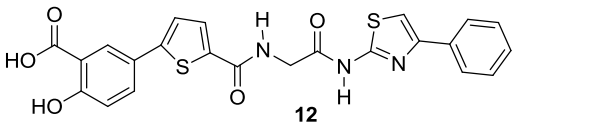
Scheme 2. Homoallylation Reaction of Chiral Dienes with Various Aldehydes



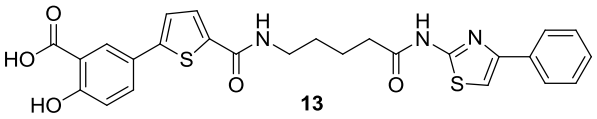
Synthesis of YopH protein inhibitors: YopH is a virulent protein excreted by pathogenic bacteria *Yersinia pestis* (the causative agent of the Black Death). A series of

bidentate ligands were designed to investigate the structure activity relationship of these ligands towards the inhibition of YopH. Several of these ligands were synthesized and tested against different protein tyrosine phosphotases (PTPs). All inhibitors prepared showed very good activity against YopH and some other human phosphatases (low to mid micro-molar range). In addition, a rapid synthesis of salicylic acid containing heterocyclic building blocks utilizing palladium catalyzed cross-coupling reactions has been achieved. This methodology can be modified to target different phosphatase enzymes enabling their application towards the development of new drugs.

Figure 2. Some YopH Protein Inhibitors



12



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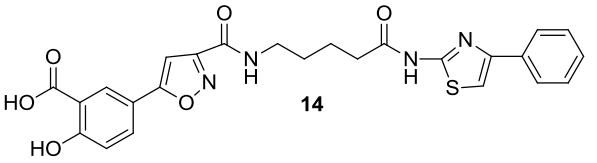

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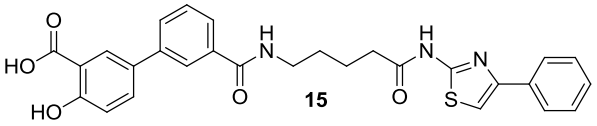

15

Acknowledgement

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Table of Contents

List of Tables

List of Figures

List of Schemes

CHAPTER I

Synthesis of C1-C9 Fragment of Amphidinolides C, C2 and F

1.1. General Objective

Substituted tetrahydrofurans are frequently occurring substructures present in several biologically active molecules and natural products. 2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofurans are embedded in a broad array of natural products such as annonaceous acetogenins[1] (mucocine **1.1**), antibiotic polyethers,[2] oxasqualenoids,[3] and macrodiolides[4]. Some specific examples of compounds are amphidinolides,[5] gymnodimine **1.2**,[6] tetronasin **1.3**,[7] monensin **1.4**,[8] and boromycin,[9] amongst others (Figure 1.1). Because of the varied activities of these molecules as antitumor, antimicrobial, antibacterial agents, considerable efforts have been made by the synthetic community towards the construction of substituted tetrahydrofurans. The general objective of this chapter of the thesis is to report the methods developed towards the stereoselective synthesis of 2,3,5-trisubstituted tetrahydrofurans present in various natural products.

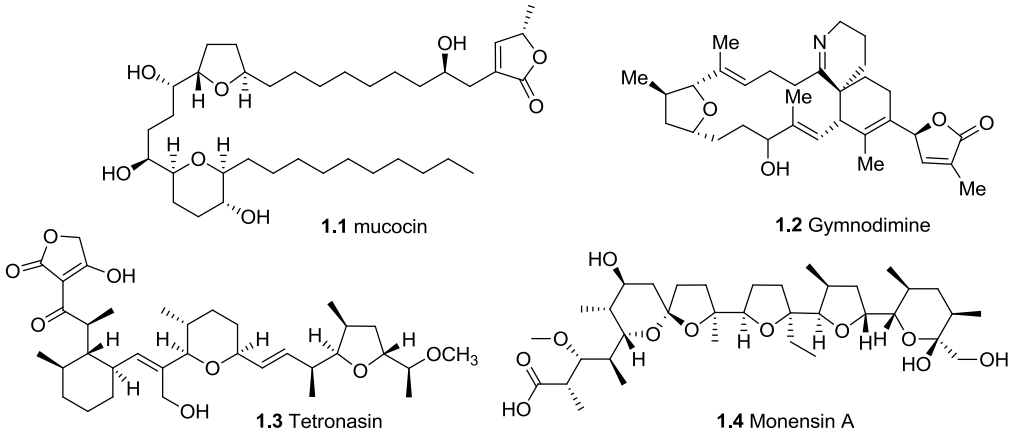
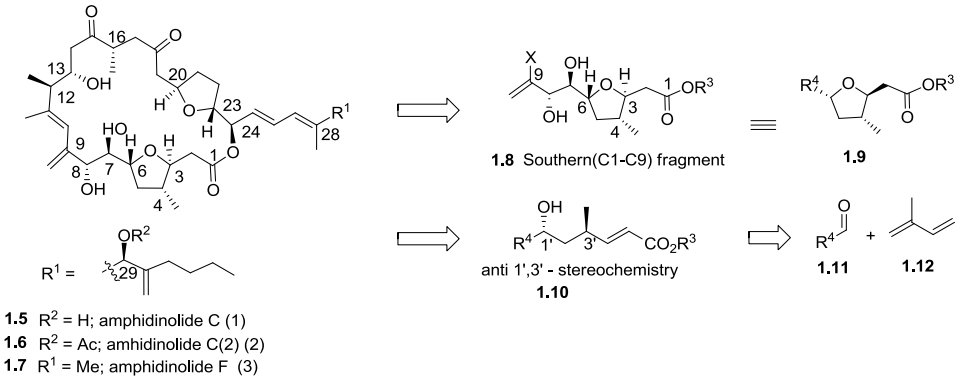


Figure 1.1. Some Substituted Tetrahydrofuran Containing Natural Products

1.2. Introduction

Amphidinolides are a series of cytotoxic macrolides possessing complex and unique structural features. These natural products are isolated from the marine dinoflagellate *Amphidinium* sp. which is symbiotic with the Okinawan acoel flatworms *Amphiscolops* sp.[5] Amphidinolides C, C2 and F possess cytotoxicity against human skin cancer cell lines and murine lymphoma cells (Scheme 1.1). Embedded within these amphidinolides are two tetrahydrofurans: *trans*-2,5-disubstituted and 2,3,5-trisubstituted tetrahydrofurans. In efforts towards the total synthesis of these amphidinolides, we needed to develop a protocol for the efficient synthesis of the 2,3,5-trisubstituted tetrahydrofuran moiety.

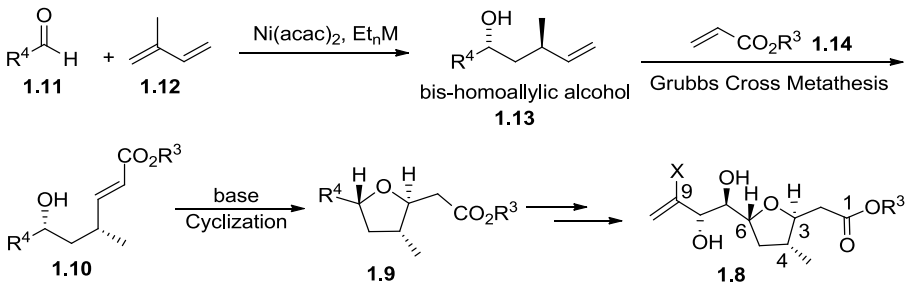


Scheme 1.1. Amphidinolides C, C2, and F and Retrosynthesis of Southern Fragment

We envisioned that if the appropriate *bis*-homoallylic alcohols could be synthesized (by the reaction of a properly functionalized aldehyde with a suitable diene), these alcohols could be cyclized to trisubstituted tetrahydrofurans with correct stereochemistry.

In this chapter, we report the nickel catalyzed reductive coupling of different aldehydes, hemiacetals and epoxyaldehydes with isoprene to give *bis*-homoallylic alcohols (Scheme 1.2). Cross metathesis with acrylates using Grubbs catalyst produced ε-hydroxy-*α*,*β*-

unsaturated esters. These esters undergo base catalyzed cyclization to yield the 2,3,5-trisubstituted tetrahydrofuran moiety present in amphidinolides C, C2 and F.



Scheme 1.2. General Representation of Homoallylation, Cross Metathesis and Cyclization Reactions

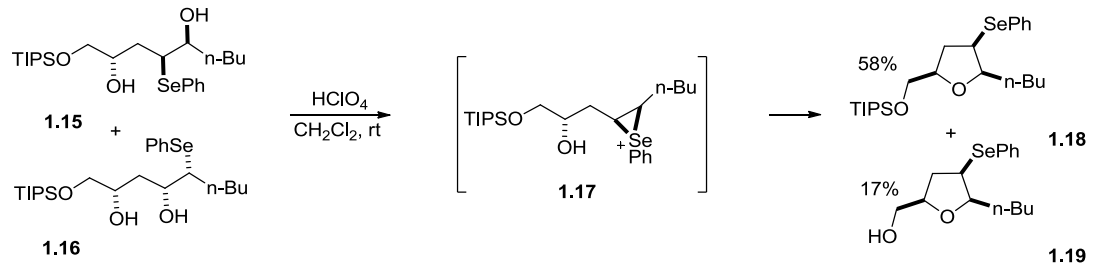
1.3. General methods for the synthesis of 2,3,5-trisubstituted tetrahydrofurans

Various methods have been developed for the stereoselective synthesis of trisubstituted tetrahydrofurans.[10] Oxidation of dienes and hydroxy alkenes, intramolecular addition of alcohols and protected diols to epoxides and alkenes, olefin metathesis, [3+2] cycloaddition and other annulation reactions are some of the most frequently used methods. Here, we describe some of these methods developed for the synthesis of trisubstituted tetrahydrofurans and, where possible, give their application in natural product synthesis.

1.3.1. Intramolecular nucleophilic addition/substitution reactions

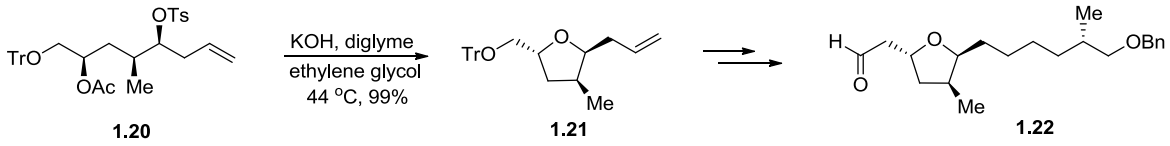
1.3.1.1. Intramolecular nucleophilic addition/substitution of hydroxyl nucleophiles

Nucleophilic substitution chemistry has been utilized in the formation of tetrahydrofurans and 2,3,5-trisubstituted tetrahydrofuran moieties of natural products. Thomas and Gruttadauria[11] developed a $HClO_4$-catalyzed synthesis of 3-phenylselenyl-2,5-*cis*-disubstituted tetrahydrofurans **1.18** from hydroxyselenide precursors (Scheme 1.3). This reaction is believed to proceed via formation of an intermediate selenonium ion followed by cyclization (5-*endo/exo* mode). As shown below, when a mixture of regioisomeric selenides **1.15** and **1.16** was treated with $HClO_4$, both regioisomers were converted to the same diastereomer **1.18**, through a common intermediate **1.17**. Loss of the TIPS-protecting group leading to tetrahydrofuran-2-yl-alcohol **1.19** was also observed.



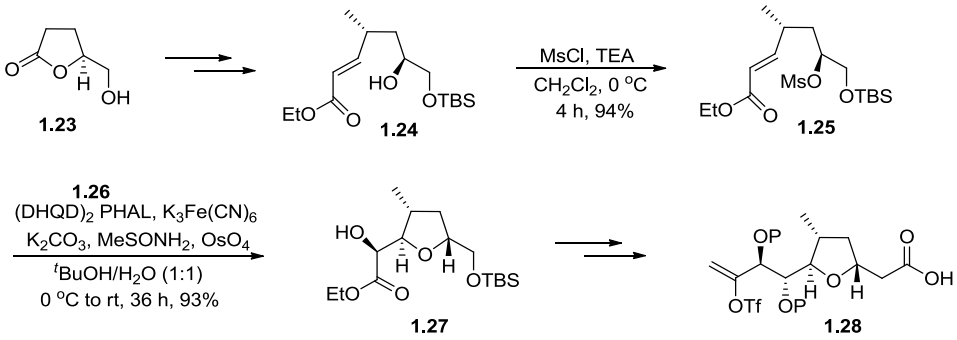
Scheme 1.3. $HClO_4$ Catalyzed Tetrahydrofuran Synthesis from Hydroxyselenide Precursor

In a report of the total synthesis of amphidinolide T3, Zhao and coworkers described the S_N2 type cyclization reaction to obtain the 2,3,5-trisubstituted tetrahydrofuran moiety (Scheme 1.4).[12] Treatment of **1.20** with potassium hydroxide in a mixed solvent of diglyme and ethylene glycol at 40 ^oC removed the acetate group, which on subsequent cyclization gave desired 3-methy-*trans*-2,5-disubstituted tetrahydrofuran **1.21** as a single isomer in excellent yield. The tetrahydrofuran **1.21** was then converted in a number of steps to one of the key building blocks **1.22** of amphidinolide T3.



Scheme 1.4. Base Mediated S_N2 Type Cyclization of 1.20

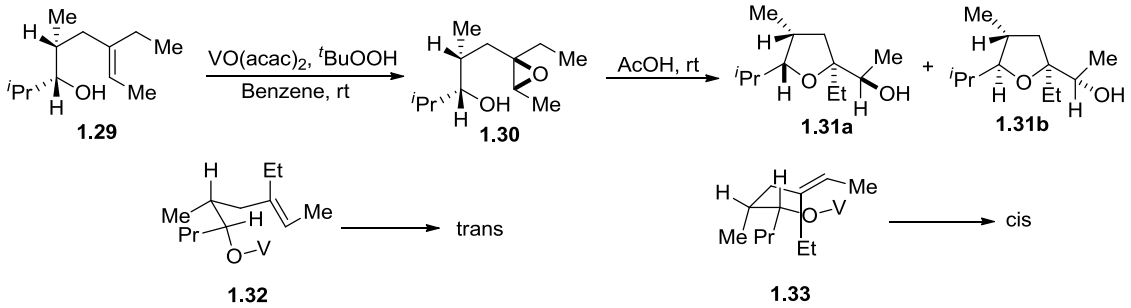
A similar nucleophilic substitution (S_N2) has been employed by Mohapatra in the stereoselective synthesis of the C1-C9 fragment of amphidinolide C.[13]As shown below, conversion of the hydroxyl group of **1.24** to a better leaving group (OMs) followed by Sharpless Asymmetric Dihydroxylation (SAD) produced a *syn*-diol, which underwent concomitant cyclization (displacement of the OMs group by OH) (Scheme 1.5). This produced the tetrahydrofuran moiety **1.27** in excellent yield as a single diastereomer with correct stereochemistry of C1-C9 fragment of amphidinolide C **1.28**.



Scheme 1.5. Intramolecular Cyclization of **1.25** to Produce Tetrahydrofuran of Amphidinolide C

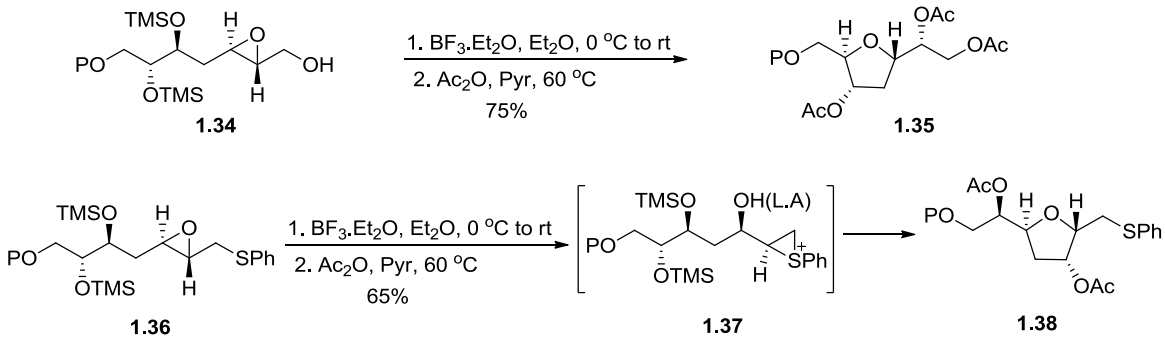
1.3.1.2. Intramolecular additions of alcohol to epoxide

In 1978, Kishi introduced a method for the synthesis of substituted tetrahydrofurans from epoxy-alcohols. He utilized this method in the total synthesis of polyether antibiotics such as the lasalocids and the monensins.[14] The epoxide mixture **1.30**, obtained by the reaction of alkene **1.29** with $VO(acac)_2$ and ^{t}BuOOH, was treated with acetic acid to produce tetrahydrofurans **1.31a** and **1.31b** with diastereoselectivity greater than 20:1 (**a**:**b**) (Scheme 1.6). It was found that the transition state (**1.33**) for the formation of the minor epoxide suffers from more steric congestion due to the interaction of the methyl and ethyl groups than the transition state (**1.32**) for the formation of the major epoxide. In other words, transition state **1.32** best fulfills the steric and geometrical constraints for the epoxidation and hence gives the *trans*-tetrahydrofuran **1.31a** as the major isomer.



Scheme 1.6. Intramolecular Addition of an Alcohol to an Epoxide

Borhan has investigated on structural factors that control regio- and stereoselectivity on Lewis-acid mediated cyclizations of protected epoxy diols.[15] He showed that the regioselectivity can be controlled by the appropriate choice of acid promoter and pedant groups adjacent to the epoxide. For example, substrate **1.34** having a C1-hydroxyl group is converted via 5-*exo*-cyclization to product **1.35** upon sequential treatment with $BF_3 \cdot Et_2O$ followed by Ac_2O (Scheme 1.7). However, when a substrate bearing a C1-thiophenyl substituent (**1.36**) is cyclized, the regioselectivity can be reversed with the formation of formal 5-*endo*-cyclization product (**1.38**). This selectivity change can be attributed to the formation of an intermediate episulphonium ion **1.37**, which then undergoes an electronically favorable 5-*endo*-cyclization to give **1.38**.[16]

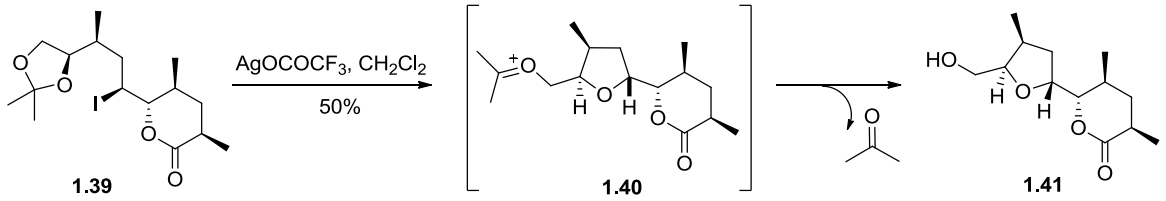


Scheme 1.7. Pedant Group Effect on the Cyclization of Epoxy-alcohols

1.3.1.3. Intramolecular addition of oxygen nucleophiles of acetonides to epoxide/Iodide

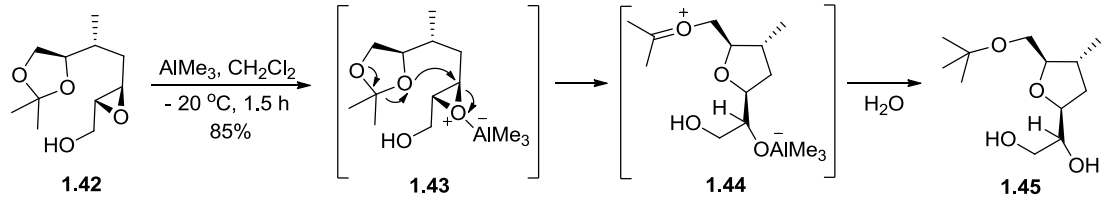
Various oxygen containing functional groups like acetonides, epoxides, etc. have been utilized as nucleophiles in tetrahydrofuran forming reactions. During the synthesis of monensin, Stille employed a silver triflate mediated intramolecular alkylation of an

acetonide oxygen atom with a tethered alkyl iodide (**1.39**) to construct the tetrahydrofuran (**1.41**) with loss of acetone (Scheme 1.8).[17]



Scheme 1.8. Silver Mediated Intramolecular Cyclization of Iodoacetal **1.39**

Parsons observed the Lewis acid mediated ring opening of the epoxide by the tethered acetonide to obtain tetrahydrofuran.[18] When the epoxyacetal **1.42** was treated with trimethylaluminium ($AlMe_3$) in CH_2Cl_2, 3-methyl-*cis*-2,5-disubstituted tetrahydrofuran **1.45** was formed as a single diastereomer (Scheme 1.9). Trimethylaluminium facilitates the ring opening of the epoxide by the tethered acetonide to generate oxonium ion **1.44** which upon methylation (via $AlMe_3$) yielded tetrahydrofuran **1.45**.



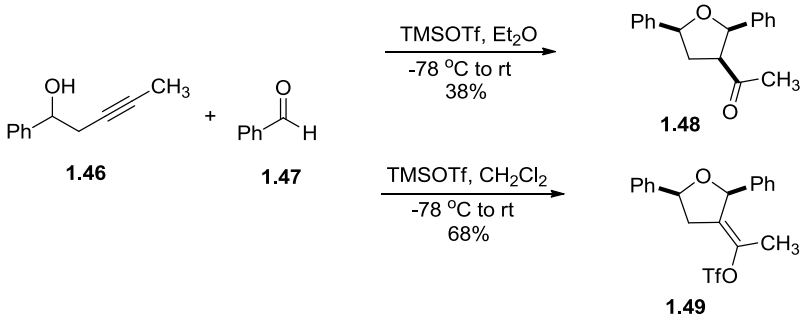
Scheme 1.9. Lewis Acid Mediated Intramolecular Cyclization of an Epoxyacetal

1.3.2. Intramolecular addition involving oxonium ions

1.3.2.1. Intramolecular addition of nucleophilic alkenes/alkynes to oxonium ions

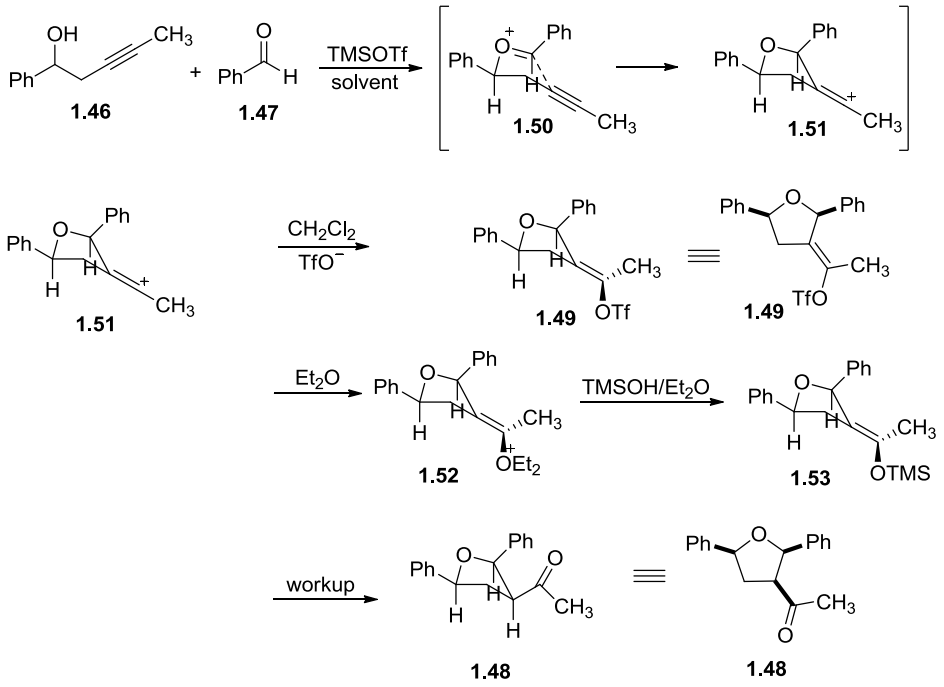
Generation of reactive oxonium ion intermediates, followed by the intramolecular capture of this ion by a tethered alkene (or alkyne) is another common approach for the construction of tetrahydrofurans. Cho and coworkers reported the synthesis of 2,3,5-

trisubstituted tetrahydrofurans from terminally substituted alkynyl alcohols and various aldehydes via Prins-type cyclizations.[19]As shown below, homopropargylic alcohol **1.46** underwent Prins-type cyclization with 1.1 equivalent of benzaldehyde in the presence of TMSOTf (3.0 equiv.) in Et_2O to give the all-*cis*-configured product **1.48** in a reasonable yield (Scheme 1.10). However, when CH_2Cl_2 was used as the solvent instead of Et_2O, the tetrahydrofuran analog with an exocyclic vinyl triflate moiety **1.49** was obtained with higher yield.



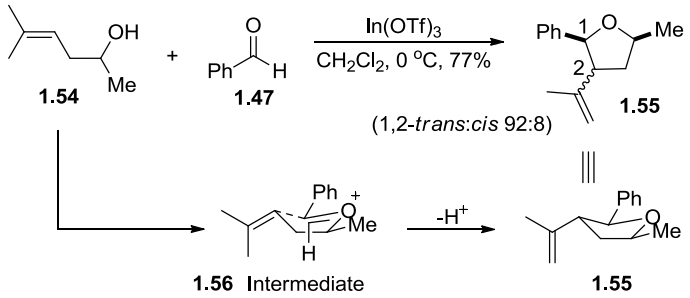
Scheme 1.10. Nucleophilic Alkyne Addition to Oxonium Ion

A plausible mechanism for these reactions has been proposed. The addition of the alkynyl alcohol **1.46** to an aldehyde **1.47** forms an oxocarbenium ion **1.50** (where both phenyl groups adopt pseudoequatorial position to avoid steric hindrance) which, after Prins-type cyclization, forms the transient vinyl cation **1.51** (Scheme 1.11). In CH_2Cl_2 solution, the exocyclic vinyl cation **1.51** is trapped by the triflate anion giving the exocyclic vinyl triflate **1.49**. On the other hand, in Et_2O solution, the exocyclic vinyl cation **1.51** would be stabilized by the ether solvent and trapped by TMSOH to give TMS-enol **1.53** which is hydrolyzed during workup to the corresponding product **1.48**.



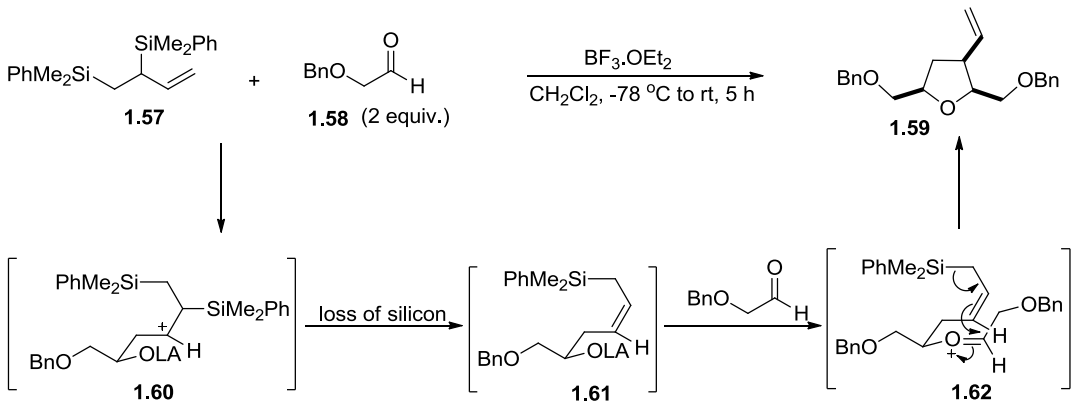
Scheme 1.11. Mechanism for the Nucleophilic Alkyne Addition to Oxonium Ion

Loh and coworkers described a $In(OTf)_3$-catalyzed oxonium-ene type cyclization to construct substituted tetrahydrofuran rings.[20] For example, when alcohol **1.54** was treated with benzaldehyde **1.47** in the presence of a catalytic amount of $In(OTf)_3$, tetrahydrofuran **1.55** was obtained in 77% yield (dr 92:8) (Scheme 1.12). This reaction proceeds through an intermediate oxonium ion **1.56**, in which the substituents occupy the pseudoequatorial orientation, resulting in the observed stereoselectivity.



Scheme 1.12. Nucleophilic Alkene Addition to an Oxonium Ion

Allylsilanes have been often utilized as the nucleophilic alkene component in oxonium ion addition reactions that afford tetrahydrofurans. Sarkar and coworkers synthesized 2,3,5-trisubstituted tetrahydrofurans by Lewis acid catalyzed one-pot reactions of silylmethyl allylic silanes and aldehydes (Scheme 1.13).[21] In an example shown below, treatment of aldehyde **1.58** with 1-silylmethyl allylic silane **1.57** in the presence of $BF_3{\cdot}OEt_2$ gave **1.59** as a single diastereomer via the shown intermediates.



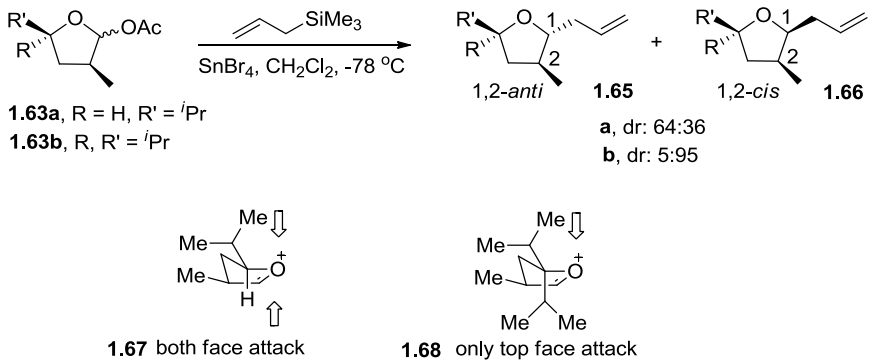
Scheme 1.13. Nucleophilic Alkene Addition to an Oxonium Ion

1.3.2.2. Nucleophilic addition to cyclic oxonium ions obtained from γ-lactols

Addition of nucleophilic reagents to five-membered ring oxonium ions derived from γ-lactol is a very common approach used in the synthesis of tetrahydrofurans.[22,23] Grignard reagent,[24] organozinc reagents[25] etc are some of the frequently used nucleophilic reagents for this purpose.

Woerpel and coworkers investigated the diastereoselectivity of the nucleophilic addition to five-membered rings derived from oxasilacyclopentane acetals[26] and γ-lactol derivatives.[27] They studied the relationship of the size of the C2-substituent on the diastereoselectivity of the allylsilane additions to oxonium ions derived from 2,2,4-

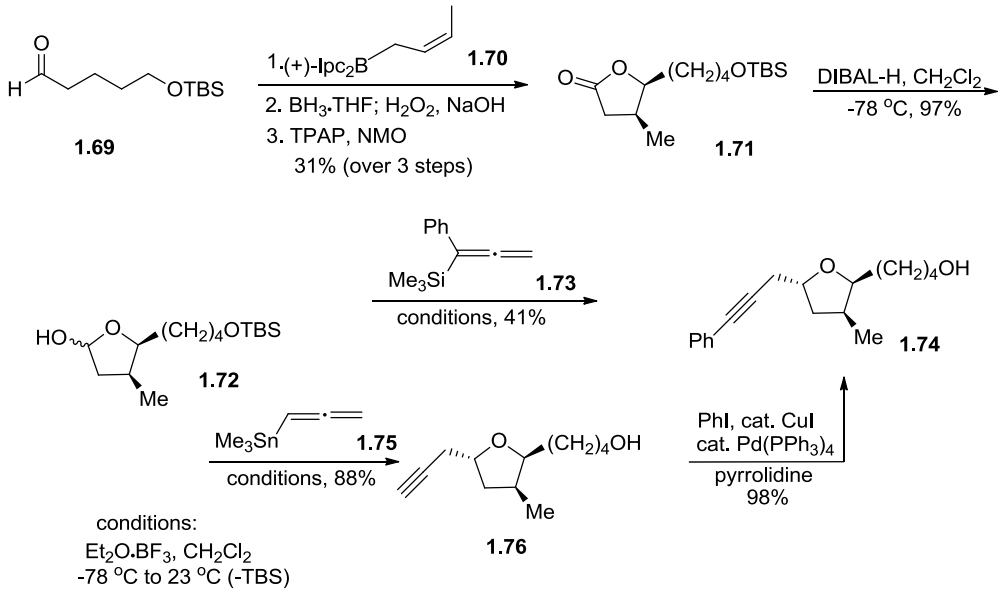
trisubstituted lactols. For example, treatment of **1.63a** with allyltrimethylsilane and $SnBr_4$ produces a 64:36 mixture of **1.65a** and **1.66a** (Scheme 1.14). In case of **1.63a**, transition state **1.67** is the predominant conformer in which both the substituent are in the pseudo-equatorial position to avoid a 1,3-diaxial interaction. In this conformer, the nucleophile can approach from both faces, leading to low diastereoselectivity. Introduction of a second isopropyl group (**1.63b**) improves the diastereoselectivity in favor of **1.66b** (5:95). The improved selectivity arises from the 1,3-diaxial interaction in transition state **1.68** which blocks attack from the lower face of the envelop conformation.



Scheme 1.14. Nucleophilic Addition of Allylsilane to Lactol Derived Cyclic Oxonium Ions **1.67** and **1.68**

Jamison employed a similar concept in the stereoselective synthesis of one of the tetrahydrofuran moieties of the amphidinolides T1 and T4.[28] The desired oxocarbenium ion precursor was made by the stereoselective addition of a chiral (*Z*)-crotyl borane **1.70** to an aldehyde **1.69** (Scheme 1.15). The crotylation product, upon hydroboration-oxidation, gave a diol which was oxidatively cyclized to give lactone **1.71**. DIBAL-H reduction of the lactone **1.71** to lactol **1.72** and subsequent treatment with allenylsilane **1.73** in the presence of $BF_3.Et_2O$ furnished the desired tetrahydrofuran **1.74** with very high diastereoselectivity (>95:5) and in 41% yield. The yield of this reaction was

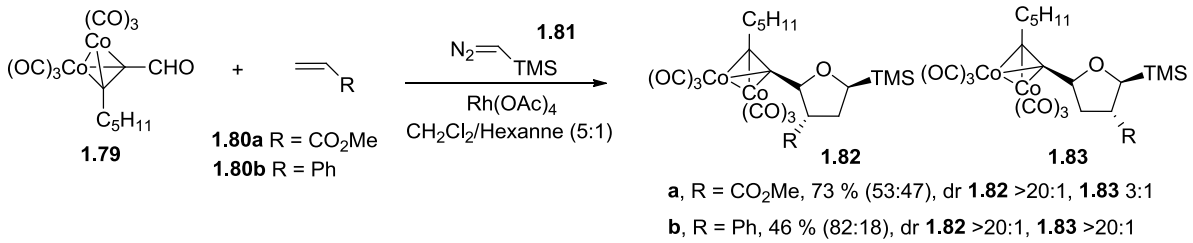
increased following a two-step conversion of lactol **1.72** to tetrahydrofuran **1.74**: treatment of lactol **1.72** with allenylstannane **1.75** followed by Sonogashira coupling of the resultant terminal alkyne **1.76** with iodobenzene.



Scheme 1.15. Nucleophilic Addition of Allenylsilane and Allenylstannane to Lactol **1.72**

1.3.3. [3+2] cycloaddition and annulations reactions

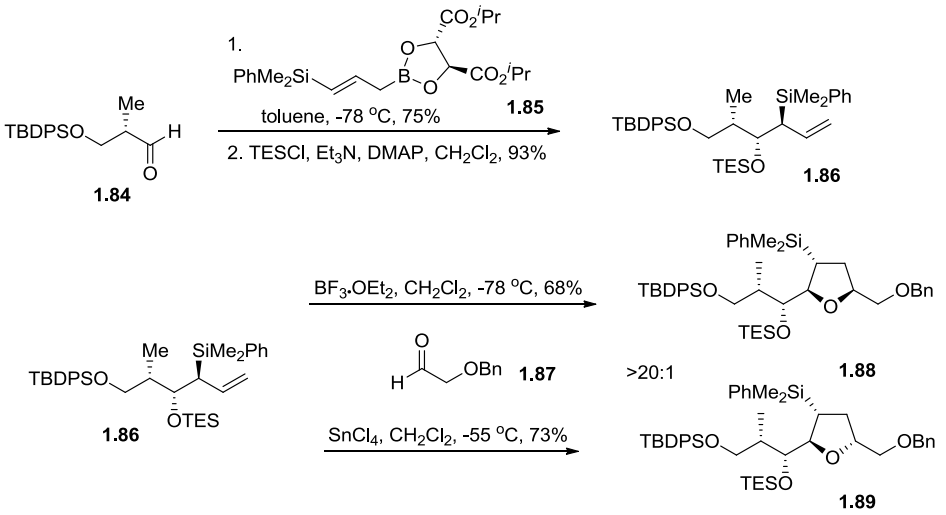
Substituted tetrahydrofuran synthesis by [3+2] cycloaddition reaction of diazo compounds and alkenes involving rhodium-catalysts is also a frequently used approach.[29] These reactions proceed through 1,3-dipolar cycloadditions between an alkene (inactivated or electron-rich) and carbonyl ylide generated *in situ*. In an example reported by Jamison, coupling of aldehyde **1.79** (cobalt carbonyl clusters containing aldehyde) with methyl acrylate **1.80a** and diazo compound **1.81** produces tetrahydrofurans **1.82a** and **1.83a** with 53:47 regioselectivity (>20:1 diastereoselectivity of the major isomer) (Scheme 1.16).[30] The same reaction with electron rich alkene **1.80b** improved the regioselectivity (**182b:1.83b** = 82:18).



Scheme 1.16. A [3+2] Cycloaddition Reaction of Aldehyde **1.79** with Different Dienes

A [3+2] annulation reaction of allylsilane and aldehydes to produce 2,3,5-trisubstituted tetrahydrofurans has been reported by Roush and coworkers. This multicomponent coupling involves a three-step coupling of two aldehydes with allyl boronate.[31] They showed that a change in Lewis acid could change the selectivity of the tetrahydrofuran ring.

For example, the reaction of allyl boronate **1.85** with aldehyde **1.84** followed by the protection of the resulting alcohol with a TES group gave intermediate product **1.86** (Scheme 1.17). Compound **1.86** upon reacting with α-benzyloxyacetaldehyde **1.87**, in the presence of $BF_3{\cdot}Et_2O$, afforded *cis*-2,5-disubstituted tetrahydrofuran **1.88** with excellent >20:1 diastereoselectivity. On the other hand, when $SnCl_4$ was used instead of $BF_3{\cdot}Et_2O$, the *trans*-2,5-disubstituted tetrahydrofuran **1.89** was obtained with the same level of selectivity. This concept has been utilized in the stereoselective synthesis of asimicin, an Annonaceous acetogenin having a *trans-threo-trans* bis-tetrahydrofuran core.[32]



Scheme 1.17. A [3+2] Annulation Reaction of an Allyl Silane with an Aldehyde

The stereochemical outcome can be explained on the basis of *syn*-clinical transition states (where the carbon bearing the silicon substituent is *syn* to the carbonyl oxygen). Transition states **1.90** are the lowest energy transition states available in the BF_3-catalyzed reactions of this type (Figure 1.2).[33] The transitions states **1.90** and **1.91** are less sterically demanding and the lowest energy transition states (formed in the presence of $BF_3{\cdot}Et_2O$ and $SnCl_4$ respectively). These transition states lead to the formation of *cis*- and *trans*-tetrahydrofurans, **1.88** and **1.89**, respectively as the major products.

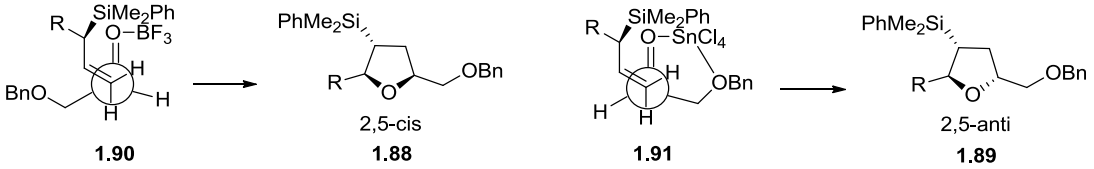
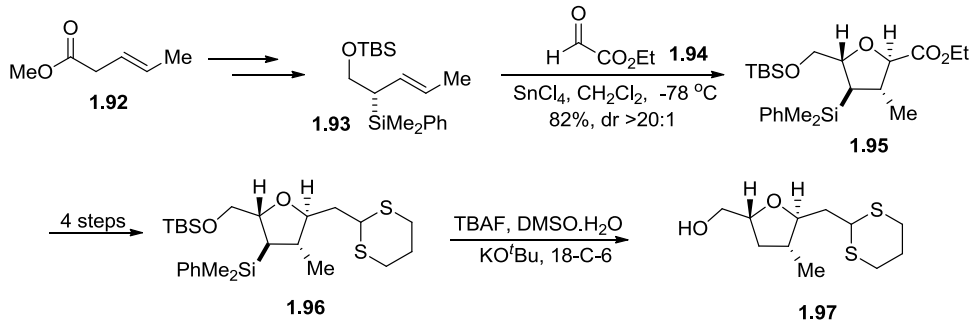


Figure 1.2. Transition States of [3+2] Annulation Reactions

During the synthesis of the C1-C9 fragment of amphidinolide C, Roush and coworkers employed the [3+2] annulation reaction for the synthesis of the 2,3,5-trisubstituted tetrahydrofuran.[34] The crotylsilane **1.93** underwent the $SnCl_4$-promoted [3+2] annulation

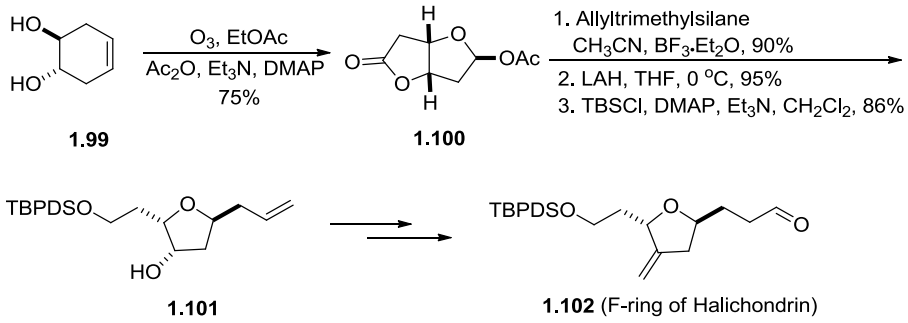
with ethyl glyoxalate **1.94** to give the required 3-methyl-*trans*-2,5-disubstituted tetrahydrofuran **1.95** (Scheme 1.18)**.** The silyl moiety at C-4 (ring numbering) of **1.96** was later removed (protiodesilylation) using modified Hudrlik conditions (TBAF, KO^{t}Bu, DMSO, H_2O, 18-crown-6).[35]



Scheme 1.18. Synthesis of *trans*-Tetrahydrofuran Ring of C1-C9 Fragment of Amphidinolide C by [3+2] Annulation Reaction

1.3.4. Oxidation of alkene

Synthesis of hydroxylated tetrahydrofuran derivatives by the oxidative cyclizations of alkenes have been reported various times.[36] In an example shown below, the oxidative cyclization of cyclohexene diol **1.99** was carried out using modified Schreiber ozonolysis[37] to give bicyclic acyloxy acetal-lactone **1.100** in 4:1 dr (75% yield) (Scheme 1.19).[38] Lactone **1.100** was then converted to the 2,3,5-trisubstituted tetrahydrofuran **1.101** by subsequent allylation and reduction. Tetrahydrofuran derivative **1.101** is the intermediate compound for the synthesis of the F ring of Halichondrin B, an anticancer compound isolated from marine sponges *Halichondria*.[39]

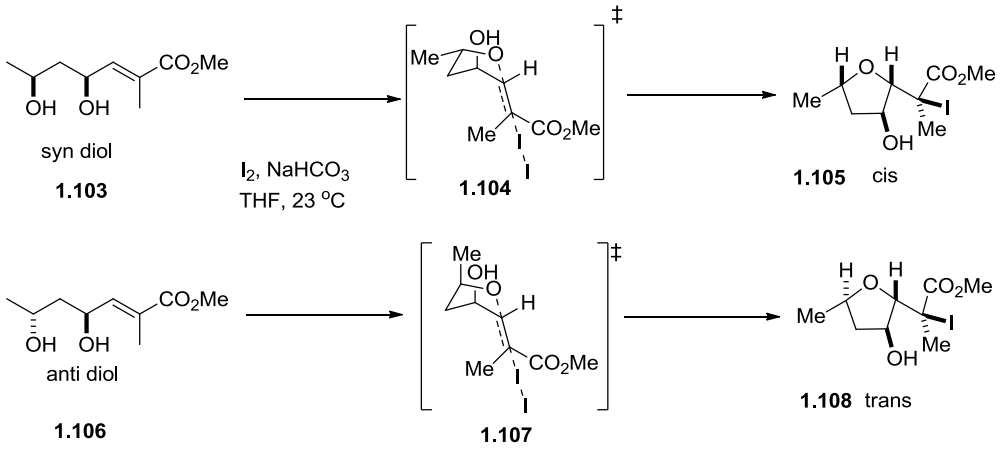


Scheme 1.19. Synthesis of Tetrahydrofuran Ring by the Oxidation of Alkene

1.3.5. Iodoetherification

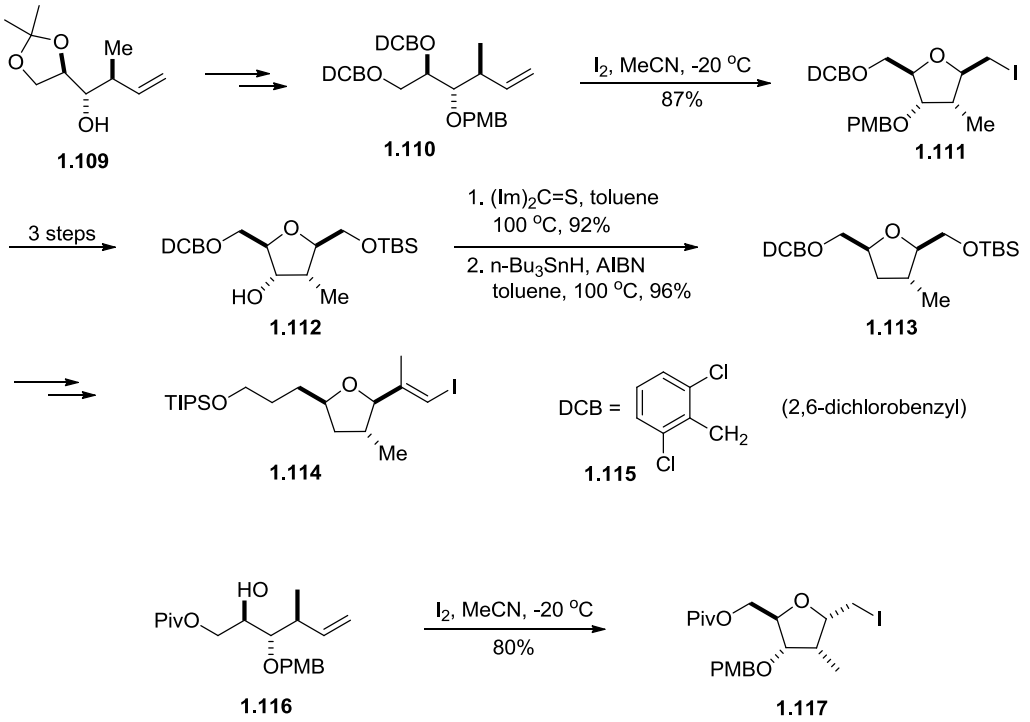
Guindon and coworkers synthesized 2,3,5-trisubstituted tetrahydrofurans from both *syn* and *anti*-diols having an electron withdrawing group at the allylic position.[40] They studied the impact of stereoelectronic effects and allylic 1,3-strain in controlling the cyclofunctionalization reaction when a hydroxyl group is at the allylic position. *Syn*-diol **1.103,** upon treatment with iodine and $NaHCO_3$ gave *cis*-tetrahydrofuran **1.105** in 86% yield after 6 h whereas *anti*-diol **1.106** produced *trans*-tetrahydrofuran **1.108** in less than 20% yield after 24 h (best yield, 55% in CH_3CN after 36 h) (Scheme 1.20).

The difference in reactivity of *syn* and *anti* diols can be explained from the reaction transition states. The transition state **1.107** obtained from *anti*-diol **1.106** has a higher energy than **1.104** (obtained from *syn*-diol **1.103**) due to the development of a transannular diaxial interaction. As a result, *syn*-diol **1.103** will react faster than *anti*-diol **1.106**.



Scheme 1.20. Iodoetherification of Hydroxyalkenes

The concept of iodoetherification has been applied by White for the synthesis of the tetrahydrofuran moiety of (-)-gymnodimine.[41] Intermediate compound **1.110** upon treating with iodine in acetonitrile underwent highly stereoselective cyclization to give 2,5-*cis*-tetrahydrofuran **1.111** as a single isomer (Scheme 1.21). However, cyclization of **1.116** under the same conditions produced the 2,5-*trans*-tetrahydrofuran **1.117** as a sole diastereomer. These results support the Barlett-Rychnovsky mechanism for the cyclization of acyclic alkenols which postulates that increasing the steric bulk attached to the oxygen incorporated into the tetrahydrofuran favors the 2,5-*cis*-tetrahydrofuran.[42]



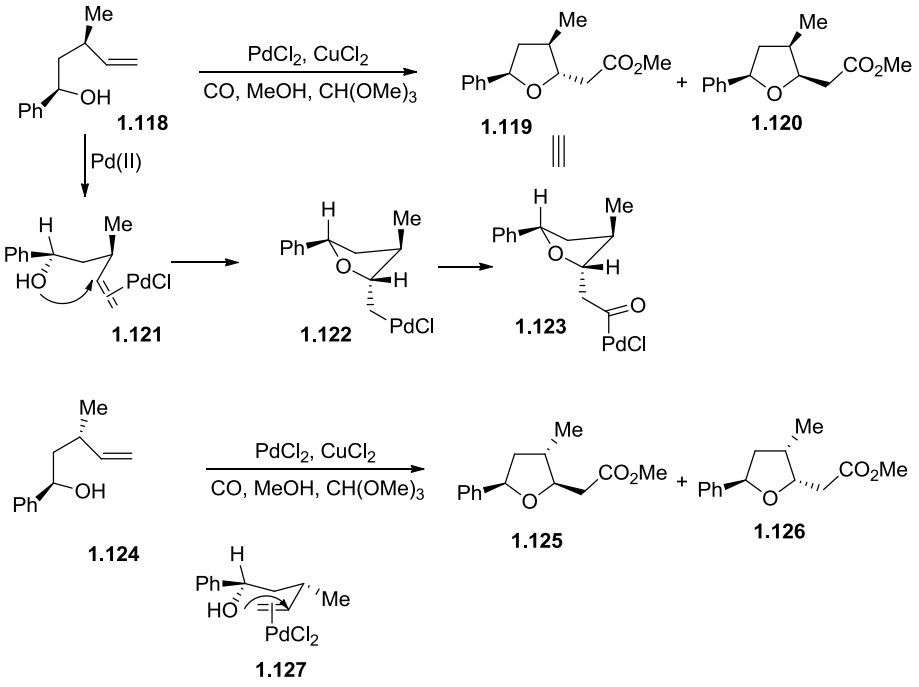
Scheme 1.21. Application of Iodoetherification in the Synthesis of the Tetrahydrofuran Ring of Gymnodimine

1.3.6. Alkene carboetherification

Semmelhack developed a palladium catalyzed cyclization of unsaturated alcohols with subsequent methoxycarbonylation at the C1' position to produce a tetrahydrofuran methyl ester.[43] As shown below, when **1.118** was treated with a catalytic amount of $PdCl_2$ and excess $CuCl_2$ under a CO atmosphere in methanol, a 9:1 mixture of **1.119** and **1.120** was obtained (Scheme 1.22). The reaction proceeds via activation of alkene by Pd(II) to give **1.121**, nucleophilic attack of the tethered alcohol to give ring product **1.122**, CO insertion to allylpalladium complex to give **1.123** followed by reductive elimination to produce the tetrahydrofurans.

The reaction will favor the *cis*- or *trans*-tetrahydrofuran depending upon the configuration at C1 center of hydroxyalkene (Scheme 1.22). For example, *anti*-precursor **1.118** proceeded via transition state **1.121** arising from the confirmation with minimum

non-bonding interaction. Therefore, the reaction led to the formation of *trans*-2,5-disubstituted tetrahydrofuran as a major product (90:10 *trans*:*cis*). On the other hand, the reaction of *syn*-precursor **1.124** proceeded via the transition state **1.127** forming the *cis*-isomer **1.125** with 87:13 *cis*:*trans* selectivity.



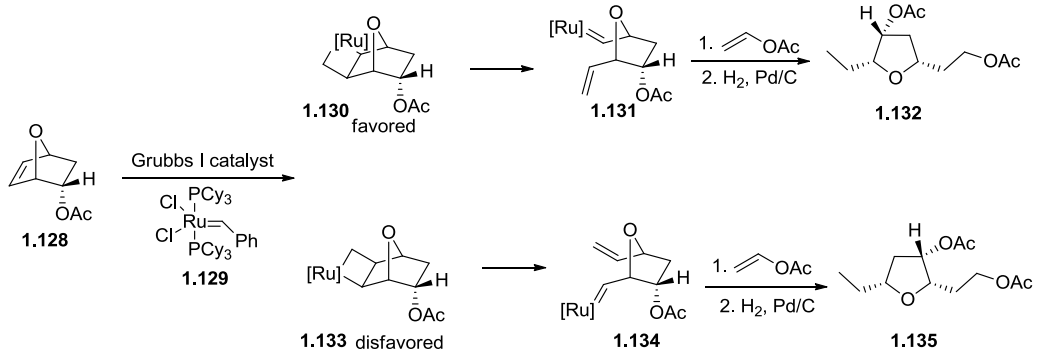
Scheme 1.22. Palladium Catalyzed Carboetherification of *syn*- and *anti*-Hydroxyalkenes

1.3.7. Olefin metathesis

Olefin metathesis is becoming a widely used method for the construction of the tetrahydrofurans.[44] Plumet studied the effect of the homoallylic substituents in the regiochemistry of the combination of ring opening and selective cross coupling metathesis, as a means of 2,3,5-trisubstituted tetrahydrofurans syntheses.[45] He showed that 2-substituted-7-oxanobornenes (with a bulky C2-*endo*-substituent) can undergo ring-opening/cross-metathesis (ROCM) to provide 2,3,5-trisubstituted tetrahydrofurans. As an example, 2-substituted-7-oxanobornenes **1.128,** upon treating with allyl acetate in the

presence of Grubbs first-generation catalyst **1.129**, afforded regioisomers **1.132** and **1.135** in a ratio of 81:19 (Scheme 1.23).

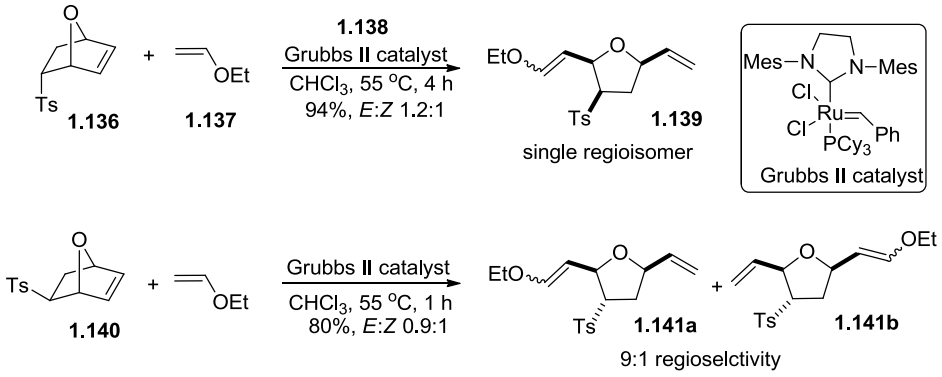
A plausible mechanism for this regioselectivity differentiation has been postulated. The irreversible cycloaddition of the carbene species [M]=CH_2 to the C=C double bond of the bicyclic alkene **1.128** forms metallacyclobutanes **1.130** and **1.133**. The ring-opening of these metallacyclobutanes lead to the formation of new carbene species **1.131** and **1.134,** respectively which then undergo cycloaddition with another alkene to afford (after hydrogenation) the tetrahydrofurans **1.132** and **1.135**. Since metallacyclobutane **1.130** is formed in preference to **1.133** for steric reasons, regioselectivity is in favor of product **1.132**.



Scheme 1.23. THF Synthesis from 2-endo-Substituted 7-Oxanobornenes

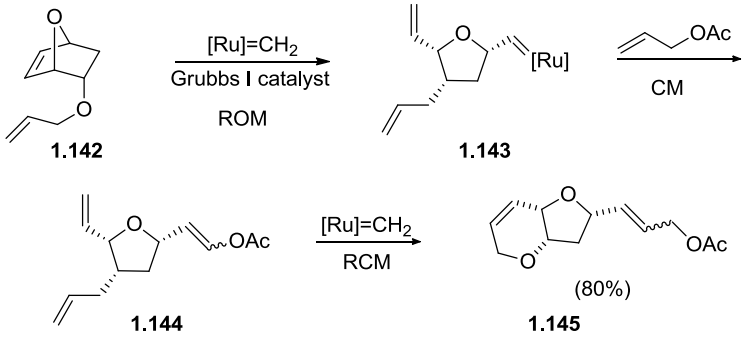
The approach of ROCM reactions between unsymmetrical oxanorbornene derivatives and olefins has also been investigated by Liu and coworkers.[46] They also studied the effect of the *endo*-substituent on the regioselectivity. As shown below (Scheme 1.24), reaction of oxanorbornene **1.136** (with an *endo*-tosyl group) with the electron-rich olefin **1.137** in the presence of Grubbs second catalyst **1.138** afforded tetrahydrofuran **1.139** as a single

isomer, but oxanorbornene **1.140** (with *exo*-tosyl group), under the same conditions, produced tetrahydrofuran **1.141a** and **1.141b** with 9:1 regioselectivity.



Scheme 1.24. Effects of Substituent Orientation of 7-Oxonobornens during Tetrahydrofuran Synthesis

Arjona observed that a more complex structure can be synthesized by the combination of ring-opening (ROM), ring-closing (RCM) and cross-metathesis (CM).[47] A *cis*-fused 2,6-dioxa[4.3.0]nonane skeleton (substructure present in many natural products and annulated nucleotide antibiotics)[48] was synthesized following this chemistry. As shown below, treatment of compound **1.142** with the allyl acetate in the presence of Grubbs I catalyst gave bicyclic product **1.145** by a tandem ROCM and RCM process (Scheme 1.25).

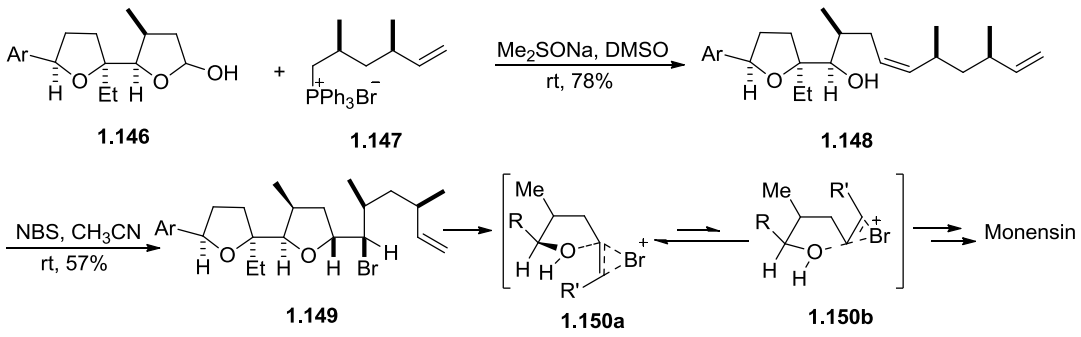


Scheme 1.25. Synthesis of Tetrahydrofuran Ring by Tandem ROCM and RCM

1.4. Synthesis of 2,3,5-trisubstituted tetrahydrofurans present in natural products

1.4.1. Monensin and boromycin via bromoetherification

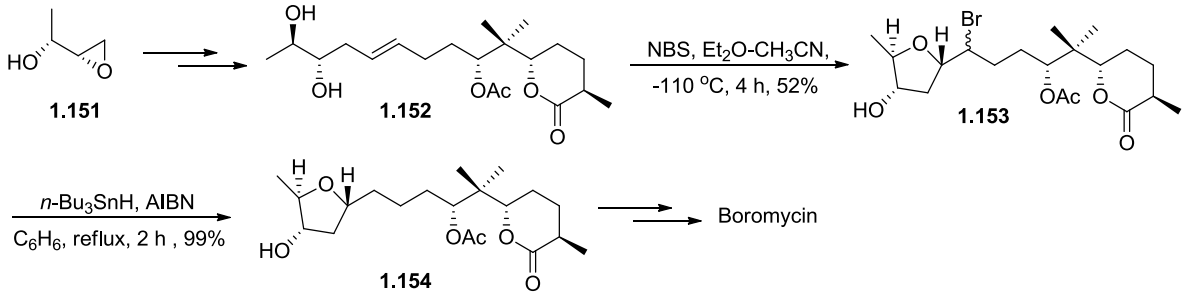
Kishi *et al.* reported the first stereocontrolled total synthesis of monensin,[49] a member of more than 40 naturally occurring polyether antibiotics.[50] The 2,3,5-trisubstituted tetrahydrofuran moiety embedded in this natural product was synthesized by *N*-bromosuccinimide (NBS) mediated cyclization of *bis*-homoallylic alcohol **1.148** (Scheme 1.26). Intermediate **1.148** was obtained by the Wittig reaction of lactol **1.146** and ylide **1.147**. The formation of the *trans*- isomer is described by the decreased steric effect experienced by **1.150a** (leading to *trans*-product) in comparison to **1.150b** that gives *cis*-isomer.



Scheme 1.26. NBS Mediated Cyclization of Homoallylic Alcohol **1.148**

N-bromosuccinimide promoted cyclization[51] has been utilized in the synthesis of substituted tetrahydrofurans of other natural products. For example, during the total synthesis of boromycin,[9] an ionophoric metabolite of *Streptomyces antibioticus*, White and coworkers treated diol **1.152** with N-bromosuccinimide in Et_2O-CH_3CN to give a

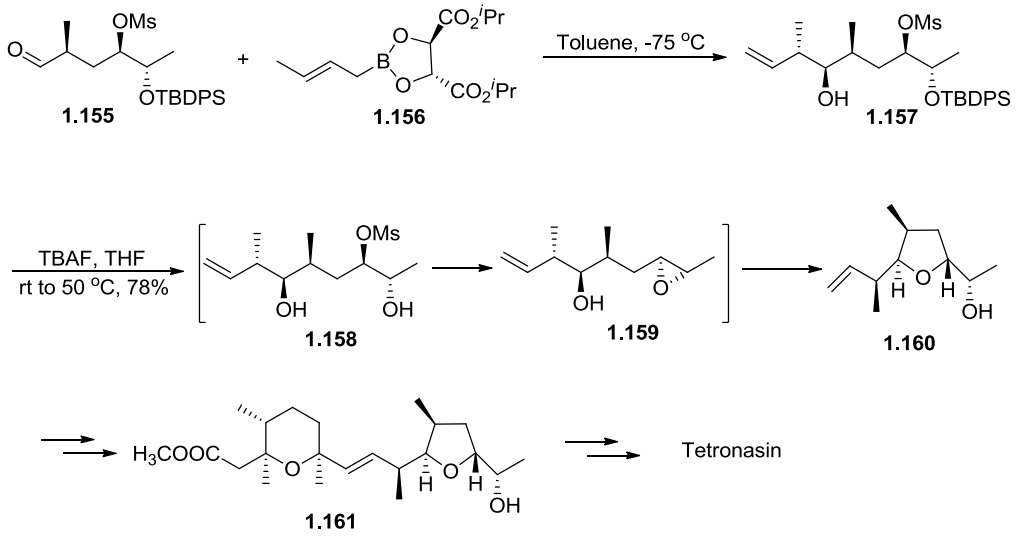
pair of easily separated bromooxalanes **1.153** (Scheme 1.27). The major isomer was reduced with tributylstannane to give desired 2,3,5-trisubstituted tetrahydrofuran **1.154**.



Scheme 1.27. NBS Mediated Cyclization of Diol **1.152** to Give Bromooxalanes

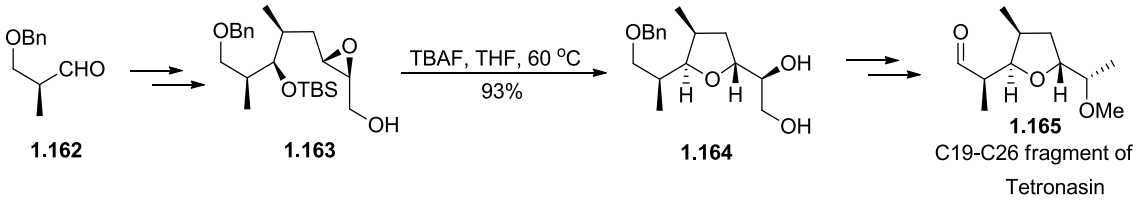
1.4.2. Tetronasin via intramolecular addition of alcohol to epoxide

Tetronasin (ICI M-139603) is a polyether ionophore antibiotic produced by *Streptomyces longisporoflavus*.[7] In the first total synthesis of tetronasin, Hori and coworkers described the synthesis of a substituted tetrahydrofuran by the intramolecular addition of alcohol to epoxide (Scheme 1.28).[52] The intermediate *syn*/*anti* homoallylic alcohol **1.157** was synthesized by the reaction of hexanal derivative **1.155** and crotylboronate **1.156**. Treatment of compound **1.157** with TBAF in THF induced a desilylation/epoxide formation/ring closure sequence to provide the 3-methyl-2,5-*trans*-tetrahydrofuran **1.160** in 78%.



Scheme 1.28. Tetrahydrofuran Synthesis of Tetronasin by Intramolecular Addition of an Alcohol to an Epoxide

Ley and coworkers also used an epoxide opening in the synthesis of the tetrahydrofuran of tetronasin.[53] Treatment of the intermediate TBS-epoxide **1.163** with TBAF at 60 °C removed the TBS group with concomitant intramolecular epoxide ring opening and produced tetrahydrofuran **1.164** with the appropriate stereochemistry for tetronasin in an excellent 93% yield (Scheme 1.29).

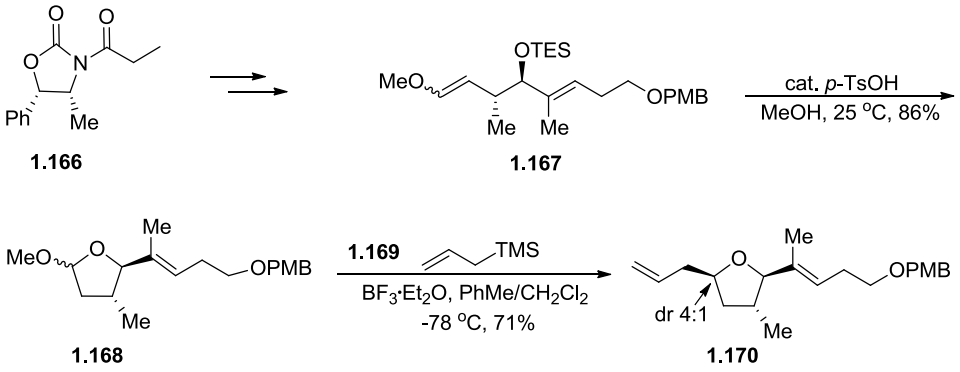


Scheme 1.29. Intramolecular S_N2 Cyclization

1.4.3. Gymnodimine by acid-catalyzed cyclization

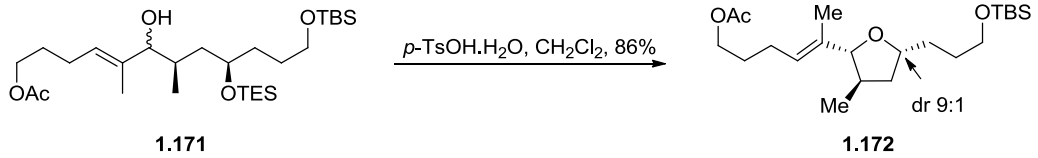
Gymnodimines are marine toxins first isolated in 1995 from *Tiostrea chilensis* oysters collected off the coast of New Zealand.[6] All the members of these spirocyclic imine containing natural products contain the 2,3,5-trisubstituted tetrahydrofuran moiety. Romo and coworkers discussed the synthesis of this moiety in their report in the first total

synthesis of gymnodimine.[54] Treatment of **1.167** with a catalytic amount of *para*-toluenesulfonic acid (*p*-TsOH) in MeOH removed the silyl group which underwent concomitant cyclization to provide the epimeric furanoses **1.168** (Scheme 1.30). Allylation of **1.168** with allyl trimethylsilane **1.169** in the presence of $BF_3{\cdot}Et_2O$ provided the allylated tetrahydrofuran **1.170** in moderate diastereoselectivity (dr, 4:1).



Scheme 1.30. *p*-TsOH Catalyzed Cyclization of Homoallylic Alcohol

A similar concept of acid catalyzed cyclization has been described by Kishi for the substituted tetrahydrofuran synthesis present in gymnodimine.[55] This one step synthesis improved the diastereoselectivity of *cis*/*trans* tetrahydrofuran formation compared to the above mentioned two step procedure.



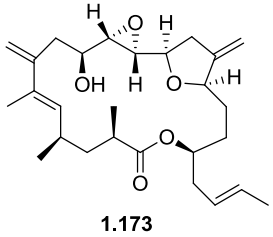
Scheme 1.31. Acid Catalyzed Cyclization of **1.171** to Give the Tetrahydrofuran of the Gymnodimine

1.5. Tetrahydrofurans synthesis embedded within amphidinolides

Amphidinolides are a series of cytotoxic macrolides possessing complex and unique structural features. These natural products are isolated from the marine dinoflagellate

Amphidinium sp. which is symbiotic with the Okinawa acoel flatworms *Amphiscolops* sp.[5] Kobayashi and coworkers have isolated more than 39 members of this family and many of them contain one or more substituted tetrahydrofurans. Herein, we will describe the synthesis of 2,3,5-trisubstituted tetrahydrofurans reported by various groups.

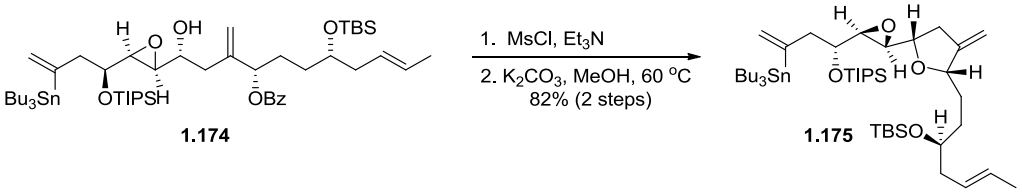
1.5.1. Amphidinolide K



1.173

Figure 1.3. Amphidinolide K

The synthesis of the cis-2,5-disubstituted-3-methylenetetrahydrofuran ring present in amphidinolide K has been described by Williams and coworkers.[56] Intermediate compound **1.174** was first converted to the corresponding mesylate followed by methanolysis of the benzoyl group (Scheme 1.32). This facilitated the intramolecular backside displacement of the mesylate group at C12 producing the desired 3-methylene-*cis*-2,5-disubstituted tetrahydrofuran **1.175**.

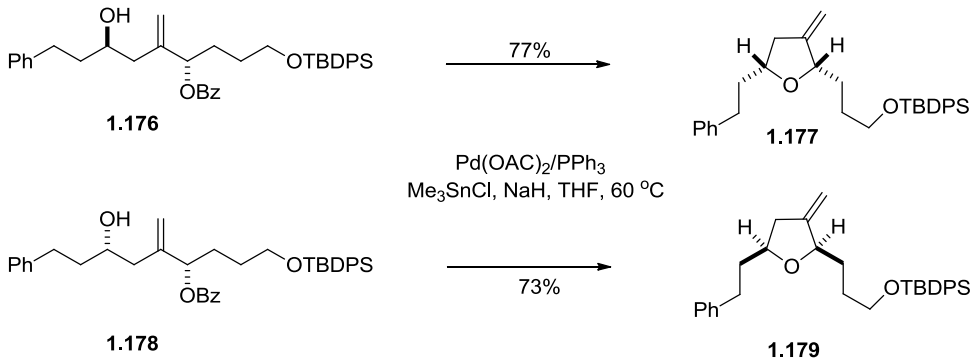


1.174 **1.175**

Scheme 1.32. Base Mediated S_N2 Type Cyclization of **1.174**

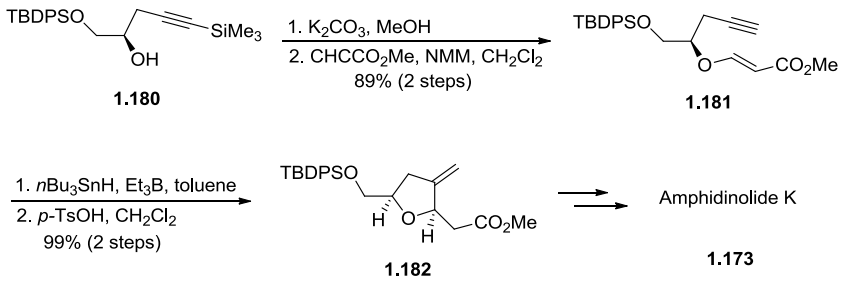
In a related study, William and coworkers described the diastereoselective synthesis of *cis*-2,5-disubstituted-3-methylenetetrahydrofurans via Pd(0)-catalyzed cyclization of

monobenzylated 2-methylene-1,4-diols (Scheme 1.33).[57] When a solution of *anti*-1,4-diol **1.176** (1.0 equiv., in THF) was slowly added to a mixture of NaH (1.0 equiv.), trimethyltin chloride (Me_3SnCl) (1.0 equiv.) and $Pd(OAc)_2/PPh_3$ (20 mol%) in THF at 60 ^oC, *cis*-2,5-disubstituted tetrahydrofuran **1.177** was formed with an 8:1 *cis*:*trans* ratio. Me_3SnCl was used as an additive that accelerated the reaction. Under the same conditions, *syn*-1,4-diol derivative **1.178** also afforded an 8:1 ratio of *cis*- and *trans*-2,5-disubstituted tetrahydrofurans **1.179.** However, the major isomer **1.177** has an antipodal relationship to **1.179** (same but opposite optical rotation values).



Scheme 1.33. Pd(0) Catalyzed Cyclization of *syn*- and *anti*-1,4-Diols

The synthesis of the substituted tetrahydrofuran ring of amphidinolide K has also been described by Lee *et al.*[58] The intermediate *β*-alkoxyacrylate **1.181** was prepared in 2 steps from the known homopropargylic alcohol **1.180** (Scheme 1.34).[59] Compound **1.181** underwent radical cyclization in the presence of tributylstannane and triethylborane to give the 3-methylene-*cis*-2,5-disubstituted tetrahydrofuran **1.182** as a major diastereomer (*cis*:*trans* 16:1) after acidic destannylation.



Scheme 1.34. Radical Cyclization of *β*-alkoxyacrylate **1.181** to Produce Tetrahydrofuran Ring of Amphidinolide K

1.5.2. Amphidinolide T

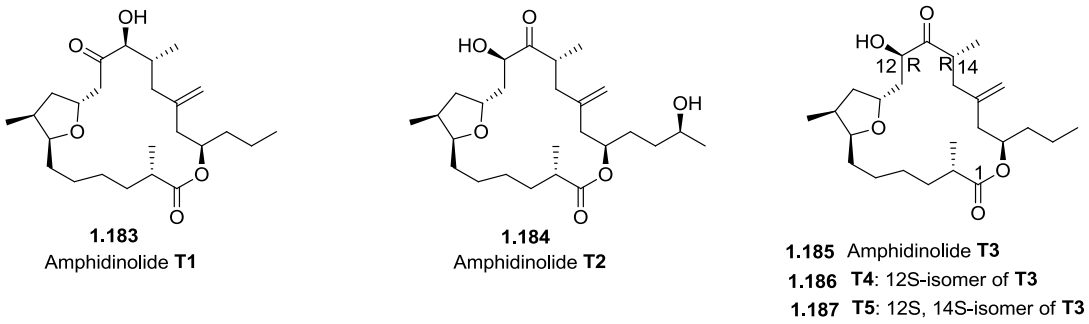
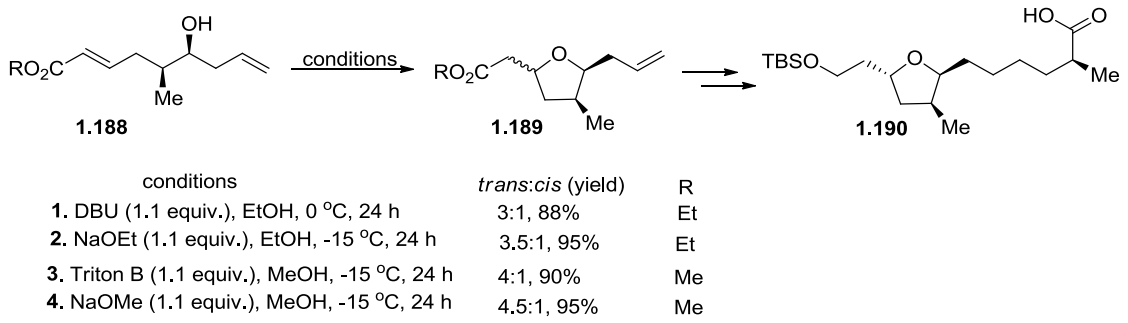


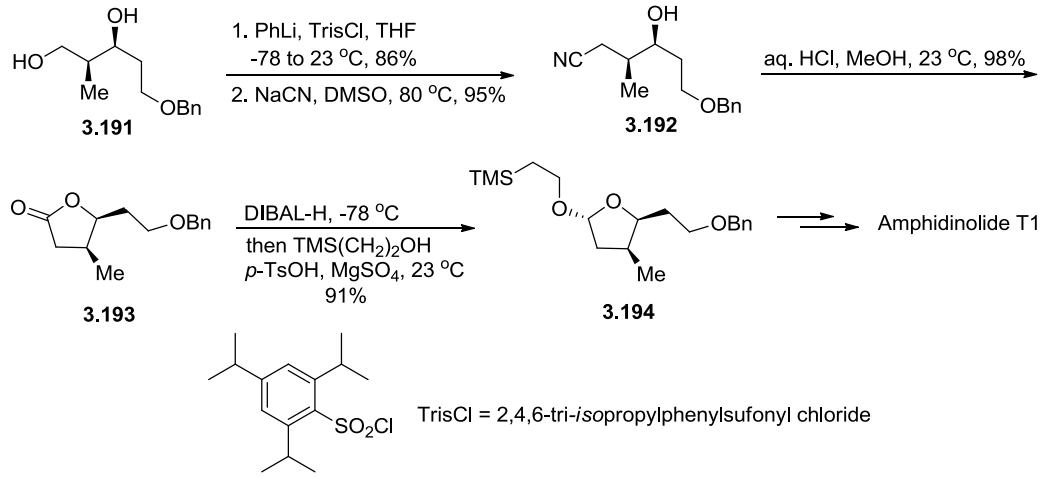
Figure 1.4. Different Members of Amphidinolide T

Synthesis of the 2,3,5-trisubstituted tetrahydrofuran found in different members of amphidinolide T has been described by many groups. Abbineni and coworkers investigated the oxy-Michael cyclization of **1.188** at different reaction conditions.[60] Cyclization of **1.188** in the presence of NaOMe in MeOH at -15 ^{o}C gave the highest *trans*-selectivity (entry 4, Scheme 1.35) with concomitant transesterification.



Scheme 1.35. Cyclization of Hydroxy Ester **1.188** at Different Basic Conditions

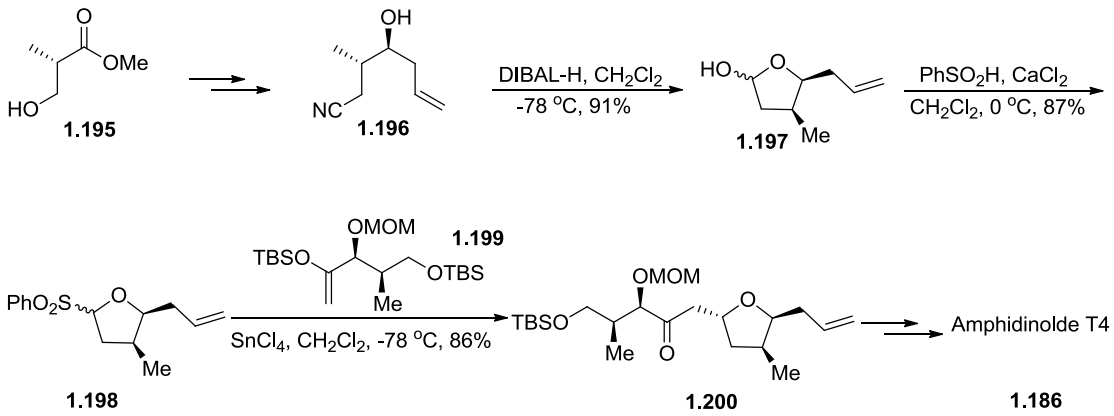
Ghosh and coworkers described the synthesis of the tetrahydrofuran of amphidinolide T1 from the lactone **1.193** which is obtained by the acid promoted lactonization of γ-hydroxy cyanide **1.192** (Scheme 1.36).[61] Reduction of lactone **1.193** with DIBAL-H followed by reaction with trimethylsilylethanol and catalytic *p*-TsOH afforded trisubstituted tetrahydrofuran **1.194** as a 3.5:1 diastereomeric mixture.



Scheme 1.36. *p*-TsOH Catalyzed Nucleophilic Addition of Alcohol to lactol **1.193**

A similar strategy has been applied by Fürstner to synthesize the tetrahydrofuran moiety of amphidinolide T4.[62] Intermediate nitrile **1.196** (prepared in 4 steps from commercially available starting material **1.195**) was converted to lactol **1.197** by treating with DIBAL-H followed by acidic work-up (Scheme 1.37). Lactol **1.197** was converted to sulfone

1.198 upon treatment with an excess of phenylsulphonic acid ($PhSO_2H$) in the presence of $CaCl_2$ (as the dehydrating agent). $SnCl_4$ mediated coupling of sulfone **1.198** with TBS-enol ether **1.199** afforded the required *trans*-tetrahydrofuran **1.200** a major diastereomer (*trans*:*cis* = 26:1).



Scheme 1.37. Synthesis of Tetrahydrofuran **1.200** of Amphidinolide T4

1.5.3. Amphidinolides C, C2 and F

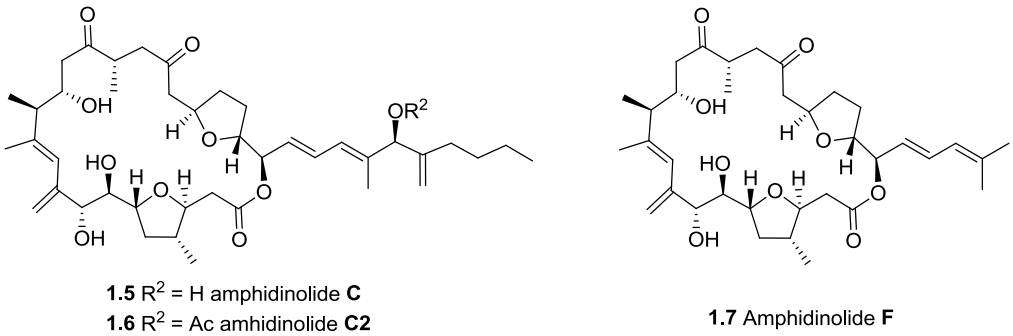
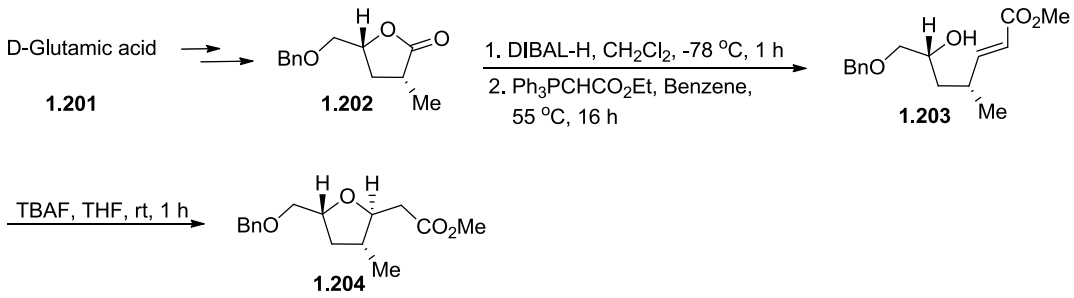


Figure 1.5. Amphidinolides C, C2 and F

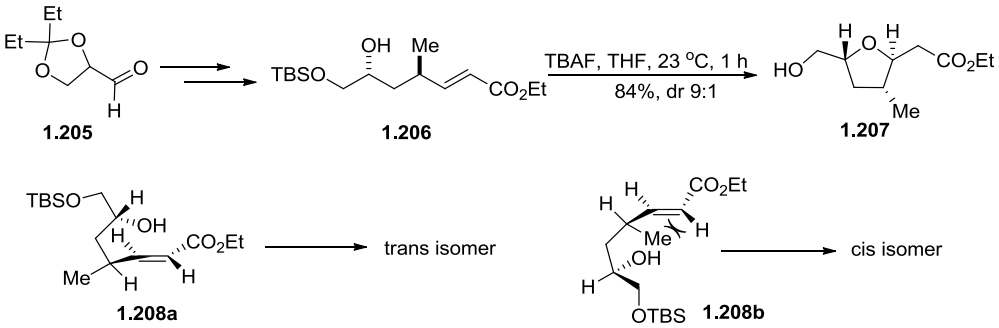
Several reports have been published on the synthesis of the tetrahydrofuran moiety of amphidinolides C, C2 and F. Kobayashi and coworkers synthesized the C1-C7 fragment to aid in the absolute configuration assignment of 12 chiral stereocenters in amphidinolide C (Scheme 1.38).[63] The 6-benzyloxymethyl-4-methyl-γ-butyrolactone

1.202 (obtained from D-glutamic acid **1.201**[64]) was reduced to a lactol and the lactol was converted to an *α,β*-unsaturated ester **1.203** by Witting reaction. The unsaturated ester **1.203** was converted to tetrahydrofuran **1.204** (via a diastereoselective Michael addition) by treating with TBAF in THF.



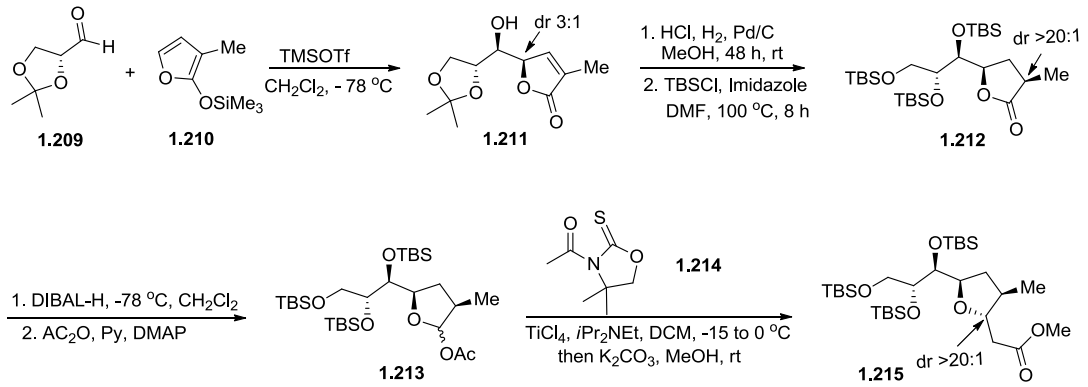
Scheme 1.38. TBAF Mediated Cyclization of Homoallylic Alcohol **1.203**

An analogous strategy of cyclization of an unsaturated ester by TBAF has been employed by Roush and coworkers.[65] When unsaturated ester **1.206** was treated with TBAF in THF, it afforded 3-methyl-2,5-*trans*-tetrahydrofuran **1.207** (an example of Michael cyclization) in excellent diastereoselectivity (*trans:cis* 9:1) with simultaneous removal of the TBS group (Scheme 1.39). The transition states (**1.208a** and **1.208b**) show that the formation of the *trans*-isomer minimizes $A_{1,3}$-strain.



Scheme 1.39. TBAF Mediated Cyclization

A completely different approach has been functionalized by Ferrie and coworkers for the trisubstituted tetrahydrofuran synthesis of amphidinolide C.[66] The vinyloguous Mukaiyama aldol reaction of chiral aldehyde **1.209** with silyloxyfuran **1.210** gave unsaturated lactone **1.211** (Scheme 1.40). The hydrogenation of lactone **1.211** gave **1.212** with excellent diastereoselectivity setting the stereochemistry at the C-3 position. The lactol derivative **1.213** was prepared by reduction followed by acylation. C-glycosylation of lactol derivative **1.213** with an acetyl oxazolidinethione **1.214** produced *trans*-2,5-disubstituted tetrahydrofuran **1.215** (60% yield).



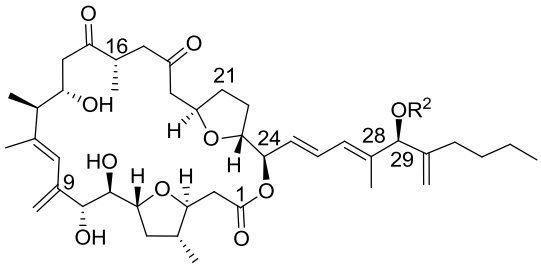
Scheme 1.40. Synthesis of Trisubstituted Tetrahydrofuran Ring by C-glycosylation of Lactol **1.213**

1.6. Results and discussion

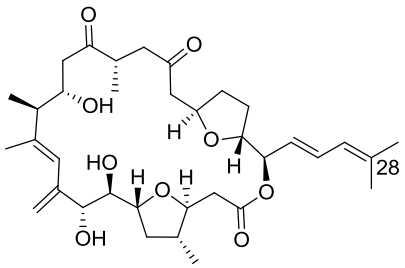
1.6.1. Introduction

Since 1986, Kobayashi and coworkers have isolated and characterized over 30 members of a structurally diverse group of natural products named amphidinolides.[5] These unique macrolides are isolated from symbiotic marine dinoflagellate *Amphidinium* species. These *Amphidinium* species are, in turn, separated from inside cells of Okinawan flatworms *Amphiscolops* sp. All amphidinolides, to some extent, possess cytotoxic activity against cancer cell lines.

Amphidinolide C (**1.5**) (Figure 1.6), one of the most cytotoxic members of this family, was first isolated from the Y-5 strain of *Amphidinium* sp.[67] Embedded within this macrolide are two *trans*-tetrahydrofurans, a vicinally located carbon branch, and 12 stereocenters. Amphidinolide C is known to possess cytotoxic activity against human tumor cell lines. The IC_{50} values of this macrolide are 0.0058 and 0.0046 μg/mL against murine lymphoma L1210 and epidermoid carcinoma KB cells, respectively, *in vitro*.



1.5 R^2 = H amphidinolide **C**
1.6 R^2 = Ac amhidinolide **C2**



1.7 Amphidinolide **F**

Figure 1.6. Amphidinolides C, C2 and F

Amphidinolides C2[68] (**1.6**) and F[69] (**1.7**) contain the same macrocylic ring as amphidinolide C, but differ in the side chain structure (Figure 1.6). Amphidinolide C2

has an acetate group at the C29 position instead of a hydroxyl group, whereas amphidinolide F has a methyl group at the C28 position. Interestingly, amphidinolides C2 and F show significantly lower activities against murine lymphoma L1210 and epidermoid carcinoma KB cell lines (0.8 and 3.0 μg/mL, respectively, for **1.6**; 1.5 and 3.2 μg/mL, respectively, for **1.7**). This suggests that the C25-C34 side chain and allylic hydroxyl group have a significant impact on the biological role of amphidinolides C, C2, and F.

Due to their unique structural scaffold and potential clinical importance, amphidinolides have attracted a significant interest among synthetic chemists. Herein, we will report the synthesis of the C1-C9 fragment of amphidinolides C, C2, and F.

1.6.2. Retrosynthetic analysis

In our retrosynthetic analysis of amphidinolide C, the molecule is divided into four different sub units (Figure 1.7). After completion of the synthesis of these subunits, the northern fragment **1.216** will be coupled to the aldehyde side chain **1.217a** (or **1.217b**) by Horner-Wadsworth-Emmons (HWE) olefination reaction. The western fragment sulfone **1.218** will be deprotonated to give a sulfone anion and added to the northern fragment. Coupling of the southern fragment **1.219** will be done by the macrocyclic Stille coupling followed by DCC esterification or *vice versa*.

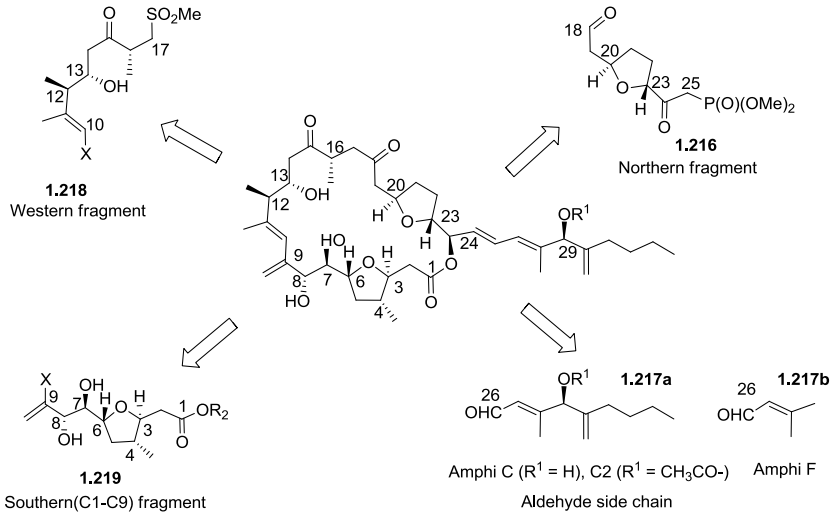
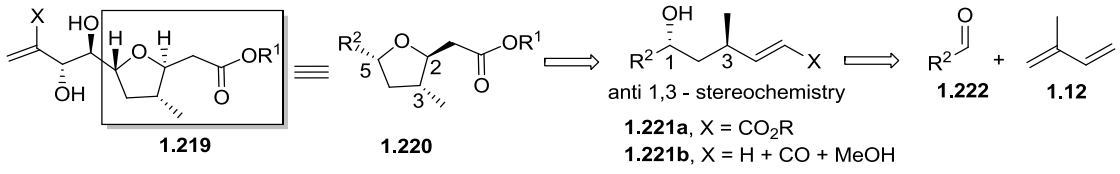


Figure 1.7. Retrosynthetic Analysis of Amphidinolides C, C2 and F

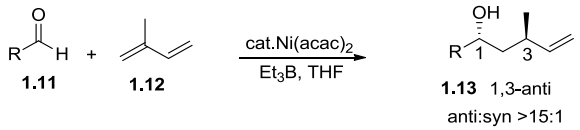
The C1-C9 fragment **1.219**, one of the core subunits of amphidinolide C, contains one trisubstituted 2,5-*trans* tetrahydrofuran and a side chain containing an 1,2-*anti*-diol. The retrosynthetic analysis of this fragment is given below (Scheme 1.41). Unfolding of the ring reveals that an alcohol with 1,3-*anti* stereochemistry and double bond in proper position cyclizes to produce the tetrahydrofuran ring. In the forward sense, the tetrahydrofuran can be formed by addition of the alcohol across the alkene. The *cis* orientation of R^2 and methyl groups, during cyclization forces the third stereocenter (position 2) in *trans*-position relative to the existing stereocenters (positions 3 and 5), resulting in the required 2,5-*trans* tetrahydrofuran ring. The alcohol can potentially be prepared from a properly functionalized aldehyde following well documented nickel chemistry.



Scheme 1.41. Retrosynthetic Analysis of C1-C9 **1.219** Fragment of Amphidinolide C

1.6.3. Nickel catalyzed homoallylation

Tamura *et al.* reported extensive work on the nickel catalyzed homoallylation of aldehydes and ketones. In homoallylation, an aldehyde (or a ketone) reacts with a diene in the presence of a nickel catalyst and triethyl borane as a promoter and reducing agent to produce a hydroxyalkene (Scheme 1.42).[70] The reductive coupling occurs between the carbonyl group of aldehyde and the C1-C2 bond of diene. A hydride that stems from the ethyl group of BEt_3 or $ZnEt_2$ is delivered at the C2 position of the diene with excellent regio– and stereoselectivity, favoring the 1,3-*anti* stereochemistry predominantly. (Note: Homoallylation reaction and its mechanism will be discussed in detail in chapter II).



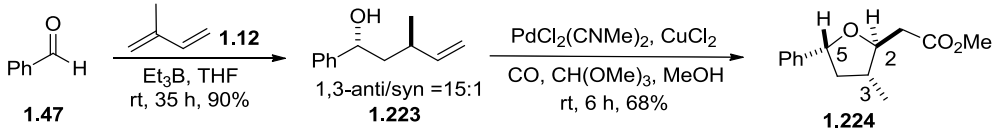
Scheme 1.42. Homoallylation of an Aldehyde **1.11** with Isoprene **1.12**

1.6.4. Synthesis of model racemic tetrahydrofuran ring

1.6.4.1. Homoallylation of benzaldehyde and Pd-catalyzed cyclization

The known homoallylation of benzaldehyde was used for a model study. Benzaldehyde reacts with isoprene catalyzed by $Ni(acac)_2$ and promoted by triethyl borane (Et_3B) to afford homoallyl alcohol **1.223** with a 1,3-*anti* to *syn* ratio of >15:1 in 90% yield (Scheme 1.43). Semmelhack and coworker have shown that hydroxyalkenes similar to **1.223** undergo Pd(II)-catalyzed intramolecular cyclization.[43] Reaction of hydroxyalkene **1.223** with Pd (II) catalyst, copper (II) chloride and carbon monoxide (methoxycarbonylation) gave *trans*-2,5-disubstituted tetrahydrofuran **1.224** in 68% yield

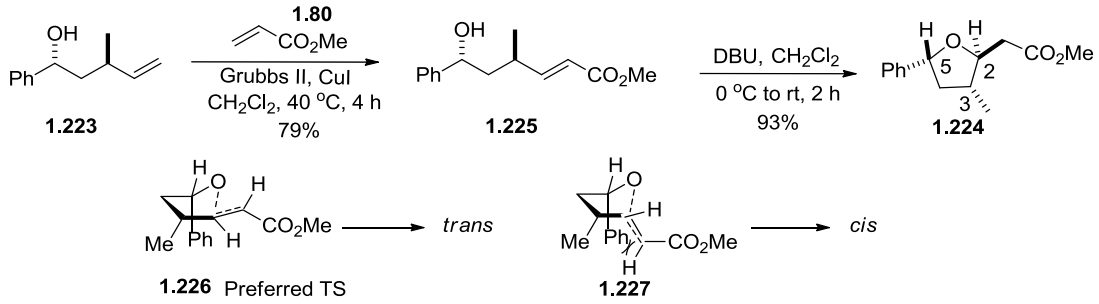
(*trans*:*cis* = 9:1) with the correct relative stereochemistry of three stereocenters of the tetrahydrofuran ring (Scheme 1.43).



Scheme 1.43. Homoallylation and Subsequent Cyclization of Benzaldehyde

1.6.4.2. Cross metathesis and base catalyzed cyclization

An alternate approach to the tetrahydrofuran ring was envisioned in which the hydroxy alkene **1.223** was converted to an unsaturated ester. The required ester **1.225** was first prepared by the Grubbs cross metathesis of the alkenol **1.223** with methyl acrylate **1.80** using Grubbs second generation catalyst and copper (I) iodide in 79% yield (Scheme 1.44).[71] Cyclization of **1.225** promoted by 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in CH_2Cl_2 gave *trans*-2,5-disubstituted tetrahydrofuran ring **1.224** as a single diastereomer in excellent 93% yield. Formation of **1.225** as a single isomer can be explained by the preferred transition state **1.226**. Transition state **1.227**, which gives *cis*-tetrahydrofuran ring, suffers from steric congestion. Thus, using either method, the required *trans*-2,5-disubstituted tetrahydrofuran ring with correct relative stereochemistry was achieved.

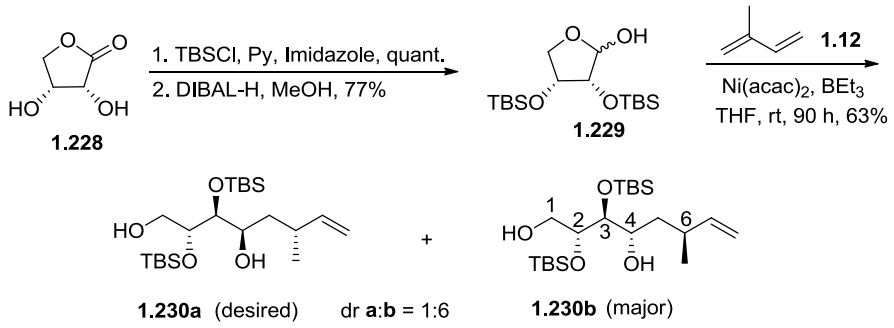


Scheme 1.44. Grubbs Cross Metathesis Followed by Cyclization of the Resulting Ester

1.6.5. Homoallylation of lactols obtained from erythronolactone with isoprene

1.6.5.1. Homoallylation of TBS protected hemiacetal 1.229

The successful racemic synthesis of the 2,5-*trans*-tetrahydrofuran ring left two challenges: synthesis of a non-racemic tetrahydrofuran ring and introduction of a side chain containing *anti*-1,2-diol. To assemble all these requirements, *tert*-butyldimethylsilyl (TBS) protected hemiacetal (lactol) **1.229** was chosen as a homoallylation substrate. Hemiacetal **1.229** was prepared in two steps from the commercially available erythronolactone **1.228** (Scheme 1.45).[72] Homoallylation of hemiacetal **1.229** with isoprene **1.12** under standard homoallylation conditions provided diastereomers **1.230a** and **1.230b**, which were separable by silica gel column chromatography, in 63% combined yield with 1:6 diastereoselectivity (based on yield after chromatography). The major diastereomer **1.230b** was crystalline and could be recrystallized to give X-ray quality crystals.



Scheme 1.45. Homoallylation of Erythronolactol **1.228** with Isoprene **1.12**

The crystal structure of major diastereomer **1.230b** clearly shows that the silyloxy groups at C2 and C3 are *anti* and the hydroxyl and methyl groups at C4 and C6 are *anti* (Figure 1.8). However, the silyloxy at C3 and the hydroxy at C4 have the wrong relative

configuration (*anti*), and thus, the minor isomer **1.230a** must have the correct relative (3,4-*syn*) and absolute configuration required for amphidinolide C.

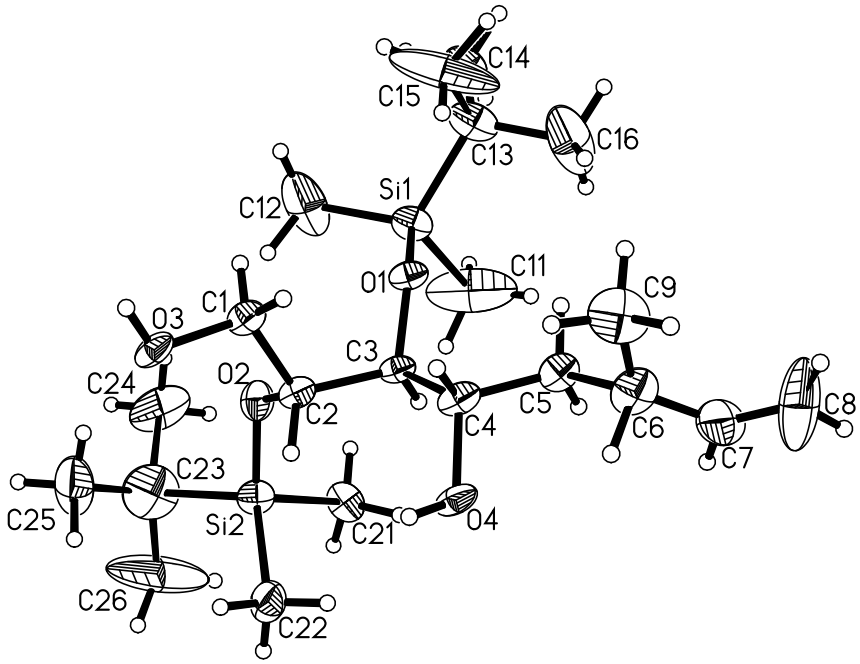
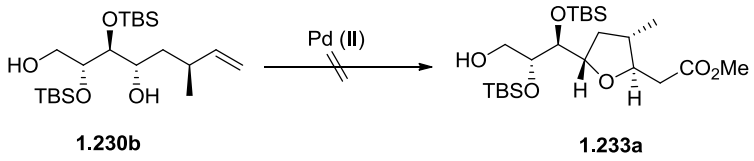


Figure 1.8. Crystal structure of **1.230a**

The observed diastereofacial selectivity was much higher than expected for the homoallylation reaction. In the limited number of chiral aldehydes investigated by Tamaru *et al.*, the diastereofacial selectivity with respect to the aldehyde was typically very low (1:1 to 1.6:1).[73] The formation of the major isomer **1.230b** appears to follow the trend observed by Evans *et al*. in the aldol reactions of a series of alkoxy and bisalkoxy aldehydes.[74,75]

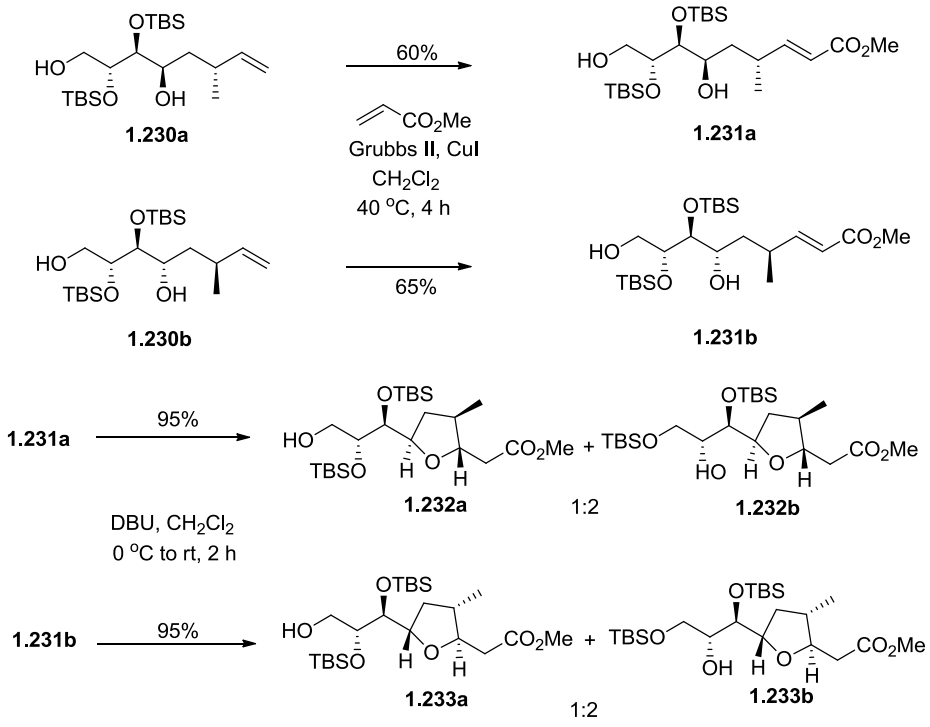
Undaunted by this setback, the cyclization of both diastereomers **1.230** was investigated. The Semmelhack Pd-catalyzed cyclization/methoxycarbonylation of major isomer **1.230b** failed to yield the tetrahydrofuran **1.233a** (Scheme 1.46).



1.230b **1.233a**

Scheme 1.46. Attempted Pd-Catalyzed Cyclization of Major Isomer **1.230b**

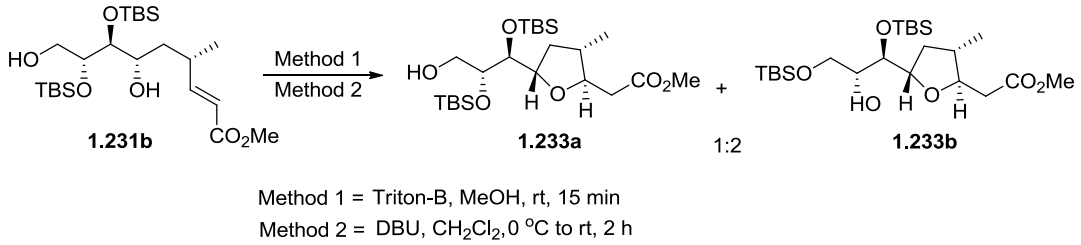
Therefore, an alternate chain extension and cyclization method was examined. Cross-metathesis of both the minor isomer **1.230a** and the major isomer **1.230b** with methyl acrylate **1.80** gave *α,β*-unsaturated methyl esters **1.231a** and **1.231b**, respectively (Scheme 1.47). Cyclization of **1.231a** and **2.231b** using DBU afforded the tetrahydrofurans **1.232a** and **1.233a** in excellent yields.



Scheme 1.47. Cross Metathesis Followed by Cyclization of Hydroxyalkenes

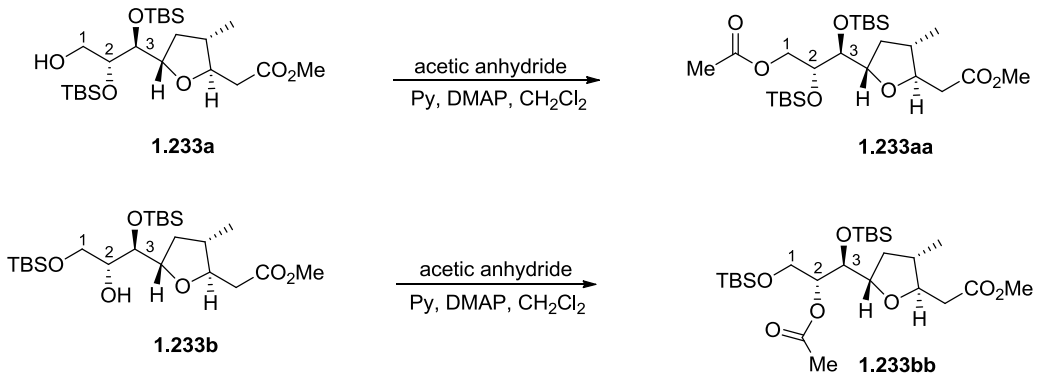
Some migration of a silyl group was observed during the cyclization process. The TBS group migrated from the secondary to the primary position (Scheme 1.48). Silyl

migration is a frequently encountered process.[76] It was found that in the presence of a strong base and polar solvent (method A), the migration was faster in comparison to a weak base and less polar solvent (method B).



Scheme 1.48. TBS Group Migration During the Cyclization of **1.231b**

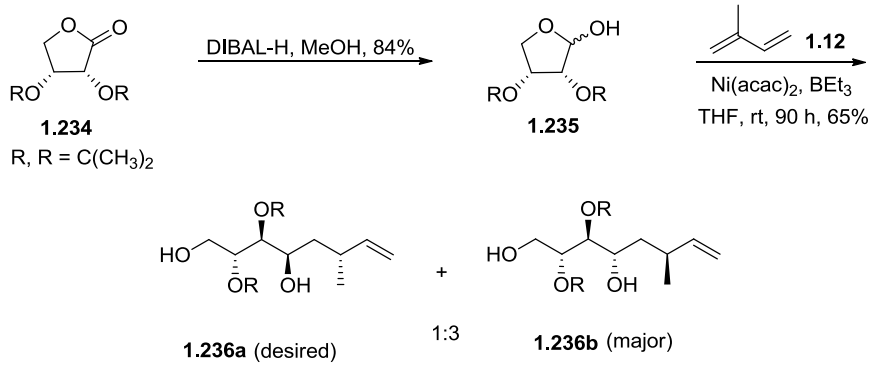
The migration of a silyl group was investigated by the change in ^{13}C chemical shifts of hydroxyl containing carbons in the starting alcohols and their acetylated derivatives. Both isomers **1.233a** and **1.233b** were acetylated by reacting with acetic anhydride in the presence of DMAP and pyridine (Scheme 1.49). The primary carbon (C-1) of **1.233a** resonated at 64.0 ppm and the secondary carbon (C-2) of **1.233b** resonated at 65.8 ppm. Upon acetylation, C-1 (primary carbon) of **1.233aa** moves downfield to resonate at 66.4 ppm but the C-2 (secondary carbon) of **1.233bb** moves upfield to resonate at 61.9 ppm.[77] It is also supported by the chemical absorption value hydrogen in ^{1}H NMR. In **1.233bb**, the secondary proton (H-2) resonates at 4.9 ppm as multiplet which is not present in **1.233aa** where all protons resonate are below 4.3 ppm. The multiplet nature of H-2 in **1.233bb** also supports the fact that C-2 TBS group migrates, not the C-3 TBS group because the H-3 would have been a doublet of doublet instead of multiplet.



Scheme 1.49. Acetylation of Alcohols

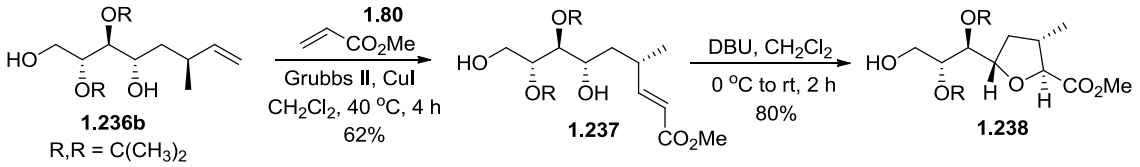
1.6.5.2. Homoallylation of acetonide protected hemiacetal 1.229

In order to avoid protecting group migration and perhaps to affect a more favorable stereochemical outcome, an alternate protecting group was examined. Homoallylation of acetonide protected hemiacetal **1.235**[78] gave a mixture of diastereomers **1.236a** and **1.236b** (1:3) (Scheme 1.50). The diastereomers were difficult to separate and required repeated silica gel column chromatography.



Scheme 1.50. Homoallylation of Erythronolactol **1.234**

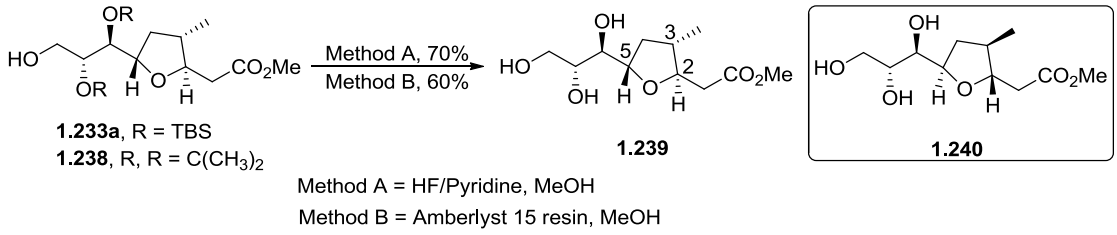
Cross metathesis of the major diastereomer **1.236b** with methyl acrylate **1.80** (Scheme 1.51) followed by cyclization with DBU gave **1.238** in 80% yield.



Scheme 1.51. Cross Metathesis and Subsequent Cyclization of **1.236b**

To compare the configuration of the tetrahydrofurans **1.238** and **1.233a,** obtained from the acetonide-protected hemiacetal **1.234** and the TBS-protected hemiacetal **1.229**, the protecting groups were removed (Scheme 1.52). The TBS- groups were cleaved using HF/pyridine in MeOH (method A) that provided triol **1.239.** The acetonide group was removed using Amberlyst 15 resin in MeOH to give the identical triol **1.239.**

The ^{1}H and ^{13}C NMR spectra of the triol **1.239** obtained by the removal of both **1.233a** and **1.238** were identical, suggesting that the tetrahydrofuran obtained from both hemiacetals have the same configuration.

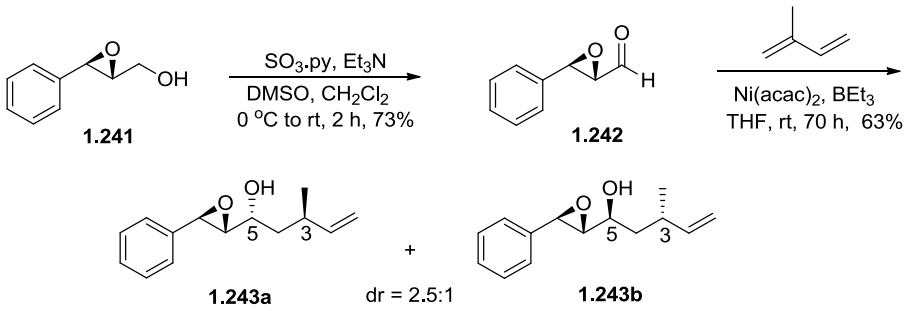


Scheme 1.52. Removal of the TBS and Acetonide Groups

The triol **1.239** has the correct orientation of the hydroxyl groups compared to the required fragment **1.240**. However, although the relative stereochemistry of stereocenters (2, 3 and 5) of the tetrahydrofuran ring is correct, the absolute configuration is reverse (Scheme 1.52).

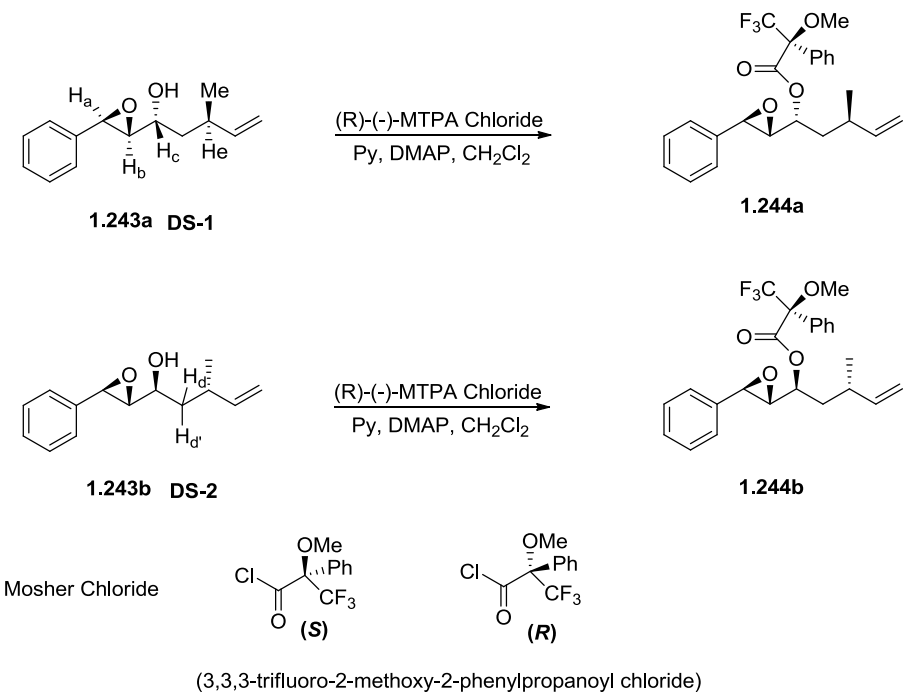
1.6.6. Homoallylation of epoxyaldehydes with isoprene

Epoxides are versatile functional groups. An epoxide can be opened with water to reveal a diol or alternatively it can be oxidatively cleaved to obtain an aldehyde. Due to this fact epoxyaldehyde **1.242** was chosen as our next substrate for homoallylation. Oxidation of commercially available (2*R*, 3*R*)-3-phenylglycidol (epoxycinnamyl alcohol) **1.241** by Moffat oxidation method gave (2*R*, 3*R*)-3-phenylglycidal **1.242** in 73% yield.[79] Homoallylation of **1.242** with isoprene gave a separable mixture of diastereomers **1.243a** and **1.243b** in 2.5:1 ratio and 63% combined yield (Scheme 1.53).



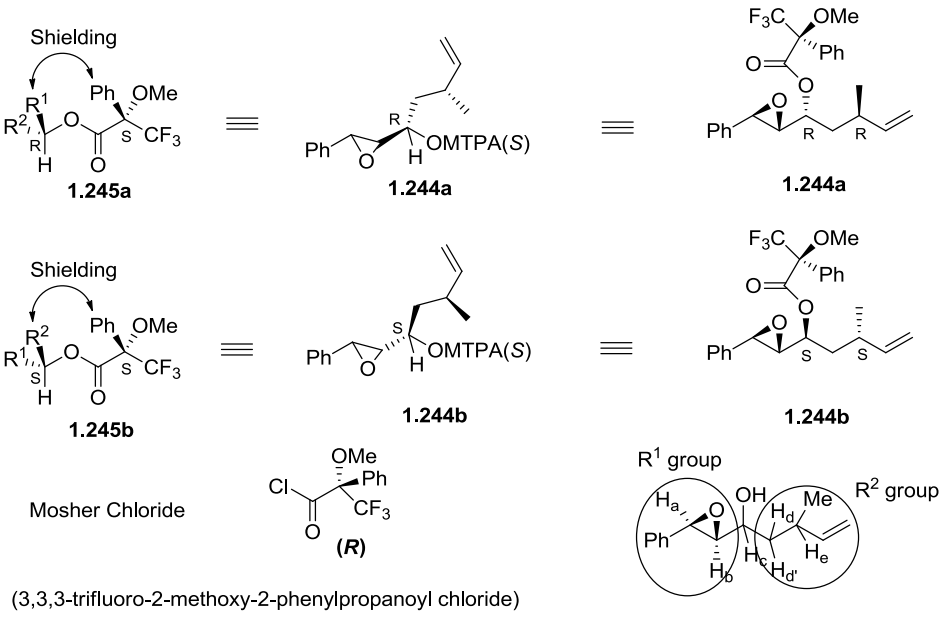
Scheme 1.53. Homoallylation of Epoxycinnamaldehyde **1.241** with Isoprene

The absolute stereochemistry of **1.243** was determined by the Mosher ester method.[80] Both diastereomeric alcohols **1.243a** and **1.243b** were treated with (*R*)-MTPA-chloride (MTPA-chloride= α-methoxy-α-(trifluoromethyl) phenylacetyl chloride) in the presence of pyridine and DMAP to give the (*S*)- Mosher ester **1.244a** and **1.244b,** respectively in good yields (Scheme 1.54) .



Scheme 1.54. Mosher Ester Formation

On the basis of the generally accepted confirmation model for Mosher esters (Scheme 1.55), the trifluoromethyl group and the carbonyl hydrogen (H_c) are eclipsed with carbonyl oxygen. The R^1-group in the (*S*)-MTPA ester **1.245a** will be shielded by the phenyl group (of MTPA) when the chiral alcohol has (*R*)-configuration. The chemical shift of proton signals of R^1-group (H_a, H_b) will consequently be upfield (smaller value in δ) and proton signal of H_d will be downfield (larger δ value). In case of another (*S*)-MTPA ester **1.245b**, the R^2 group is shielded (H_e moved upfield and the closest proton H_b of R^2-group moved downfield (change in H_a is insignificant). However, in the later case (**1.244b**), the change in chemical shift values of other protons were not as consistent as in the earlier case (**1.244a**). The chemical shift values of protons (Table 1.1) support these predictions. Therefore, **1.244a** has *R*-configuration at OH-containing center and **1.244b** has *S*-configuration at the same center.



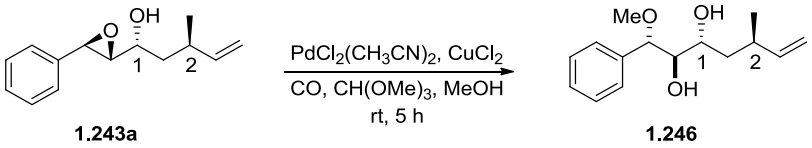
Scheme 1.55. Conformation Model of Mosher Esters from Alcohol **1.245**

Table 1.1. Chemical Shift Values of Different Protons Present in Mosher Ester

	1.243a (DS-1)			**1.243b** (DS-2)		
	SM **1.243a** (ppm)	*S*-ester **1.244a** (ppm)	Δδ (ppm)	SM **1.243b** (ppm)	*S*-ester **1.244b** (ppm)	Δδ (ppm)
H_a	3.98	3.82	-0.16	3.88	3.85	-0.03
H_b	3.09	2.93	-0.16	3.05	3.18	+0.15
H_c	4.03	5.11	+1.08	3.73	5.05	+1.32
H_d	1.57	1.75	+0.18	1.61	1.67	+0.06
$H_{d'}$	1.69	1.91	+0.22	1.65	1.79	+0.14
H_e	2.45	2.35	-0.10	2.40	2.15	-0.15
Me	1.06	1.06	0.00	1.06	1.02	-0.04

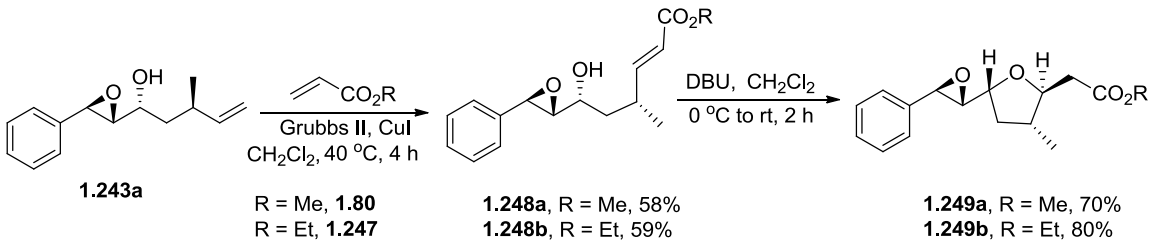
The major isomer **1.243a** with absolute configuration (3*R*, 5*R*) was the required diastereomer to obtain the tetrahydrofuran ring of correct stereochemistry of C1-C9 fragment of amphidinolide C.

Attempted cyclization of **1.243a** catalyzed by palladium (II) with concomitant chain extension with carbon monoxide was carried out as described earlier (Section 1.6.5.1). However, the epoxide ring was opened by MeOH producing **1.246** (Scheme 1.56).



Scheme 1.56. Attempted Cyclization of Hydroxyalkene **1.243a**

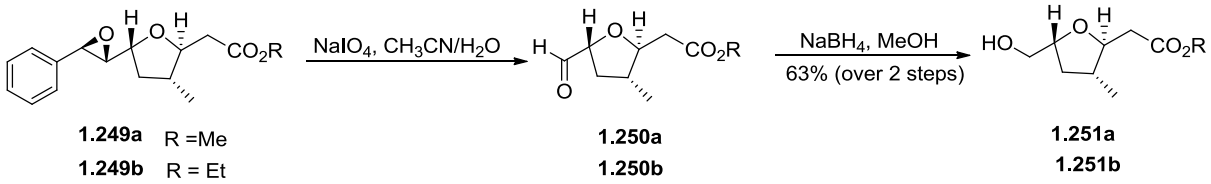
Cross metathesis of **1.243a** with methyl acrylate **1.80** (or ethyl acrylate **1.247**) gave *α,β*-unsaturated methyl (or ethyl) ester **1.248a** (or **1.248b**), which on cyclization with DBU, gave **1.249a** (or **1.249b**) as a single isomer in 70% (or 80%) yield (Scheme 1.57).



Scheme 1.57. Cross Metathesis and Subsequent Cyclization of *bis*-Homoallylic Alcohols

Oxidative cleavage of epoxide ring of **1.249a** by $NaIO_4$ in acetonitrile/water[81] gave aldehyde **1.250a** (Scheme 1.58). The pure aldehyde **1.250a** could be isolated by SiO_2 column chromatography. However, the crude aldehyde **1.250a** was subjected to

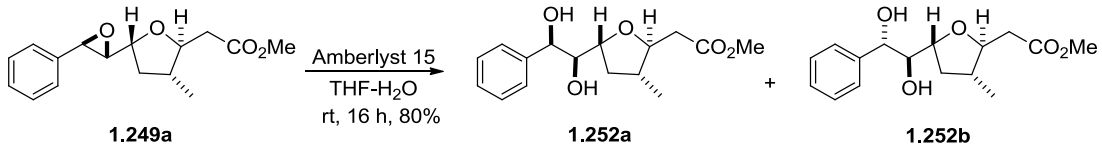
$NaBH_4$/MeOH reduction, without purification, to afford the stable alcohol **1.251a** with 63% overall yield over 2 steps in >95% ee.



Scheme 1.58. Epoxide Ring Cleavage and Subsequent Reduction

The tetrahydrofuran ring **1.251a** has the correct relative and absolute configuration of the stereocenters as required for the synthesis of the C1-C9 (southern) fragment of amphidinolide C.

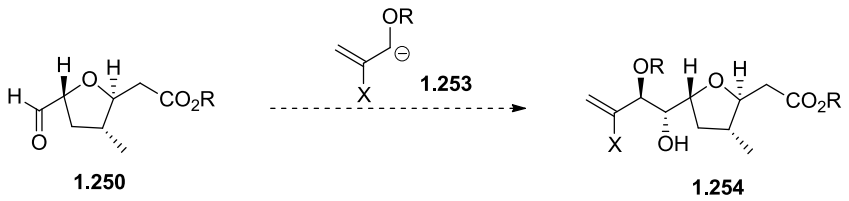
Epoxide **1.249a** was also opened with Amberlyst 15 resin in THF-water that produced diastereomers **1.252a** and **1.252b** in equal amount (Scheme 1.59).



Scheme 1.59. Acid Mediated Epoxide Ring Opening by H_2O

1.6.7. Coupling of tetrahydrofuran aldehyde 1.250a with the proper side chain partner

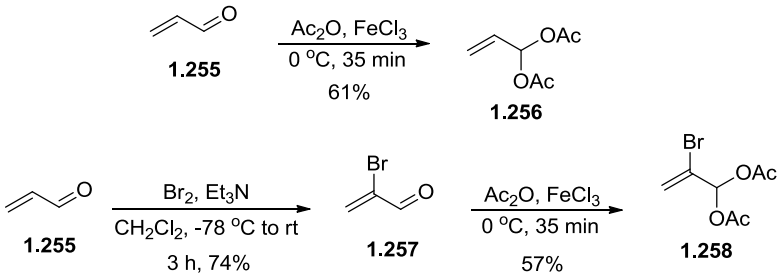
With the completion of the synthesis of tetrahydrofuran aldehyde **1.250**, the next goal was to couple aldehyde **1.250** with a properly functionalized fragment to complete the synthesis of the C1-C9 fragment of amphidinolide C (Scheme 1.60). For this synthesis, we needed a synthetic equivalent of **1.253.** Several approaches were studied.



Scheme 1.60. Coupling of Aldehyde with Properly Functionalized Side Chain Fragment

1.6.7.1. Coupling of 1.250 with diacetate/bromodiacetate

The coupling of tetrahydrofuran aldehyde **1.250** with diacetate of acrolein **1.256** and bromoacrolein **1.258** were carried out following the literature procedures (Scheme 1.61).[82,83]

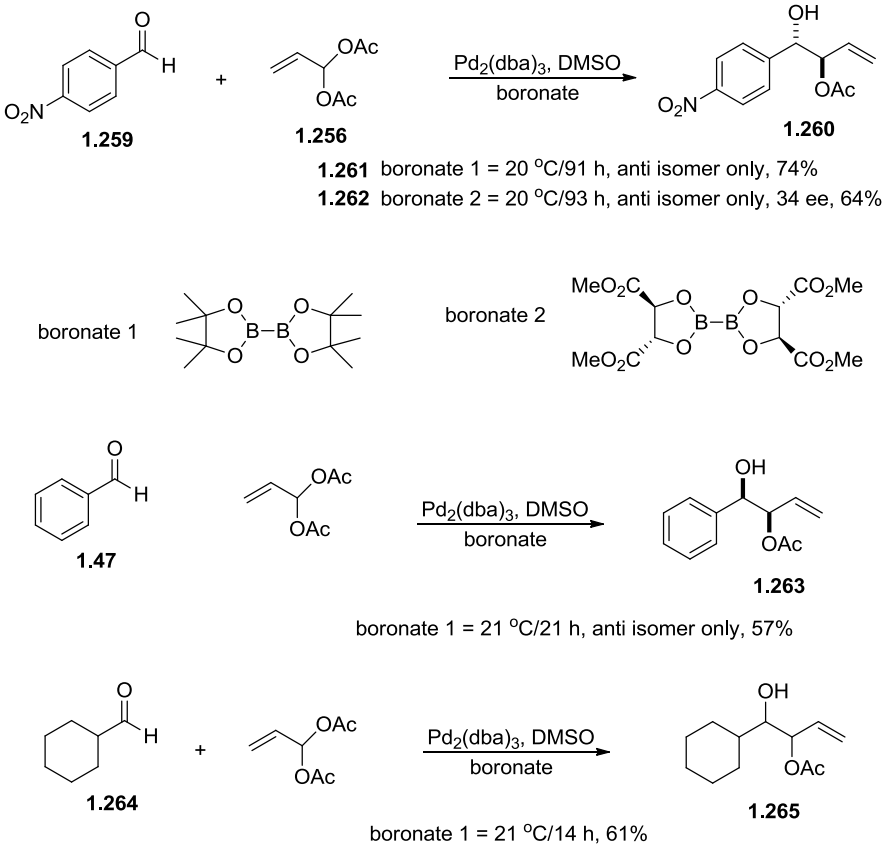


Scheme 1.61. Synthesis of Diacetate of Acrolein **1.255** and Bromoacrolein **1.257**

Szabo reported the palladium catalyzed coupling of diacetate **1.256** with different aldehydes (Scheme 1.62) in the presence of stoichiometric amount of different achiral and chiral boronates.[84] For example, diacetate **1.256** upon treating with 4-nitobenzaldehdye **1.259** and a palladium catalyst with a stoichiometric amount of $B_2(pin)_2$ **1.261** (or chiral boronate **1.262**) afforded homoallylic alcohol **1.260** as a single diastereomer (*anti* diastereoselectivity) (Scheme 1.62).

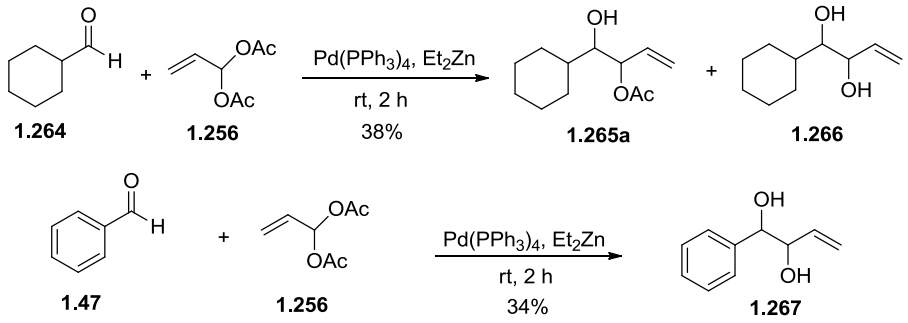
In our hands, the reaction of benzaldehyde with the diacetate under the same conditions with achiral boronate **1.261** produced only *anti*-homoallylic alcohol **1.263**. Furthermore, cyclohexanecarboxaldehyde **1.264** produced homoallylic alcohol **1.265** as a single

diastereomer in 61% yield (Scheme 1.62). Unfortunately, the diacetate of bromoacrolein **1.258** did not react with any of these aldehydes.



Scheme 1.62. Pd-Catalyzed Coupling of Diacetate **1.256** with Different Aldehydes

In another attempt, the allylation reactions between aldehydes and diacetate were carried out in the presence of a catalytic amount of palladium and diethylzinc (as a reducing agent).[85,86] When cyclohexanecarboxaldehyde **1.264** (1.0 equiv.) was reacted with diacetate **1.256** (1.2 equiv.) in the presence of 5 mol% $Pd(PPh_3)_4$ and diethyl zinc (2.4 equiv.), it produced a 3:1 mixture of **1.265a** and **1.266** (Scheme 1.63). Benzaldehyde **1.47**, on the other hand, produced diol **1.267** as a single isolated product. Again, none of these aldehydes reacted with bromodiacetate **1.258**.

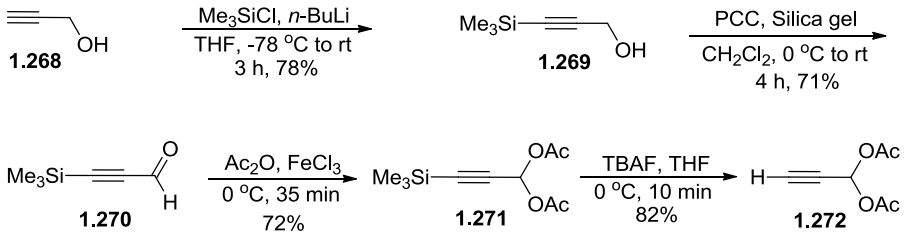


Scheme 1.63. Pd-Catalyzed Reaction of Allyl Diacetate in the Presence of Diethylzinc

Tetrahydrofuran aldehyde **1.250**, however, did not react with any of these diacetates under various reaction conditions.

1.6.7.2. Coupling of aldehyde 1.250 with diacetates 1.271 and 1.272

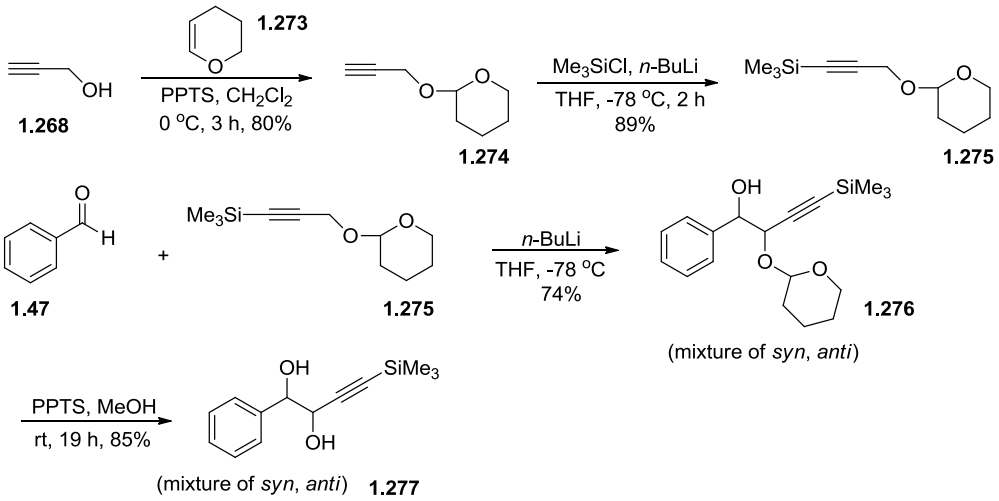
With the unsuccessful results of the coupling of tetrahydrofuran aldehyde **1.250** with diacetates **1.256** and **1.258**, different diacetates (**1.271** and **1.272**) derived from TMS-protected propargyl aldehydes were designed. The known aldehyde **1.270**[87] was converted to diacetate **1.271** using the same conditions as above (Scheme 1.64).[83] This diacetate **1.271** was converted to diacetate **1.272** by the removal of TMS using TBAF in THF. Unfortunately, none of the aldehydes reacted with either of these diacetates under different reaction conditions tested (Condition A: $Pd_2(dba)_3$, $B_2(pin)_2$, DMSO; Condition B: $Pd(PPh_3)_4$, Et_2Zn, THF).[84,85]



Scheme 1.64. Preparation of Diacetates **1.271** and **1.272** from Propargyl Aldehyde **1.268**

1.6.7.3. Coupling of aldehyde 1.248 different coupling partner

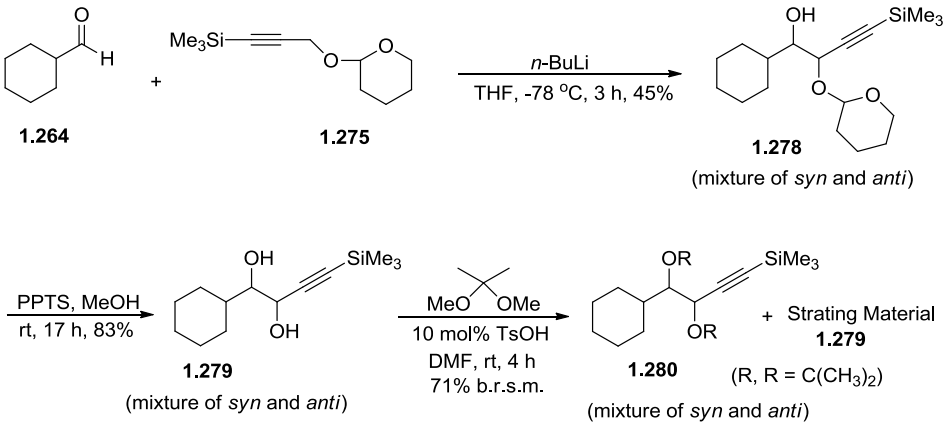
Tetrahydrofuran (THP) protected TMS-propagylic alcohol **1.275** was chosen as the next coupling partner. It was synthesized following a literature procedure[88] and first coupled with benzaldehyde **1.47**, after deprotonation with *n*-BuLi in THF (Scheme 1.65). The mono-protected diol **1.276** was formed as a mixture of *syn*- and *anti*-isomers (1:2) in 41% yield. Removal of the THP group using pyridinium *p*-toluene sulfonate (PPTS) in methanol gave diol **1.277** showing the same ratio of isomers.



Scheme 1.65. Synthesis of THP Protected TMS-Propagylic Alcohol **1.275** and Coupling with Benzaldehyde

In the next step, the THP protected TMS-propagylic alcohol **1.275** was coupled with cyclohexanecarboxaldehyde **1.264** (Scheme 1.66) to produce mono-protected diol **1.278**

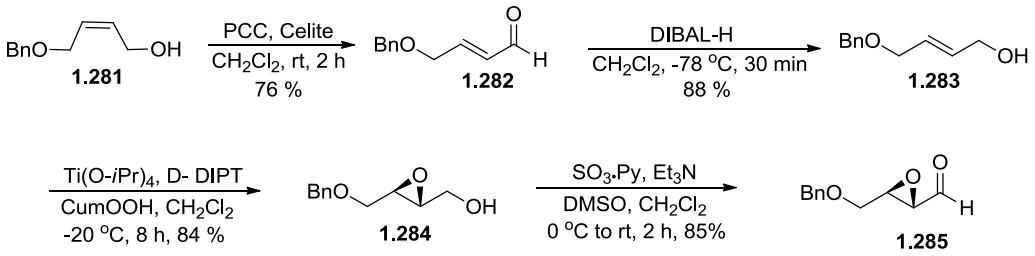
(*syn*:*anti* = 1:2) along with an unidentified product in a 1:1 ratio with **1.278**. Removal of the THP group using PPTS in methanol followed by 1,2-diol protection using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) gave **1.280**. The diol protected product **1.280** and recovered unreacted diol **1.279** has same ratio (1:2) of *syn*:*anti* isomers that confirms the same ratio in product **1.278**. However, attempts to couple tetrahydrofuran aldehyde **1.250** with the THP protected TMS-propagylic alcohol **1.275** was not successful.



Scheme 1.66. Coupling of Cyclohexanecarboxaldehyde **1.264** with **1.275**

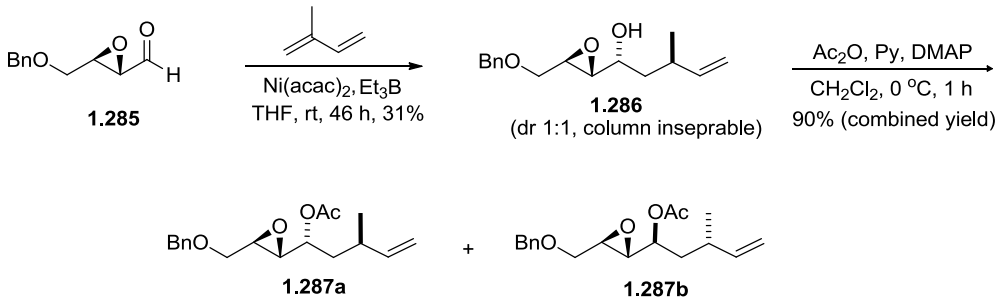
1.6.8. Stereoselective epoxide opening: New route for the C1-C9 fragment synthesis

All the attempts to couple the tetrahydrofuran aldehyde **1.250** with properly functionalized coupling partners for the side chain of the C1-C9 fragment of amphidinolide C were futile. Therefore, a different strategy of stereoselective epoxide ring opening of *α*-acetoxy aldehyde **1.287** was envisioned. The known aldehyde **1.285** was prepared in four steps from commercially available benzyl-mono-protected *cis*-diol **1.281** (Scheme 1.67).[89]



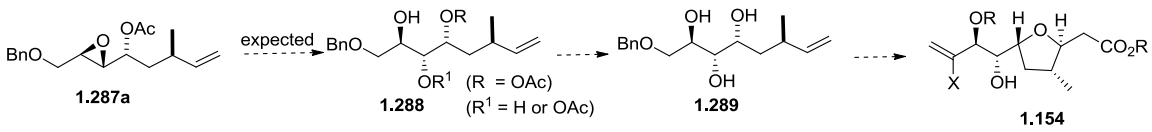
Scheme 1.67. Synthesis of Epoxyaldehyde **1.281**

Homoallylation of epoxyaldehyde **1.285** with isoprene **1.12** produced a column inseparable mixture of *bis*-homoallylic alcohol **1.286** with 1:1 diastereoselectivity in low yield (Scheme 1.68). The mixture of diastereomers **1.286** was acetylated. Careful SiO_2 column chromatography separated the acetylated diastereomers **1.287a** and **1.287b**.



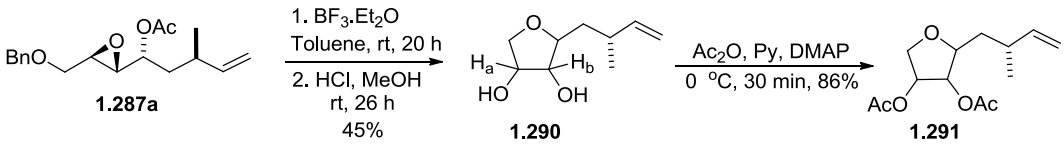
Scheme 1.68. Homoallylation and Subsequent Acetylation of Epoxyaldehyde

It was postulated that the epoxide ring could be stereoselectively opened with the assistance of the acetate group to give **1.288** (Scheme 1.69).[90] We expected that compound **1.288** could then be converted to the C1-C9 fragment of amphidinolide C **1.254**.



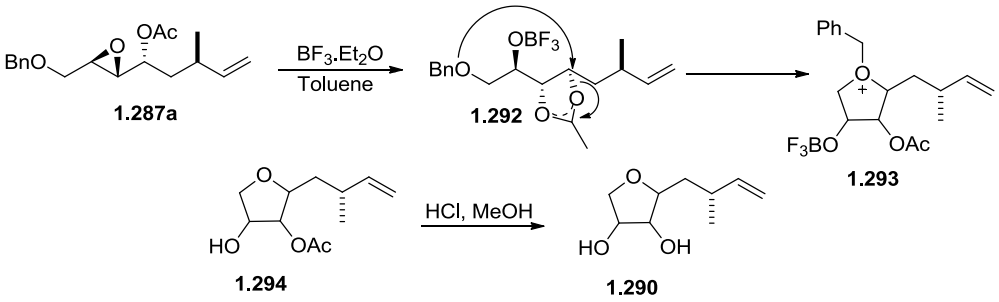
Scheme 1.69. Expected epoxide opening of **1.287a**

Therefore, one of the acetylated diastereomers **1.287a** was treated with $BF_3 \cdot Et_2O$ in dry ether and stirred at room temperature (rt) for 20 h (Scheme 1.70). Since the proton NMR of the crude material of this reaction did not show the epoxide, it was subjected to deacetylation with 1% HCl in MeOH. Surprisingly, the main product isolated after SiO_2 column chromatography did not have a benzyl group. It is probable that there is double neighboring group assistance from the benzyl and acetyl group leading to the formation of the "debenzylated" tetrahydrofuran **1.290**. The formation of tetrahydrofuran ring **1.290** was verified from the shift in position of protons (H_a and H_b) in the acetylated derivative **1.291**, incorporation of two acetyl groups in **1.291**, 2D ^1H and ^{13}C NMR.



Scheme 1.70. Stereoselective Ring Opening of **1.287a**

A plausible mechanism has been proposed for this transformation (Scheme 1.71). The α-acetoxy group attacks the Lewis acid activated epoxide from the lower face to give the dioxolane cation **1.292**. This is followed by the attack of the benzyl oxygen producing intermediate **1.293** that subsequently loses the benzyl group to give the tetrahydrofuran derivative **1.294**. Reaction of **1.294** with HCl in methanol removes the acetate group producing diol **1.290**.

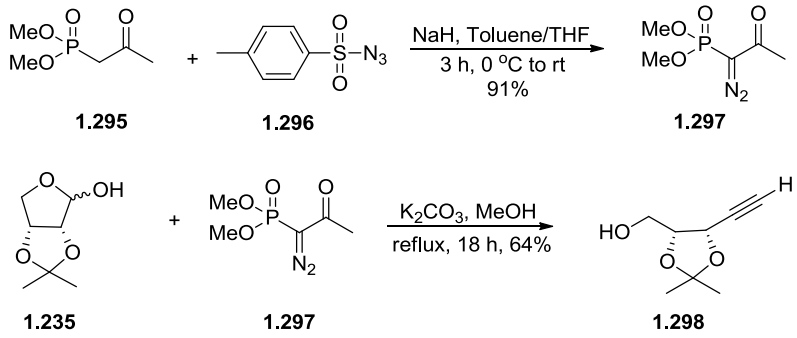


Scheme 1.71. A Proposed Mechanism for the Formation of the Tetrahydrofuran Derivative **1.290**

1.6.9. Attempted Homoallylation of an aldehyde carrying all the functionalities present in the C1-C9 fragment of amphidinolide C

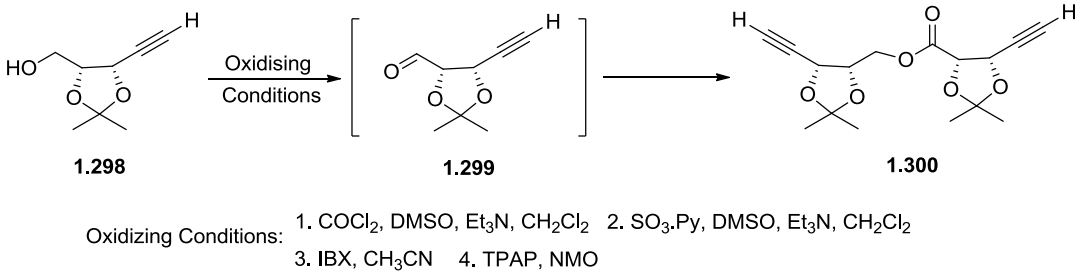
In search of a better functionalized aldehyde for the synthesis of the C1-C9 fragment, the aldehyde **1.299** with a terminal acetylene was chosen. It seemed that upon homoallylation, the *bis*-homoallylic derivative obtained would bring all the essential functionalities present in this fragment.

The Bestmann-Ohira reagent[91] was prepared by the reaction of *p*-toluenesulfonyl azide **1.296** with the phosphonate **1.295** using literature procedures (Scheme 1.72).[92,93] Treatment of lactol **1.235** with the Bestmann-Ohira reagent **1.297** in the presence of K_2CO_3 in methanol gave **1.298** in 64% yield.



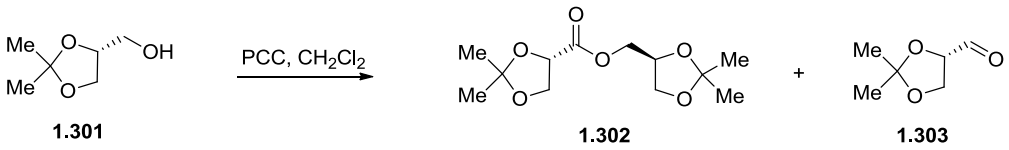
Scheme 1.72. Synthesis of Terminal Alkyne Derivative **1.298** of Alcohol **1.235**

Unfortunately, all the attempts to oxidize **1.298** to aldehyde **1.299** were futile because of the over-oxidation of the aldehyde **1.299** to the ester **1.300** in low yield.



Scheme 1.73. Over-oxidation of Alcohol **1.298** to Ester **1.300**

Ermolenko and coworkers have also observed the over-oxidation product during the PCC oxidation of (*R*)-2,3-O-isopropylideneglycerol **1.67** (Scheme 1.74).[94] They found that the oxidation of alcohol **1.301** using PCC in CH_2Cl_2 gave ester **1.302** in a 5:2 ratio with the required aldehyde **1.303**. The reaction in multigram scale followed by the careful distillation afforded the aldehyde **1.303** in 30% yield.



Scheme 1.74. Over-oxidation of Alcohol **1.301** to ester **1.302**

1.7. Summary

1) Homoallylation of aldehydes, hemiacetals and epoxyaldehydes with isoprene were carried out. Hemiacetal derivatives and epoxyaldehydes were the first substrates of homoallylation reactions. In most cases, the resulted diastereomers were separable by careful SiO_2 column chromatography. These reactions proceeded with excellent regioselectivity and low to very good diastereoselectivity.

2) Homoallylation of benzaldehyde with isoprene gave *bis*-homoallylic alcohol with excellent regio- and stereoselectivity. Palladium catalyzed cyclization of the *bis*-homoallylic alcohol followed by subsequent methoxycarbonylation obtained the 2,3,5-trisubstituted tetrahydrofuran ring in good yield. Alternatively, Grubbs cross-metathesis of the bis-homoallylic alcohol with alkyl acrylate followed by DBU cyclization of the ε-hydroxy-α,β-unsaturated ester also obtained the same 2,3,5-trisubstituted tetrahydrofuran ring. The tetrahydrofuran ring had the same relative stereochemistry as the tetrahydrofuran ring present in C1-C9 fragment of amphidinolide C.

3) The *bis*-homoallylic alcohols obtained from the homoallylation of TBS-protected hemiacetal with isoprene were subjected for Grubbs cross metathesis and DBU cyclization. The tetrahydrofuran ring obtained from the minor diastereomer had the same relative and absolute stereochemistry found in C1-C9 fragment of amphidinolide C. Therefore, the overall yield of this fragment synthesis was low.

4) Homoallylation of epoxy-cinnamaldehyde with isoprene produced two diastereomers in favor of the required diastereomer being the major one. The major diastereomer was converted to tetrahydrofuran aldehyde which has been elaborated to the C1-C9 fragment

of amphidinolide C by other groups. This is the shortest reported route for the synthesis of such tetrahydrofuran rings.

5) Attempted coupling of tetrahydrofuran aldehyde with different coupling partners bearing the essential functionalities of C1-C9 fragment of amphidinolide C were unsuccessful, although different other aldehydes (benzaldehyde, nitrobenzaldehyde, cyclohexanecarboxaldehyde etc.) obtained satisfactory results.

1.8. General Experimental

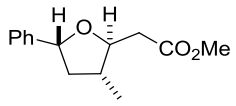
Glassware used for all experiments were oven-dried and all reactions were carried out under argon atmosphere unless otherwise mentioned. All reaction solvents were purified prior to use: CH_2Cl_2, MeOH, MeCN were dried by distillation over calcium hydride and THF over sodium-benzophenone ketyl. Reagent grade DMF was obtained from Sigma-Aldrich and used without further purification.

Proton (^{1}H) NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra at 75 MHz. Proton NMR spectra were referenced to residual $CDCl_3$ (7.27 ppm) and ^{13}C {^{1}H} NMR spectra were referenced to the center line of $CDCl_3$ (77.23 ppm). Crystal structure(s) were determined on a Bruker Apex- II CCD single crystal diffractometer. Optical rotations were measured on a polarimeter using a glass cell with 2 mL capacity and 10 cm path length. Infrared spectra were recorded on FTIR instrument using NaCl plates (liquids, oils) or using an ATR attachment (solids).

General procedure for homoallylation: Into a flask containing $Ni(acac)_2$ (0.1 mmol) in dry THF (3 mL) was added isoprene (4.0 mmol) and the resulting solution was stirred at room temperature for 10 min. A solution of aldehyde (1.0 mmol) in dry THF (2 mL) and Et_3B (1.0 M solution in hexane, 2.4 mmol) were added sequentially. The homogeneous mixture was stirred under argon atmosphere at room temperature for 70 to 90 h (monitored by ^{1}H NMR), then it was diluted with EtOAc. The mixture was washed with 2M HCl, saturated $NaHCO_3$, and saturated brine solutions sequentially. The organic layer was dried over anhydrous $MgSO_4$, concentrated in *vacuo* and purified by column chromatography (SiO_2, hexanes:EtOAc).

General procedure for Grubbs cross metathesis: To a round bottom flask equipped with a reflux condenser was charged Grubbs second generation catalyst (7 mol %) and copper iodide (10 mol %). A solution of alkenol (1.0 equiv.) in freshly distilled CH_2Cl_2 was added followed by methyl acrylate (2.0 equiv). The flask was immersed in an oil bath preheated to 40 ^oC for 4 h (TLC analysis). The solvent was evaporated in *vacuo* and the crude product was purified by column chromatography (SiO_2, hexanes:EtOAc).

General procedure for cyclization by DBU: To a stirred solution of alkenol (1.0 equiv.) in freshly distilled CH_2Cl_2 at 0 ^oC was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 1.2 equiv.). The resulting solution was stirred at 0 ^oC for 1 h and then at room temperature for another 1 h (TLC analysis). The reaction was quenched by addition of the saturated aq. NH_4Cl solution and extracted with EtOAc. The organic layer was separated and washed with brine solution, dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc).



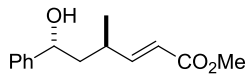
1.224

(±) Methyl 2-(3-methyl-5-phenyltetrahydrofuran-2-yl)acetate (1.224): A round bottom flask was charged copper (II) chloride (0.296 g, 2.20 mmol) and $PdCl_2(CH_3CN)_2$ (0.026 g, 0.10 mmol). The flask was flushed with carbon monoxide 3 times and then dry MeOH (3 mL) was added. To this mixture was added a solution of hydroxyalkene **1.223** (0.176 g, 1.00 mmol) in MeOH (1 mL) followed by trimethylorthoformate (0.1 mL, 1.0 mmol). The mixture was then stirred at rt for 6 h (TLC analysis) under an atmosphere of carbon monoxide (balloon). The solvent was evaporated in *vacuo* and the residue was

extracted with pentane. The pentane was concentrated in *vacuo* and the product was purified by column chromatography to afford **1.224** as colorless oil (0.159 g, 68%).

The unsaturated ester **1.225** (0.08 g, 0.341 mmol) and DBU (56 µL, 0.376 mmol) were reacted in dry CH_2Cl_2 (2 mL) following the general procedure for cyclization to give **1.224** as a colorless oil (0.075 g, 93%).

IR (neat, NaCl) 2955, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.14-7.25 (5H, m), 4.97 (1H, dd, *J* = 6.0, 9.8 Hz), 4.01-4.08 (1H, m), 3.64 (3H, s), 2.54-2.59 (2H, m), 2.39-2.50 (1H, m), 2.02-2.13 (1H, m), 1.45-1.61 (1H, m), 1.01 (3H, d, *J* = 6.5 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 172.3, 143.9, 128.7, 127.5, 126.1, 82.7, 80.4, 52.1, 44.9, 40.9, 39.7, 16.7; HRMS (FAB, MNa^+) calcd for $C_{14}H_{18}O_3Na$: 257.1154. Found 257.1159.

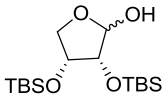


1.225

(±) (E)-Methyl 6-hydroxy-4-methyl-6-phenylhex-2-enoate (1.225): Grubbs second generation catalyst (0.034 g, 0.040 mmol), copper iodide (0.011 g, 0.057 mmol), hydroxy alkene **1.223** (0.100 g, 0.567 mmol) and methyl acrylate (0.10 mL, 1.13 mmol) were reacted in dry CH_2Cl_2 (3 mL) following the general procedure to afford **1.225** as a colorless oil (0.105 g, 79%).

IR (neat, NaCl) 3447, 3022, 2950, 2915, 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29-7.40 (5H, m), 6.94 (1H, dd, *J* = 8.0, 15.7 Hz), 5.78 (1H, dd, *J* = 1.1, 15.7 Hz), 4.68-4.74 (1H, m), 3.74 (3H, s), 2.43 (1H, app sep, *J* = 6.9 Hz), 1.91-2.05 (1H, m), 1.87 (1H, d, *J* = 3.2 Hz), 1.65-1.74 (1H, m), 1.11 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 167.6, 154.7,

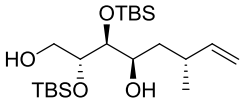
144.7, 129.0, 128.3, 126.4, 119.9, 76.5, 72.8, 51.9, 45.4, 33.8, 19.8; HRMS (FAB, MNa^+) calcd for $C_{14}H_{18}O_3Na$: 257.1154. Found 257.1162.



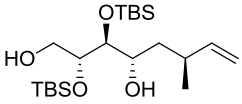
1.229

(*3R,4R*)-3,4-bis(tert-butyldimethylsilyloxy)tetrahydrofuran-2-ol (1.229): TBS-erythrono lactone **1.229a** (3.0 g, 8.6 mmol, 1.0 equiv.) and DIBAL-H (1.0 M solution in hexane, 25.9 mL, 3.0 equiv.) were reacted in dry CH_2Cl_2 (150 mL) at -78 ^oC following the literature procedure.**Error! Bookmark not defined.** Purification by column hromatography (SiO_2, hexanes: EtOAc) afforded **1.229** as a colorless oil (2.3 g, 77%).

IR (neat, NaCl) 3417, 2955, 2923 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.05 (1H, dd, *J* = 4.3, 7.4 Hz), 4.24 (1H, d, *J* = 11.7 Hz), 4.15-4.19 (1H, m), 3.92-3.98 (3H, m), 0.95 (9H, s), 0.91 (9H, s), 0.15 (6H, s), 0.11 (3H, s), 0.09 (3H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 97.1, 73.4, 73.1, 72.5, 26.1, 25.9, 18.5, 18.3, - 4.4, -4.5, -4.6, -4.81; HRMS (FAB, MNa^+) calcd for $C_{16}H_{36}O_4Si_2Na$: 371.2050. Found 371.2058.



1.230a

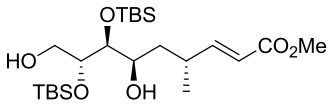


1.230b

(*2R,3S,4R,6R*) and (*2R,3S,4S,6S*) 2,3-bis(tert-butyldimethylsilyloxy)-6-methyloct-7-ene-1,4-diol (1.230a and 1.230b): $Ni(acac)_2$ (0.026 g, 0.10 mmol), isoprene (0.4 mL, 4 mmol), lactol **1.229** (0.348 g, 1.00 mmol), and Et_3B (1.0 M solution in hexanes, 2.4 mmol) were reacted in dry THF (5 mL) following the general procedure for homoallylation to afford two diastereomers **1.230a** as a liquid and **1.230b** as a colorless solid (dr, 1:6) (0.263 g, 63% combined yield).

1.230b, major isomer: IR (neat, NaCl) 3340, 2958, 2926, 2856 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.79 (1H, ddd, *J* = 7.7, 10.2, 17.2 Hz), 4.94-5.06 (2H, m), 3.86-3.91(1H, m), 3.75-3.81 (2H, m), 3.69-3.71 (1H, m), 3.51 (1H, brd s), 3.07 (1H, brd, s), 2.67 (1H, s), 2.35 (1H, sep, *J* = 6.4 Hz), 1.45-1.66 (2H, m), 1.04 (3H, d, *J* = 6.7 Hz), 0.92 (9H, s), 0.91 (9H, s), 0.12 (9H, s), 0.09 (3H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 144.9, 113.1, 78.2, 74.0, 72.2, 63.0, 39.0, 35.1, 26.1, 20.1, 18.4, -4.0, -4.2, -4.3, -4.6; HRMS (FAB, MH^+) calcd for $C_{21}H_{47}O_4Si_2$: 419.3013. Found 419.3024.

1.230a, minor isomer: ^1H NMR ($CDCl_3$): δ 5.77 (1H, ddd, *J* = 7.4, 10.3, 17.2 Hz), 4.91-5.01 (2H, m), 3.69-3.77 (4H, m), 3.51 (1H, brd d, *J* = 8.3 Hz), 2.81 (1H, brd s), 2.48 (1H, brd s), 2.34 (1H, sep, *J* = 6.9 Hz), 1.55-1.74 (1H, m), 1.23-1.40 (1H, m), 1.04 (3H, d, *J* = 6.7 Hz), 0.93 (9H, s), 0.92 (9H, s), 0.18 (3H, s), 0.14 (3H, s), 0.13 (6H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 144.7, 112.9, 75.7, 75.5, 69.3, 62.5, 41.7, 34.5, 26.4, 26.2, 19.8, 18.6, 18.4, -3.7, -4.3, -4.4.

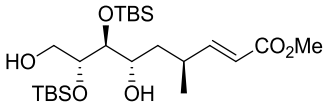


(1.231a)

(*4R,6R,7S,8R,E*) Methyl 7,8-bis(tert-butyldimethylsilyloxy)-6,9-dihydroxy-4-methylnon-2-enoate (1.231a): Grubbs second generation catalyst (9.9 mg, 12 μmol), copper iodide (3.2 mg, 17 μmol), hydroxy alkene **1.230a** (70 mg, 167 μmol) and methyl acrylate (50 μL, 501 μmol) were reacted in dry CH_2Cl_2 (1.2 mL) following the general procedure for cross metathesis to yield **1.231a** as a colorless oil (47 mg, 60%)**.**

IR (neat, NaCl) 3469, 2958, 2922, 2852, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.95 (1H, dd, *J* = 7.5, 15.7 Hz), 5.80 (1H, dd, *J* = 1.1, 15.7 Hz), 3.67-3.78 (4H, m), 3.73 (3H, s), 3.57

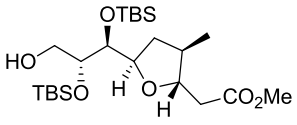
(1H, dd, *J* = 2.4, 11.0 Hz), 2.58 (1H, app sep, *J* = 7.1 Hz), 2.51 (2H, s), 1.65-1.74 (1H, m), 1.31-1.39 (1H, m), 1.09 (3H, d, *J* = 6.7 Hz), 0.92 (9H, s), 0.91 (9H, s), 0.17 (3H, s), 0.13 (3H, s), 0.11 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.5, 154.8, 119.2, 75.4, 75.1, 68.8, 62.5, 51.6, 40.8, 33.0, 26.3, 26.1, 18.6, 18.3, -3.9, -4.2, -4.3, -4.5; HRMS (FAB, MNa^+) calcd for $C_{23}H_{48}O_6Si_2Na$: 499.2887. Found 499.2884.



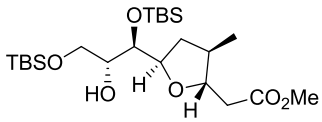
(**1.231b**)

(*4S,6S,7S,8R,E*) Methyl 7,8-bis(tert-butyldimethylsilyloxy)-6,9-dihydroxy-4-methylnon-2-enoate (1.231b): Grubbs second generation catalyst (4.3 mg, 5.0 μmol), copper iodide (1.3 mg, 7.2 μmol), hydroxy alkene **1.230b** (30 mg, 72 μmol) and methyl acrylate (13 μL, 143 μmol) were reacted in dry CH_2Cl_2 (0.5 mL) following the general procedure for cross metathesis to yield **1.230b** as a colorless solid (22 mg, 65%)**.**

IR (neat, NaCl) 3298, 2952, 2929, 2857, 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.96 (1H, dd, *J* = 7.6, 15.7 Hz), 5.82 (1H, dd, *J* = 0.9, 15.7 Hz), 3.83-3.87 (1H, m), 3.73 (3H, s), 3.70-3.79 (2H, m), 3.63 (1H, dd, *J* = 2.4, 5.1 Hz), 3.52 (1H, brd d, *J* = 10.0 Hz), 2.76 (2H, brd s), 2.61 (1H, app sep, *J* = 6.7 Hz), 1.60-1.70 (1H, m), 1.44-1.52 (1H, m), 1.08 (3H, d, *J* = 6.7Hz), 0.91 (9H, s), 0.90 (9H, s), 0.12 (9H, s), 0.09 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.7, 155.1, 119.4, 78.2, 74.9, 71.6, 63.4, 51.9, 38.6, 33.5, 26.3, 18.8, 18.6, 18.5, -3.8, -4.0, -4.2, -4.4; HRMS (FAB, MNa^+) calcd for $C_{23}H_{48}O_6Si_2Na$: 499.2887. Found 499.2876.



(1.232a)



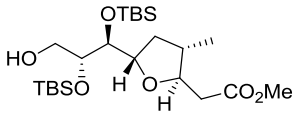
(1.232b)

Methyl-(2S,3R,5R){3-methyl-5-[(1S,2R)-3-hydroxy-1,2-bis(*tert*-butyldimethylsilyloxy) prop-1-yl]-tetrahydrofuran-2-yl)acetate (1.232a) and Methyl-(2S,3R,5R){3-methyl-5-[(1R,2R)-2-hydroxy-1,3-bis(*tert*-butyldimethylsilyloxy)prop-1-yl]-tetrahydrofuran-2-yl)acetate (1.232b): Unsaturated ester **1.231a** (28 mg, 59 μmol), DBU (10 μL, 65 μmol) were reacted in dry CH_2Cl_2 (0.5 mL) following the general procedure for cyclization (also see procedure for **1.233a/1.233b** below). Careful chromatography of the crude product afforded **1.232a** and **1.232b** in a 1:2 ratio as a colorless oil (26 mg, combined yield 95%).

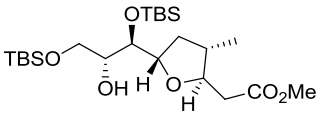
1.232a: IR (neat, NaCl) 3500, 2954, 2924, 2844, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.18-4.22 (1H, m), 3.88-3.92 (1H, m), 3.73 (1H, dd, *J* = 7.1, 11.6 Hz), 3.69 (3H, s), 3.66-3.69 (2H, m), 3.46 (1H, dd, *J* = 5.6, 9.1 Hz), 2.71 (1H, d, *J* = 5.8 Hz), 2.53 (1H, dd, *J* = 5.0, 15.0 Hz), 2.50 (1H, dd, *J* = 7.2, 14.9 Hz), 2.04-2.09 (1H, m), 1.96-2.03 (1H, m), 1.65 (1H, app q, *J* = 11.0 Hz), 1.06 (3H, d, *J* = 6.4 Hz), 0.91 (9H, s), 0.89 (9H, s), 0.09 (3H, s), 0.08 (3H, s), 0.07 (6H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 172.1, 82.2, 75.0 (2C), 73.7, 66.0, 51.8, 40.3, 39.8, 37.2, 26.2, 26.1, 18.6, 18.4, 16.5, -4.1, -4.7, -5.2; HRMS (FAB, MH^+) calcd for $C_{23}H_{49}O_6Si_2$: 477.3067. Found 477.3067.

1.232b: IR (neat, NaCl) 3486, 2947, 2931, 2849, 1755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.11-4.18 (1H, m), 3.87 (1H, td, *J* = 3.8, 8.8 Hz), 3.66-3.73 (4H, m), 3.68 (3H, s), 3.19 (1H, d, *J* = 3.7 Hz), 2.55 (1H, dd, *J* = 3.9, 14.9 Hz), 2.42 (1H, dd, *J* = 8.5, 14.9 Hz), 2.05-2.14 (1H, m), 1.86-1.93 (1H, m), 1.55-1.66 (1H, m), 1.04 (3H, d, *J* = 6.5 Hz), 0.91 (9H, s),

0.90 (9H, s), 0.11 (3H, s), 0.07 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.0, 81.8, 79.5, 74.7, 74.1, 64.4, 51.8, 40.0, 39.4, 37.0, 26.2, 26.1, 18.53, 18.49, 15.9, -4.2, -4.5, -5.1; HRMS (FAB, MNa^+) calcd for $C_{23}H_{48}O_6Si_2Na$: 499.2887. Found 499.2880.



(**1.233a**)



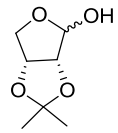
(**1.233b**)

Methyl(2R,3S,5S){3-methyl-5-[(1S,2R)-3-hydroxy-1,2-bis(*tert*-butyldimethylsilyloxy)prop-1-yl]-tetrahydrofuran-2-yl)acetate (1.233a) and Methyl(2R,3S,5S){3-methyl-5-[(1R,2R)-2-hydroxy-1,3-bis(*tert*-butyldimethylsilyloxy)prop-1-yl]-tetrahydrofuran-2-yl)acetate (1.233b): Unsaturated ester **1.231b** (10 mg, 21 μmol), DBU (3.0 μL, 23 μmol) were reacted in dry CH_2Cl_2 (0.2 mL) following the general procedure for cyclization. TLC analysis initially showed only one product spot, but as the reaction proceeded an additional product formed. After 2 h, the reaction was partitioned between saturated NH_4Cl solution and EtOAc. The layers were separated and the aq. layer was re-extracted with EtOAC. The combined organic layers were washed with brine, dried, and concentrated in *vacuo*. Careful chromatography of the crude product afforded **1.233a** and **1.233b** in a 1:2 ratio as a colorless oil (9.5 mg, combined yield 95%).

1.233a: IR (neat, NaCl) 3490, 2956, 2929, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.08-4.14 (1H, m), 3.78-3.85 (1H, m), 3.69 (3H, s), 3.60-3.74 (4H, m), 2.54 (1H, dd, J = 3.8, 14.7 Hz), 2.42 (1H, dd, J = 8.5, 14.7 Hz), 2.11 (1H, app t, J = 6.0 Hz), 1.98-2.08 (1H, m), 1.87-1.96 (1H, m), 1.54-1.65 (1H, m), 1.05 (3H, d, J = 6.3 Hz), 0.91 (18H, s), 0.13 (3H, s), 0.10 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.4, 81.9, 79.2, 76.5, 74.9, 64.0, 52.0, 40.5,

40.0, 36.7, 26.4, 26.3, 18.6, 18.5, 16.6, -3.9, -4.1, -4.2; HRMS (FAB, MH^+) calcd for $C_{23}H_{49}O_6Si_2$: 477.3068. Found 477.3061.

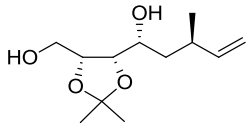
1.233b: ^{1}H NMR ($CDCl_3$): δ 4.18-4.24 (1H, m), 3.78-3.85 (2H, m), 3.73 (1H, dd, J = 3.5, 9.9 Hz), 3.68 (3H, s), 3.59 (1H, dd, J = 6.9, 9.9 Hz), 3.53-3.52 (1H, m), 2.53 (1H, dd, *J* = 3.9, 14.6 Hz), 2.38-2.48 (2H, m), 1.87-2.05 (2H, m), 1.61-1.73 (1H, m), 1.04 (3H, d, *J* = 6.2 Hz), 0.91 (18H, s), 0.10 (3H, s), 0.07 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.3, 82.2, 78.9, 75.2, 74.0, 65.8, 52.0, 40.3, 39.8, 36.1, 26.3, 26.2, 18.7, 18.6, 16.8, -3.7, -4.5, -5.0.



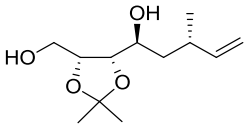
(**1.235**)

(*3aR,6aR*)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (1.235): (-)-2,3-o-isopropylidene-D-erythronolactone **1.234** (3.0 g, 0.019 mol, 1.0 equiv.) and DIBAL-H (1.0 M solution in hexanes, 22.8 mL, 1.2 equiv.) were reacted in dry CH_2Cl_2 (50 mL) following the literature procedure[78] to afford **1.235** as a colorless crystalline solid (2.55 g, 84%).

Major anomer: IR (neat, NaCl) 3421, 2993, 2945 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.42 (1H, d, *J* = 1.9 Hz), 4.85 (1H, dd, *J* = 3.4, 5.9 Hz), 4.58 (1H, d, *J* = 5.9 Hz), 3.91-4.10 (2H, m), 2.98 (1H, s), 1.47 (3H, s), 1.32 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 112.5, 102.0, 85.3, 80.1, 72.1, 26.4, 25.1; HRMS (FAB, MH^+) calcd for $C_7H_{13}O_4$: 160.0736. Found 160.0735.



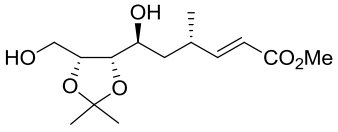
(1.236a)



(1.236b)

(*1S,3S*)-1-((*4S,5R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methylpent-4-en-1-ol (1.236b): $Ni(acac)_2$ (0.051 g, 0.20 mmol), isoprene (0.8 mL, 8 mmol), lactol **1.235** (0.32 g, 2.0 mmol), Et_3B (1.0 M solution in hexane, 4.8 mL, 4.8 mmol) were reacted in dry THF (10 mL) following the general procedure for homoallylation. After 90 h, the reaction failed to reach completion (TLC and ^1H NMR). Work up and purification afforded a mixture of diastereomers (dr 1:3, 0.3 g, combined yield 65%). Careful repeated purification gave pure **1.236b.**

1.236b, major isomer: IR (neat, NaCl) 3421, 2993, 2945 cm^{-1}; ^1H ($CDCl_3$): δ 5.88 (1H, ddd, *J* = 7.9, 10.2, 17.4 Hz), 4.99-5.17 (2H, m), 4.29-4.35 (1H, m), 3.94-4.00 (2H, m), 3.90 (1H, dd, *J* = 7.9, 11.5 Hz), 3.76 (1H, dd, *J* = 4.5, 11.5 Hz), 2.85 (1H, brd s), 2.46 (1H, app sep, *J* = 4.8 Hz), 1.79-1.86 (1H, m), 1.46-1.68 (1H, m), 1.43 (3H, s), 1.37 (3H, s), 1.08 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 145.2, 112.5, 109.9, 80.1, 76.0, 69.9, 63.5, 41.4, 33.7, 27.8, 25.2, 19.3. HRMS (FAB, MH^+) calcd for $C_{12}H_{23}O_4$: 231.1596. Found 231.1589.

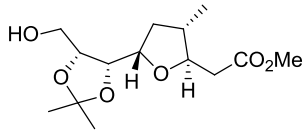


(**1.237**)

(4S,6S,E) Methyl 6-hydroxy-6-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylhex-2-enoate (1.237): Grubbs second generation catalyst (7.7 mg, 9.1 μmol), copper iodide (2.5 mg, 13 μmol), hydroxy alkene **1.236b** (30 mg, 0.13

mmol) and methyl acrylate (23 μL, 0.26 mmol) were reacted in dry CH_2Cl_2 (0.5 mL) following the general procedure for cross metathesis to afford **1.237** as a colorless oil (0.023 g, 62%).

IR (neat, NaCl) 3422, 2932, 1721, 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.00 (1H, dd, *J* = 7.5, 15.7 Hz), 5.85 (1H, dd, *J* = 1.2, 15.7 Hz), 4.28 (1H, quin, *J* = 4.3 Hz), 3.84-3.99 (3H, m), 3.74 (3H, s), 3.67-3.80 (1H, m), 3.07 (1H, d, *J* = 3.5 Hz), 2.68 (1H, app sep, *J* = 7.5 Hz), 2.42 (1H, m), 1.73-1.84 (1H, m), 1.58-1.66 (1H, m), 1.41 (3H, s), 1.35 (3H, s), 1.11 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 167.7, 155.3, 119.4, 108.7, 80.8, 67.9, 61.5, 51.8, 40.6, 33.2, 28.4, 25.8, 19.1; HRMS (FAB, MNa^+) calcd for $C_{14}H_{24}O_6Na$: 311.1471. Found 311.1465.

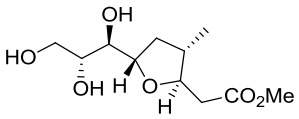


(**1.238**)

Methyl-2-((2R,3S,5S)-5-((4S,5R)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyltetrahydrofuran-2-yl)acetate (1.238): Unsaturated ester **1.237** (10 mg, 35 μmol) and DBU (5.7 μL, 38 µmol) were reacted in dry CH_2Cl_2 (0.2 mL) following the general procedure for cyclization to give **1.238** as a colorless oil (8.0 mg, 80%).

IR (neat, NaCl) 3490, 2956, 2929, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.34 (1H, dt, *J* = 5.4, 8.4 Hz), 4.10 (1H, ddd, *J* = 5.9, 9.1, 9.4), 3.99 (1H, dd, *J* = 5.6, 9.7 Hz), 3.87 (1H, dd, *J* = 3.2, 9.2 Hz), 3.74-3.82 (2H, m), 3.70 (3H, s), 3.37 (1H, dd, *J* = 5.4, 9.2 Hz), 2.60 (1H, dd, *J* = 3.2, 15.5 Hz), 2.43 (1H, dd, *J* = 9.1, 15.5 Hz), 2.37 (1H, ddd, *J* = 6.4, 6.5, 12.7 Hz), 1.87-2.02 (1H, m), 1.46-1.64 (1H, m), 1.38 (3H, s), 1.35 (3H, s), 1.06 (3H, d, *J* = 6.5 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 172.0, 108.7, 82.4, 80.7, 77. 9, 76.3, 60.8, 52.3, 40.1, 39.9,

39.2, 28.3, 25.7, 16.3; HRMS (FAB, MNa^+) calcd for $C_{14}H_{24}O_6Na$: 311.1471. Found 311.1490.



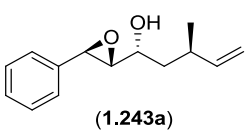
(**1.239**)

Methyl-2-((2R,3S,5S)-3-methyl-5-((1R,2R)-1,2,3-trihydroxypropyl) tetrahydrofuran-2-yl)acetate (1.239): To a stirred solution of **1.233a** (25 mg, 0.052 mmol, 1.0 equiv.) in dry MeOH (0.5 mL) at room temperature was added HF-pyridine (23 μL, 0.26 mmol, 5.0 equiv.) and the mixture was stirred for 40 h (TLC analysis). The mixture was partitioned between water and EtOAc. The layers were separated and the aq. layer was re-extracted with EtOAC. The combined organic layers were washed with brine solution and dried over Na_2SO_4. The solution was concentrated in *vacuo* and the crude product was purified by column chromatography (SiO_2, hexanes: EtOAc) to afford **1.239** as a colorless oil (9.0 mg, 70%).

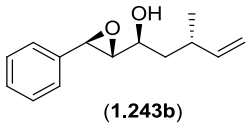
To a RBF containing **1.238** (10 mg, 35 μmol, 1.0 equiv.) and amberlyst 15 resin (10 mg, 1.0 equiv.) was added dry MeOH (0.2 mL) and the resulting mixture was stirred for 5 h (TLC analysis). The mixture was partitioned between water and EtOAc. The layers were separated and the aq. layer was re-extracted with EtOAC. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (SiO_2, hexanes: EtOAc) to afford **1.239** as a colorless oil (6.0 mg, 60%).

IR (neat, NaCl) 3401, 3328, 2951, 2924, 1709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.10 (1H, dt, *J* = 6.6, 9.0 Hz), 2.88 (1H, dd, *J* = 3.2, 8.9 Hz), 3.80-3.84 (2H, m), 3.70-3.75 (1H, m), 3.70 (3H, s), 3.62 (1H, brd d, *J* = 6.3 Hz), 3.40 (1H, brd s), 2.82 (2H, brd s), 2.60 (1H, dd, *J* =

3.3, 15.6 Hz), 2.44 (1H, dd, *J* = 8.9, 15.6 Hz), 2.32 (1H, ddd, *J* = 6.4, 6.6, 12.7 Hz), 1.90-2.0 (1H, m), 1.56-1.66 (1H, m), 1.06 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.1, 82.1, 79.4, 74.4, 73.4, 63.7, 52.1, 39.8, 39.0, 38.1, 16.2; HRMS (FAB, MNa^+) calcd for $C_{11}H_{20}O_6Na$: 271.1157. Found 271.1160.



(**1.243a**)

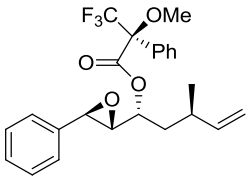


(**1.243b**)

(1R,3R)-3-methyl-1-((2R,3R)-3-phenyloxiran-2-yl)pent-4-en-1-ol (1.243a) and (1S,3S)-3-methyl-1-((2R,3R)-3-phenyloxiran-2-yl)pent-4-en-1-ol (1.243b): Epoxycinnamaldehyde **1.242** (0.33 g, 2.2 mmol), $Ni(acac)_2$ (0.057 g, 0.22 mmol), isoprene (0.9 mL, 8.9 mmol) and Et_3B (1.0 M solution in hexanes, 5.3 mL, 5.3 mmol) were reacted in dry THF (10 mL) following the general procedure for homoallylation to obtain **1.243** as a colorless oil (dr 2.5:1) (0.303 g, combined yield 63%). The diastereomers were separated by further chromatography. The absolute configuration of diastereomers was determined by the Mosher ester method.

(**1.243a**, major isomer) IR (neat, NaCl) 3422, 3062, 2963, 2928 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.37 (5H, m), 5.80 (1H, ddd, *J* = 7.5, 10.3, 17.4 Hz), 4.94-5.08 (2H, m), 3.99-4.05 (1H, m), 3.97 (1H, d, *J* = 2.1 Hz), 3.10 (1H, dd, *J* = 2.3, 3.0 Hz), 2.44 (1H, app sep, *J* = 6.8 Hz), 2.11 (1H, d, *J* = 2.4 Hz), 1.64-1.74 (1H, m), 1.56-1.60 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 144.5, 137.1, 128.7, 128.4, 125.9, 113.2, 67.2, 65.1, 54.9, 40.3, 34.5, 20.0; HRMS (FAB, MNa^+) calcd for $C_{14}H_{18}O_2Na$: 241.1204. Found 241.1213.

(**1.243b**, minor isomer) IR (neat, NaCl) 3428, 3068, 2963, 2928 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.37 (5H, m), 5.78 (1H, ddd, *J* = 7.7, 10.3, 17.4 Hz), 4.97-5.09 (2H, m), 3.89 (1H, d, *J* = 2.1 Hz), 3.72 (1H, app quin, *J* = 7.1 Hz), 3.05 (1H, dd, *J* = 2.1, 4.9 Hz), 2.40 (1H, app sep, *J* = 6.8 Hz), 2.02 (1H, d, *J* = 5.5 Hz), 1.70-1.80 (1H, m), 1.53-1.62 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 144.4, 136.9, 128.8, 128.6, 125.9, 113.5, 69.6, 65.8, 56.9, 41.2, 34.6, 20.5.

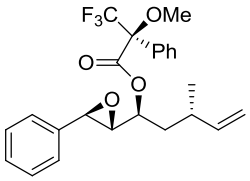


1.244a

(S)-(1R,3R)-3-methyl-1-((2R,3R)-3-phenyloxiran-2-yl)pent-4-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.244a): To a stirred solution of **1.243a** (0.023 mmol, 0.005 g) in dry CH_2Cl_2 (0.5 mL) under argon at rt was added *N*,*N*-dimethylamino pyridine (DMAP) (1 small crystal), pyridine (0.034 mmol, 3 μL) and (*R*)-MTPA chloride (0.034 mmol, 6 μL) sequentially. It was then stirred for 16 h at that temperature when the TLC analysis showed the reaction was complete. About 1 mL of water was added, the layers separated, the aq. layer was extracted with EtOAc (5 mL, 3X) and the combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to give **1.244a** as a colorless liquid (0.008 g, 80%).

^{1}H NMR ($CDCl_3$): δ 7.21-7.36 (10H, m), 5.74 (1H, ddd, *J* = 7.4, 10.3, 17.4 Hz), 4.94-5.14 (3H, m), 3.83 (1H, d, *J* = 1.9 Hz), 3.57 (3H, s), 2.94 (1H, dd, *J* = 1.9, 5.7 Hz), 2.35

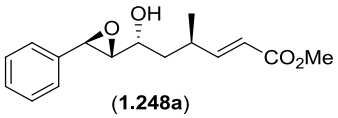
(1H, app sep, *J* = 7.0 Hz), 1.91 (1H, ddd, *J* = 6.6, 8.5, 14.4 Hz), 1.76-1.82 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz).



1.244b

(S)-(1S,3S)-3-methyl-1-((2R,3R)-3-phenyloxiran-2-yl)pent-4-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.243b): Alcohol **1.243b** (0.023 mmol, 0.005 g), DMAP (1 small crystal), pyridine (0.034 mmol, 3 μL) and (*R*)-MTPA chloride (0.034 mmol, 6 μL) were reacted in dry CH_2Cl_2 (0.5 mL) following the same procedure as above for compound **1.244a** to obtain **1.244b** as a colorless liquid (0.007 g, 70%).

^{1}H NMR ($CDCl_3$): δ 7.24-7.44 (10H, m), 5.71 (1H, ddd, *J* = 8.0, 10.2, 17.5 Hz), 4.99-5.10 (3H, m), 3.85 (1H, d, *J* = 1.7 Hz), 3.64 (3H, s), 3.18 (1H, dd, *J* = 1.7, 7.2 Hz), 2.15 (1H, app sep, *J* = 7.0 Hz), 1.76-1.91 (1H, m), 1.61-1.69 (1H, m), 1.02 (3H, d, *J* = 6.7 Hz).

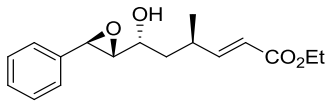


(**1.248a**)

(4R,6R,E)-methyl 6-hydroxy-4-methyl-6-((2R,3R)-3-phenyloxiran-2-yl)hex-2-enoate (1.248a): Grubbs second generation catalyst (0.068 g, 0.08 mmol), copper iodide (0.022 g, 0.11 mmol) hydroxy alkene **1.243a** (0.250 g, 1.15 mmol) and methyl acrylate (0.5 mL, 5.7 mmol) were reacted in dry CH_2Cl_2 (5 mL) following the general procedure for cross metathesis to obtain **1.248a** as a colorless oil (0.182 g, 58%).

IR (neat, NaCl) 3460, 3035, 2962, 2917, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.18-7.31 (5H, m), 6.87 (1H, dd, *J* = 7.6, 15.7 Hz), 5.75 (1H, dd, *J* = 0.9, 15.8 Hz), 3.92-3.96 (1H, m),

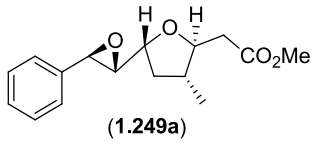
3.88 (1H, d, *J* = 2.0 Hz), 3.64 (3H, s), 3.00 (1H, t, *J* = 2.5 Hz), 2.60 (1H, app sep, *J* = 7.0 Hz), 1.99 (1H, brd s), 1.60-1.70 (1H, m), 1.46-1.55 (1H, m), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.4, 154.2, 136.8, 128.7, 128.5, 126.2, 119.6, 66.6, 64.9, 54.9, 51.7, 39.5, 32.9, 18.9; HRMS (FAB, MNa^+) calcd for $C_{16}H_{20}O_4Na$: 299.1259. Found 299.1255.



(**1.248b**)

(4R,6R,E)-Ethyl 6-hydroxy-4-methyl-6-((2R,3R)-3-phenyloxiran-2-yl)hex-2-enoate (1.248b): Grubbs second generation catalyst (0.082 g, 0.096 mmol), copper iodide (0.026 g, 0.14 mmol), hydroxy alkene **1.243a** (0.3 g, 1.4 mmol) and ethyl acrylate (0.3 mL, 2.7 mmol) were reacted in dry CH_2Cl_2 (5 mL) following the general procedure for cross metathesis to afford **1.248b** as a colorless oil (0.23 g, 59%).

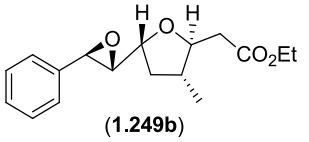
IR (neat, NaCl) 3447, 2976, 2921, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.18-7.29 (5H, m), 6.87 (1H, dd, *J* = 7.5, 15.7 Hz), 5.75 (1H, dd, *J* = 1.2, 15.7 Hz), 4.10 (2H, q, *J* = 7.1 Hz), 3.92-3.97 (1H, m), 3.87 (1H, d, *J* = 2.1 Hz), 3.00 (1H, t, *J* = 2.3 Hz), 2.60 (1H, app sep, *J* = 6.7 Hz), 2.00 (1H, s), 1.50-1.71 (2H, m), 1.21 (3H, t, *J* = 7.1 Hz), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.0, 153.9, 136.9, 128.8, 128.6, 125.9, 120.0, 66.6, 64.9, 60.5, 54.8, 39.4, 32.9, 18.9, 14.5; HRMS (FAB, MNa^+) calcd for $C_{17}H_{22}O_4Na$: 313.1416. Found 313.1407.



(**1.249a**)

Methyl2-((2S,3R,5R)-3-methyl-5-((2R,3R)-3-phenyloxiran-2-yl)tetrahydrofura-2-yl) acetate (1.249a): Unsaturated ester **1.248a** (0.10 g, 0.36 mmol), DBU (59 μL, 0.40 mmol) were reacted in dry CH_2Cl_2 (2 mL) following the general procedure for cyclization to afford **1.249a** as a colorless oil (0.07 g, 70%).

IR (neat, NaCl) 2959, 2869, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-7.36 (5H, m), 4.10-4.16 (1H, m), 3.88-3.95 (1H, m), 3.78 (1H, d, *J* = 2.0 Hz), 3.72 (3H, s), 3.12 (1H, dd, *J* = 2.0, 4.2 Hz), 2.60 (1H, dd, *J* = 4.4, 15.2 Hz), 2.51 (1H, dd, *J* = 7.6, 15.2 Hz), 2.29 (1H, dt, *J* = 6.9, 12.4 Hz), 1.97-2.08 (1H, m), 1.53-1.63 (1H, m), 1.09 (3H, d, *J* = 6.5 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 171.9, 137.2, 128.6, 128.4, 125.9, 82.2, 77.3, 64.1, 56.9, 52.0, 39.7, 39.1, 37.1, 16.3; HRMS (FAB, MNa^+) calcd for $C_{16}H_{20}O_4Na$: 299.1253. Found 299.1207.

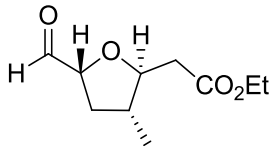


(**1.249b**)

Ethyl-2-((2S,3R,5R)-3-methyl-5-((2R,3R)-3-phenyloxiran-2-yl) tetrahydrofuran-2-yl)acetate (1.249b): Unsaturated ester **1.248b** (0. 15 g, 0.52 mmol) and DBU (85 μL, 0.57 mmol) were reacted in dry CH_2Cl_2 (3 mL) following the general procedure for cyclization to give **1.249b** as a colorless oil (0.12 g, 80%).

IR (neat, NaCl) 2960, 1735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.18-7.26 (5H, m), 4.09 (2H, q, *J* = 7.1 Hz), 4.01-4.06 (1H, m), 3.80-3.87 (1H, m), 3.70 (1H, d, *J* = 2.0 Hz), 3.03 (1H, dd, *J* = 2.0, 4.2 Hz), 2.49 (1H, dd, *J* = 4.7, 15.2 Hz), 2.41 (1H, dd, *J* = 7.4, 15.4 Hz), 2.20 (1H, dt, *J* = 6.8, 12.4 Hz), 1.88-1.99 (1H, m), 1.44-1.54 (1H, m), 1.19 (3H, t, *J* = 7.1 Hz), 1.00

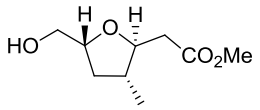
(3H, d, *J* = 6.6 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.4, 137.1, 128.6, 128.3, 125.9, 82.2, 64.1, 60.7, 56.8, 39.7, 39.3, 37.1, 16.3, 14.4; HRMS (FAB, MNa^+) calcd for $C_{17}H_{22}O_4Na$: 313.1416. Found 313.1415.



(**1.250b**)

Ethyl 2-((2*S*,3*R*,5*R*)-5-formyl-3-methyltetrahydrofuran-2-yl)acetate (1.250b): To a stirred solution of **1.249b** (29 mg, 0.10 mmol, 1.0 equiv.) in acetonitrile and water (2:1) (0.9 mL) was added $NaIO_4$ (64 mg, 0.30 mmol, 3.0 equiv.) in one portion and the resulting mixture was stirred at rt. After 22 h (TLC analysis), the mixture was partitioned between saturated sodium bicarbonate solution and CH_2Cl_2. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic phase was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to afford the crude aldehyde (20 mg) which after purification by column chromatography (SiO_2, hexanes:EtOAc) gave **1.250b** as a colorless oil (15 mg, 75%)**.** This aldehyde was used directly for the further reactions due to its instability.

^{1}H NMR ($CDCl_3$): δ 9.68 (1H, d, *J* = 2.2 Hz), 4.32 (1H, ddd, *J* = 2.1, 8.1, 8.3 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 3.98 (1H, td, *J* = 4.5, 8.0 Hz), 2.60 (1H, dd, *J* = 4.5, 15.3 Hz), 2.53 (1H, dd, *J* = 7.7, 15.3 Hz), 2.38 (1H, dt, *J* = 7.5, 15.1 Hz), 1.99-2.10 (1H, m), 1.58-1.68 (1H, m), 1.29 (3H, t, *J* = 7.1 Hz), 1.06 (3H, d, *J* = 6.4 Hz).



(**1.251a**)

Methyl2-((2S,3R,5R)-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)acetate (1.251a): Epoxide **1.249a** (10 mg, 0.036 mmol), $NaIO_4$ (23 mg, 0.11 mmol) were reacted in acetonitrile and water (2:1) (0.3 mL) following the procedure described for **1.250b** to give the crude aldehyde **1.250a** which was used for the next step without further purification.

To a stirred solution of the crude aldehyde **1.250a** (6.0 mg, 0.032 mmol, 1.0 equiv.) in dry MeOH (0.3 mL) at -78 ^{o}C was added $NaBH_4$ (1.5 mg, 39 μmol, 1.2 equiv.) and the resulting mixture was stirred at -78 ^{o}C for 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated in *vacuo*, and purified by column chromatography (SiO_2, hexanes:EtOAc) to afford **1.251a** as a colorless oil (4.0 mg, 64% over 2 steps).

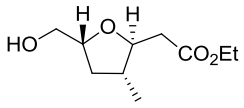
IR (neat, NaCl) 3451, 2954, 2923, 2852, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.10-4.17 (1H, m), 3.87 (1H, ddd, *J* = 4.2, 8.2, 8.4 Hz), 3.72 (3H, s), 3.68 (1H, dd, *J* = 2.9, 11.8 Hz), 3.50 (1H, dd, *J* = 5.6, 11.6 Hz), 2.58 (1H, dd, J = 4.2, 15.2 Hz), 2.49 (1H, dd, *J* = 7.9, 15.2 Hz), 2.10 (1H, ddd, *J* = 7.0, 7.1, 11.8 Hz), 1.92-2.03 (1H, m), 1.62 (1H, brd s), 1.45 (1H, ddd, *J* = 9.6, 10.4, 11.8 Hz), 1.06 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.1, 81.8, 79.0, 65.1, 51.9, 40.2, 39.3, 36.4, 16.5; HRMS (FAB, MH^+) calcd for $C_9H_{17}O_4$: 189.1127. Found 189.1126.

GC analysis:

column Rt-BDEXcst, rate 5 deg/min, Initial temp.120 ^{o}C, Final temp. 200 ^{o}C

Racemic: 38.5 min (area 47.7%) 38.9 min (area 46.2%)

Non-racemic (**1.251a**): 38.5 min (area 89.9%) 39.0 min (area 5.2%), e.e. = >95%



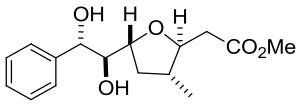
(**1.251b**)

Ethyl 2-((2S,3R,5R)-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)acetate (1.251b): Epoxide **1.249b** (0.070 g, 0.24 mmol) and $NaIO_4$ (0.155 g, 0.724 mmol) were reacted in acetonitrile and water (2:1) (1.5 mL) following the procedure described for **1.250a** to yield the crude aldehyde **2.250b** which was reduced without further purification.

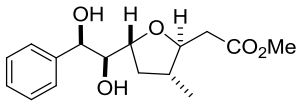
Aldehyde **1.250b** (0.045 g, 0.22 mmol) and $NaBH_4$ (0.01 g, 0.27 mmol) were reacted in dry MeOH (2 mL) following the procedure described for **1.251a** to afford **1.251b** as a colorless oil (0.03 g, 64% over 2 steps).

IR (neat, NaCl) 3451, 2954, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.17 (2H, q, *J* = 7.1 Hz), 4.08-4.14 (1H, m), 3.87 (1H, ddd, *J* = 4.3, 8.1, 8.4 Hz), 3.67 (1H, dd, *J* = 3.0, 11.7 Hz), 3.50 (1H, dd, *J* = 5.7, 11.7 Hz), 2.56 (1H, dd, *J* = 4.3, 15.2 Hz), 2.47 (1H, dd, *J* = 7.9, 15.2 Hz), 2.10 (1H, ddd, *J* = 7.0, 7.1, 11.9 Hz), 1.95-2.03 (1H, m), 1.77 (1H, brd s), 1.44 (1H, ddd, *J* = 9.6, 10.3, 11.8 Hz), 1.28 (3H, t, *J* = 7.1 Hz), 1.06 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.8, 81.8, 79.0, 65.1, 60.8, 40.1, 39.5, 36.4, 16.5, 14.4; HRMS

(FAB, MNa^+) calcd for $C_{10}H_{18}O_4Na$: 225.1102. Found 225.1114; $[\alpha]_D$ -37.3 (c 0.4, $CHCl_3$), Literature value $[\alpha]_D$ -44.9 (c 3.00, $CHCl_3$).



1.252a



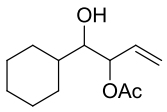
1.252b

methyl2-((2S,3R,5R)-5-((1S,2R)-1,2-dihydroxy-2-phenylethyl)-3-methyltetrahydrofuran-2-yl)acetate compound (1.252a) and methyl 2-((2S,3R,5R)-5-((1S,2S)-1,2-dihydroxy-2-phenylethyl)-3-ethyltetrahydrofuran-2-yl)acetate (1.252b): To a stirred solution of racemic **1.249a** (0.01 g, 0.036 mmol) in THF/H_2O (0.5 mL each) at rt was added Amberlyst 15 resin (after washing with dry CH_2Cl_2) (0.005 g) and stirred for 16 h when the TLC analysis showed completion of the reaction. Ethyl acetate (5 mL) was added, the layers separated, the aq. layer extracted with more EtOAc (5 mL, 3X) and the combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) two obtain to diastereomers **1.252a** and **1.252b** as a colorless liquid (1:1) (0.008 g, combined yield 80%).

1.252a: ^{1}H NMR ($CDCl_3$): δ 7.27-7.42 (5H, m), 4.74 (1H, d, *J* = 6.9 Hz), 3.90-4.02 (2H, m), 3.67-3.76 (1H, m), 3.72 (3H, s), 3.59 (1H, brd s), 2.60 (1H, dd, *J* = 3.8, 15.4 Hz), 2.48 (1H, dd, *J* = 8.6, 15.4 Hz), 2.31 (1H, app quin, *J* = 6.5 Hz), 1.92-1.97 (1H, m), 1.56-1.67 (1H, m), 1.07 (3H, d, *J* = 6.5 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.9, 140.4, 128.7, 128.4, 127.4, 82.1, 80.6, 77.0, 76.4, 52.0, 39.8, 39.2, 38.4, 16.3.

1.252b: ^{1}H NMR ($CDCl_3$): δ 7.27-7.37 (5H, m), 4.64 (1H, d, *J* = 5.8 Hz), 3.87-3.94 (2H, m), 3.79-3.85 (1H, m), 3.70 (3H, s), 3.16 (1H, brd s), 2.55 (1H, dd, *J* = 3.8, 15.3 Hz), 2.42 (1H, dd, *J* = 8.4, 15.4 Hz), 2.05-2.13 (1H, m), 1.89-1.97 (1H, m), 1.72 (1H, q, *J* =

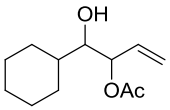
11.2 Hz), 1.59 (1H, brd s), 1.07 (3H, d, *J* = 6.4 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.0, 140.4, 128.7, 128.3, 127.0, 82.0, 79.0, 76.6, 74.3, 52.0, 40.1, 39.3, 35.4, 16.3.



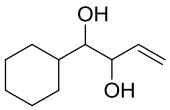
1.265

1-cyclohexyl-1-hydroxybut-3-en-2-yl-acetate (1.265): Cyclohexanecarboxaldehyde **1.264** (0.01 mL, 0.089 mmol), diacetate **1.256** (0.026 g, 0.178 mmol), $Pd_2(dba)_3$ (0.004 g, 0.004 mmol), and $B_2(pin)_2$ (0.025 g, 0.107 mmol) were reacted in dry DMSO (1 mL) following the literature procedure[84] to obtain **1.265** as a colorless oil (0.011 g, 61%).

^{1}H NMR ($CDCl_3$): δ 5.92 (1H, ddd, *J* = 6.9, 10.5, 17.4 Hz), 5.34-5.42 (3H, m), 3.48-3.53 (1H, m), 2.11 (3H, s), 1.95-2.05 (1H, m), 1.68-1.81 (4H, m), 1.35-1.42 (1H, m), 1.17-1.30 (4H, m), 1.00-1.13 (1H, m). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 170.1, 132.0, 120.2, 76.9, 76.0, 39.9, 29.2, 28.7, 26.5, 26.2, 26.0, 21.5.



1.265a

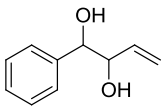


1.266

1-cyclohexyl-1-hydroxybut-3-en-2-yl-acetate (1.265a) and 1-cyclohexylbut-3-ene-1,2-diol (1.266): Cyclohexanecarboxaldehyde **1.264** (0.024 mL, 0.200 mmol), diacetate **1.256** (0.038 g, 0.240 mmol), $Pd(PPh_3)_4$ (0.012 g, 0.010 mmol), and diethylzinc (10% w/v in hexanes, 0.60 mL) were reacted in dry THF (0.5 mL) following the literature procedure[85] to obtain **1.265a** and **1.266** (3:1) as a colorless oil (0.016 g, 38%, only **1.265a**).

1.165a: ^{1}H NMR ($CDCl_3$): δ 5.90 (1H, ddd, *J* = 6.7, 10.3, 17.1 Hz), 5.23-5.36 (2H, m), 4.81 (1H, dd, *J* = 4.3, 6.8 Hz), 4.30 (1H, app q, *J* = 5.2 Hz), 2.20 (1H, t, *J* = 3.8 Hz), 2.09 (3H, s), 1.63-1.77 (6H, m), 1.05-1.24 (5H, m).

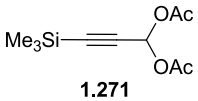
1.166: ^{1}H NMR ($CDCl_3$): δ 6.00 (1H, ddd, *J* = 6.5, 10.4, 17.1 Hz), 5.30-5.41 (2H, m), 4.23-4.26 (1H, m), 3.40-3.45 (1H, m), 2.01-2.06 (2H, m), 1.66-1.75 (6H, m), 1.05-1.26 (5H, m).



1.267

1-phenylbut-3-ene-1,2-diol (1.267): Benzaldehyde **1.47** (0.02 mL, 0.200 mmol), diacetate **1.256** (0.038 g, 0.240 mmol), $Pd(PPh_3)_4$ (0.012 g, 0.010 mmol), and diethylzinc (10% w/v in hexanes, 0.60 mL) were reacted in dry THF (0.5 mL) following the literature procedure to obtain[85] **1.267** as a colorless oil (0.011 g, 34%).

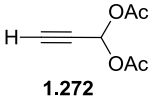
^{1}H NMR ($CDCl_3$): δ 7.31-7.38 (5H, m), 5.81 (1H, ddd, *J* = 6.5, 12.9, 17.2 Hz), 5.23-5.33 (2H, m), 4.78 (1H, t, *J* = 4.2 Hz), 4.35 (1H, app q, *J* = 5.4 Hz), 2.36 (1H, d, *J* = 3.8 Hz), 1.98 (1H, d, *J* = 4.8 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 140.1, 136.1, 128.6, 128.2, 126.9, 118.2, 77.8, 76.7.



1.271

3-(trimethylsilyl)prop-2-yne-1,1-diyl diacetate (1.271): Aldehyde **1.270** (0.700 g, 5.55 mmol), acetic anhydride (2 mL, 21.2 mmol), and $FeCl_3$ (0.04 g, 0.247 mmol) were reacted following the literature procedure to produce[83] diacetate **1.271** as a colorless oil (0.901 g, 56%).

IR (neat, NaCl) 2961, 1766 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.20 (1H, s), 2.08 (6H, s), 0.17 (9H); ^{13}C NMR ($CDCl_3$) δ 168.1, 96.8, 92.9, 79.2, 20.8, -0.4.

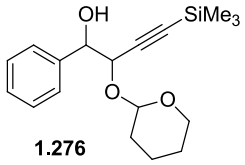


1.272

Prop-2-yne-1,1-diyl diacetate (1.272): To a stirred solution of diacetate **1.272** (0.100 g, 0.347 mmol) in dry THF (2 mL) at 0 ^{o}C was added TBAF (1.0 M solution in THF)

dropwise and stirred for 10 minutes at that temperature when the TLC analysis showed the reaction was complete. About 1 mL water and 5 mL CH_2Cl_2 was added, the layers separated and the organic layer was extracted with CH_2Cl_2 (5 mL, 3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude was purified by column chromatography (SiO_2, hexanes:EtOAc) to give **1.272** as a colorless oil (0.044 g, 83%).

^{1}H NMR ($CDCl_3$): δ 7.23 (1H, d, *J* = 1.8 Hz), 2.67 (1H, d, *J* = 1.8 Hz), 2.13 (6H, s); ^{13}C NMR ($CDCl_3$) δ 168.0, 79.0, 76.4, 75.5, 20.6.

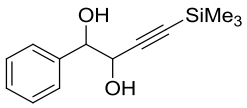


1.276

mixture of *syn* and *anti*

1-Phenyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)-4-(trimethylsilyl)but-3-yn-1-ol (1.276): To a stirred solution of **1.275** (0.023 g, 0.120 mmol) in dry THF at -78 ^{o}C was added *n*-BuLi (2.5 M in hexanes, 44 μL, 0.110 mmol) dropwise and the reaction was stirred at that temperature for 30 min. Benzaldehyde **1.47** (10 μL, 0.10 mmol) was added dropwise to this solution and the reaction was stirred for one more hour when the TLC analysis showed the reaction was complete. A few drops of aq. solution of $NaHCO_3$ was added, the layers separated and the aq. layer was extracted with Et_2O (5 mL, 3X). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to give **1.276** as a colorless liquid as a mixture of *syn*- and *anti*-isomers (1:2) (0.013 g, combined yield 41%) along with some unidentifiable product.

Major Isomer: ^{1}H NMR ($CDCl_3$): δ 7.27-7.48 (5H, m), 4.97 (1H, d, *J* = 2.9 Hz), 4.85 (1H, app q, *J* = 3.8 Hz), 4.52 (1H, t, *J* = 5.2 Hz), 3.46-3.68 (1H, m), 3.29-3.41 (1H, m), 2.93 (1H, d, *J* = 3.9 Hz), 1.53-1.67 (6H, m), 0.18 (9H, s).

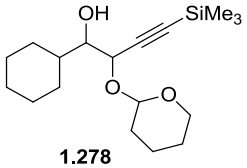


1.277

mixture of *syn* and *anti*

1-phenyl-4-(trimethylsilyl)but-3-yne-1,2-diol (1.277): To a stirred solution of THP-mono-protected diol **1.276** (0.008 g, 0.025 mmol) in dry MeOH (0.5 mL) at rt was added pyridinium *p*-toluene sulfonate (PPTS) (0.008 g, 0.031 mmol) and stirred at that temperature for 19 h (TLC analysis). Brine and water (1 mL each) was added, the layers separated and the aq. layer was extracted with Et_2O (5 mL, 3X). The combined organic layer were washed with water and brine and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to give a colorless liquid **1.277** as a mixture of *syn*- and *anti*-isomers (1:2) (0.005 g, 85%).

Major Isomer: ^{1}H NMR ($CDCl_3$): δ 4.82 (1H, t, *J* = 4.8 Hz), 4.52 (1H, dd, *J* = 4.5, 6.8 Hz), 2.60 (1H, d, *J* = 5.2 Hz), 2.28 (1H, d, *J* = 6.9 Hz), 0.15 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 138.9, 128.4, 127.2, 127.0, 102.5, 93.2, 76.5, 68.2, -0.1.

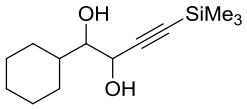


1.278

1-cyclohexyl-2-((tetrahydro-2H-pyran-2-yl)oxy)-4-(trimethylsilyl)but-3-yn-1-ol (1.278): Cyclohexanecarboxaldehyde **1.264** (24 μL, 0.20 mmol), THP- protected TMS propagylic alcohol **1.275** (0.046 g, 0.240 mmol), *n*-BuLi (2.5 M in hexanes, 88 μL, 0.22 mmol) and THF (1.0 mL) were reacted as described above to give a colorless liquid

1.278 as a mixture of *syn*- and *anti*-isomers (1:2) (0.022, 34%) along with some unidentifiable product.

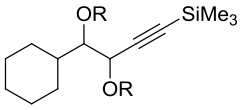
Major Isomer: ^{1}H NMR ($CDCl_3$): δ 5.00 (1H, d, *J* = 2.6 Hz), 4.53 (1H, d, *J* = 4.0 Hz), 3.73-3.81 (1H, m), 3.48-3.58 (2H, m), 2.32 (1H, d, *J* = 3.7 Hz), 2.03-2.14 (1H, m), 1.56-1.80 (10H, m), 1.01-1.30 (6H, m), 0.19 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 101.1, 95.9, 92.9, 77.1, 68.2, 62.6, 40.4, 30.5, 29.3, 28.8, 26.7, 26.4, 26.1, 25.6, 19.4, 0.15. HRMS (FAB, MNa) calcd for $C_{18}H_{33}O_3Si$: 325.2199. Found 325.2202.



1.279

1-cyclohexyl-4-(trimethylsilyl)but-3-yne-1,2-diol (1.279): The THP-mono-protected diol **1.278** (0.010 g, 0.031 mmol) and PPTS (0.009 g, 0.037 mmol) were reacted in dry MeOH (0.5 mL) as described above to give a colorless liquid **1.279** as a mixture of *cis* and *trans*-isomers (1:2) (0.006 g, combined yield 86%).

Major Isomer: ^{1}H NMR ($CDCl_3$): δ 4.44 (1H, dd, *J* = 3.8, 7.2 Hz), 3.33-3.40 (1H, m), 2.55 (1H, d, *J* = 8.0 Hz), 2.33 (1H, d, *J* = 11.8 Hz), 2.02-2.05 (1H, m), 1.60-1.87 (4H, m), 1.05-1.26 (6H, m), 0.19 (9H, s).

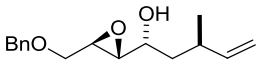


1.280 R, R = $C(CH_3)_2$

((5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethynyl)trimethylsilane (1.280): To a stirred solution of **1.279** (0.008 g, 0.033 mmol) in dry DMF (0.5 mL) at rt was added *p*-toluenesulfonic acid (*p*-TsOH) (0.001 g, 0.005 mmol) and 2,2-dimethoxypropane (10 μL, 0.083 mmol) sequentially and stirred at that temperature for 14 h. A few drops of aq. $NaHCO_3$ was added, the layers separated and the aq. layer was extracted with Et_2O (5

mL, 3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to isolate the colorless liquid **1.280** as a mixture of *syn*- and *anti*-isomers (1.2:2) (0.005 g, 71% b.r.s.m.).

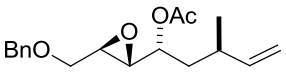
Major Isomer: ^{1}H NMR ($CDCl_3$): δ 4.68 (1H, d, *J* = 5.3 Hz), 3.68 (1H, dd, *J* = 5.3, 9.3 Hz), 1.93.2.08 (1H, m), 1.69-1.78 (6H, m), 1.54 (3H, s), 1.34 (3H, s), 1.08-1.29 (4H, m), 0.18 (9H, s).



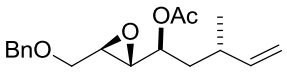
1.286

(1R,3R)-1-((2R,3R)-3-((benzyloxy)methyl)oxiran-2-yl)-3-methylpent-4-en-1-ol (1.286): Ni(acac)$_2$ (0.080 g, 0.312 mmol), isoprene **1.12** (1.3 mL, 12.0 mmol), aldehyde **1.285** (0.600 g, 3.124 mmol), and Et_3B (1.0 M solution in hexanes, 7.50 mmol) were reacted in dry THF (15 mL) following the general procedure for homoallylation to afford the column inseparable mixture of two diastereomers **1.286** as a colorless liquid (dr 1:1) (0.250 g, combined yield 31%).

Major isomer: IR (neat, NaCl) 3435, 2964, 2921, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.37 (5H, m), 5.79 (1H, ddd, *J* = 7.5, 10.3, 17.6 Hz), 4.94-5.07 (2H, m), 4.56 (2H, ABq, *J* = 12.0 Hz, Δδ = 0.05 ppm), 3.79 (1H, dd, *J* = 2.8, 11.6 Hz), 3.51 (*1*H, dd, *J* = 5.4, 15.3 Hz), 3.28 (*1*H, app quin, *J* = 2.5 Hz), 2.97 (1H, dd, *J* = 2.1, 3.3 Hz), 2.28 (1H, app sep, *J* = 6.9 Hz), 2.04 (1H, brd s), 1.44-1.60 (1H, m), 1.61-1.75 (1H, m), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 144.5, 138.0, 128.6, 127.9, 127.8, 113.1, 73.4, 69.8, 66.8, 58.2, 53.7, 40.3, 34.4, 19.9: HRMS (FAB, MNa) calcd for $C_{16}H_{22}O_3Na$: 285.1453. Found 285.11569.



1.287a



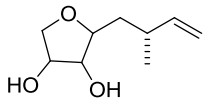
1.287b

(1R,3R)-1-((2R,3R)-3-((benzyloxy)methyl)oxiran-2-yl)-3-methylpent-4-en-1-yl acetate (1.287a) and (1S,3S)-1-((2R,3R)-3-((benzyloxy)methyl)oxiran-2-yl)-3-methylpent-4-en-1-yl acetate (1.287b): To a stirred solution of diastereomeric mixture **1.286** (0.200 g, 0.763 mmol) in dry CH_2Cl_2 at rt was added DMAP (0.009 g, 0.076 mmol). The reaction mixture was then cooled to 0 ^oC at stirred for 5 minutes before adding pyridine (7 μL, 0.915 mmol). After stirring for 5 more minutes at that temperature, acetic anhydride (107 μL, 1.14 mmol) was added and continued stirring. The TLC analysis after an additional 30 minutes showed no starting material left. A few drops of water were added, the layers separated, and the organic layer washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to give **1.287a** and **1.287b** (separately) as a colorless liquid (0.160 g, 69%).

1.287a: IR (neat, NaCl) 2963, 2932, 1741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-7.36 (5H, m), 5.73 (1H, ddd, *J* = 7.5, 10.3, 17.5 Hz), 4.91-5.04 (2H, m), 4.87 (1H, dd, *J* = 4.6, 9.1 Hz), 4.56 (2H, ABq, *J* = 12.0 Hz, Δδ = 0.05 ppm),, 3.75 (1H, dd, *J* = 2.8, 11.7 Hz), 3.47 (*1*H, dd, *J* = 5.4, 11.6 Hz), 3.20 (*1*H, app quin, *J* = 2.6 Hz), 2.93 (1H, dd, *J* = 2.1, 5.1 Hz), 2.28 (1H, app sep, *J* = 7.2 Hz), 2.05 (3H, s), 1.70-1.81 (1H, m), 1.54-1.64 (1H, m), 1.02 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 170.4, 143.8, 138.0, 128.6, 128.0, 127.9, 113.2, 73.5, 70.8, 69.6, 56.0, 55.6, 38.1, 34.4, 21.2, 20.1; HRMS (FAB, MNa) calcd for $C_{18}H_{24}O_4Na$: 327.1572. Found 327.1541.

1.287b: IR (neat, NaCl) 2954, 2924, 1746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-7.36 (5H, m), 5.72 (1H, ddd, *J* = 7.8, 10.2, 17.5 Hz), 4.94-5.05 (2H, m), 4.88 (1H, dd, *J* = 5.9, 13.3 Hz),

4.58 (2H, dd, *J* = 12.0, 16.3 Hz), 3.75 (1H, dd, *J* = 3.0, 11.7 Hz), 3.51 (*1*H, dd, *J* = 5.1, 13.7 Hz), 3.13 (*1*H, app quin, *J* = 2.4 Hz), 3.02 (1H, dd, *J* = 2.2, 5.6 Hz), 2.26 (1H, app sep, *J* = 7.4 Hz), 2.06 (3H, s), 1.69-1.82 (1H, m), 1.56-1.65 (1H, m), 1.03 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 170.4, 143.6, 137.9, 128.6, 128.0, 127.9, 113.7, 73.5, 71.5, 69.6, 56.5, 55.4, 38.1, 34.7, 21.3, 20.9.



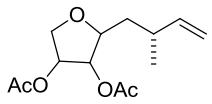
1.290

2-(2-methylbut-3-en-1-yl)tetrahydrofuran-3,4-diol (1.290): To a stirred solution of *α*-acetoxy epoxide **1.287a** (0.01 g, 0.033 mmol) in dry Et_2O at rt was added $BF_3 \cdot Et_2O$ (29 *μ*L, 0.230 mmol) and stirred at that temperature for 20 h. A few drops of aq. $NaHCO_3$ were added, the layers separated, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Proton NMR of the crude product showed no epoxide peaks. This crude product (0.012 g, quant.) was set up for the further reaction without any purification.

To the above crude product was added 0.5 mL of 1% HCl in MeOH and stirred at rt for 26 h. A few drops of aq. $NaHCO_3$ were added and the layers separated. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Column chromatography (SiO_2, hexanes:EtOAc) of the crude product produced pure **1.290** as a colorless liquid (0.005 g, 45%). Some benzyl containing unidentifiable compound was also isolated.

^{1}H NMR ($CDCl_3$): δ 5.70 (1H, ddd, *J* = 8.1, 10.2, 17.2 Hz), 4.94-5.09 (2H, m), 4.20-4.30 (1H, m), 4.13 (1H, dd, *J* = 5.3, 10.4 Hz), 3.67-3.86 (3H, m), 2.39 (1H, app sep, *J* = 6.9),

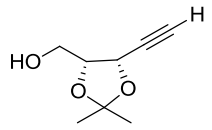
2.33 (2H, brd d, *J* = 5.3 Hz), 1.50-1.69 (2H, m), 1.06 (3H, d, *J* = 6.8 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 144.0, 113.9, 80.8, 76.4, 73.0, 71.2, 40.6, 35.5, 21.5.



1.291

2-(2-methylbut-3-en-1-yl)tetrahydrofuran-3,4-diyl diacetate (1.291): Diol **1.290** (0.005 g, 0.030 mmol), DMAP (1 small crystal), pyridine (10 μL, 0.132 mmol) and acetic anhydride (14 μL, 0.150 mmol) were reacted in dry CH_2Cl_2 (1 mL) rt following the acetylation procedure described above to produce **1.291** as a colorless liquid (0.006 g, 86 %).

IR (neat, NaCl) 2966, 2920, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.67 (1H, ddd, *J* = 8.2, 10.1, 18.1 Hz), 5.32 (1H, dd, *J* = 5.5, 10.0 Hz), 4.84-4.89 (1H, m), 4.21 (1H, dd, *J* = 5.6, 10.2 Hz), 3.92 (1H, dd, *J* = 6.9, 12.9 Hz), 3.78 (1H, dd, *J* = 4.2, 10.2 Hz), 2.34 (1H, app sep, *J* = 7.6 Hz), 2.09 (6H, s), 1.52-1.56 92H, m), 1.05 (3H, d, *J* = 6.8 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 170.3, 143.4, 114.1, 78.4, 75.6, 71.4, 70.5, 40.3, 35.3, 21.4, 21.0, 20.9.

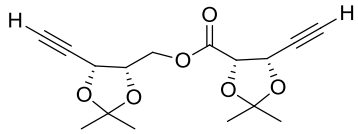


1.298

((4R,5S)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1.298): Lactol **1.235** (0.032 g, 0.200 mmol), Bestmann-Ohira reagent **1.297** (0.050 g, 0.260 mmol), and K_2CO_3 (0.036 g, 0.260 mmol) were reacted in dry MeOH (2 mL) following the literature procedure[91] to give **1.298** as a colorless liquid (0.02 g, 64%).

^{1}H NMR ($CDCl_3$): δ 4.60 (1H, dd, *J* = 2.1, 7.6 Hz), 4.19 (1H, td, *J* = 3.3, 7.6 Hz), 3.93 (1H, dd, *J* = 3.0, 4.3 Hz), 3.89 (1H, dd, *J* = 3.1, 4.3 Hz), 3.65-3.72 (1H, m), 2.54 (1H, d, *J*

= 2.10 Hz), 1.85-1.95 (1H, m), 1.51 (3H, s), 1.45 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 110.9, 82.0, 80.8, 75.0, 66.3, 60.9, 26.9, 26.3.



1.300

(4S,5S)-((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 5-ethynyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate (1.300): To a stirred solution of alcohol **1.298** (0.008 g, 0.05 mmol) in dry CH_2Cl_2 (1 mL) was added powdered 3Å molecular sieves (0.02 g), NMO (0.012 g, 0.100 mmol), and TPAP (5 mol%, 0.001 g) sequentially and stirred at rt. After 10 minutes (TLC analysis), the solvent was evaporated and the crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to afford **1.300** as a colorless liquid (0.006, 35%).

IR (neat, NaCl) 3269, 2926, 2129, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.90 (1H, dd, *J* = 2.1, 5.9 Hz), 4.67 (1H, d, *J* = 5.9 Hz), 4.54 (1H, dd, *J* = 2.1, 6.9 Hz), 4.46-4.50 (1H, m), 4.29-4.35 (2H, m), 2.62 (1H, d, *J* = 2.1 Hz), 2.58 (1H, d, *J* = 2.1 Hz), 1.57 (3H, s), 1.56 (3H, s), 1.51 (3H, s), 1.50 (3H, s), 1.50 (3H, s).

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CHAPTER II

Homoallylation of Various Chiral and Achiral Pentadienoates with Chiral and Achiral Aldehydes

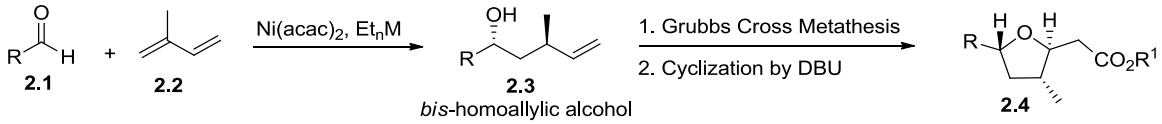
2.1. General Objective

Carbon-carbon bond formation is the most fundamental process in synthetic organic chemistry. The development of new and efficient protocols for the formation of carbon-carbon bonds for application in the rapid construction of complex natural and unnatural products has always been a formidable and enduring challenge in organic synthesis.

The vinylation, allylation and homoallylation of carbonyl compounds to produce allylic, homoallylic and *bis*-homoallylic alcohols, respectively are important reactions for the formation of carbon-carbon bonds. Various methods including asymmetric variants have been developed for the alkenylation and allylation reactions.[1] On the other hand, homoallylation of carbonyl compounds has achieved less attention, partly because of the limited availability of homoallylation methods and the limited variety of homoallylating agents CH_2=$CHCH_2CH_2M$, which are restricted to highly electropositive metals such as Li, Mg, Zr etc.[2] The development of nickel-catalyzed reductive coupling reactions of carbonyl compounds and 1,3-dienes has proven to be a successful tool for the synthesis of *bis*-homoallylic alcohols. However, very limited asymmetric variations of these reactions are known. The general objective of this chapter of the thesis is to develop diastereoselective versions of homoallylation reactions.

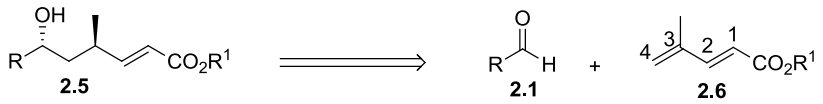
2.2. Introduction

Recently we showed that (described in chapter 1) *bis*-homoallylic alcohols **2.3** could be synthesized with good to excellent diastereoselectivity by reacting aldehydes **2.1** (hemiacetals or epoxyaldehydes) with isoprene **2.2** (Scheme 2.1).[3] The b*is*-homoallylic alcohol **2.3** obtained could be converted to trisubstituted tetrahydrofuran (THF) ring **2.4** in two steps: Grubbs cross metathesis with an alkyl acrylate followed by DBU cyclization.



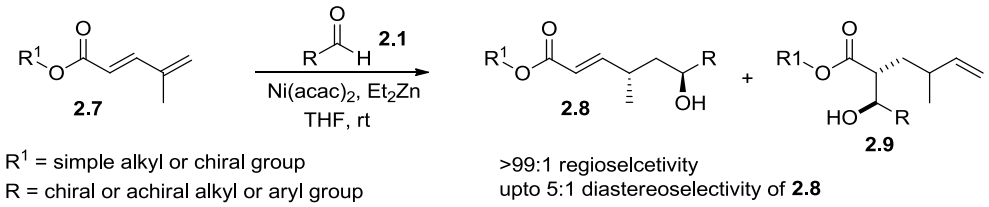
Scheme 2.1. Representation of Homoallylation, Cross Metathesis and Cyclization

It is conceivable that the metathesis reaction can be eliminated by conducting the reductive alkylation with a diene carboxylate ester (pentadienoates) **2.6** (Scheme 2.2). Reductive addition of a diene carboxylate ester (or amide) **2.6** would lead directly to the hydroxyl unsaturated ester **2.5** required for cyclization. Based on the various substituent patterns explored by Tamaru, it was predicted that the major product would result from the reaction at the 3,4-bond. The inclusion of the ester or amide moiety within the diene allows for the addition of a chiral auxiliary to control the π-facial selectivity with respect to the aldehyde.



Scheme 2.2. Retrosynthesis of ε-Hydroxy-α,β-Unsaturated Ester **2.5**

Herein, reaction of achiral and chiral aldehydes with achiral and chiral diene carboxylate esters which produce *bis*-homoallylic alcohols in excellent regioselectivity (>99:1) and modest diastereoselectivity (upto 5:1) will be discussed (Scheme 2.3).



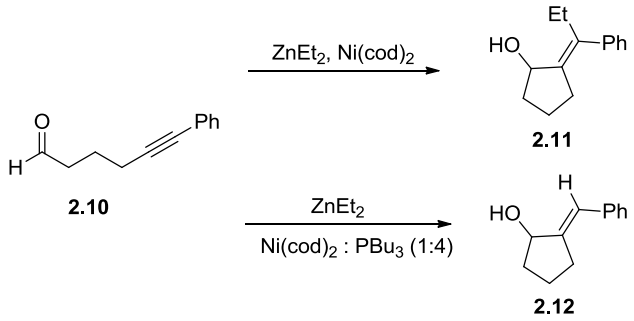
Scheme 2.3. Representation of the Homoallylation of an Aldehyde and a Pentadienoate

2.3. Nickel catalyzed reductive coupling reactions

2.3.1. Coupling of carbonyl compounds with alkynes: Allylic alcohols preparation

2.3.1.1. Intramolecular coupling of carbonyl compounds with alkynes

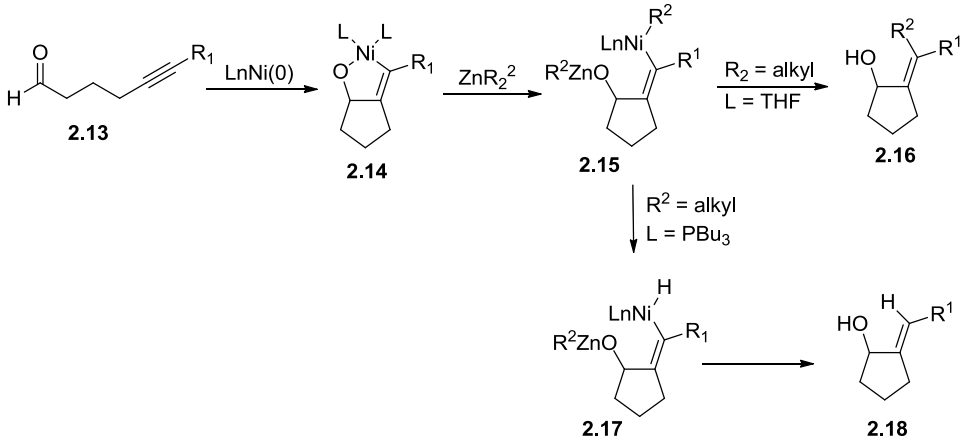
In 1997, Montgomery and coworkers reported the first example of a nickel catalyzed reductive coupling of aldehydes with alkynes to obtain cyclic allylic alcohols **2.11** and **2.12** (Scheme 2.4).[4] They observed that 5-alkynal **2.10** (1.0 equiv.) undergoes alkylative cyclization upon treatment with $Ni(cod)_2$ (5 mol %) and a variety of organozinc reagents (2.5-3.0 equiv.) at 0 ^oC in THF to give allylic alcohol **2.11** with a exocyclic tetrasubstituted alkene. However, in the presence of a catalytic phosphine additive (PBu_3, 4.0 equiv. relative to $Ni(Cod)_2$), the reductive cyclization product **2.12** (transfer of H instead of ethyl group from diethylzinc) was observed.



Scheme 2.4. Alkylative and Reductive Cyclizations of 5-Alkynyl **2.10**

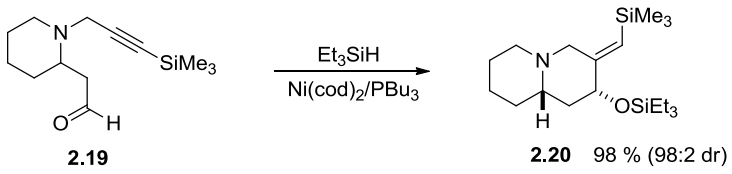
The proposed mechanism of this transformation involves the oxidative coupling of an alkyne and aldehyde with nickel(0) to obtain oxanickelacycle **2.14** (Scheme 2.5). This is followed by transmetalation of the organozinc to produce vinyl nickel species **2.15**. Reductive elimination of **2.15** produces alkylative cyclization product **2.16**. On the other

hand, β-hydride elimination of **2.15** prior to reductive elimination in the presence of tributylphosphine affords the reductive cyclization product **2.18**.[5]



Scheme 2.5. Proposed Mechanism for Ynal Cyclization

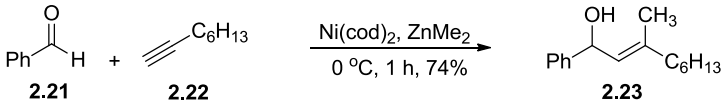
Montgomery observed that with more complex substrates, the direct 1,2-addition of diethylzinc to the aldehyde caused a significant problem. To avoid this problem of direct 1,2-addition, they developed an efficient method of reductive cyclization using triethylsilane as a reducing agent and tributylphosphine as a ligand (Scheme 2.6).[6] An example shown below gives silyl protected allylic alcohol **2.20** with excellent diastereoselectivity and yield. This concept can be employed for the stereoselective synthesis of a variety of quinolizidine, indolizidine, and pyrrolizidine alkaloids.[6]



Scheme 2.6. Ni(0) Catalyzed Cyclization of Silyl Protected Ynal **2.19**

2.3.1.2. Intermolecular coupling of carbonyl compounds with alkynes

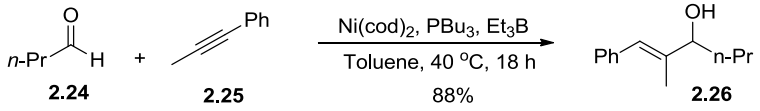
The nickel catalyzed alkylative coupling product of alkynes and aldehydes were reported by Montgomery *et al.* which uses a stoichiometric amount of dialkylzinc as a reducing agent.[4] As shown below, benzaldehyde **2.21** (3.0 equiv.) reacts with octynal-1 **2.22** (1.0 equiv.) in the presence of catalytic Ni(0) (20 mol%) and dimethylzinc (2.5 equiv.) as a reducing agent to produce **2.23** as a single regio- and stereoisomer in 74% yield.



2.21 **2.22** **2.23**

Scheme 2.7. Three Component Coupling of Aldehyde, Alkyne and Dimethylzinc

However, the first example of intermolecular reductive coupling of aldehydes and alkynes (catalyzed by $Ni(cod)_2/PBu_3$ and reduced by Et_3B) was reported by Jamison and coworkers.[7] For example, treatment of *n*-butanal **2.24** (1.0 equiv.) with 1-phenylpropyne **2.25** (1.0 equiv.) in the presence of $Ni(cod)_2$ (10 mol%), Bu_3P (0.2 equiv.), and triethylborane (2.0 equiv.) in toluene gives **2.26** in 88% yield and 98:2 regioselectivity (Scheme 2.8).

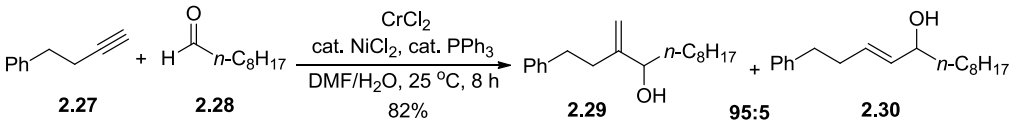


2.24 **2.25** **2.26**

Scheme 2.8. Intermolecular Reductive Coupling of an Aldehyde and an Alkyne

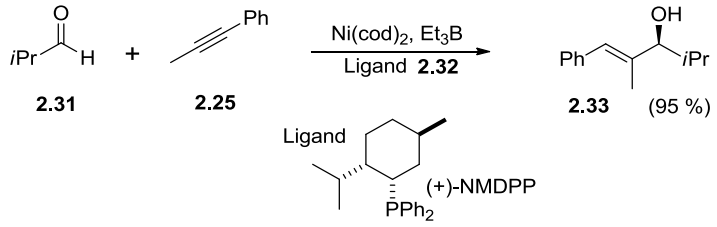
In the mean time, Takai and coworkers reported a reductive coupling of an aldehyde and a terminal alkyne with $CrCl_2$, a catalytic amount of $NiCl_2$ and triphenylphosphine to produce 1,2-disubstituted allylic alcohol regioselectively.[8] To give an example, 4-phenyl-1-butyne **2.27** (2.5 equiv.) was reacted with nonanal **2.28** (1.0 equiv.) in the presence of

$CrCl_2$ (5.0 equiv.), a catalytic amount of $NiCl_2$ (25 mol %), and triphenylphosphine (50 mol %) in DMF/water for 8 h to give allylic alcohols **2.29** and **2.30** in 95:5 regioselectivity (Scheme 2.9). An excess amount (2-3 equiv.) of alkyne was needed to avoid cyclotrimerization of alkynes, a side reaction.



Scheme 2.9. Reductive Coupling of a Terminal Alkyne and an Aldehyde

In 2003, Jamison reported the first examples of catalytic, enantioselective reductive couplings of alkynes and aldehydes employing a menthyl-based monodentate phosphine ligand **2.32** (*neo*-menthyldiphenylphosphine, (+)-NMDPP).[9] For example, treatment of *iso*-butanal **2.31** (2.0 equiv.) with 1-phenylpropyne **2.25** (1.0 equiv.) using catalytic $Ni(cod)_2$ (10 mol %), ligand **2.32** (20 mol %) and Et_3B (2.0 equiv.) in 1:1 mixture of EtOAc/DMI (1,3-dimethylimidazolidinone) at -25 °C for 36 h produced allylic alcohol **2.33** with 90% ee and >95:5 regioselectivity (Scheme 2.10).



Scheme 2.10. Enantioselective Reductive Coupling of an Aldehyde and an Alkyne

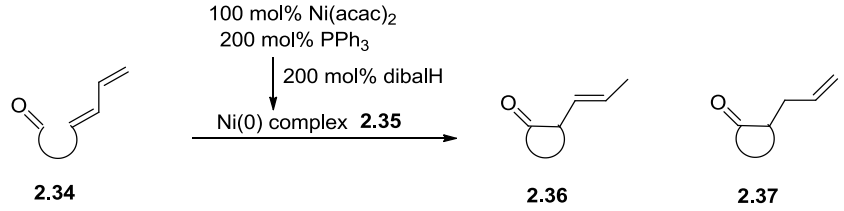
A number of diastereoselective reductive coupling reactions of alkyne and aldehyde are reported by both the Jamison and Montgomery groups.[10]

2.3.2. Coupling of carbonyl compounds with 1,3-dienes: Homoallylic and *bis*-homoallylic alcohols preparation

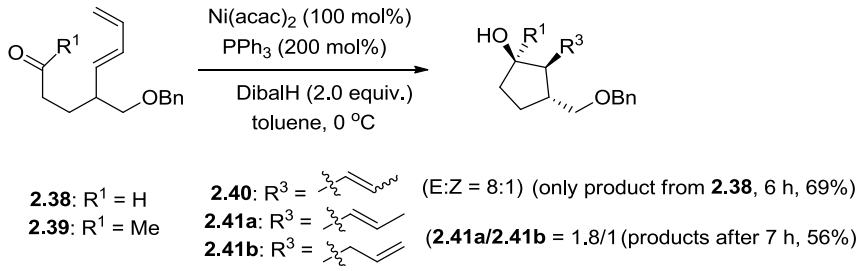
The reductive coupling reactions of aldehydes (and ketones) with 1,3-dienes are developed and extended by Mori and coworkers, Tamaru and coworkers and others.

2.3.2.1. Intramolecular coupling of 1,3-dienes and carbonyl compounds

Mori reported that 1,3-dienes undergo regio- and stereoselective reductive cyclization with a tethered carbonyl group in the presence of a stoichiometric amount of Ni(0) produced by reducing $Ni(acac)_2/PPh_3$ with dibalH (Scheme 2.11).[11] For example, treatment of aldehyde **2.38** (or ketone **2.39**) with a stoichiometric amount of hydride nickel complex **2.35**, prepared *in situ* from $Ni(acac)_2$ (100 mol%) and 2.0 equivalent of dibalH in the presence of PPh_3 (200 mol%) gave **2.40** as the only product (or a mixture of **2.41a** and **2.41b**) (Scheme 2.12).

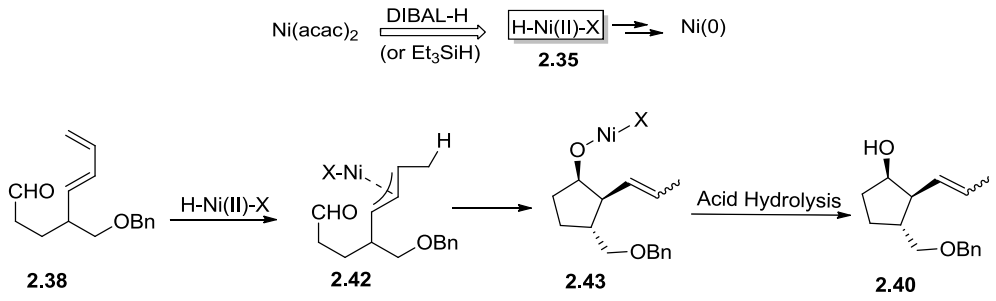


Scheme 2.11. Representation of Ni(0) Catalyzed Intramolecular Cyclization



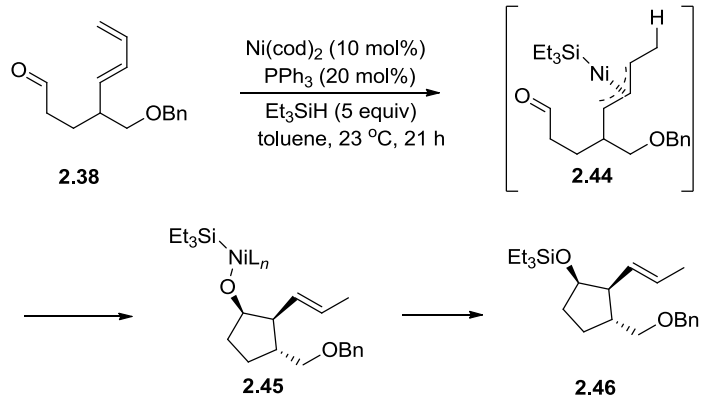
Scheme 2.12. Intramolecular Reductive Coupling of 1,3-Dienes and Aldehyde

These cyclization reactions follow the proposed mechanism (Scheme 2.13): a stoichiometric amount of hydride nickel complex **2.35** is generated from $Ni(acac)_2$ and PPh_3 by treatment with DIBAL-H.[11] The nickel complex **2.35** reacts with the diene to form a π-allylnickel complex **2.42** which reacts with the aldehyde **2.38** in the side chain giving the nickel complex **2.43**. Upon acid hydrolysis, the cyclized product **2.40** is obtained stereoselectively with respect to the three carbon centers of the cyclopentane ring.



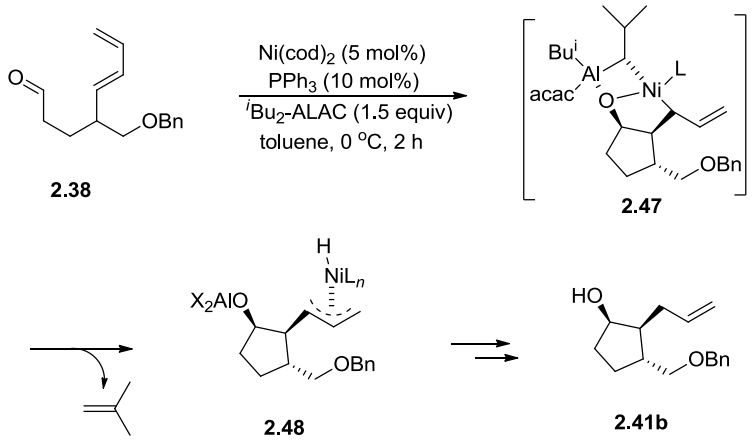
Scheme 2.13. Mechanism of Intramolecular Reductive Cyclization Reaction

Mori was also able to establish a catalytic variant of this reductive cyclization reaction preparing π-allylnickel complex **2.35** (X = $SiEt_3$) formed from a 1,3-diene and zerovalent nickel complex in the presence of Et_3SiH.[11] For example, when compound **2.38** is treated with a catalytic amounts of $Ni(cod)_2$, (10 mol%), PPh_3 (20 mol%), and Et_3SiH (5.0 equiv.), **2.46** is obtained in 70% yield (Scheme 2.14). This reaction proceeds via a π-allyl intermediate **2.44** to give **2.46** with an internal double bond in the side chain.



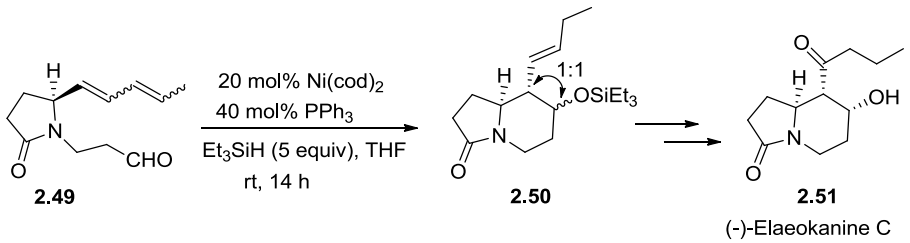
Scheme 2.14. Proposed Mechanism for the Catalytic Cyclization of **2.38**

On the other hand, when **2.38** is cyclized using a catalytic amount of $Ni(cod)_2$ (5 mol%) and PPh_3 (10 mol%) in the presence of $^{i}Bu_2$-ALAC (Diisobutylaluminum acetylacetonate) (1.5 equiv.), a cyclized product **2.41b** having a terminal olefin on the side chain can be selectively produced with 84% yield (Scheme 2.15).[12] It was proposed that in the presence of $^{i}Bu_2$-ALAC, the reaction proceeds via a transmetalation of the nickelacycle **2.47**, formed by oxidative cycloaddition of **2.38** to Ni(0) complex and $^{i}Bu_2$-ALAC.



Scheme 2.15. Proposed Mechanism of Catalytic Cyclization of **2.38**

It was found that the addition of 1,3-cyclohexyldiene (1,3-CHD) to the reaction mixture under the same reaction conditions affected the regiochemistry of olefin on the side chain and **2.37** having a terminal olefin on the side chain was exclusively produced.[13] The Mori group has successfully applied the concept of nickel catalyzed cyclization in the formal total synthesis of (-)-Elaeokanine C **2.51** (Scheme 2.16).[14]

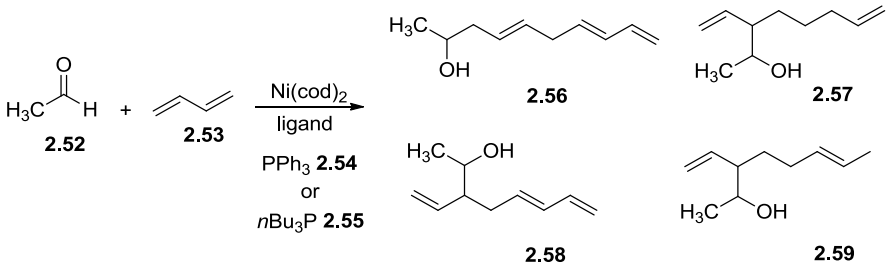


Scheme 2.16. Application of Ni(0) Catalyzed Cyclization in the Total Synthesis

2.3.2.2. Intermolecular coupling of 1,3-dienes and carbonyl compounds

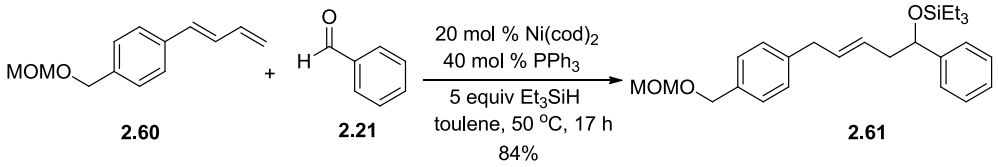
Extensive explorations have been published in the literature towards the Ni(0) catalyzed intermolecular coupling of 1,3-dienes and carbonyl compounds.

Baker and Crimmin reported the nickel-catalyzed and nickel-promoted reaction of 2 equiv. of 1,3-butadiene with 1.0 equiv. aldehydes to produce homoallylic alcohols as 2:1 adducts with good selectivity.[15] For example, reaction of acetaldehyde **2.52** (1.0 equiv.) and butadiene **2.53** (5.0 equiv.) in the presence of $Ni(cod)_2$ (25 mol %) and an organophosphorous ligand (25 mol %) at 0 ^{o}C for 16 h gave a mixture of 4 products whose ratio was dependent on nature of the ligand used (Scheme 2.17). Triphenylphosphine **2.54** and the nickel complex show a preference for the linear alcohol whereas the branched alcohol can be formed as a major isomer using tributylphosphine **2.55** and a variety of other phosphines.



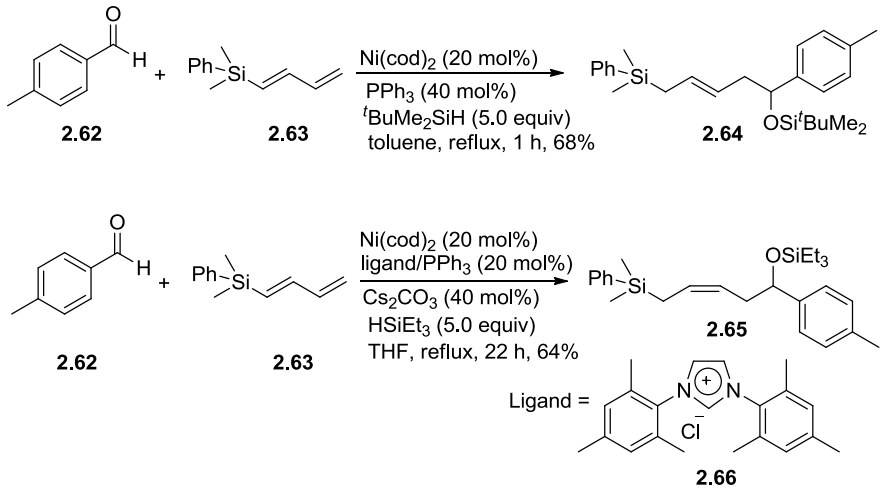
Scheme 2.17. Ni(0) Catalyzed Reaction of Acetaldehyde with Butadiene

Mori prepared homoallylic alcohol derivatives in a regio- and stereoselective manner.[16] For example, when a toluene solution of diene **2.60** (1.0 equiv.), benzaldehyde **2.21** (1.0 equiv.), and Et_3SiH (5.0 equiv.) was stirred in the presence of $Ni(cod)_2$ (20 mol %) and PPh_3 (40 mol %) at 50 ^oC for 17 h, triethylsilyl substituted homoallylic alcohol **2.61** was obtained as a sole product in 84% yield (Scheme 2.18).



Scheme 2.18. Ni(0) Catalyzed Reductive Coupling of a Diene and an Aldehyde

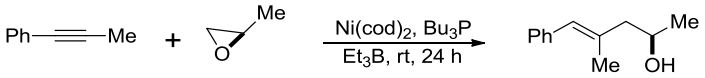
The same group also developed the Ni(0) catalyzed reactions of dienes having a silicon moiety and aldehydes which yield *E*- and *Z*-allylsilanes in a highly stereoselective manner.[17] It was found that when silyl-diene **2.63** was refluxed with aldehyde **2.62** in toluene in the presence of silane using catalytic amounts of $Ni(cod)_2$ having PPh_3, *E*-allylsilane **2.64** was obtained in good yield (Scheme 2.19). However, when the reaction mixture was heated in THF in the presence of $Ni(cod)_2$, imidazolium salt **2.66**, Cs_2CO_3 and PPh_3, *Z*-allylsilane **2.65** was formed as the sole product.



2.62 **2.63** **2.64** **2.62** **2.63** **2.65** **2.66**

Scheme 2.19. Stereoselective Formation of *E*- and *Z*- Allylsilanes

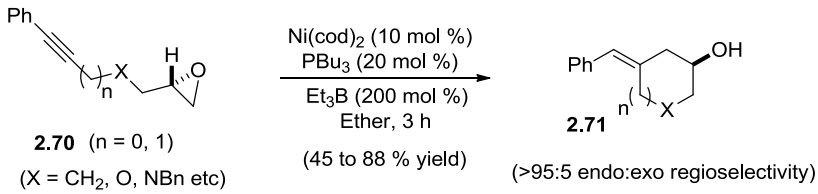
Jamison and Molinaro introduced Ni(0) catalyzed inter- and intramolecular reductive coupling of epoxides and alkynes with triethylborane as reducing agent.[18] As shown below, when phenylpropyne **2.67** (1.0 equiv.) is treated with epoxide **3.68** (2.0 equiv.) in the presence of $Ni(cod)_2$ (10 mol %), Bu_3P (20 mol %), and Et_3B (2.0 equiv.), homoallylic alcohol **2.69** is produced with >95:5 regioselectivity at both alkyne and epoxide in 71% yield (Scheme 2.20).



2.67 **2.68** **2.69**

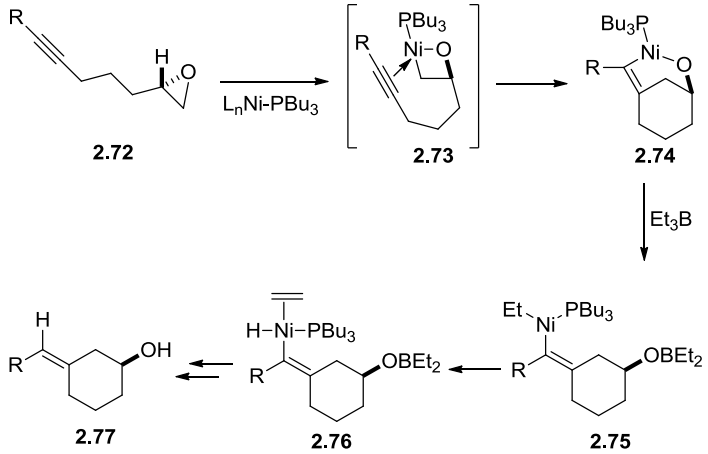
Scheme 2.20. Ni(0) Catalyzed Reductive coupling of an Alkyne and an Epoxide

Various cyclization reactions to form five- and six-membered rings were also reported by the same group. The addition always occurred at the unsubstituted epoxide position (*endo* attack) (Scheme 2.21).



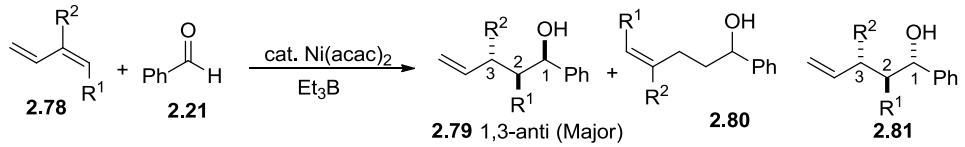
Scheme 2.21. Reductive Intramolecular Cyclization of Alkyne-Epoxide

The mechanism of this selectivity involves the regioselective oxidative addition of the phosphine-nickel(0) complex into the less hindered C-O bond of the epoxide **2.72** to form the nickelaoxetane intermediate **2.73** (Scheme 2.22). This is followed by alkyne insertion (cyclization) to give **2.74** and ethyl transfer from Et_3B to nickel giving intermediate **2.75**. Subsequent *β*-hydride elimination gives **2.76** followed by reductive elimination to give the observed product **2.77**.



Scheme 2.22. Mechanism of Ni(0) Catalyzed Intramolecular Cyclization

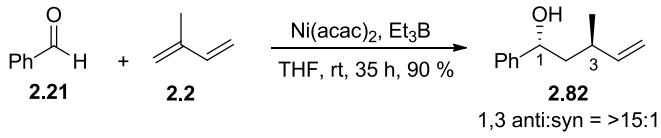
Tamaru *et al.* developed a regio- and stereoselective nickel catalyzed coupling of carbonyl compounds and 1,3-dienes using organoboron or organozinc reagents.[19] This reaction corresponds to a reductive coupling of the C1-C2 double bond of isoprene and the carbonyl group of the aldehyde to give *bis*-homoallylic alcohol with very high 1,3-*anti* (or 1,2-*anti*) diastereoselectivity (Scheme 2.23).



Scheme 2.23. Intermolecular Reductive Coupling of Diene and Benzaldehyde

The reaction is remarkable in many respects; 1) isoprene reacts with benzaldehyde exclusively at the C1 position of the diene moiety with an exclusive delivery of hydrogen at C2, 2) the reaction exhibits high 1,3-diastereoselectivity giving 1,3-*anti*-**2.79** in preference to 1,3-syn-**2.81** (15:1), 3) the 1:1 adduct of diene and aldehyde selectively is surprising because of the property of nickel complexes to promote oligomerization of simple dienes giving 2:1 and 3:1 adducts also.[15,20]

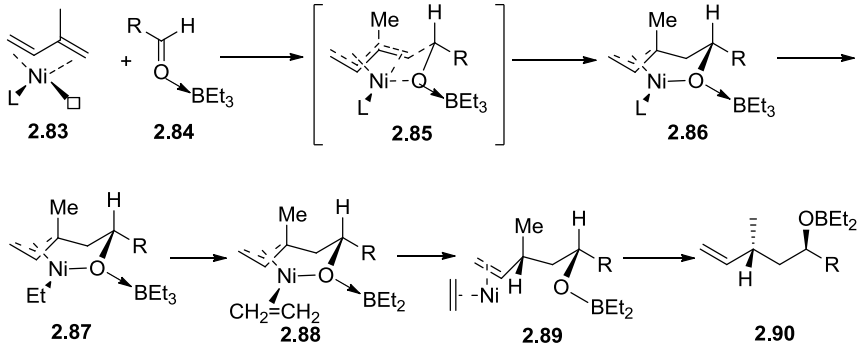
To give a specific example of such reductive coupling when benzaldehyde **2.21** (1.0 equiv.) is treated with isoprene **2.2** (4.0 equiv.) and Et_3B (2.4 equiv.) in the presence of $Ni(acac)_2$ in THF at rt, it provides the *bis*-homoallylic alcohol **2.82** (1:1 adduct of the diene and benzaldehyde) exclusively with 90% yield (Scheme 2.24).[19a]



Scheme 2.24. Homoallylation of Benzaldehyde **2.21** with Isoprene **2.2**

A plausible mechanism for this reductive coupling is outlined in scheme 2.25. The difference in the electron densities of the diene termini might control the regioselectivity and the terminal position bearing the highest electron density would react with the aldehyde (this will be discussed in detail in section **2.4.2**)**.** An oxanickellacyclopentane intermediate **2.86** is formed, from the transition state **2.85**, through oxidative cyclization

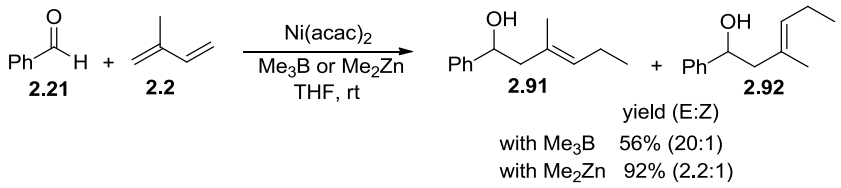
of a Ni(0) species across isoprene and an aldehyde. In the transition state **2.85**, the aldehyde is arranged to place the oxygen to the vacant site of the *s-trans*-diene-Ni(0) complex and alkyl group in a *quasi*-equatorial position to avoid a *quasi*-1,3-diaxial repulsion (between an aldehyde R and isoprene Me) that an alternate orientation of alkyl group might experience. The oxidative cyclization is enhanced by coordination of Et_3B (or Et_2Zn) to an aldehyde. One ethyl group is transferred from B to Ni followed by an ionic Ni-O bond cleavage to give an intermediate **2.87**. Intermediate **2.87** then undergoes *β*-hydrogen elimination to produce intermediate **2.88**. Reductive elimination of **2.88** delivers the hydrogen at the allylic position bound to the nickel with retention of configuration to finally produce a nickel(0)(ethylene) complex **2.89**, *bis*-homoallylic alcohol with 1,3-*anti* stereochemistry.



Scheme 2.25. Mechanism for the Ni(0)-Catalyzed Homoallylation of an Aldehyde

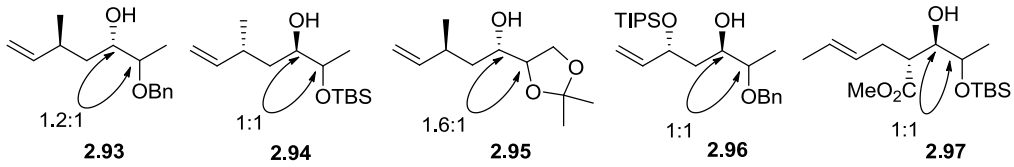
The use of Et_2Zn as a reducing agent and promoter is particularly effective for the reaction of saturated aldehydes and ketones, where the Et_3B is unsuccessful.[19b]

On the other hand, these couplings with Me_2Zn or Me_3B led to the formation of homoallylic alcohols (Scheme 2.26).[21]



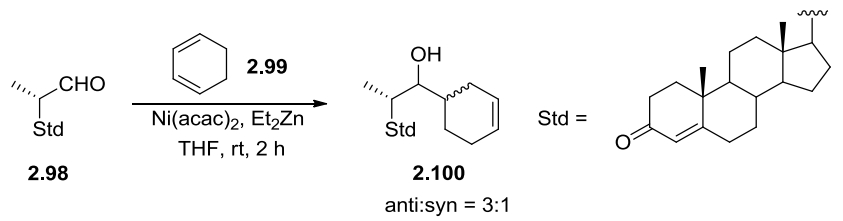
Scheme 2.26. Ni(0) Catalyzed Coupling (Me_3B or Me_2Zn as Reducing Agents)

Tamaru has extended the application of reductive coupling reaction (homoallylation) by taking a number of different types of diene and aldehydes.[19d] However, in the limited examples of chiral aldehydes studied by Tamaru gave very low π-facial selectivity (1:1 to 1.6:1) with respect to aldehyde.



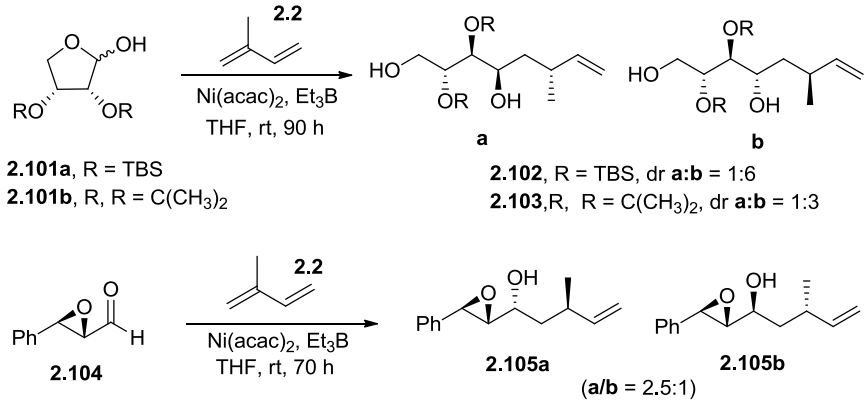
Scheme 2.27. Low Diastereoselectivity Reported by Tamaru

In some examples shown by Loh and coworkers,[22] the cyclic dienes can also undergo a reductive coupling reaction with an aldehyde which Tamaru *et al.*[19d] reported to be unreactive (or less reactive). It was shown that aldehydes like **2.98** can react with cyclic dienes like **2.99** in the presence of a catalytic amount of nickel and diethylzinc (as a promoting and reducing agent) to produce *bis*-homoallylic alcohols like **2.100** (Scheme 2.28).



Scheme 2.28. Homoallylation of Aldehyde **2.98** with Cyclohexa-1,3-diene **2.99**

We reported the nickel catalyzed diastereoselective homoallylation reactions of 1,3-dienes with hemiacetals and epoxyaldehydes (Scheme 2.29).[3] These were novel electrophiles used for this type of reductive coupling. For example, the TBS and acetonide protected hemiacetals **2.101a** and **2.101b** produced *bis*-homoallylic alcohols **2.102** and **2.103** in 1:6 and 1:3 diastereomeric ratios, respectively under normal homoallylation conditions with isoprene **2.2** developed by Tamaru *et al.*, albeit at longer reaction time. Homoallylation of isoprene **2.82** with epoxy-cinnamaldehyde **2.104** obtained *bis*-homoallylic alcohols **2.105a** and **2.105b** in 2.5:1 ratio. The *bis*-homoallylic alcohols obtained were used for the synthesis of C1-C6 fragment of cytotoxic natural products amphidinolides C, C2 and F (discussed in Chapter 1).

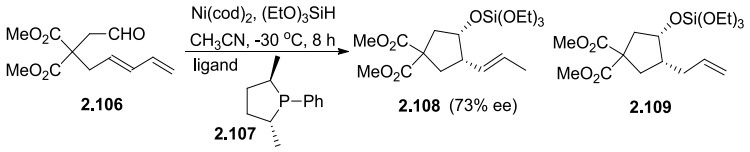


Scheme 2.29. Homoallylation of Hemiacetals and Epoxyaldehyde with Isoprene

2.3.3. Asymmetric reductive coupling reactions

2.3.3.1. Intramolecular asymmetric cyclization

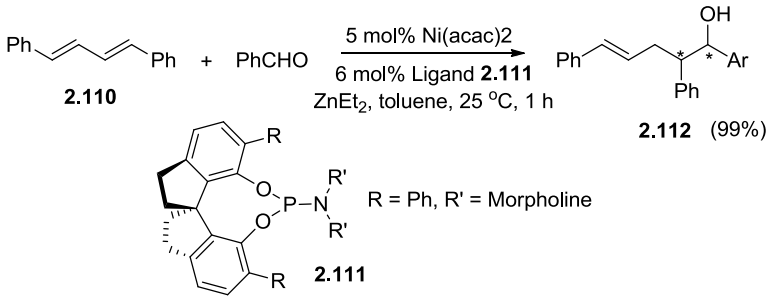
The Mori group reported the first example of nickel(0) catalyzed intramolecular asymmetric cyclizations of 1,3-dienes and tethered aldehydes in the presence of silanes employing a chiral monodentate phosphorane ligand.[23] For example, when dienal **2.106** (1.0 equiv.) was cyclized using $Ni(cod)_2$ (10 mol %) and chiral phosphorane **2.107** (20 mol %) in the presence of $(EtO)_3SiH$ (5.0 equiv.) in CH_3CN, it produced a mixture of silyl protected homoallylic alcohol **2.108** and *bis*-homoallylic alcohol **2.109** in >50/1 ratio with 73% ee (at **2.108**) and 83% combined yield (Scheme 2.30).



Scheme 2.30. Asymmetric Cyclization of a 1,3-Diene and a Tethered Aldehyde

2.3.3.2. Intermolecular asymmetric coupling

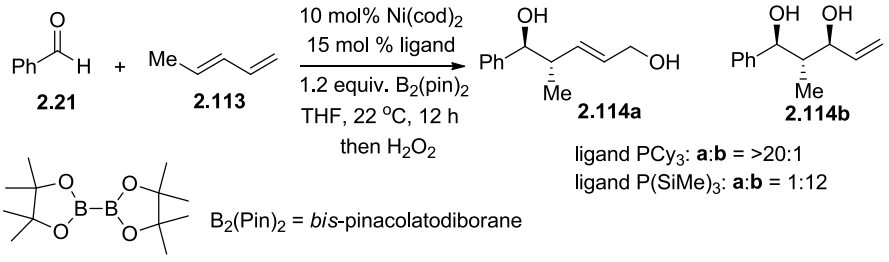
The asymmetric version of the nickel catalyzed intermolecular reductive coupling of 1,3-dienes and aldehydes was first reported by Zhou and coworkers.[24] The 6,6'-disubstituted spirobiindane phosphoramidite ligands showed low to excellent enantioselectivities (up to 96 %) in these coupling reactions. For example, when 1,4-diphenylbuta-1,3-diene **2.110** (1.0 equiv.) was treated with benzaldehyde **2.21** (2.0 equiv.) in the presence of $Ni(acac)_2$ (5 mol %), ligand **2.111** (6 mol %) and diethylzinc (2.4 equiv.), *bis*-homoallylic alcohol **2.112** was obtained in 96% ee and >99:1 anti/syn diastereoselectivity (scheme 2.31).



Scheme 2.31. Intermolecular Asymmetric Reductive Coupling

2.3.4. Diastereoselective addition of aldehyde and diene promoted by diboron reagent

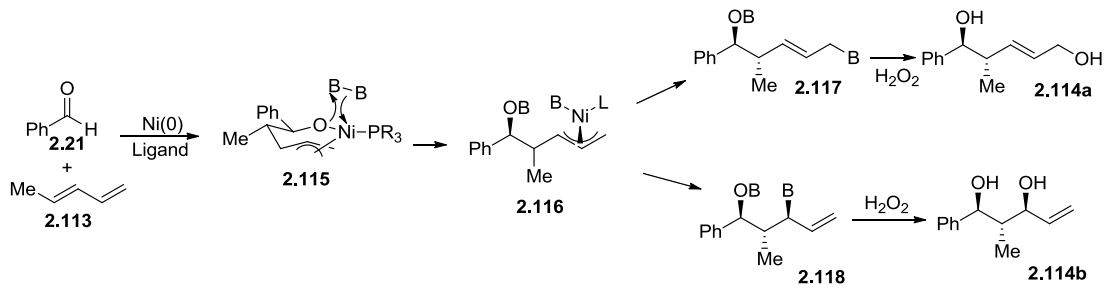
Recently, Morken and coworkers have shown that the intermolecular reductive coupling of aldehydes or ketones with dienes can be facilitated by the use of diboron reagents as the reducing agent.[25] These reactions proceed with excellent regio- and stereoselectively. As shown in the example below, benzaldehyde **2.21** (1.0 equiv.) upon treating with diene **2.113** (1.1 equiv.) in the presence of $Ni(cod)_2$ (10 mol %), PCy_3 (15 mol %) and *bis*(pinacolato)diboron (1.2 equiv.), produced homoallylic alcohol **2.114a** and *bis*-homoallylic alcohol **2.114b** (Scheme 2.32). However, when $P(SiMe_3)_3$ was employed as a ligand, a remarkable switch on regioselectivity was observed.



Scheme 2.32. Boron Reagent Mediated Asymmetric Intermolecular Coupling

The authors proposed that the difference in regioselectivity observed with these ligands may arise from electronic rather than steric differences.[25a] The reaction mechanism

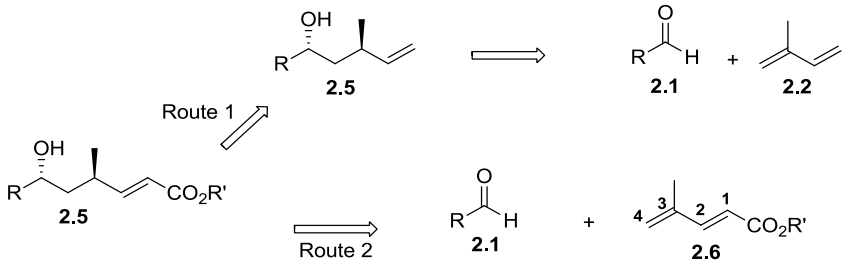
proceeds in accordance with the mechanistic studies by Ogoshi: oxidative cyclometalation to give **2.115**, subsequent transmetalation gives **2.116** and reductive elimination releases **2.117** and/or **2.118** from the catalyst, forming the C-B bond.[26] The authors proposed that the large cone angle of $P(SiMe_3)_3$ (178^o) and its ability to act as an electron acceptor may facilitate the reductive elimination of **2.118** from **2.116**, before allyl isomerization required for the formation of **2.117** (Scheme 2.33).



Scheme 2.33. Proposed Mechanism for the Diboron Reagent Promoted Intermolecular Coupling

2.4. Results and discussion

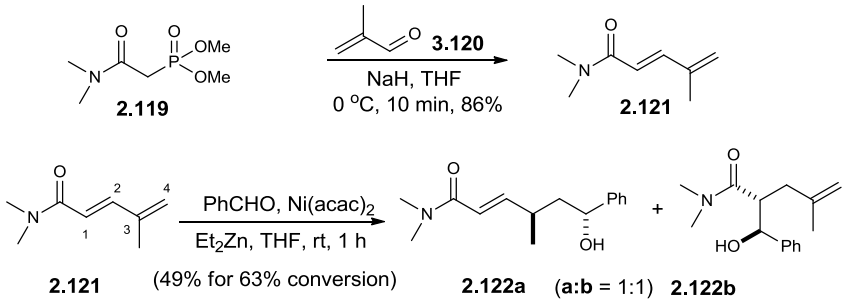
It is envisioned that the metathesis step (route 1) can be eliminated by conducting the reductive alkylation with the diene carboxylate ester (route 2) (Scheme 2.34). Reductive addition of a diene carboxylate ester **2.6** would lead directly to the hydroxyl unsaturated ester **2.5** required for cyclization. Based on the various substituent patterns explored by Tamaru, it was predicted that the major product would result from reaction of the 3,4-double bond.[19] The inclusion of the ester or amide moiety within the diene also allows for the addition of a chiral auxiliary to control the π-facial selectivity with respect to the aldehyde.



Scheme 2.34. Retrosynthetic analysis of Hydroxyl Unsaturated Ester **2.5**

2.4.1. Homoallylation with chiral and achiral dienecarboxamide

The homoallylation reaction of benzaldehyde with a simple dienecarboxamide **2.121,** prepared by the Horner-Wadsworth-Emmons (HWE) reaction of *N*,*N*-dimethyl phosphonoacetate **2.119**[27] with methacrolein **2.120**, was investigated (Scheme 2.35). This produced both regioisomers (1,2- and 3,4-addition products) **2.122a** and **2.122b**, respectively with low selectivity (1:1).



Scheme 2.35. Preparation of Dienecarboxamide **2.121** and Homoallylation with Benzaldehyde

The crystal structure of regioisomer **2.122b** shows that the newly formed stereocenters have *anti*-relative stereochemistry (Figure 2.1). Since the 3,4-addition product in all the examples reported by Tamaru[19] and Spilling[3] (Scheme 2.29) had *anti*-stereochemistry, product **2.122a** will probably have an *anti*-relationship.

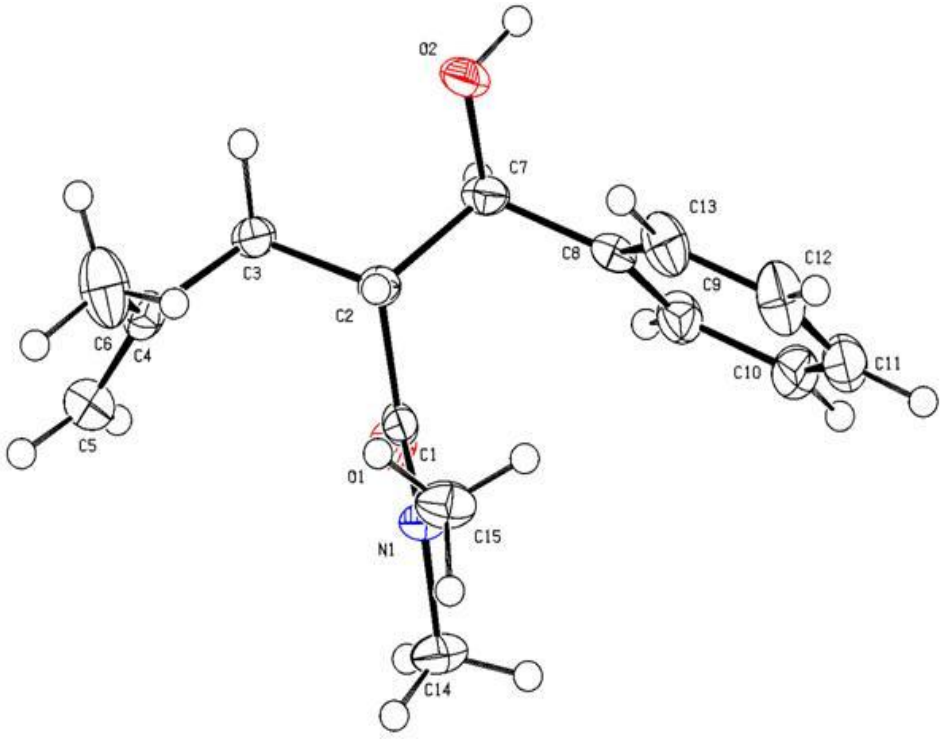
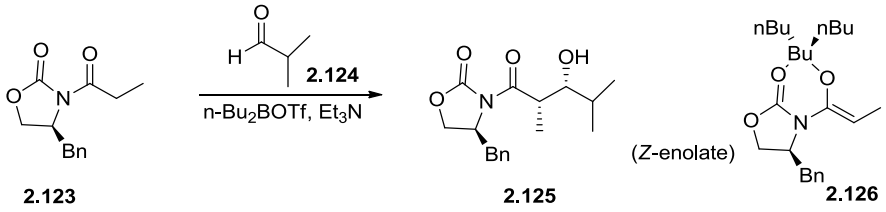


Figure 2.1. Crystal Structure of **2.122b**

Having shown that the simple dienecarboxamide **2.121** would undergo a homoallylation reaction, derivatives containing Evans and Oppolzer's chiral auxiliaries were tested next.

Introduced by Evans, Evans' chiral auxiliaries have been proven to be an excellent chiral inducer and they have been used in a number of reactions.[28]

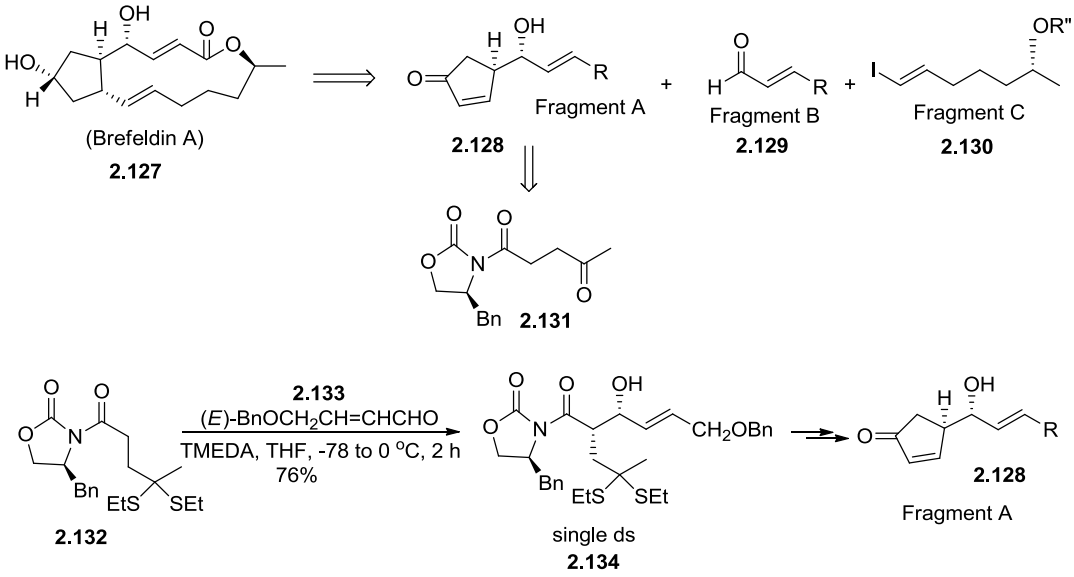
Evans *et al.* presented an application of these auxiliaries in the diastereoselective synthesis of alcohols in 1991.[29] Reaction of **2.123** having Evans' chiral auxiliary with *iso*-butyraldehyde in the presence of dibutylborontriflate and Et_3B produced **2.125** with more than 99:1 diastereoselectivity and 83% yield (Scheme 2.36). The excellent stereochemical outcome was determined by the formation *Z*-enolate and orientation of benzyl group in **2.126**.



2.123 **2.125** **2.126**

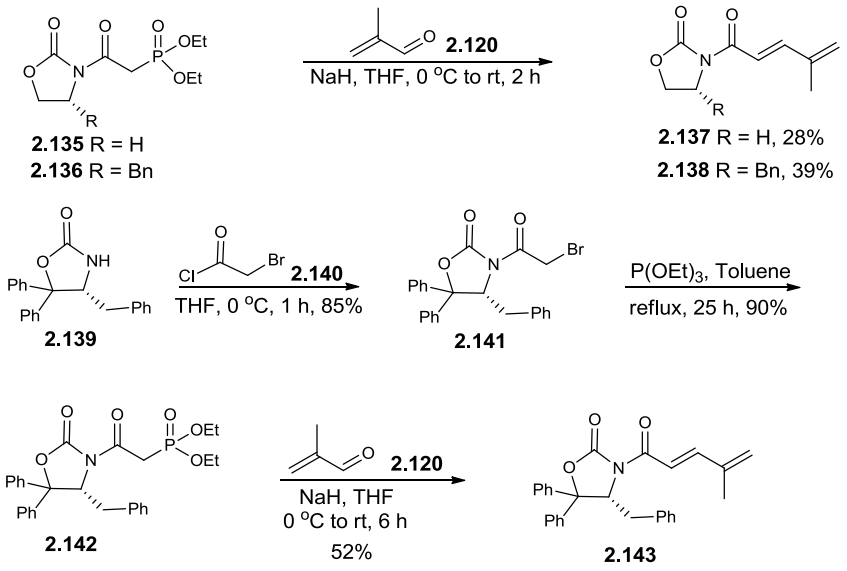
Scheme 2.36. Addition of Aldehyde **2.124** to the Enolate **2.126**

More recently, Wu *et al.* utilized Evans' chiral auxiliary in a fragment synthesis of the antiviral compound called Brefeldin A **2.127** (Scheme 2.37).[28d] Fragment A **2.128** of Brefeldin A was synthesized in steps starting from the reaction of dithiol derivative **2.132** and aldehyde **2.133** to produce a **2.134** as a single diastereomer.

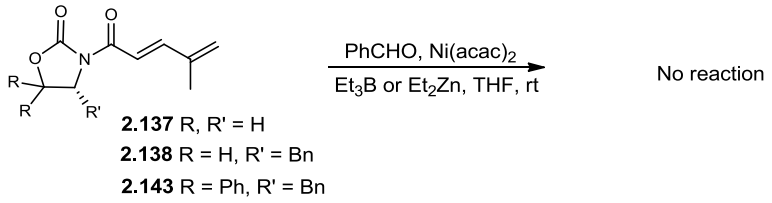


Scheme 2.37. Retrosynthesis of Brefeldin A **2.127** and Synthesis of Fragment A

In the search for chiral inducers for the homoallylation reaction, three different imide derivatives (Evans' chiral auxiliaries) were synthesized (Scheme 2.38). Diene imide derivatives **2.137** and **2.138** were synthesized by the HWE reaction of corresponding phosphono-acetates[30] **2.135** and **2.136**, respectively, whereas the derivative **2.143** was obtained in three steps starting from 5,5-diphenyl-4-benzyl oxazolidin-2-one **2.139**. Unfortunately, all these imide derivatives were completely unreactive with benzaldehyde **2.21** (Scheme 2.39).



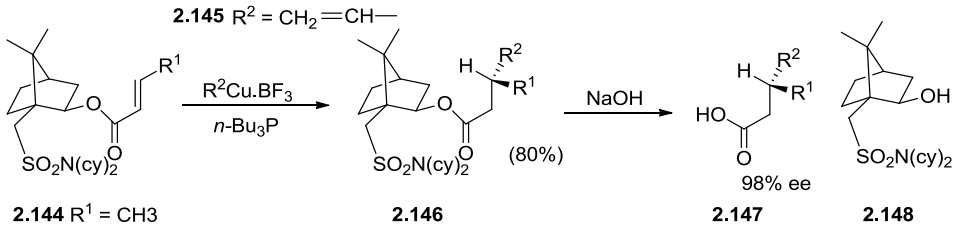
Scheme 2.38. Synthesis of Diene Derivatives of Evans' Chiral Auxiliaries



Scheme 2.39. Reaction of Imide Diene Derivatives and Benzaldehyde

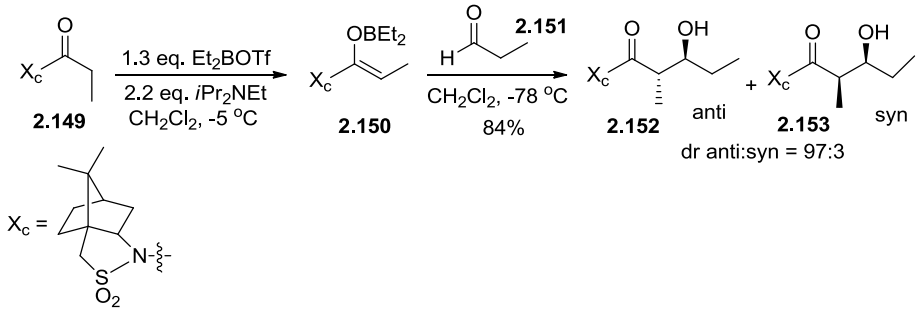
With the disappointing results from imide diene derivatives, we turned our attention towards dienes derived from Oppolzer's chiral auxiliaries. Since the developments reported by Oppolzer, he and others have beautifully applied the topological bias of the camphor skeleton in their advantage for the synthesis of enantioenriched products.[31]

In the early stage of its development, Oppolzer *et al.* showed that *β*-substituted carboxylic acids **2.147** can be synthesized with excellent enantioselectivity using camphor sulfonamide derivative **2.144**. Treatment of **2.144** with organocopper reagent **2.145** in the presence of nBu$_3$P furnished the 1,4-adduct **2.146** with 80% yield and 98% ee with complete recovery of the auxiliary **2.148** (Scheme 2.40).[32]



Scheme 2.40. Application of Oppolzer's Chiral Auxiliary

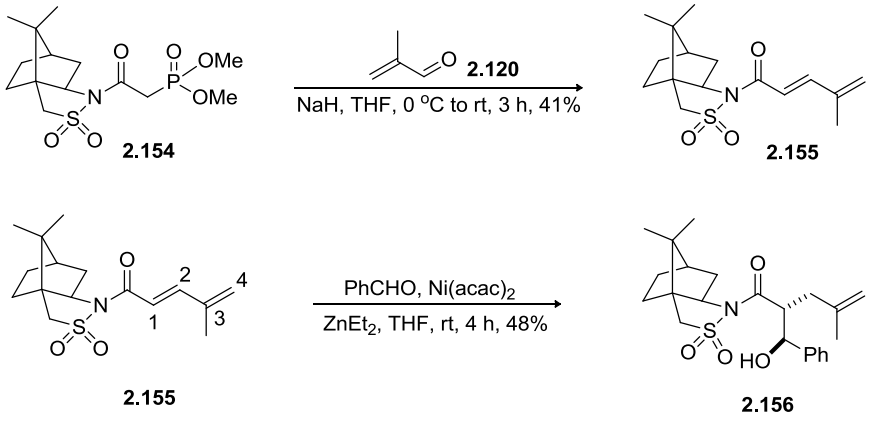
Recently, Fraser *et al.* reported the Et_2BOTf promoted *anti* selective aldol additions employing Oppolzer's sultam (Scheme 2.41).[33] The propionyl sultam **2.149** (1.0 equiv.) in CH_2Cl_2 at -78 ^oC was treated with $^iPr_2NEt$ and varying equivalents of Et_2BOTf. Propanal **2.51** (1.0 equiv.) was then added to the resulting solution. This reaction proceeded with excellent (upto 97:3) diastereoselectivity and good to excellent yield. The Et_2BOTf was generated *in situ* from triethylborane and trifluoromethane sulphonic acid (1:1).



Scheme 2.41. An Example of Aldol Reaction Employing the Oppolzer Auxiliary

The Ni(0) catalyzed reductive coupling of diene **2.155** with the Oppolzer sultam moiety was carried with benzaldehyde **2.21** (Scheme 2.42). The diene **2.155** was obtained by the HWE reaction of known phosphono-acetate **2.154**[34] with methacrolein **2.120**. After the homoallylation, only one regioisomer resulted from the addition of aldehyde across the

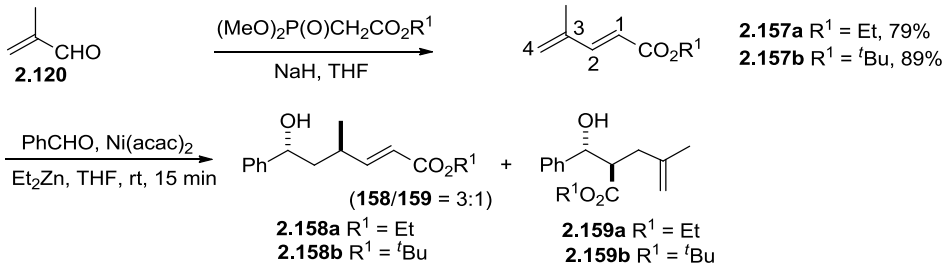
1,2-double bond, which was isolated in low yield. This clearly indicated that such substrates are only moderately reactive towards reductive coupling.



Scheme 2.42. Synthesis of Diene **2.155** and its Coupling with Benzaldehyde

2.4.2. Homoallylation with chiral and achiral dienecarboxylate esters

With the disappointing results from dienes having chiral imides and sultam moieties, we turned our attention towards chiral dienecarboxylate esters (4-methyl substituted pentadienoates). The homoallylation of achiral dienecarboxylate esters with benzaldehyde were the starting reactions to test the chemistry. Achiral pentadienoates **2.157a** and **2.157b** were synthesized by the HWE reaction of methacrolein **2.120** with phosphono-acetates (Scheme 2.42). Pentadienoates underwent a smooth homoallylation reaction with benzaldehyde to give the desired regioisomers (3,4-addition products) **2.158** in a 3:1 ratio with the 1,2-addition products **2.159**.

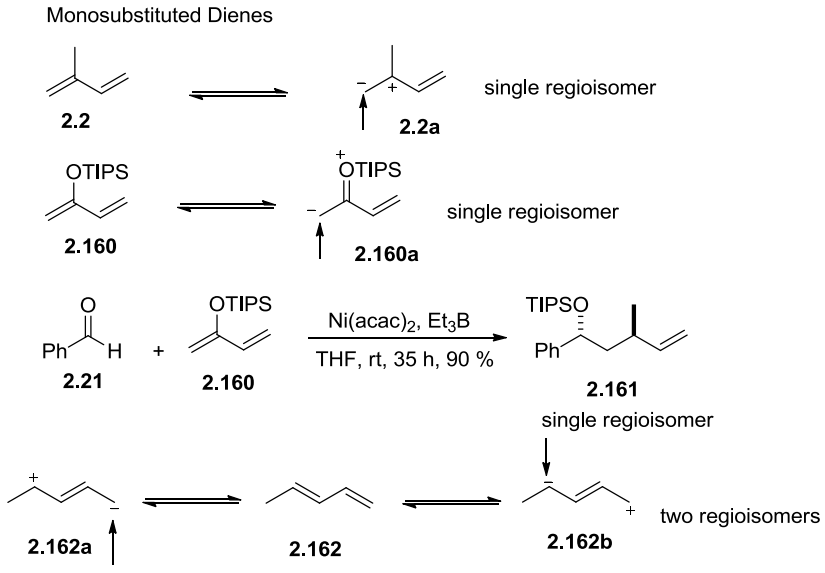


Scheme 2.43. Synthesis of Pentadienoates and Homoallylation with Benzaldehyde

Rationale for 1,2- and 3,4-attack giving two regioisomers:

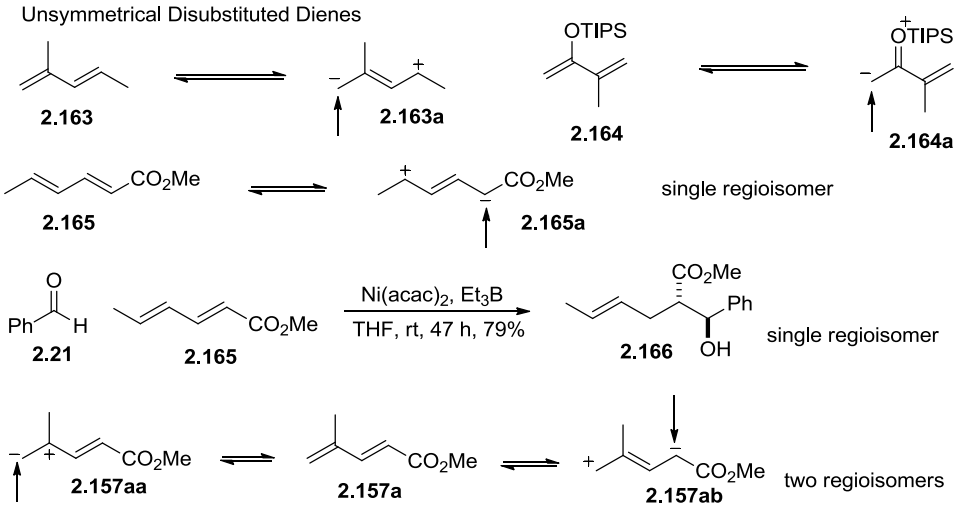
It seems that the regioselectivity is controlled by the difference in electron densities of the diene termini. This can be rationalized by examining the diene resonance structures and placing the anion and cation in the most stable positions as shown in Scheme 2.44. The position bearing the highest electron density (anion) would react with the aldehyde.

For example, isoprene **2.2** and **2.160** has the highest electron density at the terminal carbon (shown by arrow, **2.2a** and **2.160a** respectively), so only one regioisomer is obtained. On the other hand, 1,3-pentadiene **2.162** has two potential reacting sites that give two regioisomers (1:2.4) upon reacting with benzaldehyde.[19a]



Scheme 2.44. Diene Resonance Structures and Homoallylation Reaction

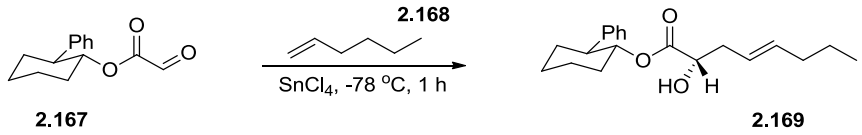
In case of the unsymmetrical disubstituted dienes such as **2.163, 2.164** and **2.165**, a single regioisomer is obtained because there is only one nucleophilic center (Scheme 2.45).[19a] However, in other cases like **2.157a**, there are two potential reacting sites that produce two regioisomers.[3] The 3:1 selectivity in case of **2.157a** favoring **2.158a** is probably stemming from steric reasons (Scheme 2.43).



Scheme 2.45. Diene Resonance Structures and Homoallylation Reaction

After obtaining successful results with achiral pentadienoates towards homoallylation, some chiral pentadienoate derivatives were synthesized and tested.

The *trans*-2-phenylcyclohexanol was introduced by Whitesell and coworkers in 1985.[35] They investigated the ene-reaction of the glyoxylate ester of *trans*-2-phenylcyclohexanol **2.167.** It was shown that when **2.167** was reacted with 1-hexene **2.168** in the presence of $SnCl_4$, it produced **2.169** as a single diastereomer in 78% yield (Scheme 2.46). This auxiliary showed the same level of asymmetric induction abilities as 8-phenylmenthol.



Scheme 2.46. Reaction of *trans*-2-phenyl Cyclohexanol Derived Glyoxylate Ester with **2.168**

The phenyl cyclohexanol chiral auxiliary has been utilized in the total synthesis of natural products like (-)-Specionin[36] **2.170** and in the stereoselective synthesis of *meso*-2,6-diaminopimelic Acid[36] **2.171** (Figure 2.2).

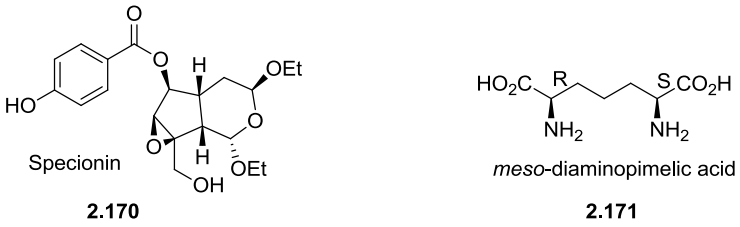
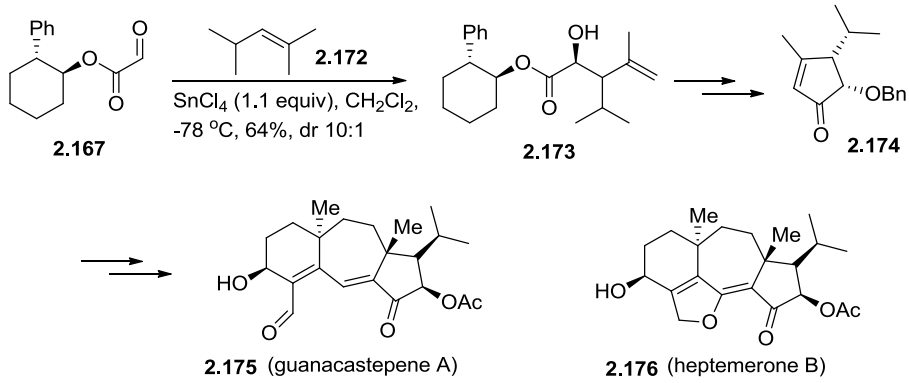


Figure 2.2. Natural Products Synthesized Using *trans*-2-Phenyl Cyclohexanol

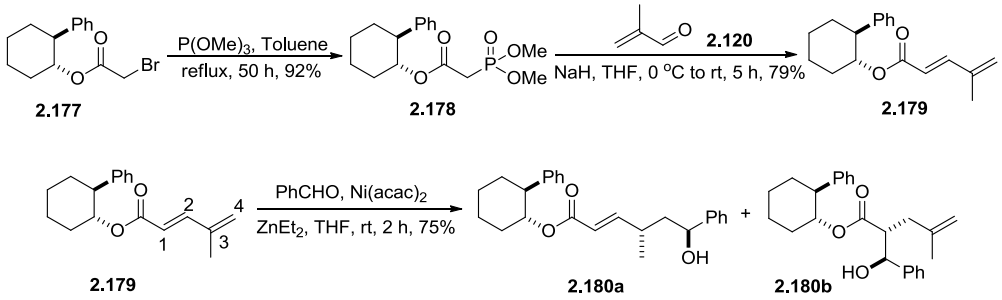
Recently Miller *et al.* used this auxiliary in the fragment synthesis of antimicrobial natural products (-)–Guanacastepene E **2.175** and Heptemerone B **1.176** (Scheme 2.47).[37]



Scheme 2.47. Application of *trans*-2-Phenyl Cyclohexanol Derivative in Natural Product Synthesis

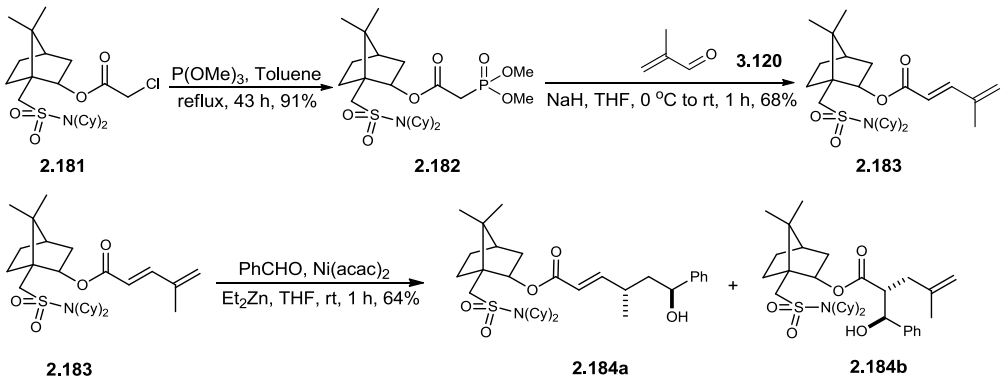
The *trans*-2-phenylcyclohexanol derived pentadienoate **2.179** was obtained in two steps from the known acetyl bromide[38] **2.177** (Scheme 2.48). Homoallylation of **2.179** with benzaldehyde gave both regioisomers **2.180a** (3,4-addition) and **2.180b** (1,2-addition) in

3:1 selectivity. The diastereoselectivity within the minor product **2.180b** (1:4) was more than the diastereoselectivity of major product **2.180a** (1:1). This difference comes from the proximity of phenyl group to the 1,2-double bond imposing more π-facial selectivity than 3,4-double bond.



Scheme 2.48. Homoallylation of Pentadienoate **2.179** with Benzaldehyde

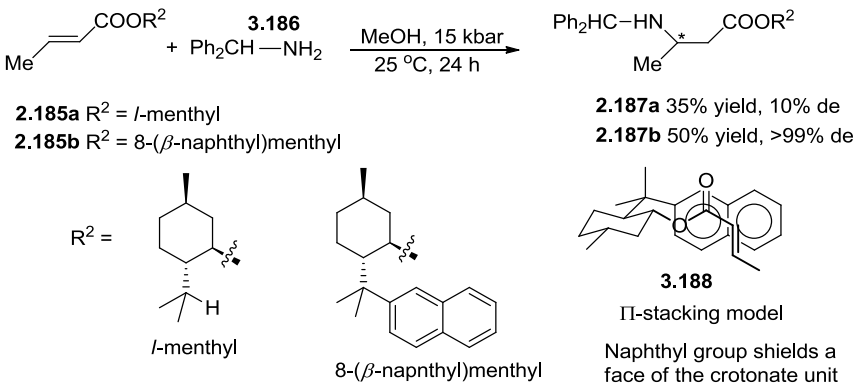
The pentadienoate derived from Oppolzer's chiral auxiliary with the sulphonamide moiety **2.183** was chosen because of the availability of both enantiomers. The known chloroacetyl ester derivative[39] **2.181** was converted to the desired chiral pentadienoate derivative **2.183** in two steps and homoallylation with benzaldehyde was carried out (Scheme 2.49). In this case the regioselectivity was improved over *trans*-2-phenylcyclohexanol derived pentadienoate **2.179** (from 3:1 to 6:1). The 1,2-addition product **2.184b** was isolated as a single diastereomer whereas the 3,4-addition product **2.184a** was formed as a 1:1 mixture. These results suggest that the cyclohexyl groups are posing steric hindrance on the 1,2-double bond but it is far away to affect the addition on the 3,4-double bond.



Scheme 2.49. Homoallylation of Pentadienoate **1.283** with Benzaldehyde

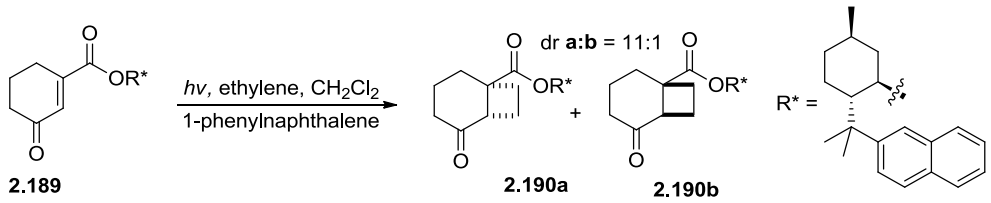
Since the introduction by Corey in 1975,[40a] 8-phenylmenthol has proved to be a versatile chiral auxiliary and has been extensively used. A variety of ether and ester derivatives of this auxiliary have been shown to undergo Diels-alder[40a,b], [2+2] cycloaddition[40c], ene[40d,e], 1,2-addition[40f], 1,4-addition[40g,h] reactions with excellent diastereoselectivity (de > 90%).

Jean d'Angelo utilized the 8-phenylmenthyl derivative for the asymmetric synthesis of *β*-amino ester group.[41] The use of 8-(*β*-naphthyl menthyl) derivative of crotonate for *β*-amino esters synthesis gave essentially complete diastereofacial control (>99% diastereoselectivity) (Scheme 2.48). The stereochemical outcome was explained by the "*π*-stacking" model in which the aryl group of the inducer shields one face of the crotonate unit, directing the amine addition to the other face.



Scheme 2.50. Diastereoselective Synthesis of *β*-Amino Ester Using Menthyl Derived Crotonate

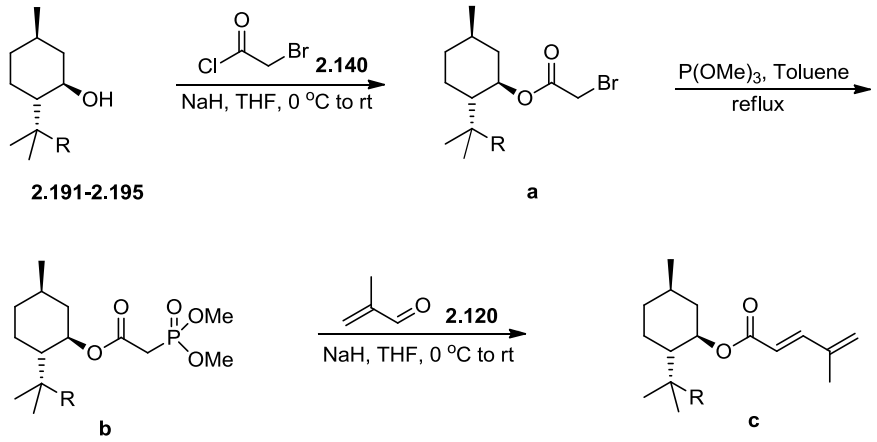
More recently, Tsutsumi and coworkers developed a fairly efficient method of increasing the diastereoselectivity of the [2+2] photocycloaddition of cyclohexanone to ethylene.[42] They showed that chiral cyclohexenone **2.189** containing the (-)-8-(*β*-naphthyl)menthyl group, shields a diastereoface effectively to produce the cyclobutane **2.190** with very good 83% diastereoselectivity.



Scheme 2.51. Diastereoselective [2+2] Cycloaddition

In search of a more effective chiral inducer for diastereoselective homoallylation reaction, a number of dienes having 8-arylmenthol derived diene carboxylate esters (pentadienoates) were synthesized (Scheme 2.52). All 8-arylmenthols were prepared from commercial *R*-(+)-pulegone using slightly modified Corey's procedure[40a] except 8-(*β*-naphthyl)menthol **2.193** and 8-(4-phenylphenyl)menthol **2.194** which had to be prepared by lithium aluminum hydride reduction of their corresponding methone.[43] The menthol derivatives were first reacted with bromoacetylchloride **2.140** to obtain the

corresponding acetyl bromides. An Arbuzov reaction of these acetyl bromides with trimethylphosphite followed by HWE reaction with methacrolein **2.120** gave the required chiral dienes **2.191c-2.195c** in good to excellent yields (Table 2.1).



Scheme 2.52. Synthesis of 8-Menthyl Derived Pentadienoates

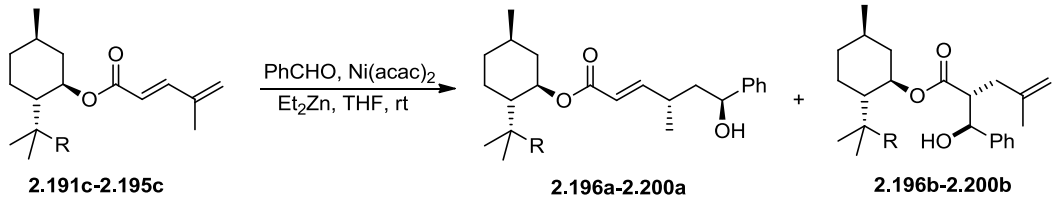
Table 2.1. Synthesis of 8-Menthyl Derived Pentadienoates

Alcohol	**Step 1 (Product a)**	**Step 2 (Product b)**	**Step 3 (Product c)**
R	t (h)/yield (%)	t (h)/yield (%)	t (h)/yield (%)
H **2.191**	X = Br, known	45, 80	0.4, 64
Phenyl **2.192**	X= Cl, known	80, 78	2, 88
Naphthyl **2.193**	4, 88	49, 96	1, 79
Biphenyl **2.194**	18, 90	43, 94	0.5, 87
p-t*B*utylphenyl **2.195**	18, 89	61, 82	0.5, 88

Reactions of the pentadienoates with benzaldehyde, $Ni(acac)_2$ and diethylzinc showed good to excellent regioselectivity and modest diastereoselectivity (Scheme 2.53, Table 2.2). As expected, the increase in the size of the *R* group increased the regioselectivity. The naphthyl group with extended π-conjugation (entry 3), gave highest regioselectivity

(**2.198a**:**2.198b** = 10:1). Except **2.196b,** all the other minor regioisomers (**2.197b-2.200b)** were isolated as a single diastereomer.

Diastereoselectivity within the major regioisomer (2.196a-2.200a): As expected, the phenyl menthol derived pentadienoate **2.192c** (entry 2) gave higher induction than menthol derived pentadienoate **2.191c** (entry 1) (dr of major product, 4:1 versus 2:1.5). This π-facial selectivity comes from the steric hindrance caused by the phenyl group which is unavailable with the hydrogen atom. But in a much surprising and dramatic way, the naphthyl menthol derived pentadienoate **2.193c** (naphthyl group with extended π-conjugation and bigger than the phenyl) gave a lower level of π-facial selectivity than the phenyl derivative **2.192c**.[41] Pentadienoate **2.194a** having a biphenyl group also did not improve the diastereoselectivity (entry 4). However, the *p*-^{t}butyl phenyl menthol derived pentadienoate **2.195c** (entry 5) showed some improvement in diastereoselectivity (4.5:1).



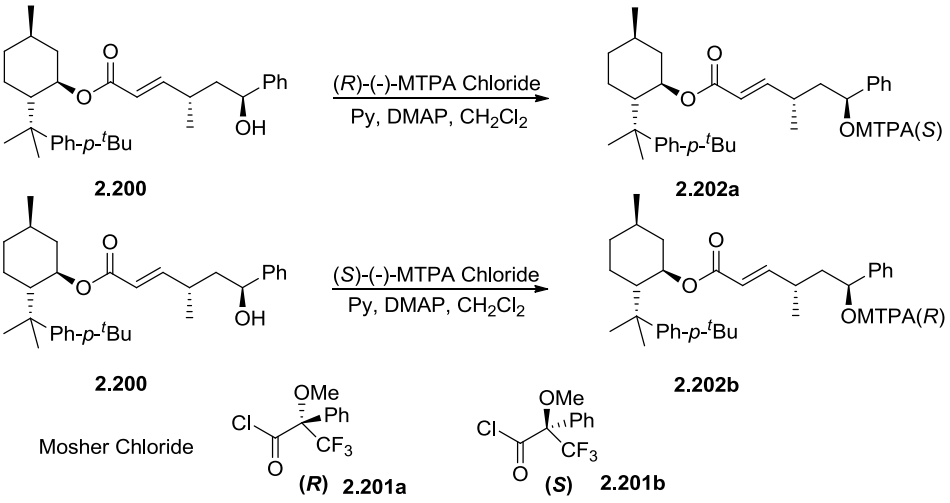
Scheme 2.53. Homoallylation of Different Pentadienoates with Benzaldehyde

Table 2.2. Results of Homoallylation of Pentadienoates with Benzaldehyde

Entry	R	**2.196a-2.200a** major product (dr)	**2.196b-2.200b** minor product (dr)	**a**:**b**	% yield (combined)
1	H **2.191c**	2:1.5	2:1	5:1	69
2	Phenyl **2.192c**	4:1	exclusive	7:1	75
3	Naphthyl **2.193c**	2.5:1	exclusive	10:1	68
4	Biphenyl **2.194c**	3.2:1	exclusive	6:1	60
5	*p*-^{t}butylphenyl **2.195c**	4.5:1	exclusive	7:1	72

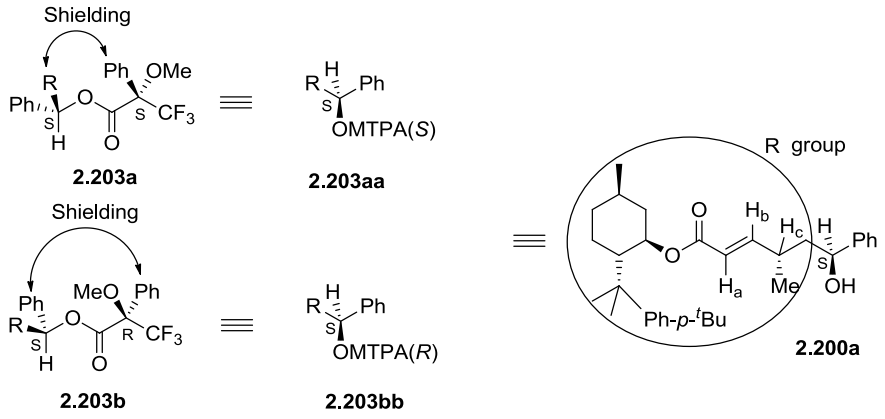
Absolute configuration determination:

The absolute stereochemistry of major isomer **2.200a** was determined by the Mosher ester method.[44] Alcohol **2.200a** was treated with both enantiomers of Mosher chloride (MTPA-chloride = α-methoxy-α-(trifluoromethyl)phenylacetyl chloride) (*R*-chloride **2.201a** and S-chloride **2.201b**) in the presence of pyridine and DMAP to give the Mosher ester **2.202a** and **2.202b** respectively in very good yields (Scheme 2.54).



Scheme 2.54. Synthesis of Mosher Ester

On the basis of the generally accepted confirmation model for Mosher esters (Scheme 2.55), the trifluoromethyl group and the carbinyl hydrogen are eclipsed with carbonyl oxygen.[45] The *R*-group in the (*S*)-MTPA ester **2.203a** will be shielded by the phenyl group (of MTPA) when the chiral alcohol has (*S*)-configuration. The chemical shift of proton signals of the *R*-group will consequently be upfield (smaller δ value). In case of (*R*)-MTPA ester **2.203b**, the phenyl group will be shielded so the proton signals of *R*-group will move downfield (higher δ value).



Scheme 2.55. Conformation Model of Mosher Esters from Alcohol **2.200a**

The chemical shift values of protons (H_a, H_b, H_c, and methyl) support this prediction (Table 2.3). All these protons are upfield (lower δ value) in case of the *S*-ester and downfield (higher δ value) in case of the *R*-ester. Therefore, the newly formed stereocenter must have *S*-configuration (Scheme 2.55).

Table 2.3. NMR Data of Proton Signal of **2.200** and its Mosher Esters

	H_c (ppm)	$\Delta\delta$ (ppm) H_c	Me	H_a (ppm)	H_b (ppm)
S.M. **2.200a**	2.24		1.00	5.16	6.71
S-ester **2.203a**	1.90	+0.34	0.96	5.11	6.60
R-ester **2.203b**	2.28	-0.04	1.10	5.23	6.74

The homoallylation reaction of pentadienoate **2.195c** with benzaldehyde was carried out at varied temperatures and solvents. Reactions were run at three different temperatures; -20 ^oC, 5 ^oC and 50 ^oC, which showed no change in regioselectivity and diastereofacial selectivity. However, at -20 ^oC the reaction was only about 50% complete after stirring for an hour whereas all other reactions were complete within 15 minutes. With all the solvents tested (Table 2.4), tetrahydrofuran (THF) was the best for the homoallylation reaction. Interestingly, only the minor regioisomer **2.200b** was isolated when the reaction was carried out in acetonitrile. Therefore, all the homoallylation reactions discussed henceforth are carried out in THF at room temperature.

Table 2.4. Solvents Effect on Homoallylation of Pentadienoate **2.195c** and Benzaldehyde

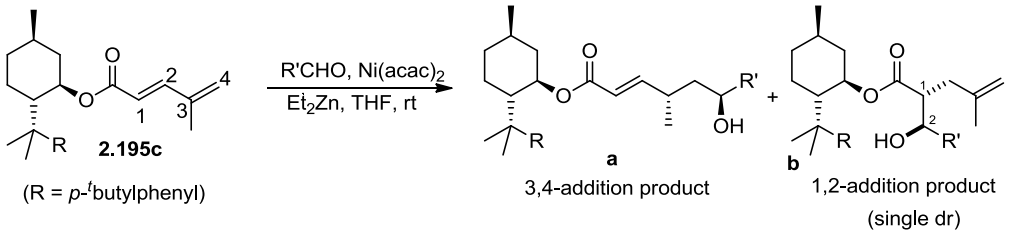
Solvent	dr of major isomer **2.200a**	Polarity Index of Solvent
Tetrahydrofuran	4:1	4.0
Dichloromethane	3.3:1	3.1
Toluene	2.3:1	2.4
Dioxane	3.0:1	4.8

Since the 4-^{t}butylphenyl menthol derived pentadienoate **2.195c** gave the highest diastereofacial selectivity with benzaldehyde, it was taken as a probe pentadienoate. The

results of homoallylation of this pentadienoate with a number of aldehydes (Scheme 2.56) are summarized in Table 2.5.

All other aldehydes, with the exception of pentanal **2.110** (entry 8), gave predominantly the 3,4-addition product with the regioselectivity from 5:1 (entry 2 and 7) to exclusive product (entry 10). The bulky aldehyde showed a tremendous effect on the regioselectivity. For example, 2-methoxyaldehyde **2.207** had 12:1 selectivity of 3,4- to 1,2-addition product (entry 5) and 2,2-dimethylpropanal **2.212** gave only 3,4- addition product (entry 10).

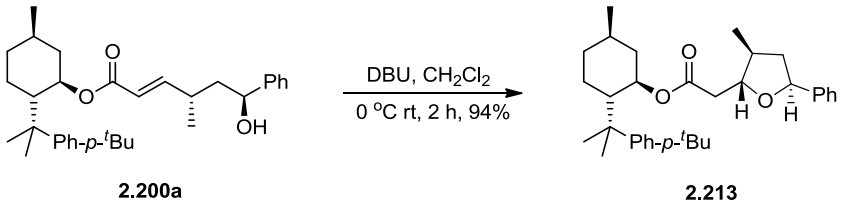
Unfortunately, the changes in diastereoselectivity were only modest. The nature and size of the aromatic ring (entry 1, 2 and 6), nature of substituent in the aromatic ring (electron withdrawing or donating group) (entry 3, 4 and 5) and increasing the bulkiness at α-position of the aldehyde (entry 10) did not have a pronounced effect on diastereofacial selectivity. Surprising and very intriguing results were shown by cyclohexanecarboxaldehyde **2.209** (entry 7) giving almost the same diastereoselectivity as pentanal **2.210** (entry 8), and 2-methoxybenzaldehyde **2.207** (entry 5) giving less diastereoselectivity than benzaldehyde **3.21** (entry 1). In theory, cyclohexanecarboxaldehyde **2.209** and 2-methoxy benzaldehyde **2.207** should have higher π-facial selectivity than pentanal **2.209** and benzaldehyde **3.21** respectively, owing to the steric hindrance on the aldehyde group.



Scheme 2.56. Homoallylation of Pentadienoate **2.195c** with Different Aldehydes

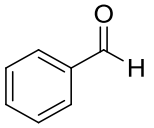
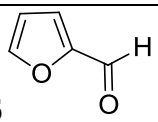
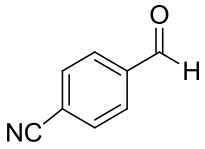
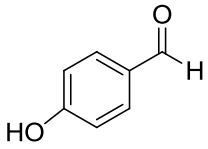
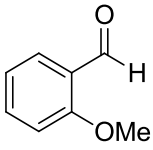
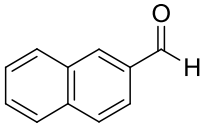
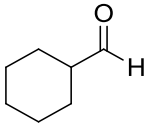
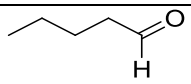
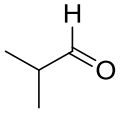
2.4.3. DBU cyclization of *bis*-homoallylic alcohol

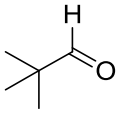
The major isomer **2.200a** obtained by the reaction of benzaldehyde **2.21** with pentadienoate **2.195c** was subjected to DBU cyclization (Scheme 2.57).[3] It underwent a very smooth cyclization with an excellent yield of 94%. During cyclization, the rate of cyclization of the diastereomers was also studied. After completion of about 50% reaction (TLC analysis), proton NMR analysis of the crude product showed the same ratio of characteristic diastereomeric peaks as in the starting *bis*-homoallylic alcohol **2.200a**. The cyclized product **2.213** and recovered starting material **2.200a** both preserved the diastereoselectivity leading to a conclusion that both diastereomers undergo the cyclization at the same rate.



Scheme 2.57. DBU Cyclization of bis-Homoallylic Alcohol **2.200a**

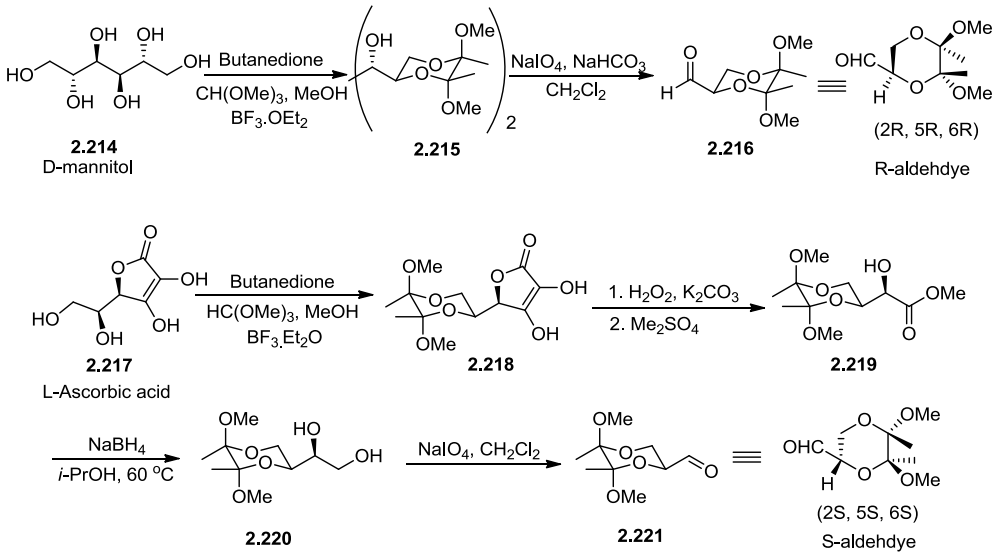
Table 2.5. Homoallylation of Pentadienoate **2.195c** with Various Aldehydes

Entry	R'CHO	**a** (dr)	**a:b**	% yield (combined)
1	**2.21** 	4.5:1	7:1	72
2	**3.196** 	2.2:1	5:1	70
3	**3.197** 	2.7:1	6:1	71
4	**3.198** 	3.1:1	6:1	70
5	**3.199** 	2.8:1	12:1	75
6	**3.200** 	3.3:1	6:1	76
7	**3.201** 	2.2:1	5:1	70
8	**3.202** 	2.4:1	2:1	79
9	**3.203** 	2.5:1	6:1	76

10	**3.204** 	4.5:1	Only a	70

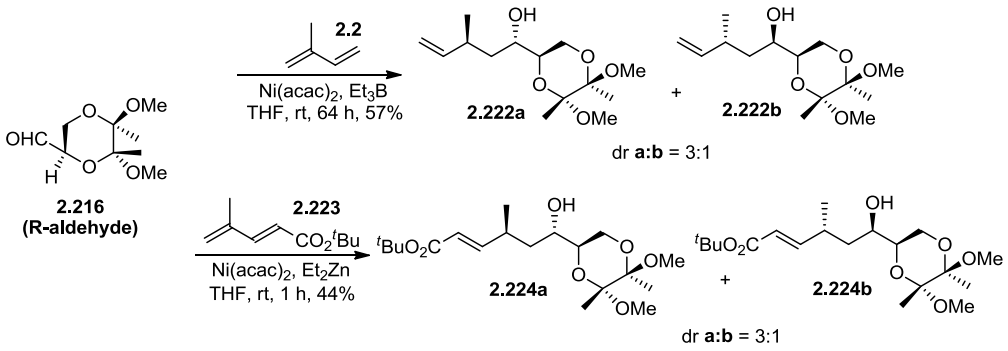
2.4.4. Homoallylation of simple and chiral dienes with chiral aldehydes

Effects of chiral aldehydes on diastereofacial selectivity during homoallylation reactions were also studied. Both enantiomers of Steve Ley aldehyde were synthesized for this study (Scheme 2.58).[46]



Scheme 2.58. Synthesis of *R*- and *S*- Aldehydes

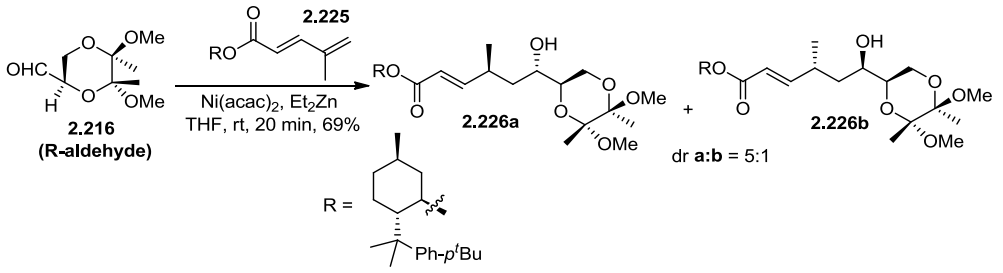
Homoallylation of *R*-aldehyde **2.216** with different dienes was carried out (Scheme 2.59). These reactions went smoothly and gave 3:1 diastereoselectivity with both isoprene **2.2** and ^{t}butyl pentadienoate **2.223**.



Scheme 2.59. Homoallylation of R-aldehyde with Isoprene and ^{t}Butyl- pentadienoate

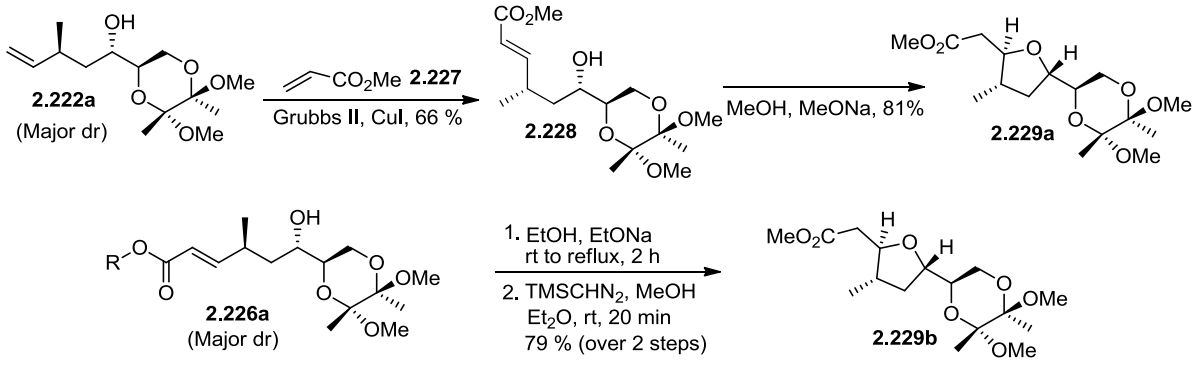
The stereochemistry of newly formed stereocenters was assigned by correlating with the known stereochemistry. The newly formed hydroxyl stereocenter in the major diastereomer (obtained from the homoallylation of TBS-, acetonide-protected hemiacetals and epoxy aldehyde with isoprene) was determined to be *anti* with the existing α-stereocenter (Scheme 2.29).[3] Assuming that these aldehydes also form similar transition states during homoallylation, the stereo-chemistry in the major isomer (**2.222a** and **2.224a**) should be *anti* between the hydroxyl and the α-stereocenter of the aldehyde **2.216**.

The homoallylation of *R*-aldehyde **2.216** with chiral pentadienoate **2.225** produced two column separable diastereomers **2.226a** and **2.226b** with good (5:1) diastereoselectivity (Scheme 2.60).



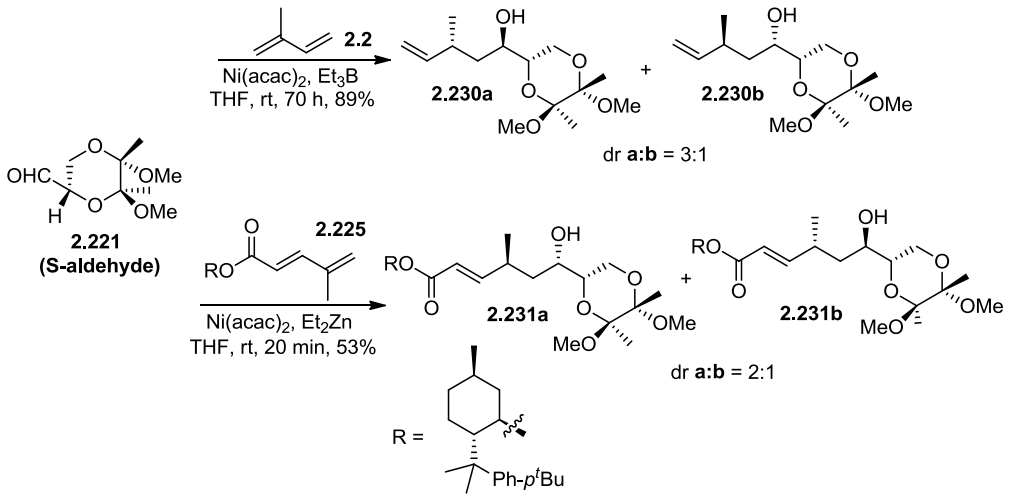
Scheme 2.60. Homoallylation of R-aldehyde with Chiral Pentadienoate

In order to determine the stereochemistry of newly formed stereocenters of the major isomer **2.226a**, both **2.222a** and **2.226a** were converted to tetrahydrofuran (THF) methyl ester **2.220** (Scheme 2.61). Cross metathesis of **2.222a** with methyl acrylate produced ester **2.228.** The ester **2.228** on subsequent cyclization with NaOMe/MeOH afforded the THF methyl ester **2.229a**. The major isomer **2.226a** was also converted to THF ester **2.229a** in two steps: ester hydrolysis by NaOEt/EtOH to give the acid followed by the conversion of the acid to methyl ester **2.229b** by TMS diazomethane in methanol and diethyl ether. Since both THF esters **2.229a** and **2.229b** have the same optical rotation value and similar proton and carbon NMR spectra, the major diastereomer **2.226a** obtained from *R*-aldehyde **2.216** and chiral diene **2.225** must have the same (*anti*) stereochemistry (between hydroxyl and existing α-stereocenter of aldehyde) similar to the major diastereomer **2.222a** (obtained from *R*-aldehyde **2.216** and isoprene **2.2**).



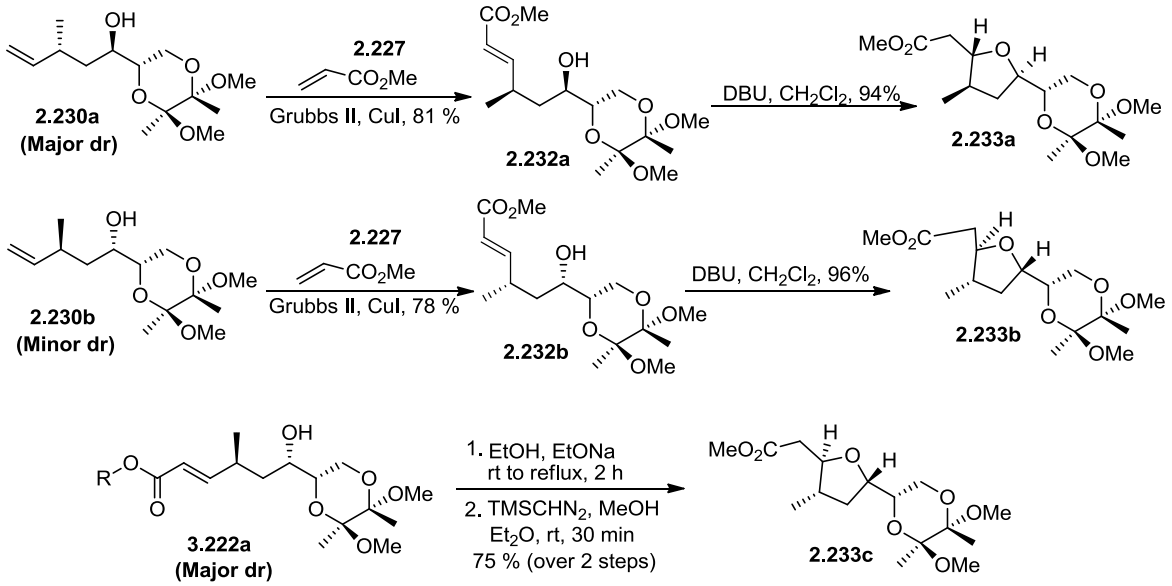
Scheme 2.61. Synthesis of THF Methyl Ester **2.229a** and **2.229b**

Not surprisingly, homoallylation of *S*- aldehyde **2.221** gave the same 3:1 diastereoselectivity with isoprene **2.2** (as *R*-aldehyde) but the selectivity decreased with chiral pentadienoate **2.225** (Scheme 2.62).



Scheme 2.62. Homoallylation of *S*-aldehyde **2.221** with Isoprene and Chiral Pentadienoate

In order to determine the stereochemistry of major diastereomer **2.231a**, the THF methyl ester **2.233c** was compared with the THF methyl esters **2.233a** and **2.233b** obtained from diastereomers **2.230a** and **2.230b**, respectively (Scheme 2.63). The THF methyl ester **2.233c** has same optical rotation and identical proton and carbon NMR spectra with the THF methyl ester **2.233b** obtained from minor isomer **2.230b**. It shows that the major diastereomer **2.231a** must have the same (*syn)* relationship between newly formed hydroxyl group and existing α-stereocenter of the aldehyde as the minor diastereomer **2.230b** (obtained from *S*-aldehyde **2.221** and isoprene **2.2**).



Scheme 2.63. Synthesis of THF Methyl Esters

The difference in diastereoselectivity between *R*- and *S*- aldehyde with chiral pentadienoate **2.225** can be best explained by whether the existing stereocenters are reinforcing or opposing each other during coupling.[47] In case of *R*-aldehyde **2.216** and chiral pentadienoate **2.225**, the stereochemical outcome is reinforced by each other giving high selectivity, called a "matched case". But for *S*-aldehyde **2.221** and chiral pentadienoate **2.225**, they are opposing each other which reduce the selectivity, called a "mis-matched case". In the latter case, the pentadienoate **2.225** "wins" which is proved by the fact that the minor isomer **2.330b** has the same stereochemistry with the major isomer **2.231a** (Scheme 2.59).

2.5. Summary

1) Homoallylation of aldehydes with achiral pentadienoates and dienecarboxamide were studied. Achiral pentadienoates underwent a smooth homoallylation with benzaldehyde to afford regioisomers with 1:3 selectivity favoring the 3,4-addition. On the other hand, achiral dienecarboxamide reacted slowly with benzaldehyde with low yield and lower regioselectivity.

2) Homoallylation of benzaldehyde with chiral dienecarboxamide containing Oppolzer's chiral auxiliary gave only the 1,2-product in low yield while diene imide derivatives having Evans' chiral auxiliaries were completely unreactive. On the other hand, chiral pentadienoates derived from *trans*-2-phenyl cyclohexanol and Oppolzer's chiral auxiliaries underwent smooth homoallylation with benzaldehyde with good to excellent regioselectivity but poor diastereoselectivity.

3) A number of 8-arylmenthol derived pentadienoates were synthesized. Homoallylation of these pentadienoates with benzaldehyde gave excellent regioselectivity and modest diastereoselectivity. The *p*-^{t}butylphenyl menthol derived pentadienoate gave the highest diastereoselectivity within the major diastereomer (3,4-addition product). Homoallylation of various aldehydes with *p*-^{t}butylphenyl menthol derived pentadienoate was studied.

4) Chiral Steve Ley aldehydes were synthesized following known literature procedures. Homoallylation of both *R* and *S*-aldehydes with achiral diene and pentadienoate gave 3:1 diastereoselectivity. However, these aldehydes show diastereodifferentiation with the chiral pentadienoate. When reacted with *p*-^{t}butylphenyl menthol derived pentadienoate, *R*-aldehyde gave higher (5:1) diastereoselectivity than *S*-aldehyde (2:1).

2.6. General Experimental

Glassware used for all experiments were oven-dried and all reactions were carried out under argon atmosphere unless otherwise mentioned. All reaction solvents were purified prior to use: CH_2Cl_2, MeOH, MeCN were dried by distillation over calcium hydride and THF over sodium-benzophenone ketyl. Reagent grade DMF was obtained from Sigma-Aldrich and used without further purification.

Proton (^1H) NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra at 75 MHz. Proton NMR spectra were referenced to residual $CDCl_3$ (7.27 ppm) and ^{13}C {^1H} NMR spectra were referenced to the center line of $CDCl_3$ (77.23 ppm). Crystal structure(s) were determined on a Bruker Apex- II CCD single crystal diffractometer. Optical rotations were measured on a polarimeter using a glass cell with 2 mL capacity and 10 cm path length. Infrared spectra were recorded on FTIR instrument using NaCl plates (liquids, oils) or using an ATR attachment (solids).

General procedure for homoallylation: Into a flask containing $Ni(acac)_2$ (0.1 mmol) in dry THF (3 mL) was added the corresponding diene (2.0 mmol) and the resulting solution was stirred at room temperature for 10 min. A solution of aldehyde (1.0 mmol) in dry THF (2 mL) and Et_2Zn (1.0 M solution in hexanes, 2.4 mmol) were added sequentially. The homogeneous mixture was stirred under argon atmosphere at room temperature 15 min to 2 h (monitored by TLC analysis), then it was diluted with EtOAc. The mixture was washed with 2M HCl, saturated aq. $NaHCO_3$, and brine solutions sequentially. The organic layer was dried over anhydrous Na_2SO_4, concentrated in *vacuo* and purified by column chromatography (SiO_2, hexanes: EtOAc).

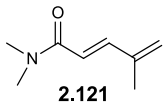
General procedure for bromoacetylation of oxazolidinone, A: Into a round bottom flask containing a suspension of oxazolidinone (1.0 equiv.) in dry THF at 0 ^{o}C was added *n*-BuLi (2.5 M solution in hexanes, 1.1 equiv.) dropwise. The resulting dark orange solution was stirred for 15 minutes when bromoacetyl chloride (1.1 equiv.) was added dropwise. The yellow solution was stirred for an additional 1 h at that temperature (monitored by TLC analysis). The reaction was quenched by saturated aq. NH_4Cl solution and the mixture was allowed to warm to room temperature. The organic layer was separated, the aqueous layer was extracted with Et_2O, the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes: EtOAc).

General procedure for bromoacetylation of alcohol, B: Into a round bottom flask containing a suspension of NaH (60% w/w dispersion in mineral oil, 1.1 equiv.) in dry THF at 0 ^{o}C was added solution of sultam (amide or alcohol) (1.0 equiv.) in dry THF while evolution of H_2 gas was seen. After stirring for 30 minutes at that temperature was added bromoacetyl chloride (1.1 equiv.) drop wise. After 30 minutes, the solution was warmed to room temperature and stirred for 2 to 18 h (monitored by TLC analysis). The reaction was quenched with saturated aq. NH_4Cl solution. The organic layer was separated, the aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes: EtOAc).

General procedure for preparation of acetyl phosphonate (Arbuzov reaction), C: Into a round bottom flask containing a solution of acetyl bromide (1.0 equiv.) in dry

toluene was added trimethyl (or triethyl) phosphite (1.1 to 3.0 equiv.) and refluxed for 22 to 80 h (monitored by TLC analysis). The solvent was removed in *vacuo* and the crude product was purified by column chromatography (SiO_2, hexanes: EtOAc).

General procedure for preparation of diene carboxylate esters and dienecarboxamides (HWE reaction), D: Into a round bottom flask containing a suspension of NaH (60% w/w dispersion in mineral oil, 1.2 equiv.) in dry THF at 0 ^oC was added solution of acetyl phosphonate (1.0 equiv.) in dry THF while evolution of H_2 gas was seen. After stirring for 30 minutes at that temperature, methacrolein (1.5 equiv.) was added dropwise. After 10 min of stirring at 0 ^oC the solution was warmed to room temperature and stirred for additional 5 min to 5 h (monitored by TLC analysis). The reaction was quenched by saturated aq. NH_4Cl solution. The organic layer was separated, the aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes: EtOAc).

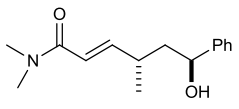


2.121

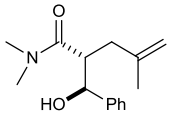
(E)-*N*,*N*,4-trimethylpenta-2,4-dienamide 2.121: Methacrolein **2.120** (3.0 mmol, 0.25 mL), sodium hydride (60% w/w in mineral oil, 2.4 mmol, 0.058 g), and phosphono-acetate[27] **2.119** (2.0 mmol, 0.390 g) were reacted in dry THF (5 mL) following the general procedure **D** to afford dienecarboxamide **2.121** as a colorless oil (0.240 g, 86%).

IR (neat, NaCl) 2935, 1642, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (1H, d, J = 15.2 Hz), 6.24 (1H, d, J = 15.3 Hz), 5.27 (1H, s), 5.22 (1H, s), 3.07 (3H, s), 2.98 (3H, s), 1.86 (3H,

d, *J* = 0.3 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.2, 144.9, 140.7, 123.1, 117.7, 37.5, 36.0, 18.4; HRMS (FAB, M^+) calcd for $C_8H_{13}NO$: 139.0997. Found 139.0999.



2.122a

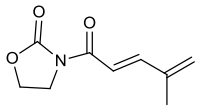


2.122b

(±)6-hydroxy-*N*,*N*,4-trimethyl-6-phenylhex-2-enamide and (±)2-(hydroxyl(phenyl)methyl)-*N*,*N*,4-trimethylpent-4-enamide (2.122a and 2.122b): Benzaldehyde **2.21** (0.20 mmol, 20 μL), $Ni(acac)_2$ (0.02 mmol, 0.005 g), diethylzinc (10% w/w in hexanes, 0.48 mmol, 0.59 mL), and dienecarboxamide **2.121** (0.40 mmol, 0.056 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.122a** and **2.122b** as a colorless liquid (rr, 2:1.5) (0.024 g, 49% for 63% conversion).

2.122b: IR (neat, NaCl) 3378, 2969, 1726, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.40 (5H, m), 4.97 (1H, d, *J* = 3.4 Hz), 4.68 (1H, d, *J* = 1. 3 Hz), 4.61 (1H, d, *J* = 1.3 Hz), 3.12 (1H, td, *J* = 3.5, 10.7 Hz), 2.94 (6H, s), 2.56 (1H, dd, *J* = 10.8, 13.9 Hz), 2.19 (1H, dd, *J* = 2.6, 13.9 Hz), 1.58 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 175.9, 143.5, 141.9, 128.4, 127.5, 126.1, 112.4, 74.1, 46.6, 37.8, 35.8, 34.4, 22.9; HRMS (FAB, MH^+) calcd for $C_{15}H_{22}NO_2$: 248.1650. Found 248.1658.

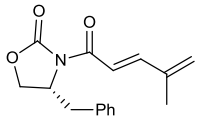
2.122a: (Mixed with column inseparable impurity) ^{1}H NMR ($CDCl_3$): δ 7.22-7.31 (5H, m), 6.73 (1H, dd, *J* = 8.2, 15.1 Hz), 6.18 (1H, d, *J* = 15.1 Hz), 5.27 (1H, d, *J* = 10.4 Hz), 2.97 (3H, s), 2.86 (3H, s), 2.22 (1H, app sep, *J* = 7.2 Hz), 1.62 (1H, broad s), 1.34-1.48 (2H, m), 1.05 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 167.2, 151.6, 141.6, 128.2, 127.5, 126.9, 119.1, 75.0, 37.8, 37.1, 36.6, 34.8, 20.0.



2.137

(*E*)-3-(4-methylpenta-2,4-dienoyloxazolidin-2-one (2.137): Methacrolein **2.120** (1.5 mmol, 0.12 mL), sodium hydride (60% w/w in mineral oil, 1.2 mmol, 0.029 g), and acetyl phosphono-acetate[30] **2.135** (1.0 mmol, 0.265 g) were reacted in dry THF (3 mL) following the general procedure **D** to afford dienecarboxamide **2.137** as a viscous colorless liquid (0.050 g, 28%).

IR (neat, NaCl) 2912, 1763, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.55 (1H, d, *J* = 15.5 Hz), 7.30 (1H, d, *J* = 15.4 Hz), 5.44 (1H, s), 5.42 (1H, s), 4.44 (2H, t, *J* = 8.0 Hz), 4.11 (2H, t, *J* = 8.4 Hz), 1.96 (3H, d, *J* = 0.3 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.8, 153.7, 148.9, 141.3, 125.9, 117.5, 62.2, 43.0, 18.4; HRMS (FAB, MNa^{+}) calcd for $C_9H_{11}NO_3Na$: 204.0637. Found 204.0634.

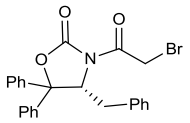


2.138

(*R*,*E*)-4-benzyl-3-(4-methylpenta-2,4-dienoyl)oxazolidin-2-one (**2.138)**: Methacrolein **2.120** (1.5 mmol, 0.12 mL), sodium hydride (60% w/w in mineral oil, 1.2 mmol, 0.029 g), and phosphono-acetate[30] **2.136** (1.0 mmol, 0.355 g) were reacted in dry THF (3 mL) following the general procedure **D** to afford dienecarboxamide **2.138** as a viscous colorless liquid (0.105 g, 39%).

IR (neat, NaCl) 2984, 1776, 1742, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.51 (1H, d, *J* = 15.5 Hz), 7.15-7.29 (6H, m), 5.39 (1H, s), 5.36 (1H, s), 4.65-4.73 (1H, m), 4.09-4.18 (1H, m), 3.28 (1H, dd, *J* = 3.2, 13.4 Hz), 2.74 (1H, dd, *J* = 9.5, 13.4 Hz), 1.89 (3H, d, *J* = 0.4 Hz);

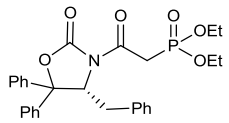
^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.6, 153.6, 149.0, 141.3, 135.5, 129.6, 129.1, 127.5, 125.9, 117.9, 66.3, 55.6, 38.1, 18.4; HRMS (FAB, MNa^+) calcd for $C_{16}H_{17}NO_3Na$: 294.1106. Found 294.1098.



2.141

(R)-4-benzyl-3-(2-bromoacetyl)-5,5-diphenyloxazolidine-2-one (2.141): *n*-Butyl lithium (2.5 M solution in hexanes, 5.5 mmol, 2.2 mL), bromoacetyl chloride **2.140** (5.5 mmol, 0.46 mL), and oxazolidinone **2.139** (5.0 mmol, 1.65 g) were reacted in dry THF (20 mL) following the general procedure **A** to afford **2.141** (mixture of acetyl bromide and chloride isomer, 4:1) as a viscous brown oil (1.90 g, 85%).

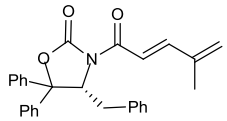
IR (neat, NaCl) 3065, 1780, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.12-7.44 (13H, m), 6.75 (2H, dd, *J* = 2.1, 4.9 Hz), 5.65 (1H, dd, *J* = 3.3, 4.9 Hz), 4.42 (2H, ABq, *J* = 12.8 Hz, Δδ = 0.07 ppm), 2.94 (1H, dd, *J* = 7.9, 14.2 Hz), 2.81 (1H, dd, *J* = 7.9, 14.2 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.4, 151.8, 141.1, 137.2, 135.9, 129.2, 129.15, 129.13, 128.6, 128.5, 128.5, 126.8, 126.6, 126.1, 89.5, 62.7, 36.5, 28.4.



2.142

(*R*)-diethyl-(2-(4-benzyl-2-oxo-5,5-diphenyloxazolidin-3-yl)-2-oxoethyl) phosphonate (2.142): Triethylphosphite (9.9 mmol, 1.7 mL) and acetyl bromide **2.141** (3.3 mmol, 1.482 g) were reacted in dry toluene (2 mL) following the general procedure **C** to afford phosphono-acetate **2.142** as a viscous yellow oil (1.500 g, 90%).

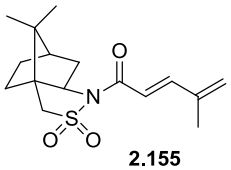
IR (neat, NaCl) 3058, 1784, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.99-7.36 (10H, m), 7.00 (3H, dd, *J* = 1.8, 4.9 Hz), 6.60-6.64 (2H, m), 5.57 (1H, dd, *J* = 4.0, 8.6 Hz), 3.88-4.01 (4H, m), 3.72 (1H, dd, J_{HH} = 14.2, J_{HP} = 22.0 Hz), 3.51 (1H, dd, J_{HH} = 14.2, J_{HP} = 22.5 Hz), 2.88 (1H, dd, *J* = 3.9, 14.2 Hz), 2.69 (1H, dd, *J* = 8.6, 14.3 Hz),1.20 (3H, t, *J* = 7.0 Hz), 1.07 (3H, t, *J* = 7.0 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 164.4 (d, J_{CP} = 6.8 Hz), 152.1, 141.3, 137.4, 136.3, 129.1, 129.0, 128.43, 128.36, 126.7, 126.6, 126.3, 88.6, 62.95 (d, J_{CP} = 6.2 Hz), 62.72 (d, J_{CP} = 6.2 Hz), 62.5, 36.5, 34.4 (d, J_{CP} = 131.6 Hz), 16.5 (d, J_{CP} = 6.4 Hz), 16.39 (d, J_{CP} = 6.0); ^{31}P {^{1}H}: NMR ($CDCl_3$) δ 19.0; HRMS (FAB, MH^+) calcd for $C_{28}H_{31}NO_6P$:508.1889. Found 508.1881.



2.143

(*R*,*E*)-4-benzyl-3-(4-methylpenta-2,4-dienoyl)-5,5-diphenyloxazolidin-2-one (**2.143)**: Methacrolein (0.513 mmol, 42 μL), sodium hydride (60% w/w in mineral oil, 0.376 mmol, 0.009 g), and phosphono-acetate **2.142** (0.342 mmol, 0.164 g) were reacted in dry THF (1 mL) following the general procedure **D** to afford dienecarboxamide **2.143** as a viscous colorless liquid (0.075 g, 52%).

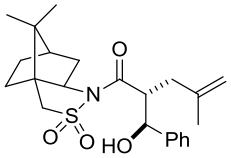
IR (neat, NaCl) 3024, 1764, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.35-7.40 (3H, m), 7.25 (3H, d, *J* = 7.5 Hz), 7.17 (2H, d, *J* = 5.1 Hz), 7.13 (1H, d, *J* = 15.4 Hz), 7.11-7.18 (3H, m), 7.00 (3H, dd, *J* = 1.8, 5.1 Hz), 6.62-6.65 (2H, m), 5.62 (1H, dd, *J* = 4.1, 7.9 Hz), 5.31 (2H, s), 2.88 (1H, dd, *J* = 4.3, 14.2 Hz), 2.73 (1H, dd, *J* = 4.1, 8.1 Hz), 1.84 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.2, 152.5, 149.2, 141.9, 141.6, 137.9, 136.7, 129.4, 129.3, 129.2, 128.62, 128.60, 127.0, 126.8, 126.4, 126.1, 118.0, 88.8, 62.7, 36.9, 18.6.



2.155

(*E*)-1-((3a*R*,6*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c] isothiazol-1-yl)-4-methylpenta-2,4-dien-1-one (2.155): Methacrolein **2.120** (0.945 mmol, 80 μL), sodium hydride (60% w/w in mineral oil, 0.756 mmol, 0.018 g), and acetyl phosphono-acetate[34] **2.154** (0.63 mmol, 0.230 g) were reacted in dry THF (2 mL) following the general procedure **D** to afford dienecarboxamide **2.155** as a colorless viscous oil (0.080 g, 41%).

IR (neat, NaCl) 2962, 1677, 1601, 1329 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45 (1H, d, *J* = 15.2 Hz), 6.59 (1H, d, *J* = 15.2 Hz), 5.41 (s, 1H), 5.40 (1H, s), 3.96 (1H, dd, *J* = 5.4, 7.3 Hz), 3.49 (2H, ABq, *J* = 13.8 Hz, Δδ = 0.06 ppm), 2.11-2.15 (2H, m). 1.93 (3H, s), 1.89-1.93 (3H, m), 1.38-1.45 (2H, m), 1.18 (3H, s), 0.98 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 164.7, 148.2, 141.0, 125.9, 118.2, 65.4, 53.4, 48.7, 48.0, 44.9, 38.7, 33.1, 26.7, 21.1, 20.1, 18.3; HRMS (FAB, MNa^+) calcd for $C_{16}H_{23}NO_3SNa$: 332.1296. Found 332.1306.

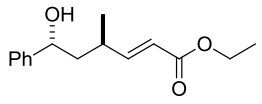


2.156

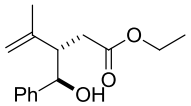
(2*R*)-1-((3a*R*,6*R*)-8,8-dimethyl-2,2-dioxidohexahydro-1*H*-3a,*R*-methanobenzo[c]isothiazol-1-yl)-2-((S)-hydroxy(phenyl)methyl)-4-methylpent-4-en-1-one (2.156): Benzaldehyde **2.21** (0.050 mmol, 5.0 μL), $Ni(acac)_2$ (0.005 mmol, 0.001 g), diethylzinc (10% w/w in hexanes, 0.12 mmol, 0.15 mL), and dienecarboxamide **2.155**

(0.075 mmol, 0.023 g) were reacted in dry THF (0.5 mL) following the general procedure of homoallylation to afford **2.156** as a colorless liquid (dr 1:3) (0.010 g, 48%).

IR (neat, NaCl) 3517, 2957, 1674, 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.47 (2H, d, *J* = 4.6 Hz), 7.36 (3H, d, *J* = 4.6 Hz), 5.30 (1H, s), 4.70 (1H, s), 4.65 (1H, s), 3.99 (1H, t, *J* = 3.7 Hz), 3.49-3.59 (3H, m), 2.69 (1H, app t, *J* = 7.2 Hz), 2.06 (2H, app d, *J* = 4.1 Hz), 1.87-1.95 (5H, m), 1.59 (3H, s), 1.14 (3H,s), 0.96 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 176.1, 142.6, 140.8, 128.4, 127.4, 126.1, 113.4, 71.9, 65.6, 53.5, 49.6, 48.6, 48.0, 44.9, 38.6, 34.1, 33.2, 26.7, 22.2, 20.8, 20.1.



2.158a



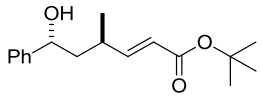
2.159a

(±)-(*E*)-ethyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.158a) and (±)-ethyl-3-(hydoxy(phenyl)methyl)-4-methylpent-4-enoate (2.159a): Benzaldehyde **2.21** (0.30 mmol, 30 μL), $Ni(acac)_2$ (0.03 mmol, 0.008 g), diethylzinc (1.0 M solution in hexanes, 0.72 mmol, 0.72 mL), and pentadienoate **2.157a** (0.60 mmol, 0.084 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.158a** and **2.159a** as a colorless liquid (rr, 3:1) (0.056 g, combined yield 76%).

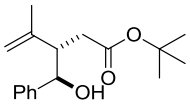
2.158a: IR (neat, NaCl) 3448, 2969, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.29-7.39 (5H, m), 6.94 (1H, dd, *J* = 7.9, 15.7 Hz), 5.79 (1H, dd, *J* = 1.1, 15.7 Hz), 4.72 (1H, dd, *J* = 6.2, 7.8 Hz), 4.21 (2H, q, *J* = 7.1 Hz), 2.44 (1H, app sep, *J* = 7.0 Hz), 1.92-2.02 (1H, m), 1.90 (1H, brd s), 1.66-1.75 (1H, m), 1.31 (3H, t, *J* = 7.1 Hz), 1.12 (3H, d, *J* = 6.7 Hz); ^{13}C

{^{1}H} NMR ($CDCl_3$): δ 167.0, 154.2, 144.5, 128.8, 128.0, 126.2, 120.1, 72.6, 60.5, 45.2, 33.5, 19.5, 14.5; HRMS (FAB, MNa^+) calcd for $C_{15}H_{20}O_3Na$: 271.1310. Found 271.1301.

2.159a: IR (neat, NaCl) 3499, 2967, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.40 (5H, m), 4.97 (1H, d, *J* = 5.7 Hz), 4.74 (1H, s), 4.73 (1H, s), 3.98-4.09 (2H, m), 2.97 (1H, ddd, *J* = 4.2, 5.7, 9.9 Hz), 2.92 (1H, brd s), 2.52 (1H, dd, *J* = 11.2, 14.3 Hz), 2.34 (1H, dd, *J* = 4.0, 14.3 Hz), 1.70 (3H, s), 1.12 (3H, t, *J* = 7.1 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 174.6, 143.2, 141.5, 128.5, 128.0, 126.4, 112.3, 74.5, 60.7, 51.7, 35.7, 22.4, 14.2; HRMS (FAB, MNa^+) calcd for $C_{15}H_{20}O_3Na$: 271.1310. Found 271.1317.



2.158b



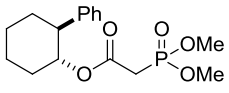
2.159b

(±)-(*E*)-*tert*-butyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.158b) and (±)-*tert*-butyl-3-(hydoxy(phenyl)methyl)-4-methylpent-4-enoate (2.159b): Benzaldehyde **2.21** (0.10 mmol, 10 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.157b** (0.20 mmol, 0.034 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.158b** and **2.159b** as a colorless liquid (rr, 3:1) (0.021 g, combined yield 78%).

2.158b: IR (neat, NaCl) 3436, 2984, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.29-7.37 (5H, m), 6.84 (1H, dd, *J* = 7.8, 15.7 Hz), 5.72 (1H, dd, *J* = 1.1, 15.7 Hz), 4.72 (1H, dd, J = 6.2, 7.8 Hz), 2.40 (1H, app sep, *J* = 7.0 Hz), 1.91-2.00 (2H, m), 1.64-1.73 (1H, m), 1.51 (9H, s), 1.11 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 152.9, 144.6, 128.8, 128.0,

126.1, 121.7, 80.4, 72.5, 45.2, 33.2, 28.3, 19.5; HRMS (FAB, MNa^+) calcd for $C_{17}H_{24}O_3Na$: 299.1623. Found 299.1628.

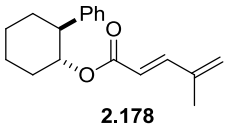
2.159b: IR (neat, NaCl) 3467, 2965, 1714 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-7.40 (5H, m), 4.91 (1H, dd, *J* = 1.7, 5.6 Hz), 4.73 (2H, s), 2.94 (1H, d, *J* = 1.6 Hz), 2.84 (1H, ddd, *J* = 4.1, 5.7, 9.9 Hz), 2.47 (1H, dd, *J* = 11.2, 14.3 Hz), 2.30 (1H, dd, *J* = 3.8, 14.3 Hz), 1.69 (3H, s), 1.29 (9H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 173.9, 143.3, 141.6, 128.4, 127.9, 126.7, 112.3, 81.4, 74.6, 51.9, 36.0, 28.1, 22.3; HRMS (FAB, MNa^+) calcd for $C_{17}H_{24}O_3Na$: 299.1623. Found 299.1614.



2.177

(±)-*trans*-2-phenylcyclohexyl-2-(dimethoxyphosphoryl)acetate (2.177): Trimethyl phosphite (10.133 mmol, 1.2 mL) and acetyl bromide[38] **2.176** (4.053 mmol, 1.20 gm) were reacted in dry toluene (1 mL) following the general procedure **C** to afford phosphono-acetate **2.177** as a highly viscous yellow oil (1.21 gm, 92%).

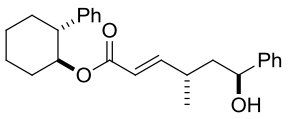
IR (neat, NaCl) 2935, 1726, 1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.12-7.28 (5H, m), 5.04 (1H, dt, *J* = 4.5, 10.7 Hz), 3.63 (3H, d, J_{HP} = 11.2 Hz), 3.54 (3H, d, J_{HP} = 11.2 Hz), 2.61-2.81 (1H, m), 2.72 (1H, dd, J_{HH} = 9.1 Hz, J_{HP} = 21.7 Hz), 2.69 (1H, dd, J_{HH} = 9.1, J_{HP} = 21.4 Hz), 2.14-2.17 (1H, m), 1.74-1.93 (3H, m), 1.30-1.58 (4H, m); ^{13}C {^1H} NMR ($CDCl_3$): δ 164.8 (d, J_{CP} = 6.0 Hz), 142.9, 128.3, 127.4, 126.4, 77.2, 53.0 (d, J_{CP} = 6.3 Hz), 52.8 (d, J_{CP} = 6.3 Hz), 49.4, 34.3, 32.2 (d, J_{CP} = 133.8 Hz), 32.0, 25.7, 24.6; ^{31}P {^1H} NMR ($CDCl_3$): δ 22.34; HRMS (FAB, MNa^+) calcd for $C_{16}H_{24}O_5P$: 327.1361. Found 327.1366.



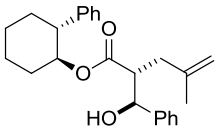
2.178

(±)-(*E*)-*trans*-2-phenylcyclohexyl-4-methylpenta-2,4-dienoate (**2.178)**: Methacrolein **2.120** (4.599 mmol, 0.38 mL), sodium hydride (60% w/w in mineral oil, 3.679 mmol, 0.088 g), and phosphono-acetate **2.177** (3.066 mmol,1.000 g) were reacted in dry THF (9 mL) following the general procedure **D** to afford pentadienoate **2.178** as a colorless viscous oil (0.650 g, 79%).

IR (neat, NaCl) 2935, 1709, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.09-7.20 (5H, m), 7.05 (1H, d, *J* =15.7 Hz), 5.55 (1H, d, *J*= 15.7 Hz), 5.17 (2H, s), 4.97 (1H, dt, *J* = 4.4, 10.5 Hz), 2.65 (1H, dt, *J* = 3.7, 11.9 Hz), 2.10-2.13 (1H, m), 1.72-1.90 (3H, m), 1.70 (3H, s), 1.47 (1H, dq, *J* = 2.9, 13.0 Hz), 1.29-1.46 (3H, m); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.6, 146.7, 143.3, 140.7, 128.4, 127.6, 126.5, 124.1, 119.0, 76.0, 49.9, 34.3, 32.6, 26.0, 24.9, 18.1; HRMS (FAB, MH^+) calcd for $C_{18}H_{23}O_2$: 271.1698. Found 271.1694.



2.179

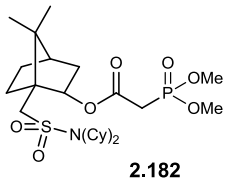


2.180

(±)-(*E*)-*trans*-2-phenylcyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.179) and (±)-*trans*-2-phenylcyclohexyl-2-(hydroxyl(phenyl)methyl)-4-methylpent-4-enoate (2.180): Benzaldehyde **2.21** (0.30 mmol, 30 μL), $Ni(acac)_2$ (0.03 mmol, 0.008 g), diethylzinc (10% w/w in hexanes, 0.72 mmol, 0.88 mL), and pentadienoate **2.178** (0.60 mmol, 0.162 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.179** and **2.180** as a colorless liquid (rr, 3:1) (0.085 g, combined yield 75%).

2.179: IR (neat, NaCl) 3461, 2938, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$): (major isomer) δ 7.18-7.37 (10H, m), 6.68 (1H, dd, *J* = 7.9, 15.7 Hz), 5.53 (1H, dd, *J* = 1.0, 15.7 Hz), 5.04 (1H, dt, *J* = 4.6, 10.6 Hz), 4.57 (1H, t, *J* = 7.0 Hz), 2.74 (1H, dt, *J* = 3.4, 11.5 Hz), 2.20-2.30 (2H, m), 1.80-2.00 (5H, m), 1.55-1.68 (3H, m), 1.29-1.52 (2H, m), 1.02 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): 166.1, 153.4, 144.1, 143.2, 128.6, 128.3, 127.8, 127.5, 126.3, 126.0, 120.0, 75.9, 72.4, 49.8, 44.9, 33.9, 33.2, 32.4, 25.9, 24.8, 19.3; HRMS (FAB, MNa^{+}) calcd for $C_{25}H_{30}O_3Na$: 401.2093. Found 401.2090.

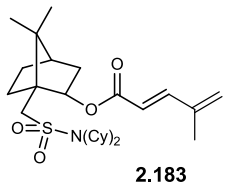
2.180: IR (neat, NaCl) 3459, 2935, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.18-7.34 (10H, m), 4.91 (1H, dt, *J* = 4.3, 10.9 Hz), 4.67 (1H, app dd, *J* = 2.8, 5.5 Hz), 4.35 (2H, s), 2.60-2.76 (2H, m), 2.24-2.32 (1H, m), 2.28 (1H, d, *J* = 2.9 Hz), 2.01-2.14 (1H, m), 1.76-1.93 (5H, m), 1.39-1.53 (3H, m), 1.36 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 173.4, 143.4, 142.7, 141.4, 128.7, 128.4, 127.8, 127.6, 126.8, 126.4, 111.9, 77.4, 74.5, 52.1, 49.7, 34.9, 34.7, 31.9, 26.0, 24.8, 22.1; HRMS (FAB, MNa^{+}) calcd for $C_{25}H_{30}O_3Na$: 401.2092. Found 401.2110.



2.182

(1*R*,2*S*,4*R*)-1-((N,N-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-yl-2-(dimethoxyphosphoryl)acetate (2.182): Trimethylphosphite (2.417 mmol, 0.28 mL) and acetyl chloride **2.181** (0.967 mmol, 0.500 g) were reacted in dry toluene (1 mL) following the general procedure **C** to afford phosphono-acetate **2.182** as a highly viscous yellow oil (0.480 g, 91%).

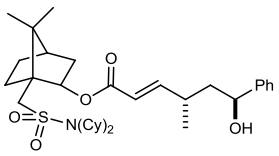
IR (neat, NaCl) 2932, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.99 (1H, dd, *J* = 3.2, 9.2 Hz), 3.80 (6H, d, J_{HP} = 11.2 Hz), 3.25 (1H, d, *J* = 13.3 Hz), 3.21-3.27 (2H, m), 2.96 (2H, dd, J_{HH} = 1.6 Hz, J_{HP} = 21.2 Hz), 2.67 (1H, d, *J* = 13.3 Hz), 1.96-2.07 (2H, m), 1.71-1.80 (14H, m), 1.62-1.65 (3H, m), 1.25-1.32 (5H, m), 1.15-1.22 (1H, m), 1.08-1.13 (2H, m), 1.02 (3H, s), 0.88 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 164.2 (d, J_{CP} = 6.1 Hz), 80.1, 57.7, 54.0, 52.35 (d, J_{CP} = 6.6 Hz), 53.18 (d, J_{CP} = 6.0 Hz), 49.6, 49.4, 44.6, 39.3, 34.21 (d, J_{CP} = 134.6 Hz), 33.0, 30.4, 27.2, 26.7, 25.4, 20.6, 20.0; ^{31}P {^{1}H} NMR ($CDCl_3$): δ 23.4; HRMS (FAB, MH^+) calcd for $C_{26}H_{47}NO_7PS$: 548.2817. Found 548.2817.



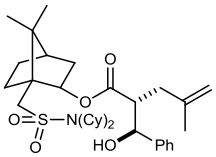
2.183

(*E*)-(1*R*,2*S*,4*R*)-1-((N,N-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-yl-4-methylpenta-2,4-dienoate (2.183): Methacrolein **2.120** (0.077 mmol, 6 μL), sodium hydride (60% w/w in mineral oil, 0.060 mmol, 0.001 g) and phosphono-acetate **2.182** (0.050 mmol, 0.027 g) were reacted in dry THF (0.5 mL) following the general procedure **D** to afford **2.183** as a colorless solid (0.017 g, 68%).

IR (neat, NaCl) 2937, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33 (1H, d, *J* = 15.9 Hz), 5.84 (1H, d, *J* = 15.6 Hz), 5.33 (2H, s), 5.13 (1H, dd, *J* = 3.2, 9.8 Hz), 3.29 (1H, d, *J* = 13.4 Hz), 3.23 (2H, quin, *J* = 6.6 Hz), 2.69 (1H, d, *J* = 13.2 Hz), 1.96-2.05 (2H, m), 1.88 (3H, s), 1.72-1.84 (14H, m), 1.55-1.66 (4H, m), 1.21-1.29 (5H, m), 0.99-1.11 (2H, m), 1.04 (3H, s), 0.91 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.6, 146.8, 140.6, 124.3, 119.4, 78.5, 57.7, 53.9, 49.7, 49.3, 44.8, 39.7, 33.1, 33.0, 30.2, 27.3, 26.7, 25.4, 20.7, 20.4, 18.2; HRMS (FAB, MNa^+) calcd for $C_{28}H_{45}NO_4SNa$: 514.2967. Found 514.2950.



2.184a



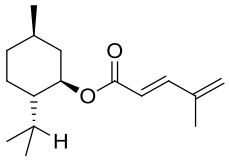
2.184b

(1*R*,2*S*,4*R*)-1-((*N*,*N*-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-yl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.184a) and (1*R*,2*S*,4*R*)-1-((*N*,*N*-dicyclohexylsulfamoyl)methyl)-7,7-dimethylbicyclo [2.2.1] heptan-2-yl-2-(hydroxyl(phenyl)methyl)-4-methylpent-4-enoate (2.184b): Benzaldehyde **2.21** (0.150 mmol, 15 μL), $Ni(acac)_2$ (0.015 mmol, 0.004 g), diethylzinc (10% w/w in hexanes, 0.36 mmol, 0.44 mL), and pentadienoate **2.183** (0.300 mmol, 0.147 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.184a** and **2.184b** as a colorless liquid (rr, 6:1) (0.058 g, combined yield 64%).

2.184a: IR (neat, NaCl) 3502, 2932, 1714 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.27-7.36 (5H, m), 6.99 (1H, dd, *J* = 6.9, 15.7 Hz), 5.77 (1H, d, *J* = 15.7 Hz), 5.06 (1H, dd, *J* = 2.7, 9.4 Hz), 4.77 (1H, dd, *J* = 4.5, 9.1 Hz), 3.27 (1H, d, *J* = 13.3 Hz), 3.23 (2H, app quin, *J* = 9.2 Hz), 2.69 (1H, d, *J* = 13.3 Hz), 2.59 (1H, app sep, *J* = 6.8 Hz), 1.94-2.05 (4H, m), 1.70-1.77 (14H, m), 1.56-1.66 (5H, m), 1.18-1.26 (5H, m), 1.13 (3H, d, *J* = 6.7 Hz), 1.05-1.10 (2H, m), 1.01 (3H, s), 0.90 (3H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 165.5, 154.1, 144.9, 128.8, 128.0, 125.9, 119.8, 78.4, 72.2, 57.7, 53.8, 49.6, 49.3, 45.1, 44.8, 39.8, 33.04, 33.00, 32.9, 30.1, 27.2, 26.76, 26.72, 25.4, 20.7, 20.4, 18.7; HRMS (FAB, MNa^+) calcd for $C_{35}H_{53}NO_5SNa$: 622.3542. Found 622.3536.

2.184b: IR (neat, NaCl) 3525, 2945, 1716 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.43 (2H, d, *J* = 7.7 Hz), 7.34 (2H, t, *J* = 7.5 Hz), 7.25 (1H, t, *J* = 7.5 Hz), 5.31 (1H, s), 4.91

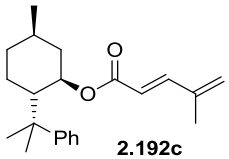
(1H, dd, *J* = 3.2, 7.7 Hz), 4.68 (1H, s), 4.59 (1H, s), 3.55 (1H, d, *J* = 3.4 Hz), 3.32-3.36 (2H, m), 3.34 (1H, d, *J* = 13.3 Hz), 2.99 (1H, dt, *J* = 2.7, 11.1 Hz), 2.66 (1H, d, *J* = 13.3 Hz), 2.48 (1H, dd, *J* = 11.2, 17.0 Hz), 1.93-2.01 (2H, m), 1.72-1.92 (14H, m), 1.64-1.69 (3H, m), 1.61 (3H, s), 1.36-1.41 (4H, m), 1.11-1.29 (5H, m), 0.93 (3H, s), 0.87 (3H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.5, 143.5, 141.4, 127.7, 126.6, 125.4, 109.1, 78.9, 73.5, 57.1, 53.9, 51.7, 49.0, 48.8, 43.9, 38.9, 33.0, 31.7, 30.8, 30.7, 26.6, 26.0, 25.9, 24.7, 23.2, 20.0, 19.2.



2.191c

(*E*)-(1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl-4-methylpenta-2,4-dienaote (2.191c): Methacrolein **2.120** (0.980 mmol, 80 μL), sodium hydride (60% w/w in mineral oil, 0.784 mmol, 0.019 g), and phosphono-acetate[48] **2.191b** (0.653 mmol, 0.200 g) were reacted in dry THF (2 mL) following the general procedure **D** to afford pentadienoate **2.191c** as a viscous colorless liquid (0.105 g, 64%).

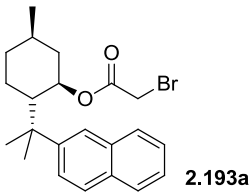
IR (neat, NaCl) 2957, 1707 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34 (1H, d, *J* = 15.7 Hz), 5.86 (1H, d, *J* = 15.7 Hz), 5.35 (1H, s), 5.32 (1H, s), 4.78 (1H, dt, *J* = 4.4, 10.9 Hz), 2.01-2.04 (1H, m), 1.86-1.91 (1H, m), 1.88 (3H, s), 1.67-1.70 (2H, m), 1.49-1.53 (1H, m), 1.39-1.44 (1H, m), 1.08 (1H, dq, *J* = 2.8, 12.6 Hz), 0.97-1.04 (1H, m), 0.90 (3H, d, *J* = 6.4 Hz), 0.89 (3H, d, *J* = 7.0 Hz), 0.85-0.91 (1H, m), 0.77 (3H, d, *J* = 6.9 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.9, 147.0, 140.8, 124.3, 119.4, 74.3, 47.4, 41.2, 34.5, 31.6, 26.5, 23.7, 22.2, 21.0, 18.3, 16.6; HRMS (FAB, MH^+) calcd for $C_{16}H_{27}O_2$: 251.2011. Found 251.2013.



2.192c

(*E*)-(1*R*,2*R*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-4-methyl-penta-2,4-dienaote (2.192c): Methacrolein **2.120** (0.667 mmol, 55 μL), sodium hydride (60% w/w in mineral oil, 0.534 mmol, 0.013 g), and phosphono-acetate[48] **2.192b** (0.445 mmol, 0.170 g) were reacted in dry THF (2 mL) following the general procedure **D** to afford pentadienoate **2.192c** as a colorless solid (0.125 g, 86%).

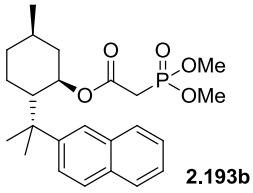
IR (neat, NaCl) 2952, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.01-7.21 (5H, m), 6.85 (1H, d, *J* = 15.7 Hz), 5.19 (1H, s), 5.16 (1H, s), 5.13 (1H, d, *J* = 15.7 Hz), 4.79 (1H, dt, *J* = 4.3, 10.7 Hz), 1.96-2.05 (1H, m), 1.80-1.87 (1H, m), 1.69 (3H, s), 1.56-1.71 (2H, m), 1.37-1.46 (1H, m), 1.24 (3H, s), 1.14 (3H, s), 1.06 (1H, dq, *J* = 3.1, 12.6 Hz), 0.75-0.91 (2H, m), 0.79 (3H, d, *J* = 6.6 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 152.0, 146.3, 140.7, 128.1, 125.5, 125.0, 124.0, 119.5, 74.3, 50.8, 41.9, 39.7, 34.8, 31.5, 28.6, 26.7, 24.4, 22.0, 18.2; HRMS (FAB, MH^+) calcd for $C_{22}H_{31}O_2$: 327.2324. Found 327.2312.



2.193a

(1*R*,2*R*,5*R*)-5-methyl-2-(2-naphthalen-2-yl)propan-2-yl)cyclohexyl-2-bromoacetate (2.193a): Sodium hydride (60% w/w in mineral oil, 1.091 mmol, 0.026 g), bromoacetyl chloride **2.140** (1.191 mmol, 0.1 mL) and alcohol[43] **2.188** (9.922 mmol, 0.280 g) were reacted in dry THF (3 mL) following the general procedure **B** to afford acetyl bromide **2.193a** as a viscous brown oil (0.350 g, 88%).

IR (neat, NaCl) 2958, 1728, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.71 (3H, d, *J* = 8.6 Hz), 7.54 (1H, d, *J* = 1.2 Hz), 7.43 (1H, dd, *J* = 1.8, 8.7 Hz), 7.32-7.38 (2H, m), 4.85 (1H, dt, *J* = 4.6, 10.8 Hz), 2.58 (2H, ABq, *J* = 12.4 Hz, $\Delta\delta$ = 0.08 ppm), 2.10 (1H, dt, *J* = 3.6, 12.2 Hz), 1.74-1.84 (2H, m), 1.64 (1H, td, *J* = 2.8, 12.8 Hz), 1.39-1.44 (1H, m), 1.36 (3H, s), 1.23 (3H, s), 1.07-1.20 (1H, m), 0.87-0.99 (2H, m), 0.82 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.5, 149.2, 133.4, 131.5, 128.0, 127.5, 127.4, 126.2, 125.5, 125.2, 122.6, 76.0, 50.1, 41.4, 39.8, 34.5, 31.4, 29.1, 26.4, 26.2, 23.5, 21.9; HRMS (FAB, MNa^{+}) calcd for $C_{22}H_{27}BrO_2Na$: 425.1092. Found 425.1099.

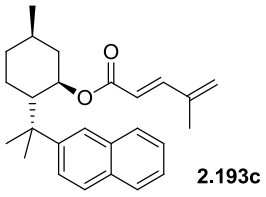


2.193b

(1*R*,2*R*,5*R*)-5-methyl-2-(2-naphthalen-2-yl)-propan-2-yl)cyclohexyl-2-(dimethoxyphosphoryl)acetate (2.193b): Trimethylphosphite (2.114 mmol, 0.25 mL) and acetyl bromide **2.193a** (0.845 mmol, 0.340 g) were reacted in dry toluene (1mL) following the general procedure **C** to afford acetyl phosphonate **2.193b** as a highly viscous yellowish oil (0.350 g, 96%).

IR (neat, NaCl) 2959, 1726, 1277 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.79 (3H, d, *J* = 8.6 Hz), 7.65 (1H, d, *J* = 1.2 Hz), 7.53 (1H, dd, *J* = 1.8, 8.7 Hz), 7.29-7.48 (2H, m), 4.92 (1H, dt, *J* = 4.5, 10.7 Hz), 3.62 (3H, d, J_{HP} = 11.2 Hz), 3.59 (3H, d, J_{HP} = 11.2 Hz), 2.18 (1H, dt, *J* = 3.5, 12.2 Hz), 2.02 (1H, dd, J_{HH} = 14.5 Hz, J_{HP} = 21.2 Hz), 1.85-1.90 (2H, m), 1.70 (1H, dd, J_{HH} = 14.5 Hz, J_{HP} = 21.2 Hz), 1.63-1.71 (1H, m), 1.45-1.52 (1H, m), 1.45 (3H, s), 1.32 (3H, s), 1.22 (1H, dq, *J* = 3.2, 13.1 Hz), 0.96-1.08 (2H, m), 0.90 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.0 (d, J_{CP} = 5.9 Hz), 149.3, 133.5, 131.5, 127.9, 127.4,

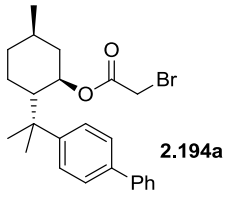
126.2, 125.5, 125.3, 122.8, 75.5, 53.05 (d, J_{CP} = 6.9 Hz), 53.01 (d, J_{CP} = 6.4 Hz), 50.1, 41.4, 39.9, 34.6, 32.8 (d, J_{CP} = 132.9 Hz), 31.5, 28.9, 26.5, 23.6, 22.0; ^{31}P {^{1}H} NMR ($CDCl_3$): δ 22.81; HRMS (FAB, MNa^+) calcd for $C_{24}H_{33}O_5PNa$: 455.1963. Found 455.1965.



2.193c

(*E*)-(1*R*,2*R*,5*R*)-5-methyl-2-(2-naphthalen-2-yl)propan-2-yl)cyclohexyl-4-methyl-penta-2,4-dienaote (2.193c): Methacrolein **2.120** (1.145 mmol, 95 μL), sodium hydride (60% w/w in mineral oil, 0.916 mmol, 0.022 g), and phosphonate **2.193b** (0.763 mmol, 0.330 g) were reacted in dry THF (2 mL) following the general procedure **D** to afford pentadienoate **2.193c** as a highly viscous liquid (0.246 g, 86%).

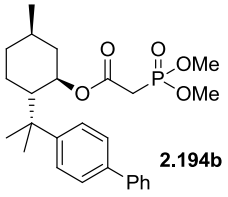
IR (neat, NaCl) 3057, 2956, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.69-7.78 (3H, m), 7.60 (1H, s), 7.53 (1H, dd, *J* = 1.9, 8.7 Hz), 7.27-7.40 (2H, m), 6.75 (1H, d, *J* = 15.8 Hz), 5.09 (1H, s), 5.00 (1H, s), 4.94 (1H, dt, *J* = 4.3, 10.7 Hz), 4.77 (1H, d, *J* = 15.8 Hz), 2.23 (1H, dt, *J* = 3.5, 12.2 Hz), 1.85-1.91 (2H, m), 1.72 (1H, td, *J* = 2.8, 12.8 Hz), 1.50-1.55 (1H, m), 1.44 (3H, s), 1.31 (3H, s), 1.30 (3H, s), 1.20-1.30 (1H, m), 0.94-1.06 (2H, m), 0.89 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 149.6, 146.2, 140.5, 133.3, 131.5, 128.1, 127.45, 127.40, 125.9, 125.2, 125.1, 123.7, 122.8, 118.8, 74.0, 50.3, 41.9, 39.8, 34.8, 31.5, 29.1, 26.6, 23.6, 22.0, 17.6; HRMS (FAB, MH^+) calcd for $C_{26}H_{32}O_2Na$: 399.2300. Found 399.2298.



2.194a

(1*R*,2*R*,5*R*)-2-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-5-methylcyclohexyl-2-bromoacetate (2.194a): Sodium hydride (60% w/w in mineral oil, 0.500 mmol, 0.012 g), bromoacetyl chloride **2.140** (0.540 mmol, 45 μL) and alcohol **2.194** (0.454 mmol, 0.140 g) were reacted in dry THF (2 mL) following the general procedure **B** to afford acetyl bromide **2.194a** as a viscous brown oil (0.175 g, 90%).

IR (neat, NaCl) 2957, 1729, 1272 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.52 (2H, d, *J* = 8.5 Hz), 7. 46 (2H, d, *J* = 8.5 Hz), 7.37 (2H, t, *J* = 7.2 Hz), 7.19-7.30 (3H, m), 4.82 (1H, dt, *J* = 4.6, 10.9 Hz), 2.96 (2H, ABq, *J* = 12.6 Hz, $\Delta\delta$ = 0.13 ppm), 2.03 (1H, dt, *J* = 3.6, 12.4 Hz), 1.75-1.87 (2H, m),1.65 (1H, td, *J* = 2.8, 12.7 Hz), 1.39-1.47 (1H, m), 1.28 (3H, s), 1.18 (3H, s), 1.06-1.17 (1H, m), 0.88-1.00 (2H, m), 0.83 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.5, 151.1, 141.0, 138.1, 129.0, 127.3, 127.1, 126.8, 126.0, 76.0, 50.3, 41.4, 39.5, 34.6, 31.4, 29.8, 26.6, 26.4, 23.0, 22.0; HRMS (FAB, MNa^{+}) calcd for $C_{24}H_{29}BrO_2Na$: 451.1249. Found 451.1244.

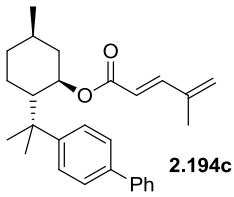


2.194b

(1*R*,2*R*,5*R*)-2-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-5-methylcyclohexyl-2-(dimethoxyphosphoryl)acetate (2.194b): Trimethylphosphite (1.022 mmol, 0.12 mL) and acetyl bromide **2.194a** (0.409 mmol, 0.175 g) were reacted in dry toluene (1mL)

following the general procedure **C** to afford acetyl phosphonate **2.194b** as a highly viscous yellowish oil (0.175 g, 94%).

IR (neat, NaCl) 2950, 1725, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.59 (2H, d, *J* = 8.5 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 7.29-7.47 (5H, m), 4.88 (1H, dt, *J* = 4.4, 10.8 Hz), 3.70 (3H, d, J_{HP} = 11.2 Hz), 3.69 (3H, d, J_{HP} = 11.2 Hz), 2.39 (1H, dd, J_{HH} = 14.6 Hz, J_{HP} = 21.0 Hz), 2.20 (1H, dd, J_{HH} = 14.6, J_{HP} = 21.3 Hz), 2.06-2.15 (1H, m), 1.85-1.95 (2H, m), 1.72 (1H, td, *J* = 2.8, 12.9 Hz), 1.46-1.52 (1H, m), 1.37 (3H, s), 1.27 (3H, s), 1.20 (1H, dq, *J* = 3.2, 12.9 Hz), 0.96-1.08 (2H, m), 0.91 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.1 (d, J_{CP} = 5.4 Hz), 151.1, 141.0, 138.1, 128.9, 127.2, 127.0, 126.7, 126.1, 75.5, 53.1 (d, J_{CP} = 6.2 Hz), 53.0 (d, J_{CP} = 6.2 Hz), 50.5, 41.4, 39.5, 34.6, 33.2 (d, J_{CP} = 134.4 Hz), 31.4, 29.2, 26.5, 23.5, 21.9; ^{31}P {^{1}H} NMR ($CDCl_3$): δ 22.78; HRMS (FAB, MNa^{+}) calcd for $C_{26}H_{35}O_5PNa$: 481.2120. Found 481.2133.

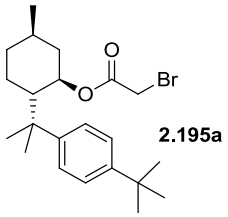


2.194c

(E)-(1*R*,2*R*,5*R*)-2-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-5-methylcyclohexyl-4-methylpenta-2,4-dienaote (2.194c): Methacrolein **2.140** (0.556 mmol, 46 μL), sodium hydride (60% w/w in mineral oil, 0.445 mmol, 0.011 g), and acetyl phosphonate **2.194b** (0.371 mmol, 0.170 g) were reacted in dry THF (2 mL) following the general procedure **D** to afford pentadienoate **2.194c** as a white solid (0.130 g, 87%).

IR (neat, NaCl) 3051, 2948, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (2H, d, *J* = 8.5 Hz), 7.42 (2H, d, *J* = 8.5 Hz), 7.16-7.33 (5H, m), 6.92 (1H, d, *J* = 15.7 Hz), 5.14 (1H, d, *J*

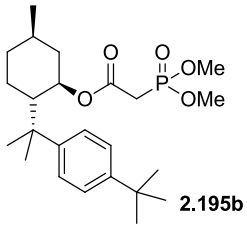
=15.7 Hz), 5.09 (1H, s), 5.07 (1H, s), 4.83 (1H, dt, *J* = 4.4, 10.7 Hz), 2.02 (1H, dt, *J* = 3.5, 12.2 Hz), 1.82-1.87 (1H, m), 1.70-1.77 (1H, m), 1.61 (1H, td, *J* = 2.9, 12.8 Hz), 1.49 (3H, s), 1.37-1.46 (1H, m), 1.27 (3H, s), 1.17 (3H, s), 1.09 (1H, dq, *J* = 3.2, 12.8 Hz), 0.86-0.98 (2H, m), 0.80 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 151.2, 146.4, 140.9, 140.6, 137.6, 128.7, 127.0, 126.9, 126.6, 126.0, 124.1, 119.3, 74.2, 50.8, 41.9, 39.6, 34.8, 31.5, 28.7, 26.7, 24.4, 22.0, 18.0; HRMS (FAB, MNa^+) calcd for $C_{28}H_{34}O_2Na$: 425.2457. Found 425.2441.



2.195a

(1*R*,2*R*,5*R*)-2-(2-(4(tet-butylphenyl)propan-2-yl)-5-methylcyclohexyl-2-bromoacetate (2.195a): Sodium hydride (60% w/w in mineral oil, 7.260 mmol, 0.174 g), bromoacetyl chloride **2.140** (7.920 mmol, 0.66 mL), and alcohol **2.195** (6.600 mmol, 1.902 g) were reacted in dry THF (20 mL) following the general procedure **B** to afford acetyl bromide **2.195a** as a viscous brown oil (2.400 g, 89%).

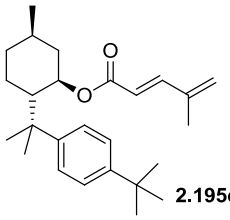
IR (neat, NaCl) 2963, 1754, 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33 (2H, d, *J* = 6.6 Hz), 7.21 (2H, d, *J* = 6.7 Hz), 4.91 (1H, dt, *J* = 4.6, 10.7 Hz), 3.06 (2H, ABq, *J* = 15.1 Hz, Δ*δ* = 0.4 ppm), 2.04-2.12 (1H, m), 1.93-2.03 (1H, m), 1.70-1.92 (2H, m), 1.44-1.69 (1H, m), 1.33 (9H, s), 1.32 (3H, s), 1.19 (3H, s), 1.04-1.23 (1H, m), 0.92-1.0 (2H, m), 0.89 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.7, 148.9, 147.8, 125.1, 125.0, 75.8, 50.4, 41.8, 40.9, 39.1, 34.6, 34.4, 31.5, 31.4, 30.6, 26.2, 22.1, 22.0; HRMS (FAB, MNa^+) calcd for $C_{22}H_{33}ClO_2Na$: 387.2067. Found 387.2062.



2.195b

(1*R*,2*R*,5*R*)-2-(2-(4(tet-butylphenyl)propan-2-yl)-5-methylcyclohexyl-2-(dimethoxyphosphoryl)acetate (2.195b): Trimethylphosphite (14.749 mmol, 1.74 mL) and acetyl bromide **2.195a** (5.899 mmol, 2.408 g) were reacted in dry toluene (1 mL) following the general procedure **C** to afford acetyl phosphonate **2.195b** as a highly viscous yellow oil (2.100 g, 82%).

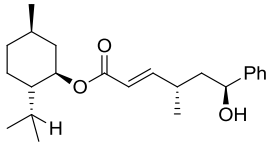
IR (neat, NaCl) 2954, 1719, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.23 (2H, d, J = 6.6 Hz), 7.21 (2H, d, J = 6.7 Hz), 4.75 (1H, dt, J = 4.5, 10.8 Hz), 3.63 (3H, d, J_{HP} = 11.2 Hz), 3.61 (3H, J_{HP} = 11.2 Hz), 2.21 (1H, dd, J_{HH} = 14.6, J_{HP} = 21.2 Hz), 1.95 (1H, dd, J_{HH} = 14.5, J_{HP} = 21.2 Hz), 1.93-2.02 (1H, m), 1.77-1.84 (2H, m), 1.59-1.65 (1H, m), 1.32-1.44 (1H, m), 1.23 (9H,s), 1.22 (3H, s), 1.11 (3H, s), 1.11 (1H, dq, J = 3.1, 13.2 Hz), 0.8-0.91 (2H, m), 0.8 (3H, d, J = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 165.1 (d, J_{CP} = 5.4 Hz), 148.9, 147.7, 125.1, 124.9, 75.3, 53.2, 53.1 (d, J_{CP} = 6.0 Hz), 53.0 (d, J_{CP} = 6.1 Hz), 50.4, 41.4, 39.1, 34.6, 34.3, 33.2 (d, J_{CP} = 134.4 Hz), 31.5, 31.4, 29.9, 26.3, 22.7, 21.9; ^{31}P {^{1}H} NMR ($CDCl_3$): δ 23.01; HRMS (FAB, MH^+) calcd for $C_{24}H_{40}O_5$: 439.2613. Found 439.2621.



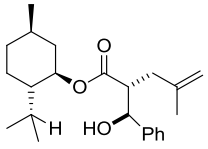
2.195c

(E)-(1*R*,2*R*,5*R*)-2-(2-(4(tet-butylphenyl)propan-2-yl)-5-methylcyclohexyl-4-methylpenta-2,4-dienoate (2.195c): Methacrolein **2.120** (1.164 mmol, 96 μL), sodium hydride (60% w/w in mineral oil, 0.931 mmol, 0.022 g), and acetyl phosphonate **2.195b** (0.776 mmol, 0.340 g) were reacted in dry THF (3 mL) following the general procedure **D** to afford pentadienoate **2.195c** as a colorless solid (0.260 g, 88%).

IR (neat, NaCl) 2953, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22-7.32 (5H, m), 5.50 (1H, d, *J* = 15.7 Hz), 5.36 (2H, s), 4.96 (1H, dt, *J* = 4.3, 10.7 Hz), 1.96-2.09 (2H, m), 1.86 (3H, s), 1.62-1.68 (2H, m), 1.28-1.59 (1H, m), 1.35 (3H, s), 1.32 (9H, s), 1.24 (3H, s), 0.95-1.16 (2H, m), 0.89 (3H, d, *J* = 6.4 Hz), 0.83- 0.90 (1H, m); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.5, 148.4, 147.6, 146.7, 140.6, 125.3, 124.8, 124.2, 119.5, 74.7, 50.8, 42.0, 39.6, 34.8, 34.3, 31.6, 31.5, 27.1, 27.0, 26.5, 22.0, 18.3; HRMS (FAB, MNa^{+}) calcd for $C_{26}H_{38}O_2Na$: 405.2769. Found 405.2764.



2.196a



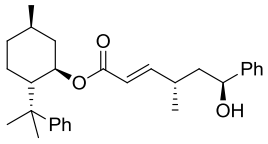
2.196b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.196a) and (1*R*,2*R*,5*R*)-2-isopropyl-5-methylcyclohexyl-2-(hydroxy(phenyl)methyl)-4-methylpent-4-enoate (2.196b): Benzaldehyde **2.21** (0.10 mmol, 10 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (10% w/w solution in

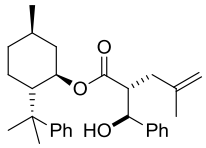
hexanes, 0.24 mmol, 0.30 mL), and pentadienoate **2.191c** (0.20 mmol, 0.050 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.196a** and **2.196b** as a colorless liquid (rr, 5:1) (0.024 g, combined yield 69%).

2.196a: IR (neat, NaCl) 3467, 2956, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$): (major isomer) δ 7.19-7.28 (5H, m), 6.84 (1H, dd, *J* = 7.8, 15.7 Hz), 5.68 (1H, d, *J* = 15.7 Hz), 4.67 (1H, dt, *J* = 4.4, 11.1 Hz), 4.65 (1H, app q, *J* = 5.3 Hz), 2.37 (1H, app sep, *J* = 7.0 Hz), 1.75-1.97 (3H, m), 1.72 (1H, broad s), 1.56-1.65 (3H, m), 1.26-1.33 (2H, m), 1.04 (3H, d, *J* = 6.7 Hz), 0.97 (2H, dq, *J* = 2.3, 11.3 Hz), 0.83 (6H, d, *J* = 6.7 Hz), 0.69 (3H, d, *J* = 6.9 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.6, 153.9, 144.6, 128.9, 128.1, 126.2, 120.5, 74.2, 72.6, 47.3, 45.3, 41.2, 34.5, 33.4, 31.6, 26.5, 23.8, 22.3, 21.0, 19.4, 16.7; HRMS (FAB, MNa^{+}) calcd for $C_{23}H_{34}O_3Na$: 381.2406. Found 381.2408.

2.196b: IR (neat, NaCl) 3462, 2953, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7 (37 (5H, m), 4.89 (1H, dd, *J* = 2.4, 6.4 Hz), 4.73 (2H, s), 4.52 (1H, dt, *J* = 4.4, 10.9 Hz), 2.90-2.97 (1H, m), 2.71 (1H, dd, *J* = 2.6, 13.8 Hz), 2.48 (1H, dd, *J* = 4.0, 10.4 Hz), 2.30-2.53 (1H, m), 1.72-1.82 (1H, m), 1.70 (3H, s), 1.49-1.65 (2H, m), 1.20-1.39 (4H, m), 0.96 (1H, dq, *J* = 2.8, 12.7 Hz), 0.84 (6H, d, *J* = 6.9 Hz), 0.64 (3H, d, *J* = 6.9 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 174. 0, 142.9, 141.5, 128.6, 128.1, 126.7, 112.7, 74.9, 74.7, 52.2, 46.8, 40.4, 36.1, 34.3, 31.4, 25.7, 23.5, 23.2, 23.0, 22.4, 16.5; HRMS (FAB, MNa^{+}) calcd for $C_{23}H_{34}O_3Na$: 381.2406. Found 381.2410.



2.197a



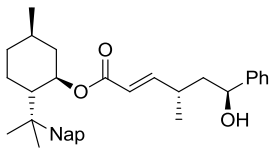
2.197b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.197a) and (1*R*,2*R*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2-(hydroxy(phenyl)methyl)-4-methylpent-4-enoate (2.197b): Benzaldehyde **2.21** (0.20 mmol, 20 μL), $Ni(acac)_2$ (0.02 mmol, 0.005 g), diethylzinc (10% w/w solution in hexanes, 0.48 mmol, 0.59 mL), and pentadienoate **2.192c** (0.40 mmol, 0.130 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.197a** and **2.197b** as a colorless liquid (rr, 7:1) (0.065 g, combined yield 75%).

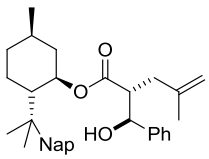
1.297a: IR (neat, NaCl) 3444, 2957, 1703 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.33-7.39 (5H, m), 7.26-7.32 (4H, m), 7.10 (1H, app t, J = 7.1 Hz), 6.61 (1H, dd, J = 7.5, 15.7 Hz), 5.20 (1H, d, J = 15.7 Hz), 4.86 (1H, dt, J = 4.1, 10.7 Hz), 4.68 (1H, t, J = 7.1 Hz), 2.35 (1H, app sep, J = 7.1 Hz), 2.04-2.07 (1H, m), 1.87-1.95 (3H, m), 1.60-1.73 (4H, m), 1.50-1.52 (1H, m), 1.33 (3H, s), 1.24 (3H, s), 1.10-1.15 (1H, m), 1.06 (3H, d, J = 6.6 Hz), 0.96-1.09 (1H, m), 0.89 (3H, d, J = 6.5 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.2, 153.5, 151.9, 144.7, 128.9, 128.2, 128.1, 126.2, 125.7, 125.2, 120.5, 74.4, 72.6, 50.8, 45.2, 42.0, 40.0, 34.8, 33.2, 31.5, 28.1, 26.8, 25.3, 22.0, 19.2; HRMS (FAB, MNa^+) calcd for $C_{29}H_{38}O_3Na$: 457.2719. Found 457.2719.

1.297b: IR (neat, NaCl) 3466, 2950, 1719 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26-7.33 (9H, m), 7.17 (1H, app t, J = 7.1 Hz), 4.77 (1H, d, J = 4.5 Hz), 4.75 (2H, s), 4.68 (1H, dt, J = 4.1, 10.7 Hz), 2.63 (1H, app pent, J = 4.6 Hz), 2.46 (1H, dd, J = 9.9, 14.2 Hz), 2.41 (1H, d, J

= 3.7 Hz), 2.16 (1H, dd, *J* = 4.2, 14.5 Hz), 1.86-1.90 (1H, m), 1.66 (3H, s), 1.50-1.57 (2H, m), 1.40-1.43 (1H, m), 1.29 (3H, s), 1.26-1.35 (1H, m), 1.18 (3H, s), 0.80-0.95 (2H, m), 0.77 (3H, d, *J* = 6.5 Hz), 0.71 (1H, m); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 173.2, 151.6, 143.4, 141.4, 128.5, 128.2, 128.0, 126.8, 125.8, 125.4, 113.0, 75.9, 75.1, 51.6, 50.4, 41.1, 40.2, 35.0, 34.7, 31.4, 27.8, 27.2, 25.8, 22.8, 21.9; HRMS (FAB, MNa^+) calcd for $C_{29}H_{38}O_3Na$: 457.2719. Found 457.2699.



1.298a



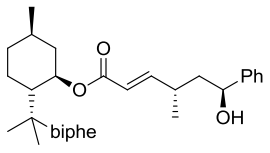
1.298b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-5-methyl-2-(2-(naphthalene-2-yl)cyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (1.298a) and (1*R*,2*R*,5*R*)-5-methyl-2-(2-(naphthalene-2-yl)cyclohexyl-2-(hydroxy(phenyl)methyl)-4-methylpent-4-enoate (1.298b): Benzaldehyde **3.21** (0.20 mmol, 20 μL), $Ni(acac)_2$ (0.02 mmol, 0.005 g), diethylzinc (10% w/w solution in hexanes, 0.48 mmol, 0.59 mL), and pentadienoate **2.193c** (0.40 mmol, 0.150 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.198a** and **2.198b** as a colorless liquid (rr, 10:1) (0.068 g, combined yield 68%).

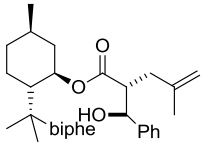
2.198a: IR (neat, NaCl) 3454, 3057, 2963, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$): (major isomer) δ 7.72-7.79 (3H, m), 7.61(1H, d, *J* = 1.4 Hz), 7.54 (1H, dd, *J* = 1.7, 8.7 Hz), 7.27-7.41 (7H, m), 6.38 (1H, dd, *J* = 7.1, 15.8 Hz), 4.92 (1H, dt, *J* = 4.3, 10.7 Hz), 4.80 (1H, dd, *J* = 1.1, 15.8 Hz), 4.51-4.56 (1H, m), 2.18-2.27 (1H, m), 1.86-1.96 (2H, m), 1.79-1.84 (1H, m), 1.63-1.79 (2H, m), 1.51-1.61 (1H, m), 1.44 (3H, s), 1.15-1.38 (3H, m), 1.30 (3H, s), 0.95-1.07 (2H, m), 0.90 (3H, d, *J* = 6.4 Hz), 0.77 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR

($CDCl_3$): δ 166.2, 153.4, 153.3, 149.6, 144.7, 133.7, 131.6, 128.8, 128.2, 127.9, 127.5, 126.1, 125.9, 125.3, 125.2, 122.9, 119.8, 74.1, 72.3, 50.2, 45.0, 42.0, 40.0, 34.8, 32.7. 31.5, 28.7, 26.7, 24.2, 22.0, 18.4; HRMS (FAB, MNa^+) calcd for $C_{33}H_{40}O_3Na$: 507.2875. Found 507.2886.

2.198b: IR (neat, NaCl) 3462, 2945, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.69-7.77 (3H, m), 7.49 (1H, s), 7.45 (1H, dd, *J* = 1.8, 8.7 Hz), 7.32-7.41 (2H, m), 7.02-7.12 (3H, m), 6.64-6.67 (2H, m), 4.81 (1H, dt, *J* = 4.3, 10.7 Hz), 4.57 (1H, broad s), 4.47 (1H, s), 4.43 (1H, s), 3.65 (1H, d, *J* = 1.7 Hz), 2.05-2.19 (2H, m), 1.64-1.79 (4H, m), 1.53-1.62 (1H, m), 1.31 (3H, s), 1.25 (3H, s), 1.03-1.21 (2H, m), 1.11 (3H, s), 0.74-0.89 (2H, m), 0.78 (3H, d, *J* = 6.5 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 172.2, 149.4, 141.5, 133.5, 131.6, 128.5, 128.1, 127.8, 127.5, 127.4, 126.5, 126.0, 125.4, 125.0, 123.0, 112.9, 81.8, 75.3, 53.1, 50.2, 43.4, 41.8, 39.9, 34.8, 31.5, 28.8, 28.5, 27.5, 26.9, 25.3, 22.0 HRMS (FAB, MNa^+) calcd for $C_{33}H_{40}O_3Na$: 507.2875. Found 507.2865.



2.199a



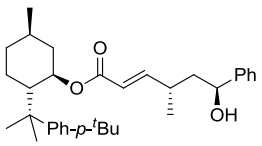
2.199b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.199a) and (1*R*,2*R*,5*R*)-2-(2-([1,1'-biphenyl]-4-yl)propan-2-yl)-5-methylcyclohexyl-2-(hydroxy(phenyl)methyl)-4-methylpent-4-enoate (2.199b): Benzaldehyde **2.21** (0.10 mmol, 10 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.194c** (0.20 mmol, 0.080 g) were reacted in dry THF (1 mL) following the

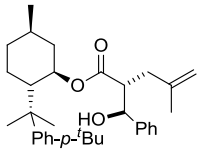
general procedure of homoallylation to afford two regioisomers **2.199a** and **2.199b** as a colorless liquid (rr, 6:1) (0.031 g, combined yield 60%).

2.199a: IR (neat, NaCl) 3456, 2958, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$): (major isomer) δ 7.41-7.53 (6H, m), 7.14-7.35 (8H, m), 6.59 (1H, dd, *J* = 7.7, 15.7 Hz), 5.14 (1H, dd, *J* = 1.0, 15.7 Hz), 4.81 (1H, dt, *J* = 4.4, 10.8 Hz), 4.84 (1H, app quin, *J* = 7.6 Hz), 2.10-2.24 (1H, m), 1.95-2.08 (1H, m), 1.81-1.90 (1H, m), 1.57-1.76 (3H, m), 1.35-1.51 (3H, m), 1.27 (3H, s), 1.19 (3H, s), 0.89-1.14 (3H, m), 0.84 (3H, d, *J* = 6.7 Hz), 0.81 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.0, 153.3, 151.0, 144.3, 140.8, 137.4, 128.7, 128.6, 127.7, 127.0, 126.8, 126.7, 125.9, 125.7, 120.2, 73.9, 72.2, 50.6, 44.9, 41.8, 39.6, 34.6, 33.0, 32.0, 31.3, 27.9, 26.6, 25.0, 21.8, 18.7; HRMS (FAB, MNa^+) calcd for $C_{35}H_{42}O_3Na$: 533.3032. Found 533.3015.

2.199b: IR (neat, NaCl) 3456, 2958, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66 (2H, d, *J* = 8.3 Hz), 7.60 (2H, d, *J* = 8.3 Hz), 7.48 (2H, t, *J* = 7.3 Hz), 7.39 (4H, dd, *J* = 1.3, 7.2 Hz), 7.26-7.37 (4H, m), 4.72-4.84 (2H, m), 4.78 (2H, s), 2.66 (1H, app quin, *J* = 4.1 Hz), 2.51 (1H, dd, *J* = 10.3, 14.0 Hz), 2.33-2.48 (1H, m), 2.10-2.19 (1H, m), 2.01 (1H, dt, *J* = 3.2, 12.0 Hz), 1.69 (3H, s), 1.56-1.57 (2H, m), 1.24-1.44 (2H, m), 1.38 (3H, s), 1.27 (3H, s), 0.88-1.10 (3H, m), 0.85 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 173.1, 150.8, 143.4, 141.3, 140.9, 138.0, 128.9, 128.4, 127.9, 127.2, 127.1, 126.7, 126.5, 126.2, 112.7, 75.9, 75.0, 51.5, 50.3, 41.1, 39.9, 34.7, 34.4, 31.4, 27.2, 27.1, 26.3, 22.8, 21.9; HRMS (FAB, MNa^+) calcd for $C_{35}H_{42}O_3Na$: 533.3032. Found 533.3038.



2.200a



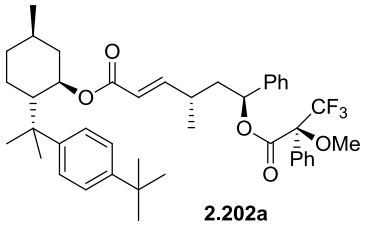
2.200b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenylpropan-2-yl)-5-methylcyclohexyl-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.200a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(hydroxy(phenyl)methyl)-4-methylpent-4-enoate (2.200b): Benzaldehyde **2.21** (0.20 mmol, 20 μL), $Ni(acac)_2$ (0.02 mmol, 0.005 g), diethylzinc (1.0 M solution in hexanes, 0.48 mmol, 0.48 mL), and pentadienoate **2.195c** (0.40 mmol, 0.153 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.200a** and **2.200b** as a colorless liquid (rr, 7:1) (0.071 g, combined yield 72%).

2.200a: IR (neat, NaCl) 3468, 2963, 1709 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.08-7.29 (9H, m), 6.71 (1H, dd, *J* = 8.1, 15.8 Hz), 5.17 (1H, dd, *J* = 0.9, 15.7 Hz), 4.79 (1H, dt, *J* = 4.3, 10.7 Hz), 4.60 (1H, t, *J* = 5.9 Hz), 2.25 (1H, app sep, *J* = 7.0 Hz), 1.77-1.96 (4H, m), 1.45-1.62 (3H, m), 1.33-1.44 (1H, m), 1.22 (3H, s), 1.20 (9H, s), 1.14 (3H, s), 1.0 (3H, d, *J* = 6.7 Hz), 0.89-0.95 (2H, m), 0.78 (3H, d, *J* = 6.4 Hz), 0.76-0.80 (1H, m); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.2, 153.8, 148.4, 147.6, 144.5, 128.8, 128.0, 126.1, 125.3, 124.9, 120.6, 74.6, 72.5, 50.8, 45.3, 41.9, 39.6, 34.8, 34.3, 33.4, 31.6, 31.5, 26.9, 26.8, 26.7, 22.0, 19.5; HRMS (FAB, MNa^+) calcd for $C_{33}H_{46}O_3Na$: 513.3345. Found 513.3331.

2.200b: IR (neat, NaCl) 3470, 2958, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.19-7.27 (7H, m), 7.09 (2H, d, *J* = 8.5 Hz), 4.71 (1H, d, *J* = 5.3 Hz), 4.68 (2H, s), 4.59 (1H, dt, J = 4.1, 10.6 Hz), 2.62-2.68 (1H, m), 2.39 (1H, dd, *J* = 10.2, 14.2 Hz), 2.33 (1H, brd s), 2.11 (1H, dd, *J* = 3.9, 14.1 Hz), 1.72-1.81 (1H, m), 1.60 (3H, s), 1.40-1.49 (3H,

m), 1.24 (9H, s), 1.20-1.32 (1H, m), 1.20 (3H, s), 1.09 (3H, s), 0.81-0.97 (2H, m), 0.69 (3H, d, J = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 173.2, 148.1,148.0, 143.2, 141.4, 128.5, 128.0, 126.8, 125.4, 125.0, 113.1, 76.1, 75.1, 51.8, 50.3, 41.1, 39.8, 35.1, 34.7, 34.4, 31.6, 31.3, 28.4, 27.2, 25.4, 22.8, 21.9; HRMS (FAB, MNa^+) calcd for $C_{33}H_{46}O_3Na$: 513.3345. Found 513.3349.

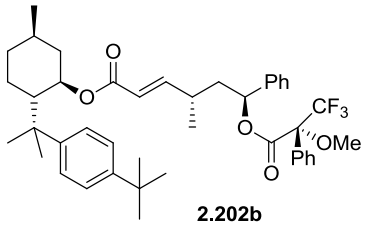


2.202a

4S,6S,E)-(1R,2R,5R)-2-(2-(4-(tert-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl 4-methyl-6-phenyl-6-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-2-enoate (2.202a): To a stirred solution of **2.200a** (0.020 mmol, 0.010 g) in dry CH_2Cl_2 (0.5 mL) under argon at rt was added *N*,*N*-dimethylamino pyridine (DMAP) (0.004 mmol, 0.005 g), pyridine (0.031 mmol, 3 μL) and (*R*)-MTPA chloride **2.201a** (0.031 mmol, 6 μL) sequentially. The resulting solution was stirred for 23 h at that temperature when the TLC analysis showed the reaction was complete. About 1 mL of water was added, the layers separated, the aq. layer was extracted with EtOAc (5 mL, 3X) and the combined organic layers were dried over anhydrous Na_2SO_4. The crude product was purified by SiO_2 column chromatography to give **2.202a** as a colorless liquid (0.01 g, 71%).

^{1}H NMR ($CDCl_3$): (major isomer) δ 7.08-7.28 (14H, m), 6.60 (1H, dd, J = 7.5, 15.7 Hz), 5.83 (1H, t, J = 6.2 Hz), 5.11 (1H, d, J = 15.7 Hz), 4.79 (1H, dt, J = 4.2, 10.7 Hz), 3.3 (3H, s), 1.95-2.03 (3H, m), 1.84-1.93 (2H, m), 1.62-1.67 (1H, m), 1.39-1.53 (3H, m),

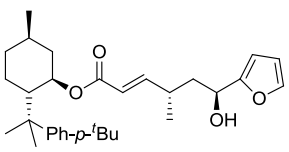
1.21 (3H, s), 1.20 (3H, s), 1.18 (9H, s), 0.89-1.00 (2H, m), 0.96 (3H, d, J = 6.4 Hz), 0.79 (3H, d, J = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.06, 166.02, 152.2, 148.3, 147.7, 138.7, 132.5, 129.7, 128.9, 128.8, 128.5, 127.5, 127.3, 125.3, 124.8, 121.1, 76.5, 74.7, 55.6, 50.8, 41.9, 41.8, 39.7, 34.8, 34.3, 32.6, 31.6, 31.5, 27.0, 26.6, 22.0, 19.1.



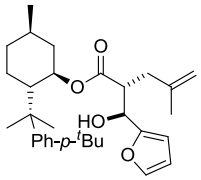
2.202b

(4S,6S,E)-(1R,2R,5R)-2-(2-(4-(tert-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl 4-methyl-6-phenyl-6-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-2-enoate (2.202b): Alcohol **2.202b** (0.032 mmol, 0.016 g), DMAP (0.007 mmol, 0.008 g), pyridine (0.049 mmol, 4 μL), and MTPA chloride (0.049 mmol, 9 μL) were reacted in dry CH_2Cl_2 (0.5 mL) following the above mentioned procedure for **2.202a** to afford **2.202b** as a colorless liquid (0.018 g, 82%).

^{1}H NMR ($CDCl_3$): (major isomer) δ 7.18-7.41 (14H, m), 6.74 (1H, dd, J = 7.5, 15.7 Hz), 5.85 (1H, t, J = 7.2 Hz), 5.23 (1H, d, J = 15.7 Hz), 4.90 (1H, dt, J = 4.2, 10.7 Hz), 3.51 (3H, s), 2.13-2.25 (3H, m), 1.92-2.10 (2H, m), 1.75-1.86 (1H, m), 1.59-1.65 (2H, m), 1.46-1.52 (2H, m), 1.30 (6H, s), 1.27 (9H, s), 1.10 (3H, d, J = 6.5 Hz), 0.93-1.06 (2H, m), 0.90 (3H, d, J = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.0, 165.8, 152.0, 148.4, 147.7, 138.7, 132.1, 129.7, 128.9, 128.7, 128.4, 127.5, 127.1, 125.3, 124.8, 121.4, 76.9, 74.8, 55.7, 50.8, 42.1, 42.0, 39.9, 39.7, 34.8, 34.3, 34.3, 31.61, 31.58, 26.96, 26.91, 26.6, 22.0, 19.5, 18.9.



2.204a



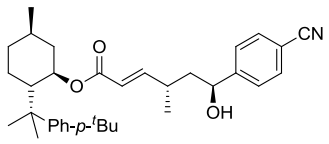
2.204b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenylpropan-2-yl)-5-methylcyclohexyl-6-(furan-2-yl)-6-hydroxy-4-methyl-6-phenylhex-2-enoate (2.204a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(furan-2-yl(hydroxyl)methyl)-4-methylpent-4-enoate (2.204b): Furfuraldehyde **2.204** (0.10 mmol, 8 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.204a** and **2.204b** as a colorless liquid (rr, 5:1) (0.036 g, combined yield 75%).

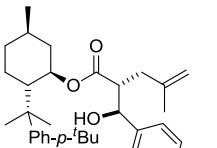
2.204a: IR (neat, NaCl) 3456, 2958, 1713 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.08-7.30 (5H, m), 6.67 (1H, dd *J* = 8.2, 15.7 Hz), 6.23-6.26 (1H, m), 6.13 (1H, d, *J* = 3.2 Hz), 5.13 (1H, dd, *J* = 0.9, 15.7 Hz), 4.78 (1H, dt, *J* = 4.3, 10.7 Hz), 4.58 (1H, t, *J* = 7.1 Hz), 2.26 (1H, app sep, *J* = 7.1 Hz), 1.77-1.97 (5H, m), 1.49-1.56 (2H, m), 1.42-1.48 (1H, m), 1.23 (9H, s), 1.21 (3H, s), 1.14 (3H, s), 1.00 (3H, d, *J* = 6.6 Hz), 0.97-1.02 (1H, m), 0.89-0.96 (1H, m), 0.77-0.80 (1H, m), 0.79 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 164.2, 156.3, 153.4, 148.5, 147.7, 142.3, 125.3, 124.9, 120.8, 110.4, 106.5, 74.7, 65.8, 50.8, 42.0, 41.6, 39.8, 34.8, 34.4, 33.2, 31.6, 31.5, 26.9, 26.6, 22.0, 19.4; HRMS (FAB, MNa^+) calcd for $C_{31}H_{44}O_4Na$: 503.3137. Found 503.3146.

2.204b: IR (neat, NaCl) 3463, 2962, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 -7.27 (3H, m), 7.10 (2H, d, *J* = 8.6 Hz), 7.21-7.27 (1H, m), 6.15 (1H, d, *J* = 4.3 Hz), 4.74 (1H, dt, *J* =

4.3, 10.9 Hz), 4.71 (1H, s), 4.61 (1H, s), 4.53 (1H, brd s), 2.26-2.28 (1H, s), 2.35 (1H, dd, *J* = 8.3, 14.3 Hz), 2.05 (1H, dd, *J* = 6.1, 14.5 Hz), 1.88 (1H, dt, *J* = 3.2, 11.9 Hz), 1.70-1.76 (1H, m), 1.65 (3H, s), 1.43-1.59 (5H, m), 1.23 (9H, s), 1.21 (3H, s), 1.10 (3H, s), 0.75 (3H, d, *J* = 6.4 Hz), 0.64-0.81 (2H, m); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.6, 154.0, 148.3, 148.1, 142.8, 142.1, 125.2, 125.1, 113.0, 110.3, 107.7, 76.2, 68.6, 50.4, 48.6, 41.5, 39.6, 35.2, 34.7, 34.4, 31.5, 31.4, 27.1, 26.5, 22.7, 21.9; HRMS (FAB, MNa^+) calcd for $C_{31}H_{44}O_4Na$: 503.3137. Found 503.3128.



2.205a



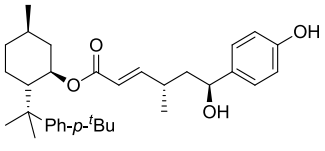
2.205b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-(4-cyanophenyl)-6-hydroxy-4-methylhex-2-enoate (2.205a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-((4-cyanophenyl)(hydroxy) methyl)-4-methylpent-4-enoate (2.205b): 4-Cyanobenzaldehyde **2.205** (0.10 mmol, 0.013 g), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 gm) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.205a** and **2.205b** as a colorless liquid (rr, 6:1) (0.036 g, combined yield 71%).

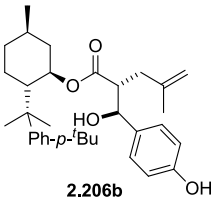
2.205a: IR (neat, NaCl) 3482, 2963, 2227, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.56 (2H, d, *J* = 8.3 Hz), 7.36 (2H, d, *J* = 8.3 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 6.69 (1H, dd, *J* = 7.5, 15.7 Hz), 5.12 (1H, dd, *J* = 0.8, 15.7 Hz), 4.78 (1H, dt, *J* = 4.2, 10.7 Hz), 4.66 (1H, t, *J* = 6.6 Hz), 2.27 (1H, app sep, *J* = 7.0 Hz), 1.73-1.96 (4H, m), 1.49-

1.58 (3H, m), 1.34-1.43 (1H, m), 1.23 (3H, s), 1.20 (9H, s), 1.14 (3H, s), 1.02 (3H, d, *J* = 6.7 Hz), 0.83-0.96 (3H, m), 0.79 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.1, 152.9, 149.9, 148.4, 147.5, 132.6, 126.7, 125.2, 124.8, 121.0, 118.9, 111.7, 74.8, 71.9, 50.8, 45.4, 41.9, 39.6, 34.8, 34.3, 33.4, 31.6, 31.5, 27.1, 26.9, 26.3, 22.0, 19.5; HRMS (FAB, MNa^+) calcd for $C_{34}H_{45}NO_3Na$: 538.3297. Found 538.3289.

2.205b: IR (neat, NaCl) 3482, 2952, 2221, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.54 (2H, d, *J* = 8.3 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.10 (2H, d, *J* = 8.4 Hz), 4.73 (1H, t, *J* = 4.1 Hz), 4.69 (1H, s), 4.65 (1H, s), 4.62 (1H, dt, *J* = 4.2, 10. 7 Hz), 2.56 (1H, app quin, *J* = 4.8 Hz), 2.49 (1H, d, *J* = 3.5 Hz), 2.34 (1H, dd, *J* = 9.6, 14.2 Hz), 1.97 (1H, dd, *J* = 5.9, 14.2 Hz), 1.78-1.87 (2H, m), 1.57 (3H, s), 1.38-1.48 (2H, m), 1.22 (9H, s), 1.19 (3H, s), 1.07-1.14 (1H, m), 1.09 (3H, s), 0.68-0.90 (3H, m), 0.74 (3H, d, *J* = 6.5 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.6, 148.0, 147.9, 146.4, 142.4, 132.1, 127.3, 125.1, 124.9, 118.7, 113.3, 11.6, 76.3, 73.9, 51.0, 50.1, 41.2, 39.5, 34.6, 34.4, 34.2, 31.4, 31.2, 27.3, 26.9, 26.0, 22.5, 21.7; HRMS (FAB, MNa^+) calcd for $C_{34}H_{45}NO_3Na$: 538.3297. Found 538.3279.



2.206a



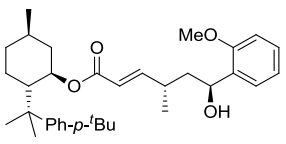
2.206b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-6-(4-hydroxyphenyl)-4-methylhex-2-enoate (2.206a) and (1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(hydroxy(4-hydroxyphenyl) methyl)-4-methylpent-4-enoate (2.206b): 4-Hydroxybenzaldehyde **2.206** (0.10 mmol, 0.012 g), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24

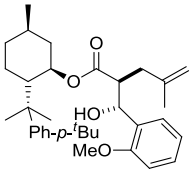
mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.206a** and **2.206b** as a viscous colorless liquid (rr, 6:1) (0.036 g, combined yield 70%).

2.206a: IR (neat, NaCl) 3369, 2958, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.17 (2H, d, *J* = 8.4 Hz), 7.09 (4H, d, *J* = 8.7 Hz), 6.71 (2H, d, *J* = 8.4 Hz), 6.70 (1H, dd, *J* = 7.5, 15.7 Hz), 5.8 (1H, brd s), 5.14 (1H, d, *J* = 15.7 Hz), 4.79 (1H, dt, *J* = 4.2, 10.6 Hz), 4.46 (1H, t, *J* = 7.1 Hz), 2.17 (1H, app sep, *J* = 7.1 Hz), 1.83-1.98 (3H, m), 1.73-1.80 (1H, m), 1.48-1.61 (3H, m), 1.33-1.44 (1H, m), 1.22 (9H, s), 1.20 (3H, s), 1.15 (3H, s), 0.97 (3H, d, *J* = 6.7 Hz), 0.77-0.80 (3H, m), 0.79 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.6, 155.7, 153.9, 148.4, 147.7, 136.3, 127.6, 125.3, 124.9, 120.6, 115.7, 74.9, 72.2, 50.8, 45.1, 42.0, 39.7, 34.8, 34.4, 33.5, 31.8, 31.5, 27.0, 26.8, 21.3, 19.6; HRMS (FAB, MNa^{+}) calcd for $C_{33}H_{46}O_4Na$: 529.3294. Found 529.3300.

2.206b: IR (neat, NaCl) 3476, 2949, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.29 (2H, d, *J* = 8.5 Hz), 7.17 (4H, d, *J* = 8.5 Hz), 6.78 (2H, d, *J* = 8.5 Hz), 4.77 (2H, s), 4.72 (1H, d, *J* = 5.9 Hz), 4.65 (1H, dt, *J* = 4.1, 10.6 Hz), 2.71 (1H, ddd, *J* = 4.2, 5.9, 10.1 Hz), 2.46 (1H, dd, *J* = 10.2, 14.0 Hz), 2.23 (1H, dd, *J* = 3.8, 14.1 Hz), 1.76-1.97 (2H, m), 1.70 (3H, s), 1.34-1.65 (3H, m), 1.31 (9H, s), 1.27 (6H, s), 1.09-1.22 (2H, m), 0.81-1.01 (3H, m), 0.77 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 173.3, 155.5, 148.04, 148.0, 143.2, 133.6, 128.3, 125.4, 124.9, 115.2, 113.2, 76.0, 74.9, 51.9, 50.3, 41.0, 39.8, 35.6, 34.6, 34.4, 31.6, 31.3, 28.6, 27.2, 25.2, 22.7, 21.9.



2.207a



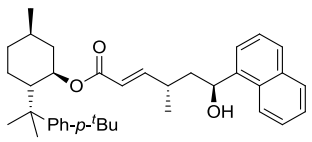
2.207b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-6-(2-methoxyphenyl)-4-methylhex-2-enoate (2.207a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(hydroxy(2-methoxyphenyl)methyl)-4-methylpent-4-enoate (2.207b): 2-Methoxybenzaldehyde **2.207** (0.10 mmol, 0.014 g), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.207a** and **2.207b** as a colorless liquid (rr, 12:1) (0.039 g, combined yield 75%).

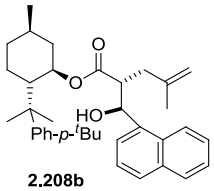
2.207a: IR (neat, NaCl) 3472, 2960, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.14-7.21 (4H, m), 7.10 (2H, d, *J* = 8.4 Hz), 6.87 (1H, t, *J* = 7.4 Hz), 6.79 (1H, t, J = 7.4 Hz), 6.75 (1H, dd, *J* = 7.8, 15.7 Hz), 5.20 (1H, d, *J* = 15.7 Hz), 4.78 (1H, dt, *J* = 4.3, 10.6 Hz), 4.74-4.83 (1H, m), 3.76 (3H, s), 2.44 (1H, brd s), 2.37 (1H, app sep, *J* = 6.8 Hz), 1.79-1.94 (3H, m), 1.32-1.67 (4H, m), 1.23 (9H, s), 1.21 (3H, s), 1.15 (3H, s), 1.02 (3H, d, *J* = 6.7 Hz), 0.81-0.96 (3H, m), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.4, 156.7,154.2, 148.4, 147.7, 132.2, 128.7,127.1, 125.3, 124.8, 121.0, 120.3, 110.7, 74.5, 69.0, 55.4, 50.8, 43.6, 42.0, 39.7, 34.8, 34.3, 33.5, 31.6, 31.5, 27.0, 26.9, 26.7, 22.0, 19.0; HRMS (FAB, MNa^+) calcd for $C_{34}H_{48}O_4Na$: 543.3450. Found 543.3442.

2.207b: ^1H NMR ($CDCl_3$): δ 7.12-7.24 (4H, m), 7.09 (2H, d, *J* = 8.4 Hz), 6.71-6.95 (3H, m), 4.91 (1H, d, *J* = 5.7 Hz), 4.78 (1H, s), 4.72 (1H, s), 4.64 (1H, dt, *J* = 4.3, 10.7 Hz),

3.78 (3H, s), 3.02 (1H, q, *J* = 7.5 Hz), 2.30 (1H, dd, *J* = 8.0, 14.0 Hz), 2.16 (1H, dd, *J* = 7.1, 14.0 Hz), 1.64 (3H, s), 1.29-1.58 (4H, m), 1.23 (9H, s), 1.21 (3H, s), 1.12 (3H, s), 0.73-0.89 (4H, m), 0.67 (3H, d, *J* = 6.4 Hz).



2.208a



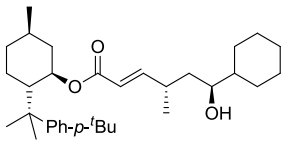
2.208b

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenylpropan-2-yl)-5-methylcyclohexyl-6-hydroxy-4-methyl-6-(naphthalene-1-yl)hex-2-enoate (2.208a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(hydroxy(naphthalene-1-yl)-methyl)-4-methylpent-4-enoate (2.208b): 2-Naphthaldehyde **2.208** (0.10 mmol, 14 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.2 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.208a** and **2.208b** as a colorless liquid (rr, 6:1) (0.041 g, combined yield 76%).

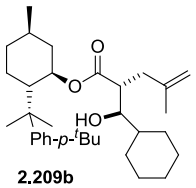
2.208a: IR (neat, NaCl) 3469, 2955, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.01 (1H, d, *J* = 8.2 Hz), 7.77 (1H, d, *J* = 7.1 Hz), 7.69 (1H, d, *J* = 8.2 Hz), 7.55 (1H, d, *J* = 7.1 Hz), 7.35-7.45 (3H, m), 7.15 (2H, d, *J* = 8.4 Hz), 7.06 (2H, d, *J* = 8.4 Hz), 6.75 (1H, dd, *J* = 7.8, 15.7 Hz), 5.41 (1H, dd, *J* = 4.6, 8.8 Hz), 5.19 (1H, d, *J* = 15.7 Hz), 4.76 (1H, dt, *J* = 4.2, 10.7 Hz), 2.49 (1H, app sep, *J* = 6.7 Hz), 1.74-1.95 (5H, m), 1.47-1.52 (2H, m), 1.31-1.43 (1H, m), 1.20 (9H, s), 1.19 (3H, s), 1.13 (3H, s), 1.10 (3H, d, *J* = 7.8 Hz), 0.86-0.94 (2H, m), 0.73-0.80 (1H, m), 0.77 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.2, 153.7,148.4, 147.6, 140.3, 134.0,130.4, 129.1, 128.3, 126.2, 125.7, 125.6, 125.2, 124.8,

123.2, 120.5, 74.6, 69.2, 50.8, 44.5, 41.9, 39.6, 34.8, 34.3, 33.7, 31.6, 31.4, 26.9, 26.8, 26.7, 22.0, 19.0; HRMS (FAB, MNa^+) calcd for $C_{37}H_{48}O_3Na$: 563.3501. Found 563.3495.

2.208b: IR (neat, NaCl) 3456, 2962, 1720 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10 (1H, d, *J* = 8.2 Hz), 7.89 (1H, d, *J* = 7.1 Hz), 7.81 (1H, d, *J* = 8.2 Hz), 7.70 (1H, d, *J* = 7.1 Hz), 7.44-7.63 (3H, m), 7.30 (2H, d, *J* = 8.4 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 5.71 (1H, t, *J* = 4.0 Hz), 4.70 (2H, s), 4.73 (1H, dt, *J* = 4.3, 10.7 Hz), 3.03-3.08 (1H, m), 2.62 (1H, dd, *J* = 10.6, 14.3 Hz), 2.44 (1H, d, *J* = 3.1 Hz), 2.26 (1H, dd, *J* = 3.1, 14.3 Hz), 1.79-1.86 (1H, m), 1.57 (3H, s), 1.40-1.50 (3H, m), 1.34 (3H, s), 1.30 (9H, s), 1.28-1.34 (2H, m), 1.20 (3H, s), 0.86-0.98 (2H, m), 0.72 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 173.6, 148.0, 147.8, 143.3, 137.0, 134.0, 130.5, 129.3, 128.6, 126.5, 125.8, 125.5, 125.4, 125.0, 124.7, 123.2, 112.7, 76.1, 71.8, 50.9, 50.4, 41.1, 40.0, 34.7, 34.5, 31.6, 31.3. 29.4, 27.4, 24.8, 22.8, 21.9; HRMS (FAB, MNa^+) calcd for $C_{37}H_{48}O_3Na$: 563.3501. Found 563.3489.



2.209a

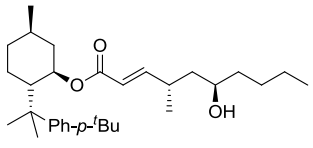


2.209b

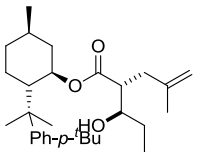
(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-cyclohexyl-6-hydroxy-4-methylhex-2-enoate (2.209a) and (1*R*,2*R*,5*R*)-2-(2-(4(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(cyclohexyl(hydroxy)methyl)-4-methylpent-4-enoate (2.209b): Cyclohexanecarboxaldehyde **2.209** (0.20 mmol, 24 μL), $Ni(acac)_2$ (0.02 mmol, 0.005 g), diethylzinc (1.0 M solution in hexanes, 0.48 mmol, 0.48 mL), and pentadienoate **2.195c** (0.40 mmol, 0.153 g) were reacted in dry THF (2 mL) following the general procedure of homoallylation to afford two regioisomers **2.209a** and **2.209b** as a colorless liquid (rr, 5:1) (0.062 g, combined yield 70%).

2.209a: IR (neat, NaCl) 3475, 2952, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.21 (2H, d, *J* = 8.4 Hz), 7.11 (2H, d, *J* = 8.4 Hz), 6.74 (1H, dd, *J* = 7.8, 15.7 Hz), 5.21 (1H, dd, *J* = 1.1, 15.7 Hz), 4.78 (1H, dt, *J* = 4.3, 10.7 Hz), 3.34 (1H, m), 2.36 (1H, app sep, *J* = 7.1 Hz), 1.81-1.94 (2H, m), 1.66-1.73 (3H, m), 1.47-1.61 (5H, m), 1.28-1.45 (5H, m), 1.24 (9H, s), 1.20-1.24 (1H, m), 1.22 (3H, s), 1.13-1.17 (1H, m), 1.15 (3H, s), 0.88-0.98 (4H, m), 0.97 (3H, d, *J* = 6.8 Hz), 0.73-0.79 (1H, m), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 154.5, 148.5, 147.7, 125.3, 124.9, 120.0, 74.6, 73.8, 50.8, 44.2, 42.0, 40.6, 39.7, 34.8, 34.4, 33.4, 31.6, 31.5, 29.4, 27.7, 26.7, 26.5, 26.4, 22.0, 18.7; HRMS (FAB, MNa^{+}) calcd for $C_{33}H_{52}O_3Na$: 519.3814. Found 519.3816.

2.209b: IR (neat, NaCl) 3436, 2957, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.21 (2H, d, *J* = 8.4 Hz), 7.11 (2H, d, *J* = 8.4 Hz), 4.70 (1H, dt, *J* = 4.1, 10.7 Hz), 4.70 (2H, s), 3.37 (1H, t, *J* = 7.4 Hz), 2.28-2.54 (1H, m), 2.37 (1H, app dd, *J* = 10.8, 14.1 Hz), 2.07-2.14 (1H, m), 1.81-1.97 (4H, m), 1.67 (3H, s), 1.59-1.73 (3H, m), 1.42-1.49 (4H, m), 1.27-1.37 (2H, m), 1.23 (9H, s), 1.22 (3H, s), 1.13 (3H, s), 1.07-1.14 (3H, m), 0.84-1.03 (4H, m), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 174.5, 147.9, 143.6, 125.4, 124.9, 112.8, 77.4, 76.1, 50.4, 47.3, 41.6, 40.8, 39.9, 34.8, 34.4, 34.3, 31.6, 31.5, 29.7, 28.9, 28.1, 27.4, 26.5, 26.4, 26.1, 25.0, 23.0, 22.0; HRMS (FAB, MNa^{+}) calcd for $C_{33}H_{52}O_3Na$: 519.3814. Found 519.3822.



2.210a



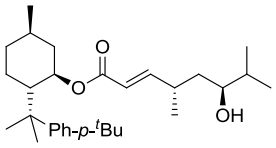
2.210b

(4*S*,6*R*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-4-methyldec-2-enoate (2.210a) and (1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-

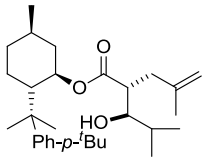
butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-3-hydroxy-2-(2-methylallyl) heptanoate (2.210b): Pentanal **2.210** (0.10 mmol, 11 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.210a** and **2.210b** as a colorless liquid (rr, 2:1) (0.037 g, combined yield 79%).

2.210a: IR (neat, NaCl) 3471, 2965, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (2H, d, *J* = 8.5 Hz), 7.10 (2H, d, *J* = 8.5 Hz), 6.71 (1H, dd, *J* = 7.9, 15.7 Hz), 5.19 (1H, dd, *J* = 0.9, 15.7 Hz), 4.78 (1H, dt, *J* = 4.3, 10.6 Hz), 3.52-3.58 (1H, m), 2.38 (1H, app sep, *J* = 7.1 Hz), 1.83-1.97 (2H, m), 1.12-1.55 (14H, m), 1.24 (9H, s), 1.22 (3H, s), 1.15 (3H, s), 0.75-1.03 (4H, m), 0.98 (3H, d, *J* = 6.8 Hz), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.3, 154.2, 148.5, 147.7, 125.3, 124.9, 120.2, 74.6, 69.7, 50.8, 43.8, 42.0, 39.7, 37.7, 34.8, 34.4, 33.5, 31.7, 31.5, 27.9, 27.0, 26.9, 26.6, 22.9, 22.0, 19.2; HRMS (FAB, MNa^+) calcd for $C_{31}H_{50}O_3Na$: 493.3658. Found 493.3662.

2.210b: IR (neat, NaCl) 3474, 2969, 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22 (2H, d, *J* = 8.5 Hz), 7.11 (2H, d, *J* = 8.5 Hz), 4.73 (1H, dt, *J* = 4.1, 10.8 Hz), 4.70 (1H, s), 4.67 (1H, s), 3.45-3.55 (1H, m), 2.18-2.36 (2H, m), 1.86-2.07 (4H, m), 1.65 (3H, s), 1.10-1.53 (8H, m), 1.23 (12H, s), 1.10 (3H, s), 0.68-0.98 (7H, m), 0.77 (3H, d, *J* = 6.6 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 173.7, 148.2, 148.0, 143.3, 125.3, 125.0, 112.7, 76.0, 72.4, 50.5, 49.7, 41.7, 39.7, 35.0, 34.8, 34.4, 33.7, 31.6, 31.5, 28.4, 27.6, 27.2, 26.2, 22.8, 22.0, 14.2; HRMS (FAB, MNa^+) calcd for $C_{31}H_{50}O_3Na$: 493.3658. Found 493.3666.



2.211a



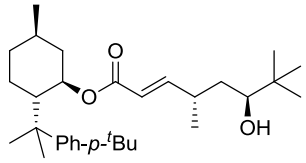
2.211b

(4*S*,6*R*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-4,7-dimethyloct-2-enoate (2.211a) and (1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-(1-hydroxy-2-methylpropyl)-4-methylpent-4-enoate (2.211b): 2-Methylpropanal **2.211** (0.10 mmol, 9 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford two regioisomers **2.211a** and **2.211b** as a colorless liquid (rr, 6:1) (0.035 g, combined yield 76%).

2.211a: IR (neat, NaCl) 3505, 2950, 1703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19 (2H, d, *J* = 8.5 Hz), 7.10 (2H, d, *J* = 8.5 Hz), 6.73 (1H, dd, *J* = 7.8, 15.7 Hz), 5.22 (1H, dd, *J* = 1.1, 15.7 Hz), 4.78 (1H, dt, *J* = 4.3, 10.7 Hz), 3.32-3.41 (1H, m), 2.40 (1H, app sep, *J* = 6.9 Hz), 1.83-1.94 (2H, m), 1.49-1.60 (3H, m), 1.36-1.48 (2H, m), 1.27-1.33 (3H, m), 1.24 (9H, s), 1.23 (3H, s), 0.98 (3H, d, *J* = 6.7 Hz), 0.73-0.88 (2H, m), 0.83 (3H, d, *J* = 6.7 Hz), 0.82 (3H, d, *J* = 6.7 Hz), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.3, 154.4, 148.5, 147.6, 125.3, 124.8, 120.0, 74.6, 74.2, 50.8, 42.0, 40.6, 39.7, 34.8, 34.4, 34.0, 33.5, 31.6, 31.5, 27.0, 26.8, 26.7, 22.0, 18.9, 18.8, 17.1; HRMS (FAB, MNa^+) calcd for $C_{30}H_{48}O_3Na$: 479.3501. Found 479.3505.

2.211b: IR (neat, NaCl) 3456, 2958, 1710 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20 (2H, d, *J* = 8.5 Hz), 7.11 (2H, d, *J* = 8.5 Hz), 4.70 (1H, dt, *J* = 4.1, 10.8 Hz), 4.71 (1H, s), 4.70 (1H, s), 3.33 (1H, app q, *J* = 4.6 Hz), 2.48-2.54 (1H, m), 2.36 (1H, dd, *J* = 10.6, 14.1 Hz), 2.12

(1H, dd, *J* = 2.9, 14.1 Hz), 1.86-1.98 (4H, m), 1.67 (3H, s), 1.59-1.63 (1H, m), 1.19-1.44 (3H, m), 1.25 (3H, s), 1.23 (9H, s), 1.13 (3H, s), 0.74-0.94 (2H, m), 0.90 (3H, d, *J* = 6.6 Hz), 0.82 (3H, d, *J* = 6.8 Hz), 0.78 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 174.4, 148.1, 148.0, 143.6, 125.5, 125.0, 112.9, 77.8, 76.2, 50.5, 47.9, 41.5, 40.0, 34.9, 34.3, 31.6, 31.5, 31.4, 29.0, 27.5, 25.0, 23.0, 22.0, 19.8, 17.9; HRMS (FAB, MNa^+) calcd for $C_{30}H_{48}O_3Na$: 479.3501. Found 479.3520.

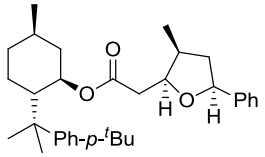


2.212a

(4*S*,6*S*,*E*)-(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-hydroxy-4,7,7-trimethylhept-2-enoate (2.212a): 2,2-Dimethylpropanaldehyde **2.212** (0.10 mmol, 11 μL), $Ni(acac)_2$ (0.01 mmol, 0.003 g), diethylzinc (1.0 M solution in hexanes, 0.24 mmol, 0.24 mL), and pentadienoate **2.195c** (0.20 mmol, 0.076 g) were reacted in dry THF (1 mL) following the general procedure of homoallylation to afford single regioisomer **2.212a** as a colorless liquid (0.033 g, 70%).

IR (neat, NaCl) 3501, 2957, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.29 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 6.85 (1H, dd, *J* = 7.6, 15.7 Hz), 5.35 (1H, d, *J* = 15.7 Hz), 4.88 (1H, dt, *J* = 4.3, 10.7 Hz), 3.30 (1H, app dd, *J* = 3.5, 8.5 Hz), 2.51 (1H, app sep, *J* = 7.0 Hz), 1.93-2.04 (2H, m), 1.54-1.63 (2H, m), 1.40-1.47 (4H, m), 1.33 (9H, s), 1.32 (3H, s), 1.25 (3H, s), 1.07 (3H, d, *J* = 6.7 Hz), 0.98-1.06 (2H, m), 0.90 (9H, s), 0.85-0.89 (1H, m), 0.88 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 166.4, 154.7, 148.5, 147.7, 125.3, 124.9, 119.8, 77.4, 74.6, 50.8, 42.0, 39.7, 38.0, 35.1, 34.8, 34.4, 33.6, 31.6, 31.5, 27.0,

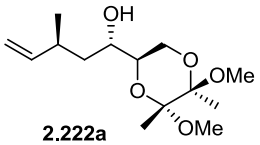
26.8, 25.8, 22.0, 18.3; HRMS (FAB, MNa^+) calcd for $C_{31}H_{50}O_3Na$: 493.3658. Found 493.3651.



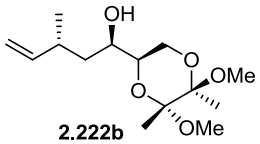
2.213

(1*R*,2*R*,5*R*)-2-(2-(4-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-2-((2*R*,3*S*,5*S*)-3-methyl-5-phenyltetrahydrofuran-2-yl)acetate (2.213): To a stirred solution of *bis*-homoallylic alcohol **2.200a** (0.035 mmol, 0.017 g) in freshly distilled CH_2Cl_2 at 0 ^oC was added 1,8-diazabicyclo[5.4.0]-undec-7-ene, DBU (0.038 mmol, 6 μL). The resulting solution was stirred at 0 ^oC for 1 h and then at room temperature for another 1h (TLC analysis). The reaction was quenched with few drops of saturated aq. NH_4Cl solution and extracted with EtOAc (5 mL, 3X). The combined organic layers were separated and washed with brine solution (5 mL, 1X), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to afford **2.213** as a colorless liquid (0.016 g, 94%).

IR (neat, NaCl) 2958, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): (major isomer) δ 7.22-7.32 (9H, m), 4.94 (1H, dd, *J* = 6.2, 9.6 Hz), 4.86 (1H, dt, *J* = 4.3, 10.7 Hz), 3.88-3.95 (1H, m), 2.48 (1H, app quin, *J* = 3.1 Hz), 2.00-2.07 (4H, m), 1.94 (1H, dd, *J* = 7.7, 15.2 Hz), 1.71-1.75 (1H, m), 1.63-1.69 (1H, m), 1.45-1.53 (2H, m), 1.34 (9H, s), 1.32 (3H, s), 1.22 (3H, s), 0.94-1.16 (3H, s), 1.03 (3H, d, *J* = 6.5 Hz), 0.86 (3H, d, *J* = 6.6 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 171.1, 148.8, 147.6, 144.1, 128.4, 127.1, 125.5, 125.2, 124.9, 82.3, 79.7, 74.6, 50.4, 44.5, 42.0, 40.6, 39.6, 39.4, 34.8, 34.4, 31.6, 31.5, 28.6, 26.7, 24.8, 22.0, 16.7; HRMS (FAB, MNa^+) calcd for $C_{33}H_{46}O_3Na$: 513.3344. Found 513.3348.



2.222a

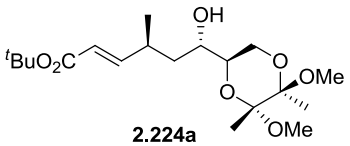


2.222b

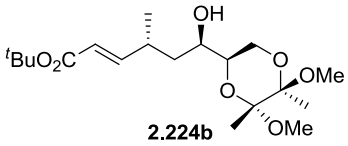
(1*S*,3*S*)-1-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methylpent-4-en-1-ol (2.222a) and (1*R*,3*R*)-1-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methylpent-4-en-1-ol (2.222b): $Ni(acac)_2$ (0.008 g, 0.030 mmol), isoprene (0.12 mL, 1.200 mmol), *R*-aldehyde **2.216** (0.061 g, 0.300 mmol), Et_3B (1.0 M solution in hexanes, 0.720 mmol) were reacted in dry THF (2 mL) following the general procedure for homoallylation to afford two diastereomers **2.222a** and **2.222b** as a colorless liquid (dr 3:1) (0.047 g, combined yield 57%).

2.222a: IR (neat, NaCl) 3464, 2941, 1120 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.77 (1H, ddd, *J* = 7.9, 10.2, 17.7 Hz), 4.92-5.06 (2H, m), 3.71-3.86 (3H, m), 3.55 (1H, dd, *J* = 1.7, 10.1 Hz), 3.26 (6H, s), 2.35 (1H, app sep, *J* = 7.2 Hz), 2.20 (1H, d, *J* = 2.5 Hz), 1.38-1.48 (2H, m), 1.29 (6H, s), 1.01 (3H, d, *J* = 6.7 Hz), ^{13}C {^1H} NMR ($CDCl_3$): δ 144.8, 113.0, 99.3, 97.9, 70.3, 69.6, 59.3, 48.0, 38.9, 35.0, 19.9, 17.8, 17.6; HRMS (FAB, MNa) calcd for $C_{14}H_{26}O_5Na$: 297.1678. Found 297.1689.

2.222b: IR (neat, NaCl) 3489, 2966, 1135 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.75 (1H, ddd, *J* = 7.3, 10.3, 17.4 Hz), 4.89-5.01(2H, m), 3.66-3.78 (2H, m), 3.49-3.61 (1H, m), 3.42 (1H, dd, *J* = 1.4, 9.4 Hz), 3.27 (3H, s), 3.26 (3H, s), 2.41 (1H, app sep, *J* = 6.9 Hz), 2.38 (1H, d, *J* = 5.2 Hz), 1.55-1.64 (1H, m), 1.30 (3H, s), 1.28 (3H, s), 1.15-1.1.23 (1H, m), 1.00 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 144.8, 112.7, 99.3, 98.1, 70.4, 68.8, 60.6, 48.3, 39.4, 33.9, 19.2, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{14}H_{26}O_5Na$: 297.1678. Found 297.1672.



2.224a



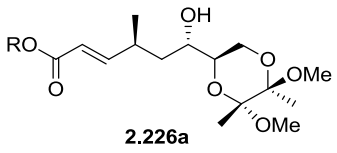
2.224b

(4*S*,6*S*,*E*)-*tert*-butyl-6-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.224a) and (4*R*,6*R*,*E*)-*tert*-butyl-6-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.224b): $Ni(acac)_2$ (0.006 g, 0.025 mmol), pentadienoate **2.223** (0.084 g, 0.500 mmol), *R*-aldehyde **2.216** (0.051 g, 0.250 mmol), and $ZnEt_2$ (1.0 M solution in hexane, 0.620 mmol) were reacted in dry THF (1.5 mL) following the general procedure for homoallylation to afford two diastereomers **2.224a** and **2.224b** as a colorless liquid (dr 3:1) (0.041 g, combined yield 44%).

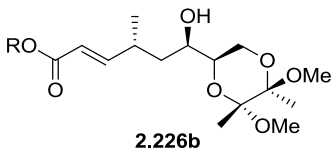
2.224a IR (neat, NaCl) 3478, 2946, 1707, 1641 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.81 (1H, dd, *J* = 7.7, 15.7 Hz), 5.73 (1H, dd, *J* = 1.2, 15.7 Hz), 3.70-3.85 (3H, m), 3.53 (1H, dd, *J* = 1.7, 10.1 Hz), 3.26 (6H, s), 2.55 (1H, app sep, *J* = 6.8 Hz), s), 2.06 (1H, d, *J* = 2.6 Hz), 1.47 (9H, s), 1.40-1.50 (1H, m), 1.28 (6H, s), 1.25-1.32 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz), ^{13}C {^1H} NMR ($CDCl_3$): δ 166.4, 153.0, 121.5, 99.5, 98.1, 80.4, 69.9, 69.6, 59.3, 48.3, 48.2, 38.3, 32.9, 28.3 (3C), 18.6, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{19}H_{34}O_7Na$: 397.2202. Found 397.2200.

2.224b IR (neat, NaCl) 3486, 2969, 1707, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.83 (1H, dd, *J* = 7.3, 15.7 Hz), 5.73 (1H, dd, *J* = 1.3, 15.7 Hz), 3.68-3.74 (2H, m), 3.57-3.63 (1H, m), 3.44 (1H, dd, *J* = 1.8, 6.2 Hz), 3.29 (3H, s), 3.28 (3H, s), 2.59-2.66 (1H, m), 2.37 (1H, d, *J* = 5.3 Hz), 1.67-1.75 (1H, m), 1.49 (9H, s), 1.32 (3H, s), 1.30 (3H, s), 1.14-1.23 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.5, 153.2, 121.4, 99.4, 98.2,

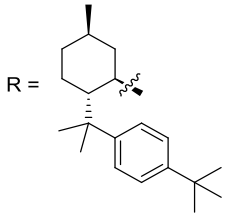
80.4, 70.6, 68.4, 60.6, 48.3 (2C), 38.8, 32.3, 28.4 (3C), 18.2, 18.0, 17.7. HRMS (FAB, MNa) calcd for $C_{19}H_{34}O_7Na$: 397.2202. Found 397.2209.



2.226a



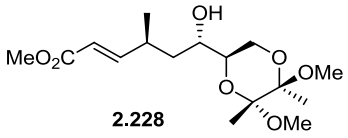
2.226b



(4*S*,6*S*,*E*)-(1R,2S,5R)-2-(2-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.226a) and (4*R*,6*R*,*E*)-(1R,2S,5R)-2-(2-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.226b): $Ni(acac)_2$ (0.003 g, 0.010 mmol), chiral pentadienoate **2.225** (0.076 g, 0.200 mmol), aldehyde **2.216** (0.020 g, 0.100 mmol), and Et_2Zn (1.0 M solution in hexanes, 0.240 mmol) were reacted in dry THF (1 mL) following the general procedure for homoallylation to afford two diastereomers **2.226a** and **2.226b** as a colorless liquid (dr 5:1) (0.041 g, combined yield 69%).

2.226a: IR (neat, NaCl) 3517, 2970, 1711, 1642 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (2H, d, *J* = 8.5 Hz), 7.17 (2H, d, *J* = 8.5 Hz), 6.78 (1H, dd, *J* = 8.0, 15.7 Hz), 5.30 (1H, dd, *J* = 0.7, 15.7 Hz), 4.85 (1H, dt, *J* = 4.3, 10.6 Hz), 3.69-3.85 (3H, m), 3.51 (1H, dd, *J* = 1.8, 10.3 Hz), 3.26 (3H, s), 3.25 (3H, s), 2.48 (1H, app sep, *J* = 7.1 Hz), 1.90-2.01 (3H, m), 1.48-1.62 (3H, m), 1.43-1.48 (3H, m), 1.31 (9H, s), 1.30 (3H, s), 1.29 (6H, s), 1.22 (3H, s), 1.06 (3H, d, *J* = 6.6 Hz), 0.89-1.02 (2H, m), 0.86 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.2, 153.7, 148.4, 147.7, 125.3, 124.8, 120.4, 99.5, 98.1, 74.6, 69.9, 69.6, 59.3, 50.8, 48.23, 48.21, 41.9, 39.6, 38.3, 34.8, 34.4, 33.2, 31.6, 31.5, 26.9, 26.7, 22.0, 18.7, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{35}H_{56}O_7Na$: 611.3924. Found 611.3934.

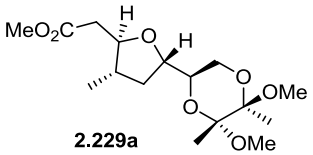
2.226b: IR (neat, NaCl) 3468, 2945, 1711, 1646 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (2H, d, *J* = 8.2 Hz), 7.18 (2H, d, *J* = 8.5 Hz), 6.81 (1H, dd, *J* = 7.4, 15.7 Hz), 5.35 (1H, dd, *J* = 1.1, 15.7 Hz), 4.86 (1H, dt, *J* = 4.3, 10.7 Hz), 3.70-3.73 (2H, m), 3.52-3.60 (1H, m), 3.39-3.44 (1H, m), 3.29 (3H, s), 3.28 (3H, s), 2.55-2.61 (1H, m), 2.36 (1H, broad J = 3.3 Hz), 1.92-2.00 (2H, m), 1.40-1.64 (6H, m), 1.32 (9H, s), 1.31 (6H, s), 1.26 (3H, s), 1.23 (3H, s), 0.96-1.09 (2H, m), 1.02 (3H, d, *J* = 6.7 Hz), 0.86 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.4, 154.0, 148.3, 147.7, 125.3, 124.9, 120.1, 99.3, 98.2, 74.7, 70.7, 68.3, 60.5, 50.8, 48.3, 42.0, 39.7, 38.6, 34.8, 34.4, 32.2, 31.6, 31.5, 29.9, 27.3, 27.0, 22.0, 18.01, 17.96, 17.7.



2.228

(4*S*,6*S*,*E*)-methyl-6-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.228): Grubbs second generation catalyst (0.024 g, 0.028 mmol), copper iodide (0.008 g, 0.040 mmol), *bis*-homoallylic alcohol **2.222a** (0.110 g, 0.400 mmol) and methyl acrylate **2.227** (0.11 mL, 1.200 mmol) were reacted in dry CH_2Cl_2 (4 mL) following the general procedure to afford **2.228** as a colorless liquid (0.088 g, 66%).

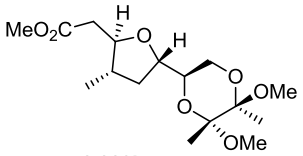
IR (neat, NaCl) 3468, 2941, 1728, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.92 (1H, dd, *J* = 7.7, 15.7 Hz), 5.80 (1H, dd, *J* = 1.2, 15.7 Hz), 3.69-3.84 (3H, m), 3.71 (3H, s), 3.52 (1H, dd, *J* = 1.8, 10.1 Hz), 3.25 (6H, s), 2.58 (1H, app sep, *J* = 6.7 Hz), 2.20 (1H, d, *J* = 3.1 Hz), 1.45-1.51 (2H, m), 1.271 (3H, s), 1.270 (3H, s), 1.07 (3H, d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 167.4, 154.6, 119.3, 99.4, 98.1, 70.0, 69.5, 59.3, 51.6, 48.22, 48.17, 38.2, 33.1, 18.5, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1728.



2.229a

Methyl-2-((2*R*,3*S*,5*S*)-5-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methyltetrahydrofuran-2-yl)acetate (2.229a): To a small piece of sodium under argon was added 0.5 mL of dry methanol and then a solution of **2.228** (0.076 g, 0.23 mmol) in dry methanol was added on it. TLC analysis after 10 min showed the reaction was complete. Ethyl acetate (5 mL) was added followed by 0.5 mL of saturated aq. NH_4Cl solution, the layers separated, the aq. layer extracted with EtOAc (5 mL, 3X), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to isolate **2.229a** as a colorless liquid (0.061 g, 81 %).

IR (neat, NaCl) 2953, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69-3.89 (3H, m), 3.66 (3H, s), 3.52-3.65 (2H, m), 3.26 (3H, s), 3.24 (3H, s), 2.50 (1H, dd, *J* = 4.5, 14.9 Hz), 2.41 (1H, dd, *J* = 7.9, 14. 9 Hz), 2.31 (1H, td, *J* = 7.1, 12. 4 Hz), 1.83-1.94 (1H, m), 1.43-1.54 (1H, m) , 1.26 (6H, s), 1.02 (3H, d, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 99.1, 98.1, 81.9, 77.6, 70.3, 62.1, 51.8, 48.11, 48.06, 39.6, 39.2, 38.0, 18.0, 17.7, 16.6; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1736. Optical rotation: -135.5 (c = 0.65, $CHCl_3$).



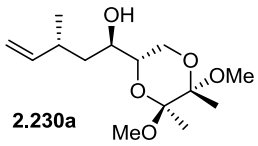
2.229b

Methyl-2-((2*R*,3*S*,5*S*)-5-((2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methyltetrahydrofuran-2-yl)acetate (2.229b): To a small piece of sodium under argon was added 0.5 mL of dry methanol and then a solution of **2.226a** (0.011 g, 0.019 mmol)

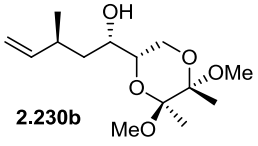
in dry methanol was added. After stirring for 10 min at rt., the reaction mixture was refluxed for a total 2 h. The mixture was then cooled down to rt, diluted with 5 mL EtOAc and acidified with 1M HCl (pH 0-1), the layers separated, the aq. layer extracted with EtOAc (5 mL, 3X), the combined organic layers were with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. To this crude product was added 0.5 mL each of dry methanol and dry ether and stirred for 2 minutes at rt before adding 10 μL of TMS diazomethane (2.0 M solution in diethyl ether). The reaction was complete in 20 min (TLC analysis). The solvents were evaporated and the crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to give **2.229a** as a colorless liquid (0.005 g, 79 %).

IR, proton and carbon spectra: same as **2.229a**

Optical rotation: -116.1 (c = 0.15, $CHCl_3$)



2.230a



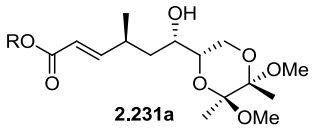
2.230b

(1*R*,3*R*)-1-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methylpent-4-en-1-ol (2.230a) and (1*S*,3*S*)-1-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methylpent-4-en-1-ol (2.230b): $Ni(acac)_2$ (0.026 g, 0.10 mmol), isoprene (0.4 mL, 4.00 mmol), aldehyde **2.221** (0.204 g, 1.00 mmol), and Et_3B (1.0 M solution in hexanes, 2.40 mmol) were reacted in dry THF (5 mL) following the general procedure for homoallylation to afford two diastereomers **2.230a** and **2.230b** as a colorless liquid (dr 3:1) (0.274 g, combined yield 89%).

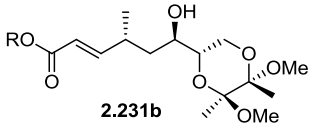
2.230a: IR (neat, NaCl) 3472, 2913, 1127 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.77 (1H, ddd, J = 7.9, 10.2, 17.5 Hz), 4.91-5.06 (2H, m), 3.70-3.85 (3H, m), 3.55 (1H, dd, J = 1.9, 10.2

Hz), 3.25 (6H, s), 2.34 (1H, app sep, *J* = 7.1 Hz), 2.21 (1H, broad s), 1.42-1.47 (2H, m), 1.28 (3H, s), 1.27 (3H, s), 1.01 (3H, d, *J* = 6.7 Hz), ^{13}C {^{1}H} NMR ($CDCl_3$): δ 145.0, 113.2, 99.4, 98.1, 70.4, 69.7, 59.5, 48.2, 39.0, 35.1, 20.1, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{14}H_{26}O_5Na$: 297.1678. Found 297.1670.

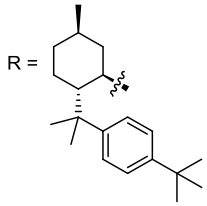
2.230b: IR (neat, NaCl) 3575, 2970, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.76 (1H, ddd, *J* = 7.3, 10.3, 17.4 Hz), 4.89-5.02 (2H, m), 3.67-3.79 (2H, m), 3.55-3.60 (1H, m), 3.43 (1H, dd, *J* = 1.4, 9.4 Hz), 3.28 (3H, s), 3.26 (3H, s), 2.42 (1H, app sep, *J* = 7.2 Hz), 2.41 (1H, broad s), 1.55-1.65 (1H, m), 1.31 (3H, s), 1.28 (3H, s), 1.16-1.26 (1H, m), 1.00 (3H, d, *J* = 6.7 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 144.8, 112.7, 99.3, 98.1, 70.4, 68.8, 60.6, 48.3, 39.4, 33.9, 19.2, 18.0, 17.7; HRMS (FAB, MNa) calcd for $C_{14}H_{26}O_5Na$: 297.1678. Found 297.1687.



2.231a



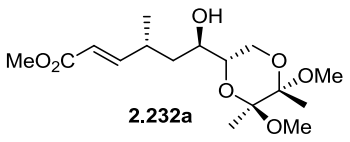
2.231b



(4*S*,6*S*,*E*)-(1R,2S,5R)-2-(2-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-((2*S*,5*S*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.231a) and (4*R*,6*R*,*E*)-(1R,2S,5R)-2-(2-(*tert*-butyl)phenyl)propan-2-yl)-5-methylcyclohexyl-6-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.231b): $Ni(acac)_2$ (0.003 g, 0.010 mmol), chiral pentadienoate **2.225** (0.076 g, 0.200 mmol), aldehyde **2.221** (0.020 g, 0.100 mmol), and Et_2Zn (1.0 M solution in hexanes, 0.240 mmol) were reacted in dry THF (1 mL) following the general procedure for homoallylation to afford two diastereomers **2.231a** and **2.231b** as a colorless solid (dr 2:1) (0.031 g, combined yield 53%).

2.231a: IR (neat, NaCl) 3475, 2972, 1712, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 (2H, d, *J* = 8.5 Hz), 7.17 (2H, d, *J* = 8.6 Hz), 6.78 (1H, dd, *J* = 7.6, 15.7 Hz), 5.29 (1H, dd, *J* = 1.2, 15.7 Hz), 4.85 (1H, dt, *J* = 4.3, 10.7 Hz), 3.66-3.75 (2H, m), 3.50-3.59 (1H, m), 3.40-3.46 (1H, m), 3.27 (6H, s), 2.50-2.62 (1H, m), 2.32 (1H, brd d, J = 3.3 Hz), 1.90-2.01 (2H, m), 1.50-1.70 (6H, m), 1.31 (12H, s), 1.29 (6H, s), 1.22 (3H, s), 1.09-1.20 (1H, s), 1.05 (3H, d, *J* = 6.7 Hz), 0.89-1.02 (1H, m), 0.86 (3H, d, *J* = 6.3 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.4, 153.9, 148.5, 147.7, 125.4, 124.9, 120.3, 99.4, 98.2, 74.7, 70.6, 68.4, 60.6, 50.8, 48.3 (2H), 42.0, 39.7, 38.9, 34.9, 34.4, 32.5, 31.7, 31.5, 27.0, 26.9, 26.8, 22.0, 18.2, 18.0, 17.7; HRMS (FAB, MNa) calcd for $C_{35}H_{56}O_7Na$: 611.3924. Found 611.3928.

2.231b: IR (neat, NaCl) 3497, 2962, 1711, 1646 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.26 (2H, d, *J* = 8.5 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 6.82 (1H, dd, *J* = 7.7, 15.7 Hz), 5.39 (1H, dd, *J* = 1.0, 15.7 Hz), 4.86 (1H, dt, *J* = 4.3, 10.6 Hz), 3.71-3.86 (3H, m), 3.54 (1H, dd, *J* = 2.1, 10.5 Hz), 3.27 (6H, s), 2.53 (1H, app sep, *J* = 7.1 Hz), 1.92-2.03 (3H, m), 1.38-1.61 (6H, m), 1.31 (12H, s), 1.29 (6H, s), 1.22 (3H, s), 1.04 (3H, d, *J* = 6.7 Hz), 0.89-1.01 (2H, m), 0.85 (3H, d, *J* = 6.4 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 166.3, 154.0, 148.3, 147.8, 125.4, 124.9, 120.4, 99.6, 98.2, 74.8, 70.1, 69.6, 59.4, 50.9, 48.32, 48.26, 42.0, 39.8, 38.2, 34.9, 34.4, 33.0, 31.7, 31.5, 27.6, 27.1, 26.2, 22.0, 18.6, 17.9, 17.8; HRMS (FAB, MNa) calcd for $C_{35}H_{56}O_7Na$: 611.3824. Found 611.3929.

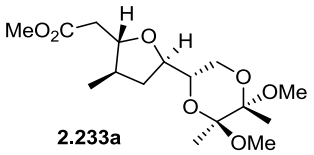


2.232a

(4*R*,6*R*,*E*)-methyl-6-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.232a): Grubbs second generation catalyst (0.023 g, 0.027 mmol), copper iodide (0.007 g, 0.038 mmol), *bis*-homoallylic alcohols **2.230a**

(0.104 g, 0.380 mmol), and methyl acrylate **2.227** (0.10 mL, 1.140 mmol) were reacted in dry CH_2Cl_2 (3 mL) following the general procedure to afford **2.232a** as a colorless oil (0.102 g, 81%).

IR (neat, NaCl) 3464, 2945, 1715, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.91 (1H, dd, *J* = 7.7, 15.7 Hz), 5.78 (1H, dd, *J* = 1.2, 15.7 Hz), 3.68-3.79 (3H, m), 3.71 (3H, s), 3.51 (1H, dd, *J* = 1.8, 10.1 Hz), 3.23 (6H, s), 2.56 (1H, app sep, *J* = 6.7 Hz), 2.26 (1H, d, *J* = 3.4 Hz), 1.44-1.50 (2H, m), 1.26 (3H, s), 1.25 (3H, s), 1.06 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 167.4, 154.7, 119.3, 99.4, 98.1, 70.0, 69.5, 59.4, 51.6, 48.2, 48.1, 38.2, 33.0, 18.5, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1729.

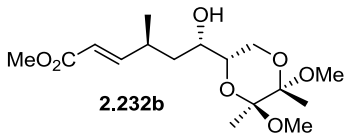


2.233a

Methyl-2-((2*S*,3*R*,5*R*)-5-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methyltetrahydrofuran-2-yl)acetate (2.233a): The unsaturated ester **2.232a** (0.100 g, 0.300 mmol) and DBU (49 μL, 0.330 mmol) were reacted in dry CH_2Cl_2 (2 mL) following the general procedure for cyclization to give **2.233a** as a colorless oil (0.094 g, 94%).

IR (neat, NaCl) 2962, 1736, 1113 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.69-3.87 (3H, m), 3.65 (3H, s), 3.52-3.64 (2H, m), 3.26 (3H, s), 3.23 (3H, s), 2.50 (1H, dd, *J* = 4.5, 14.9 Hz), 2.41 (1H, dd, *J* = 7.9, 14. 9 Hz), 2.29 (1H, td, *J* = 7.1, 12. 4 Hz), 1.83-1.94 (1H, m), 1.43-1.53 (1H, m) , 1.25 (6H, s), 1.02 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 171.8, 99.1, 98.1, 81.9, 77.6, 70.3, 62.0, 51.8, 48.1, 48.0, 39.6, 39.2, 38.0, 18.0, 17.7, 16.6; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1742.

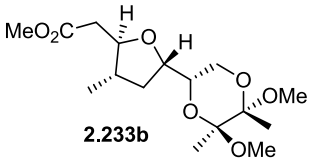
Optical rotation: + 124.6 (c = 0.65, $CHCl_3$).



2.232b

(4*S*,6*S*,*E*)-methyl-6-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-6-hydroxy-4-methylhex-2-enoate (2.232b): Grubbs second generation catalyst (0.009 g, 0.011 mmol), copper iodide (0.003 g, 0.015 mmol), *bis*-homoallylic alcohols **2.230b** (0.041 g, 0.150 mmol), and methyl acrylate **2.227** (0.04 mL, 0.450 mmol) were reacted in dry CH_2Cl_2 (2 mL) following the general procedure to afford **2.232b** as a colorless oil (0.039 g, 78%).

IR (neat, NaCl) 3460, 2948, 1711, 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.93 (1H, dd, *J* = 7.4, 15.7 Hz), 5.79 (1H, dd, *J* = 1.3, 15.7 Hz), 3.65-3.76 (2H, m), 3.71 (3H, s), 3.55-3.58 (1H, m), 3.41 (1H, dd, *J* = 1.9, 6.2 Hz), 3.27 (3H, s), 3.26 (3H, s), 2.60-2.69 (1H, m), 2.41 (1H broad d, *J* = 3.5 Hz), 1.64-1.73 (1H, m), 1.30 (3H, s), 1.28 (3H, s), 1.13-1.24 (1H, m), 1.06 (3H, d, *J* = 6.7 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 167.5, 154.7, 119.2, 99.3, 98.1, 70.6, 68.4, 60.5, 51.7, 48.3, 38.6, 32.5, 18.1, 17.9, 17.7; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1735.

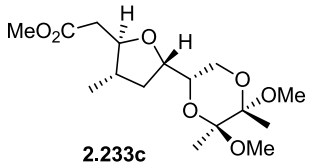


2.233b

Methyl-2-((2*R*,3*S*,5*S*)-5-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methyltetrahydrofuran-2-yl)acetate (2.233b): The unsaturated ester **2.232b** (0.026 g, 0.080 mmol) and DBU (13 μL, 0.088 mmol) were reacted in dry CH_2Cl_2 (1 mL) following the general procedure for cyclization to give **2.233b** as a colorless oil (0.025 g, 96%).

IR (neat, NaCl) 2954, 1728, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.88-3.97 (1H, m), 3.77-3.86 (2H, m), 3.64-3.71 (1H, m), 3.67 (3H, s), 3.37 (1H, dd, *J* = 2.8, 10.8 Hz), 3.28 (3H, s), 3.25 (3H, s), 2.55 (1H, dd, *J* = 6.9, 15.1Hz), 2.49 (1H, dd, *J* = 5.5, 15.1 Hz), 1.96-2.09 (1H, m), 1.88-1.94 (1H, m), 1.36-1.46 (1H, m), 1.29 (3H, s), 1.28 (3H, s), 1.03 (3H, d, *J* = 6.4 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.9, 99.2, 98.1, 81.5, 77.1, 70.0, 60.3, 51.8, 48.14, 48.09, 39.7, 39.1, 36.3, 18.0, 17.8, 16.5; HRMS (FAB, MNa) calcd for $C_{16}H_{28}O_7Na$: 355.1733. Found 355.1730.

Optical rotation: +138.8 (c = 0.35, $CHCl_3$)



2.233c

Methyl-2-((2*R*,3*S*,5*S*)-5-((2*S*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-3-methyltetrahydrofuran-2-yl)acetate (2.233c): To a small piece of sodium under argon was added 0.5 mL of dry methanol and then a solution of **2.231a** (0.015 g, 0.025 mmol) in dry methanol was added. After stirring for 10 min at rt, the reaction mixture was refluxed for a total 2 h. The mixture was then cooled to rt, diluted with 5 mL EtOAc and acidified with 1M HCl (pH 0-1), the layers separated, the aq. layer extracted with EtOAc (5 mL, 3X), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. To this crude product was added 0.5 mL each of dry methanol and dry ether and stirred for 2 minutes at rt before adding 10 μL of TMS diazomethane (2.0 M solution in diethyl ether). The reaction was complete in total 30 min (TLC analysis). The solvents were evaporated and the crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to isolate **2.233c** as colorless liquid (0.006 g, 75 %).

IR, proton and carbon spectra: same as **2.233b**

Optical rotation: +146.6 (c = 0.15, $CHCl_3$)

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CHAPTER III

Synthesis of Potent Inhibitors of YopH

3.1. General objective

Yersinia is the pathogenic bacteria causing human diseases ranging from gastrointestinal syndromes to bubonic plague.[1] *Yersinia pestis*, one of the three species of genus *Yersinia*, is responsible for the bubonic plague. Also known as the Black Death, bubonic plague killed millions of people in the 15th century in Europe.[2]

The pathogenicity of *Yersinia* depends on the activity of a bacterial virulence factor known as Yersinia outer membrane protein H (YopH).[3] YopH is homologous to eukaryotic protein tyrosine phosphatase (PTP) with potent tyrosine phosphatase activity.[4] In humans, protein tyrosine phosphatases (PTPs) constitute a large family of signaling enzymes. When YopH is secreted into the body, it disrupts signal transduction pathways by removing a phosphate group (dephosphorylation) from a variety of proteins including PTPs. This deregulates the PTP activity and decreases immune response. It has already been shown that blocking the YopH protein of this bacterium can render it avirulent. Therefore, the design and synthesis of potent and selective YopH inhibitors are of prime importance to serve as anti-plague agents. The general objective of this chapter of the thesis is to report the synthesis of YopH inhibitors and their activity against different PTPs including YopH.

3.2. Introduction

Among the three species of genus *Yersinia*; *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*, *Y. pestis* is the most virulent and was responsible for the bubonic, pneumonic, and septicemic plague.[5] Also known as the Black Death, the bubonic plague alone reduced the population of Europe by about 25 million in the 15th century.[2] The number of people killed by this bacterium during the course of human history approaches 200 million.[6] The plague had long been considered an eradicated disease until an outbreak in Surat, India.[7] Moreover, this pathogen could be misused as a biological weapon and an agent for mass destruction in warfare.[8] The World Health Organization (WHO) has recognized the plague as a re-emerging public health concern.

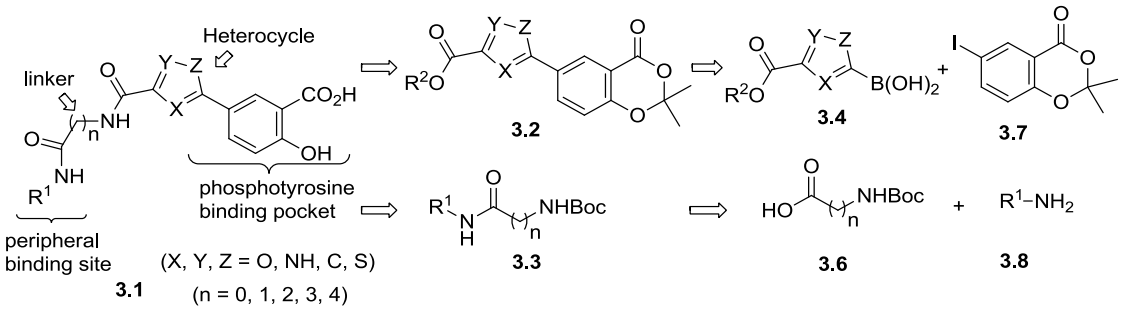
Y. pestis contains a plasmid that encodes several of the bacterial virulence factors known as Yersinia outer membrane proteins (Yops); YopE, YopH, YopM, YopJ/P, YopT, and YpkA. This bacterium utilizes a contact-dependent (type III) secretion apparatus to inject these six cytotoxic effectors into the cytosol of mammalian cells.[9] YopH, the most active virulence factor, is homologous to eukaryotic protein tyrosine phosphatase (PTP) and has potent tyrosine phosphatase activity.[4]

Protein tyrosine phosphatases (PTPs) constitute a large family of signaling enzymes which are involved in the regulation of various cell functions including cell-cell interactions, growth, metabolism, neuronal development, and the gene transcription, amongst others.[10] The opposing actions of protein tyrosine kinases (PTKs) and PTPs regulate the phosphorylation states of proteins *in vivo*: PTKs catalyze protein tyrosine phosphorylation and PTPs catalyze the dephosphorylation. Several PTKs, PTPs and tyrosine substrates form a family of signal transduction enzymes.

When YopH is injected into mammalian cells, it dephosphorylates a variety of proteins such as focal adhesion kinase and focal adhesion protein $p130^{Cas}$. This deregulates the human PTP activity, disrupts the signal transduction processes, and disarms the immune responses. In general, deregulation of PTP activity increases the risk of numerous diseases including diabetes, cancer, and immune system dysfunction, amongst others.

Since the PTPase activity is essential for the virulence of *Yersinia*,[4] YopH is a valid molecular target for antiplague therapeutics. The specific inhibitors targeted to the *Yersinia* PTPs are expected to make the bacteria avirulent. Therefore, the design and synthesis of potent and selective YopH inhibitors is of prime importance to stop the spread of *Y. pestis*, and hence to serve as anti-plague agents.

Based upon previous results,[11] a series of salicylic acid derived ligands (inhibitors) were designed (Scheme 3.1). These bidentate ligands were designed to achieve higher binding affinity and specificity, and thus were expected to increase the inhibitory activity against YopH protein of *Y. pestis*. In this chapter, we report the synthesis of a number of heterocyclic building blocks **3.2** and coupling them to a wide variety of amines **3.3** using parallel chemistry to obtain the desired inhibitors. We also include the activity of these inhibitors towards different types of phosphotases, YopH of *Y. pestis*, PTP1B of humans, etc.



Scheme 3.1. General Design of YopH Inhibitors and Retrosynthetic Analysis

3.3. Background

3.3.1. *Yersinia* PTPase (YopH) and inhibitors design

YopH is a 51 kDa protein containing 468 amino acids. It is composed of two independently folded domains. The N-terminal domain (residues 1-130) binds tyrosine-phosphorylated proteins in a phosphoryl dependent manner.[12] The structure of N-terminal domain of YopH does not resemble those of eukaryotic PTPs such as Src homology 2 (SH2), nor does it bind phosphotyrosine in a similar manner.[13] The C-terminal catalytic domain (residues 164-468) is the center of the PPTase activity and is very similar to the structures of eukaryotic PTPs.[14]

The catalytic domain of *Yersinia* PTP (YopH) is only about 20% identical to the human PTP1B but it contains all of the invariant residues present in eukaryotic PTP.[15] The central feature of the *Yersinia* PTP tertiary fold is a highly twisted, eight-stranded, mixed β-sheet flanked by five α-helixes on one side and two α-helixes on the other side (Figure 3.1).[16] The PTP signature sequence (Ile/Val)His-Cys-Xxx-Ala-Gly-Xxx-Gly-Arg(Ser/Thr)(Gly/Ala) is centered within the catalytic domain. Residues 403-410 form the PTP phosphate-binding loop (P-loop) containing the invariant Cys 403 thiol centered within the P-loop.[17,16a]

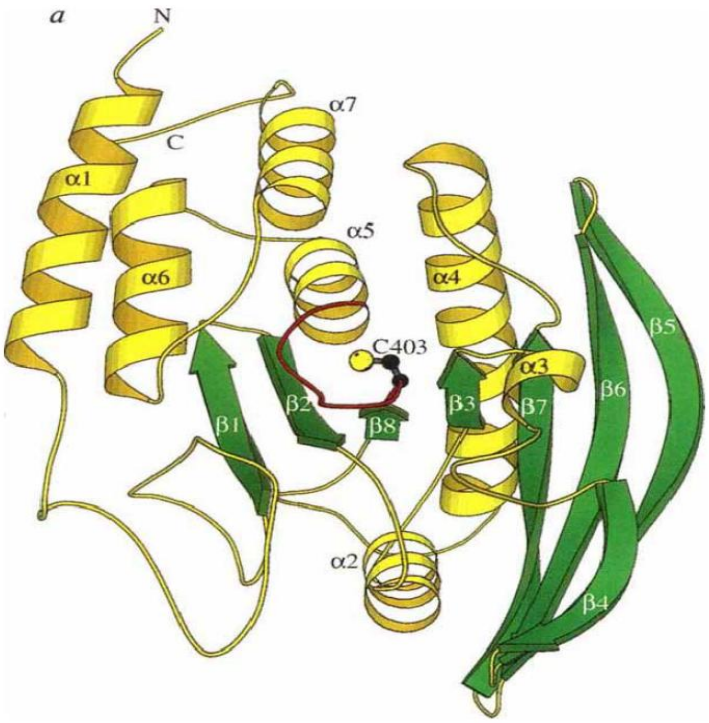


Figure 3.1. Ribbon Diagram of the Unliganded Yersinia PTPase Structure[16a]

The main target for PTPs inhibitor design is the phosphotyrosine (pTyr) binding pocket (also called phosphate-binding loop, P-loop) that is the highly conserved binding active site present in all PTPs. Since this pocket is relatively small, it is hard to achieve high binding affinity by targeting this pocket alone.

Most inhibitors designed and synthesized share a pharmacophore structurally similar to the pTyr substrate. These pTyr mimics are often charged bidentate anions that competitively bind to the pTyr pocket. Some of these pTyr mimics include salicylic acids (SA) and its derivatives (carboxymethylene benzoic acids, CMBA), benzoic acid derivatives such as 2-(oxalylamino)-benzoic acids (OBA), difluoromethylene phosphonates (DFMP), bis-(*para*-phosphophenyl) methane (BPPM), etc (Figure 3.2).[18]

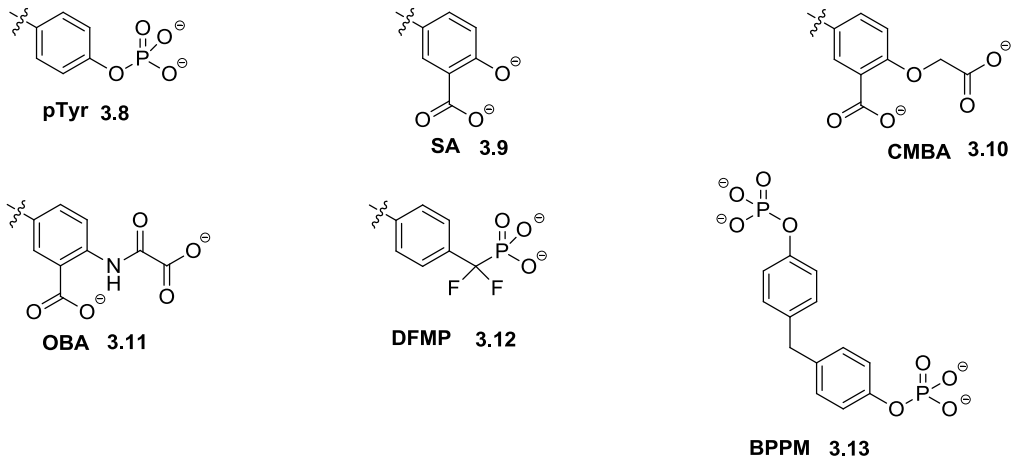


Figure 3.2. The Phosphotyrosine (pTyr) Mimics

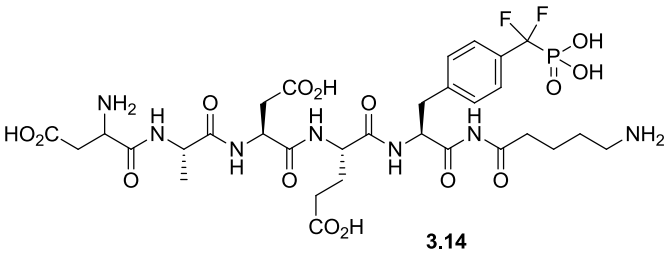
3.3.2. Known YopH inhibitors

Stuckey and coworkers first reported the unliganded and tungstate-bound crystal structure of the catalytic domain of YopH protein which was among the first PTP structures to be solved.[16a] Crystal structures of bound protein with vanadate,[19] nitrate,[20] sulfate,[21] and a phosphotyrosyl mimetic-containing hexapeptide[22] were subsequently determined. All these structures provided valuable information about the enzyme, revealing Cys 403 is positioned at the center of the phosphate-binding loop. This loop is at the hub of several hydrogen-bonded arrays that stabilizes a bound oxyanion and may activate Cys 403 as a reactive thiolate.[16a] Several YopH inhibitors have already been identified over the last few years. Some of these are discussed below.

3.3.2.1. Hexapeptide mimic designed by Phan *et al.*

Phan and coworkers designed a nonhydrolyzable phosphotyrosine substrate analog, hexapeptide mimetic (Ac-Asp-Ala-Asp-Glu-F_2Pmp-Lys-NH_2) **3.14** (Figure 3.14) and determined its co-crystal structure with the YopH (F_2Pmp stands for difluoro-substituted phosphonomethylphenylalanine).[22] They noted that the binding mode of this ligand to the

active site of PTP is similar to the binding of corresponding hexapeptide to structurally homologous human PTP1B. The crystal structure of this hexapeptide with YopH revealed a second substrate binding site in YopH that is not present in PTP1B.

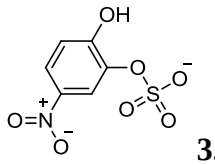


3.14

Figure 3.3. Hexapeptide Mimetic

3.3.2.2. *p*-Nitrocatechol sulfate (*p*NCS) inhibitor designed by Sun *et al.*

Sun and coworkers found that *p*-nitrocatechol sulfate (*p*-NCS) **3.15** was an inhibitor of YopH protein.[23] The co-crystal structure of p-NCS with YopH was also determined. The inhibition activity of this molecule against YopH and a number of mammalian PTPs were measured (Table 3.1) that displayed a 13-60-fold selectivity in favor of YopH.



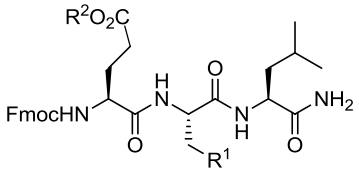
3.15

Table 3.1. Selectivity of *p*-NCS **3.15** Against Different PTPs

PTPs	**K_i (μM)**
YopH	25±0.7
SHP1	750±56
HePTP	1500±24
PTP1B	1200±120
TCPTP	330±42
CD45	500±68
LAR	830±270
VHR	350±49
CDC14	1400±60

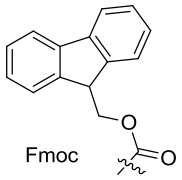
3.3.2.3. Tripeptide inhibitors developed by Lee *et al.*

Mono-anionic tripeptide inhibitors of YopH have been reported by Lee and coworkers.[24] Several of the tripeptides with the mono-anionic peptide, Fmoc-Glu(OBn)-Xxx-Leu-amide [Xxx = 4-(carboxymethyloxy)Phe, a pTyr mimetic] showed very good activity against YopH (Table 3.2). Interestingly, Glu residues with an unprotected side chain carboxyl were inactive towards YopH, but exhibited good IC_{50} value against PTP1B (**a** versus **b** values in Table 3.2). Also, the dicarboxy pTyr mimetic-containing tripeptide exhibited sub-micromolar PTP1B IC_{50} values.



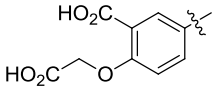
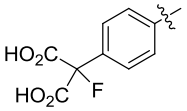
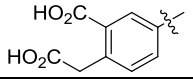
a R^2 = H

b R^2 = Bn



3.16

Table 3.2. Inhibitory Activities of Tripeptides in YopH and PTP1B Assays

R^1	Entry No.	YopH (IC_{50}, μM)	PTP1B (IC_{50}, μM)
	**3.17a** **3.17b**	>100 10.5±3.9	54.7±15.3 8.3±2.1
	**3.18a** **3.18b**	>>800 3.1±0.17	0.7 3.1±1.0
	**3.19a** **3.19b**	>>800 142±51	0.7 44±13

In a more recent study, Lee *et al.* synthesized N-terminally modified and pTyr mimetic derivatives of the above tripeptides (**3.17-3.19**) and tested against YopH and human PTP1B proteins.[25] This change in the tripeptide platform resulted in increased inhibitory potencies against both proteins but it did not improve the selectivity (Table 3.3).

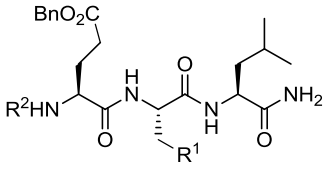
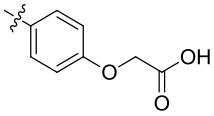
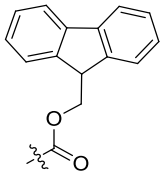
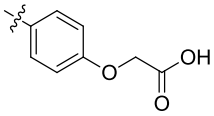
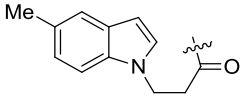
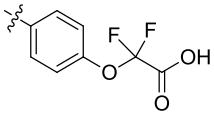
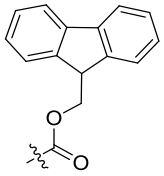


Table 3.3. Inhibitory Potencies of Tripeptides Against YopH and PTP1B

Entry No.	R^1	R^2	YopH (IC_{50}, μM)	PTP1B (IC_{50}, μM)
3.20			1.8±1.0	2.9±1.3
3.21			5.6±1.2	4.3±0.7
3.22			1.9±1.3	3.8±1.8

3.3.2.4. Aurintricarboxylic acid inhibitor designed by Liang *et al.*

Liang and coworkers screened a library of 720 commercially available and structurally diverse carboxylic acids and identified 26 YopH inhibitors with IC_{50} values less than 100 μM.[26] They identified aurintricarboxylic acid (ATA) as the most potent and specific small molecule YopH inhibitor which exhibited a K*i* value of 5 nM for YopH and displayed 6-120-fold selectivity in favor of YopH against a panel of mammalian PTPs (Figure 3.4).

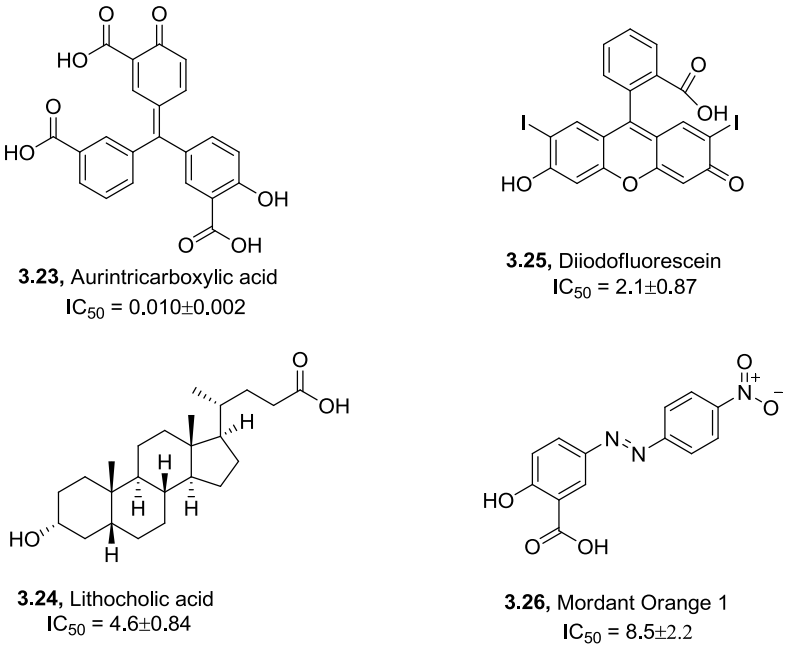


Figure 3.4. Structure and IC_{50} (μM) Values of Some Carboxylic Acid Inhibitors

3.3.2.5. Furanyl salicylate pharmacophore containing inhibitors

Tautz *et al*. developed furanyl salicylate containing YopH inhibitors after screening thousands of drug-like compounds of the DIVERSet™ library (Figure 3.5).[27] The lead compounds of this chemical library screening were analyzed and computationally docked into the crystal structure of YopH. This identified the furanyl salicylate moiety as a novel pharmacophore (a pTyr mimetic) for PTPs inhibitor design.

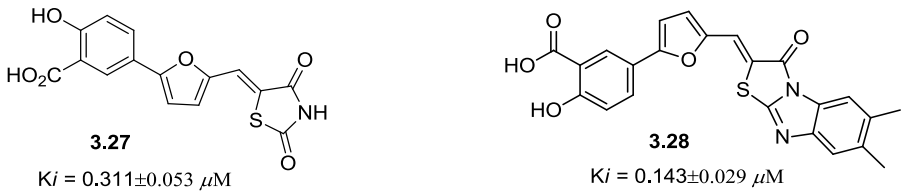


Figure 3.5. Furanyl Salicylate Containing Small molecule Inhibitors of YopH Protein

Pellecchia and coworkers designed furanyl salicylate derivative chemically linked to the 'spin label' TEMPO (the 2,2,6,6-tetramethylpiperidine-1-oxyl) as a probe for NMR-

based second-site screening against different PTPS including YopH (for example **3.29**, Figure 3.6**)**.[28] This technique, in combination with molecular docking studies, was used to synthesize a series of novel bidentate compounds as potential inhibitors of YopH (for example **3.30**, Figure 3.6).[29]

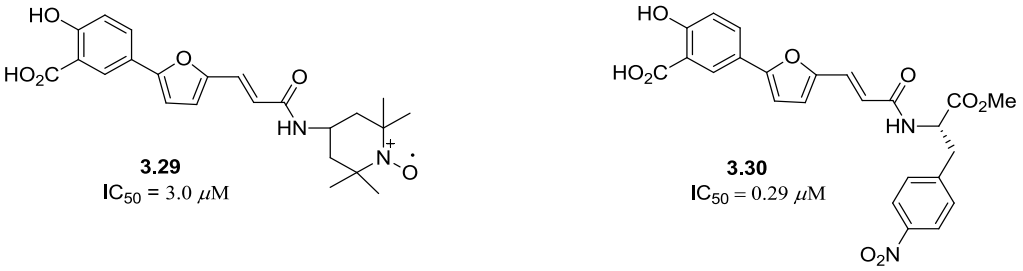


Figure 3.6. Small Molecule Inhibitors Containing Furanyl Salicylate Derivatives

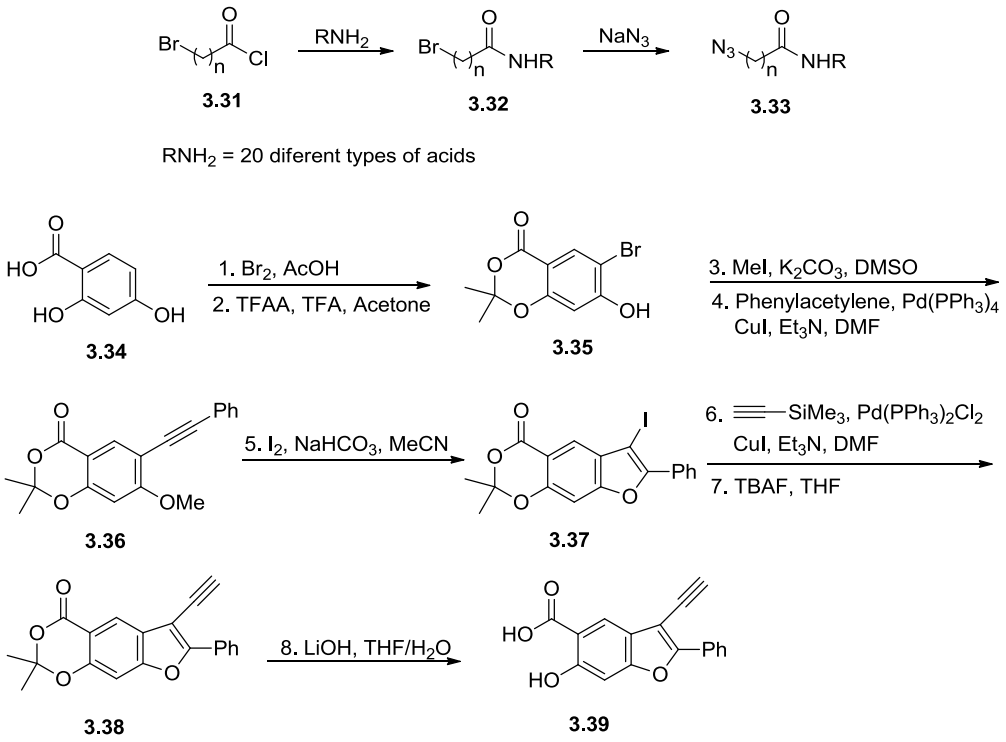
In this context, we were motivated to design and synthesize a new set of small molecule inhibitors to achieve higher activity. This project is in collaboration with Dr. Chung F. Wong's laboratory at the University of Missouri-St. Louis.

3.3.3. Rationale of new design

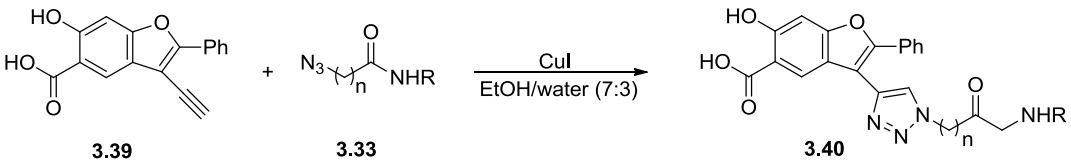
3.3.3.1. Previous results: Benzofuran salicylate derived YopH inhibitors

Huang *et al.* designed benzofuran salicylic acid based ligands having two chemical moieties connected by a flexible hydrocarbon linker.[11] These two moieties target two different pockets in the active site of the protein; the salicylic acid core targeted the phosphotyrosine binding pocket and the other moiety targeted the secondary pockets that are present adjacent to the catalytic side. Based on the results from molecular docking, these bidentate ligands designed to achieve higher binding affinity and specificity targeting the primary phosphotyrosine binding pocket and secondary peripheral pocket.

Two series of forty salicylic acid derivatives having hydrocarbon linkers with different length were synthesized by Huang and coworkers. The benzofuran salicylic acid core was prepared in 8 steps from commercially available 4-hyroxysalicylic acid as shown in scheme 3.2. The benzofuran was then coupled with azide **3.33** (prepared in two steps from commercially available compounds, Scheme 3.2) using click chemistry (Cu(I)-catalyzed [3+2] azide-alkyne cycloaddition) to complete the synthesis of the inhibitors (11 total steps, Scheme 3.3). Out of the 80 compounds synthesized and tested, 16 showed micromolar inhibitory activity. Some of these molecules with their IC_{50} values are given in figure 3.7.



Scheme 3.2. Synthesis of Benzofuran Salicylic Acid Core and Azide



Scheme 3.3. Coupling of the Benzofuran Salicylic Acid Core with Azide

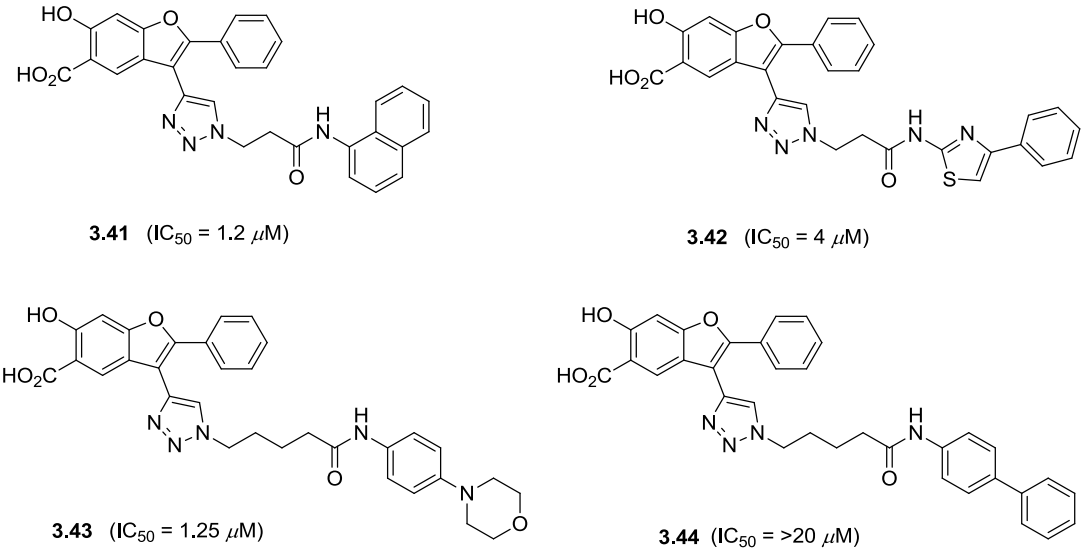


Figure 3.7. Benzofuran Core Containing Small molecule Inhibitors and Their IC_{50} Values Against YopH

3.3.3.2. Limitations of the method of Huang and coworkers and new design

The synthesis of benzofuran-salicylate core was tedious requiring 11 steps from the commercially available compounds (Scheme 3.2). From the docking studies, it was found that the phenyl group does not appear to assist in the interaction of these molecules with the binding site of the protein, though it aids in the synthesis. Furthermore, these inhibitors failed to show potency higher that the most literature reported inhibitors (all in low to mid micromolar range).

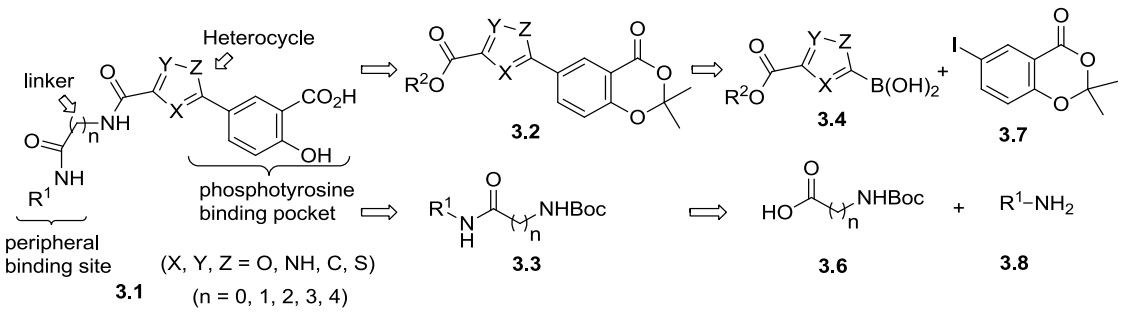
This prompted some changes of these inhibitors design, retaining the useful features of the above mentioned inhibitors. Many challenges to consider were

i) to keep the size of the inhibitors more or less the same (no increase in molecular weight),

ii) to improve the synthetic route for the rapid synthesis of inhibitors and easy modification if needed during the course of optimization,

iii) to incorporate different chemical moieties with possibly more binding affinities and hence to increase the inhibitory activity against YopH protein.

A series of compounds were proposed which retain the salicylic acid moiety which is a proven pharmacophore for binding to the active site of the enzyme (Scheme 3.4). Instead of fused furan ring (benzofuran), five membered aromatic heterocycles possessing oxygen, sulfur or nitrogen atoms in the different positions (or six membered aromatic rings) and a carboxylic acid in one of the two orientations were chosen. This synthetic design has the following features: a) many salicylic derivatives are commercially available inexpensive starting materials, b) the boc-protected amino acids with different carbon lengths are also commercial available and ready for coupling, c) several amines needed to couple with the acids for the side chain (peripheral binding site) are easily available, and d) many five membered heterocycles or six membered aromatics are coupled to salicylic acid part in one step following Suzuki cross coupling reactions.



Scheme 3.4. Newly Designed YopH Inhibitors and Retrosynthetic Analysis

3.4. Results and discussion

3.4.1. Synthesis of building block acids

Different building blocks were chosen with various heterocyclic aromatic rings and simple arenes with different orientation of the carboxylic acid (Figure 3.8). The syntheses of these building blocks were achieved as described below.

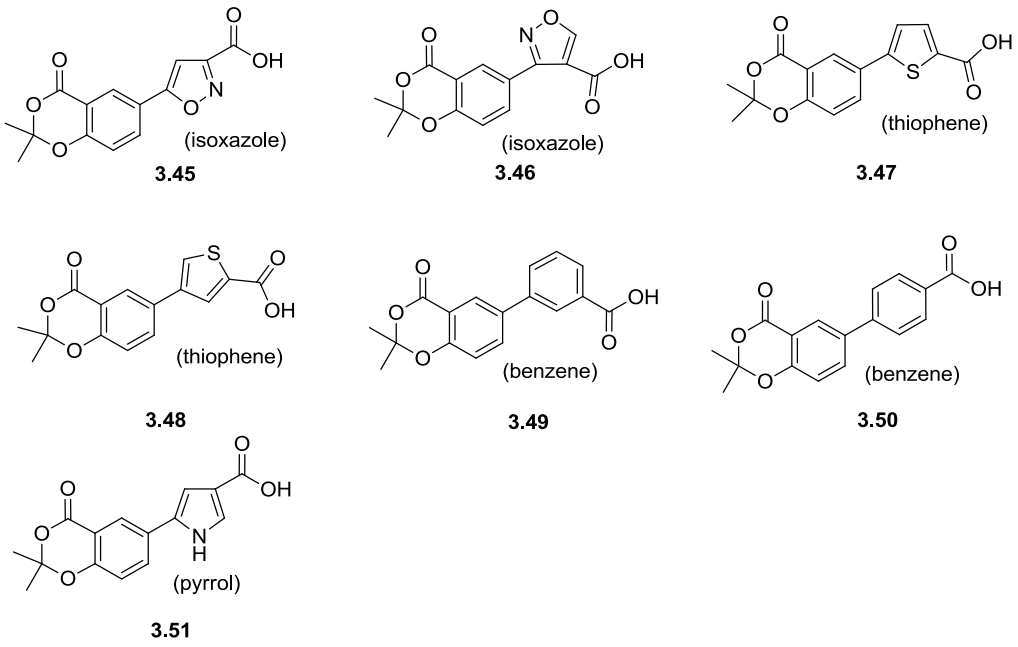
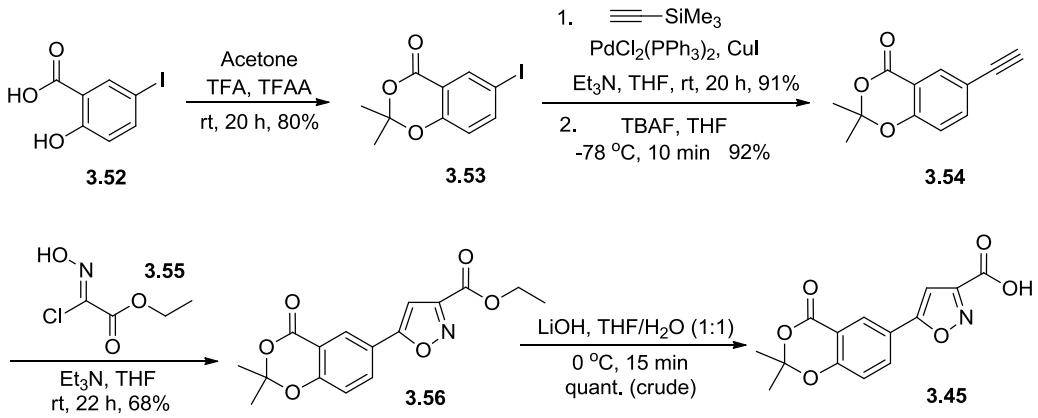


Figure 3.8. Building Blocks Containing Different Heterocycles

3.4.1.1. Isoxazole heterocycles containing building blocks

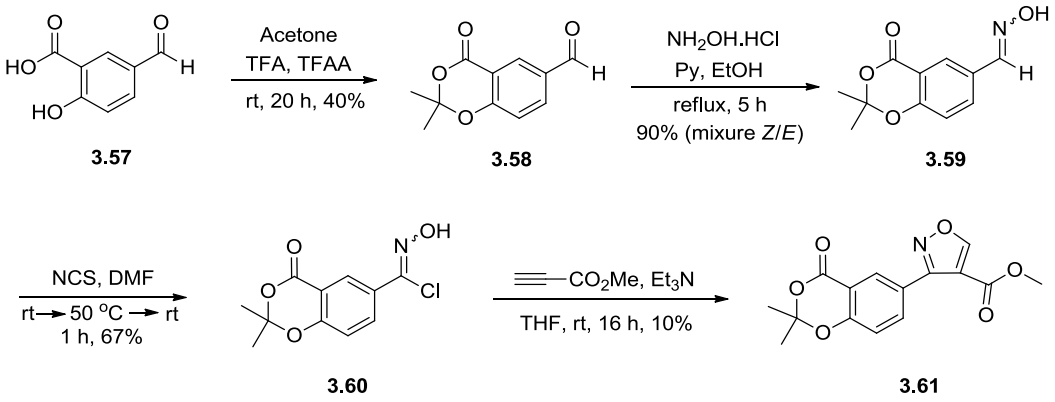
The building block **3.45** was synthesized in four steps from the 5-iodo-salicylic acid **3.52** (Scheme 3.5). The salicylic acid was protected as acetonide (2,2-dimethyl-1,3-benzodioxan-4-one) by reacting with acetone in trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) to give **3.53**.[30] Sonogashira coupling of **3.53** with trimethylacetylene in the presence of a catalytic amount of palladium and copper iodide followed by TMS removal produced phenyl acetylene **3.54.**[31] [3+2] polar cycloaddition

of acetylene **3.54** with chlorooxime (nitrile-oxide) **3.55** afforded isoxazole **3.56** in 68% yield.[32] Hydrolysis of **3.56** by LiOH in THF/water produced desired acid **3.45** ready for coupling.



Scheme 3.5. Synthesis of Isoxazole Heterocycle Containing Building Block **3.45**

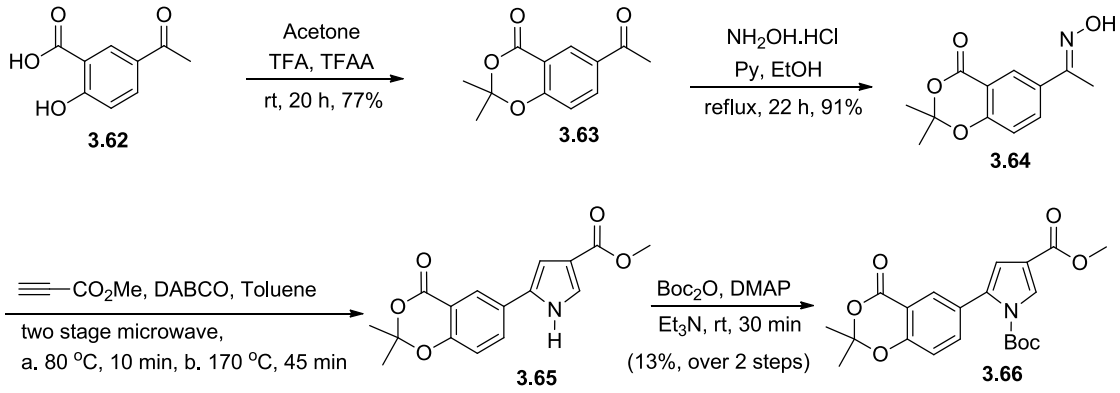
A building block containing isoxazole heterocycle with a different orientation of phenyl and carboxylic acid **3.45** was also synthesized (Scheme 3.6). 5-formyl-salicylic acid **3.57** was first protected as described above to give **3.58** followed by the treatment with hydroxylamine hydrochloride in ethanol to give oxime **3.59**. The oxime **3.59** was converted to chlorooxime **3.60** reacting with *N*-chlorosuccinimide (NCS) in DMF.[33] [3+2] cycloaddition of chlorooxime (nitrile-oxide) **3.60** with methyl propiolate[32] gave isoxazole derivative **3.61.** However, the cycloaddition step produced with very low yield.



Scheme 3.6. Isoxazole Containing Building Block Synthesis

3.4.1.2. Pyrrole heterocycle containing building block

The pyrrole derivative of building block **3.66** was synthesized by the reaction of oxime **3.64** with methyl propiolate in the presence of DABCO, followed by a two stage microwave irradiation (Scheme 3.7).[34] The pyrrole **3.65** was protected by reacting with boc-anhydride in the presence of dimethylaminopyridine (DMAP) and triethylamine to give **3.66** albeit in very low yield.

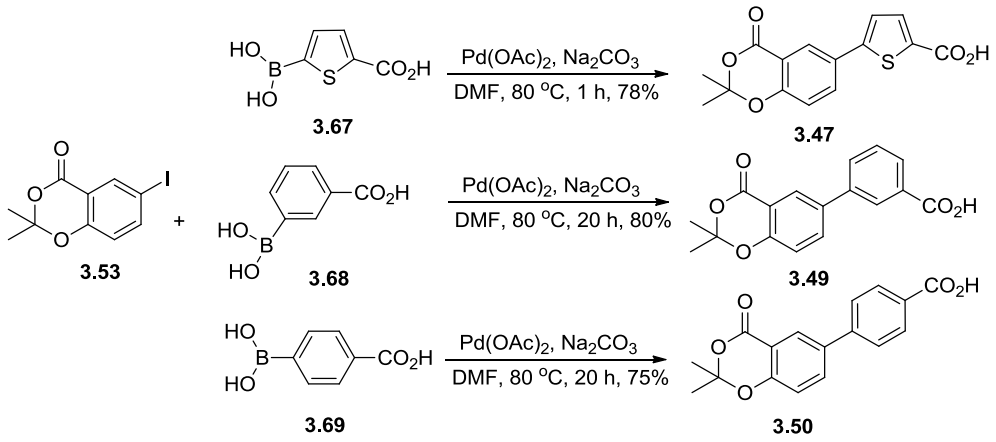


Scheme 3.7. Synthesis of Building Block Containing Pyrrol Derivative

Since the overall yield of building blocks **3.61** and **3.66** were low, these were not employed in the inhibitor synthesis.

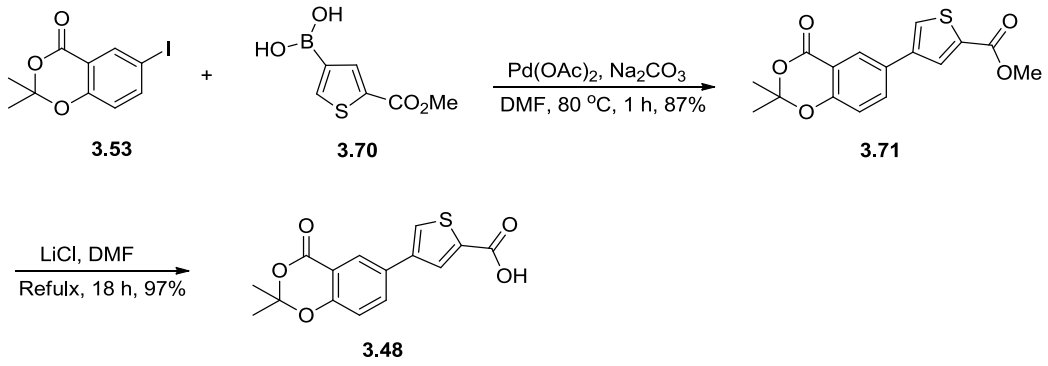
3.4.1.3. Thiophene heterocycles containing building blocks

The thiophene heterocycle and phenyl containing building blocks were synthesized by Suzuki coupling of the acetonide protected salicylic acid **3.53** with corresponding boronic acids **3.67**-**3.70** (Scheme 3.8).[35]



Scheme 3.8. Suzuki Coupling of Iodide **3.53** with Different Boronic Acids

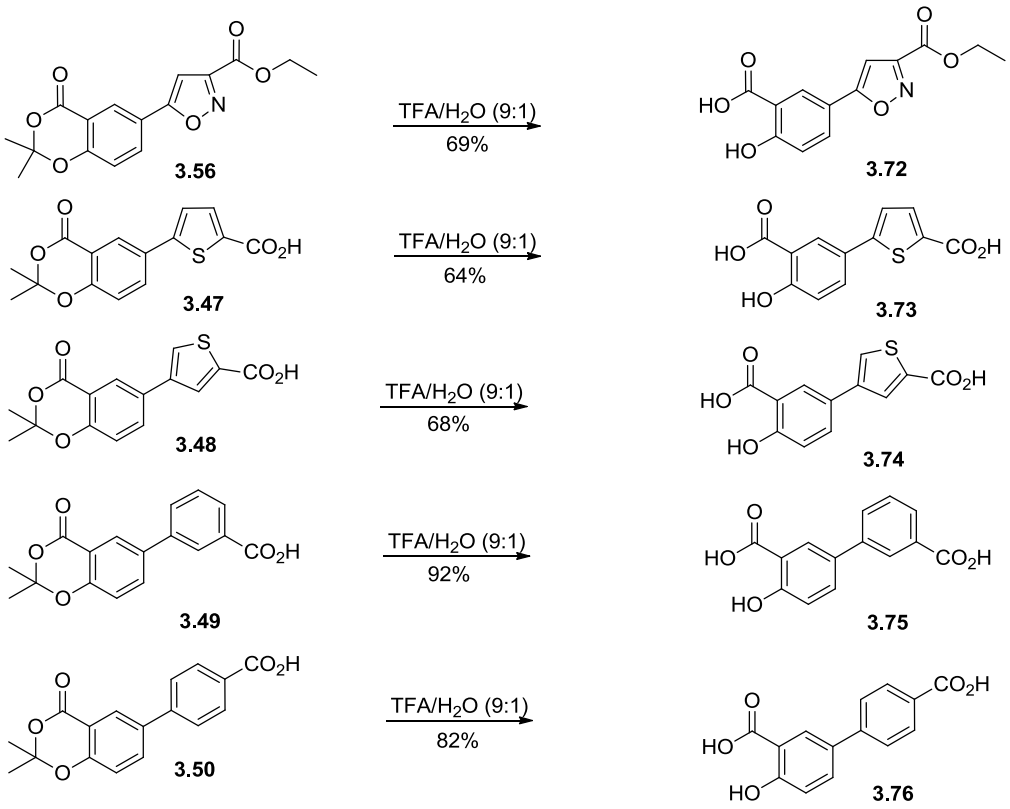
The ester moiety in **3.71** was hydrolyzed selectively using anhydrous lithium chloride in DMF (Scheme 3.9).[36]



Scheme 3.9. Suzuki Coupling Followed by Ester Hydrolysis

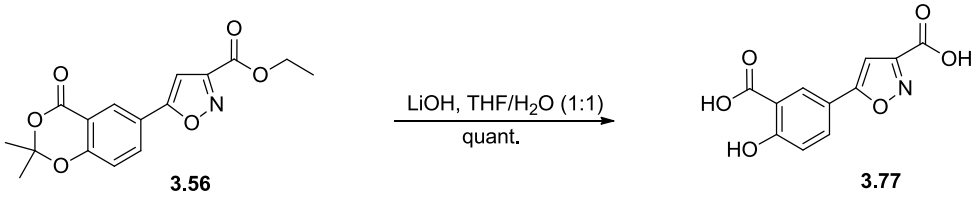
3.4.2. Acetonide group removal from building block acid

The acetonide protecting groups were removed from the building blocks by treating with trifluoroacetic acid (TFA) and water (9:1) to obtain free salicylic acid (Scheme 3.10).



Scheme 3.10. Removal of Acetonide Protecting Groups

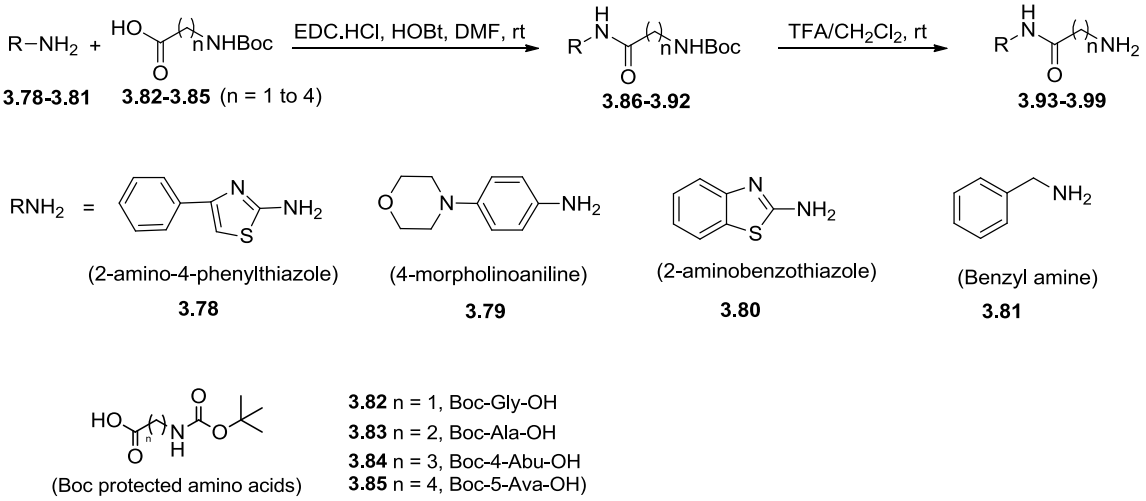
The building block **3.56** was fully deprotected by reacting with 5.0 equivalents of lithium hydroxide in THF/water at 0 ^{o}C (Scheme 3.11).



Scheme 3.11. Full Deprotection of Building Block **3.56**

3.4.3. Coupling of amines with linker acids

The commercially available amines **3.78-3.81** were coupled with the boc-protected *α*, *β*, *γ*, *δ* amino acids **3.82-3.85** in different combinations using 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC·HCl) and *N*-hydroxybenzotriazole (HOBt) in DMF to afford amides **3.86-3.92** (Scheme 3.12)**.** Boc-removal of **3.86-3.92** by trifluoroacetic acid (TFA) in CH_2Cl_2 produced free amines **3.93-3.99** that is ready for coupling with building block acids.

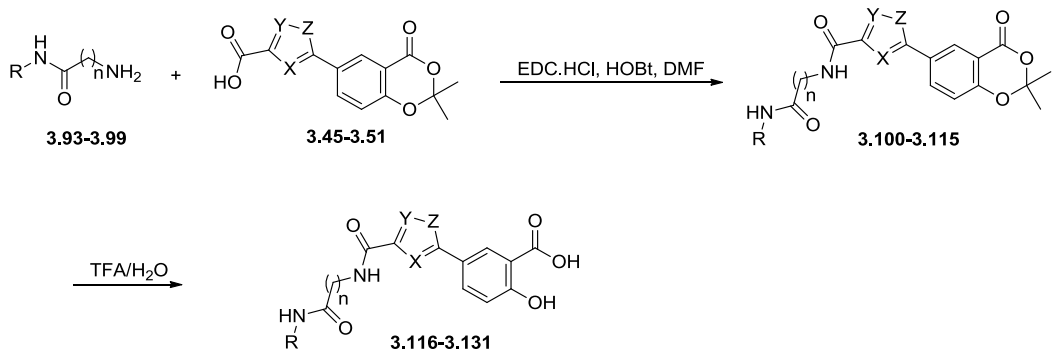


Scheme 3.12. Coupling of the Amines and Acids Followed by Boc-Removal

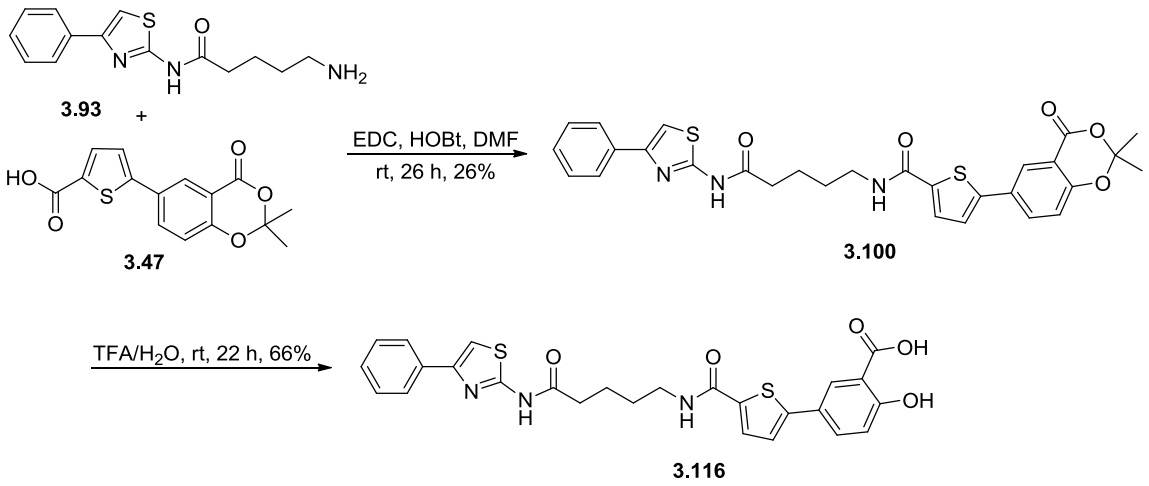
3.4.4. Coupling of building block acids with amines carrying linker and peripheral amines

The building block acids were coupled with the amines (that carry the linker) by reacting with EDC·HCl and HOBt in DMF. Finally, the acetonide group was removed by treating with TFA/H_2O (9:1) at room temperature to complete the synthesis. A representative example is shown below (Scheme 3.13).

General Scheme



A Specific Example



Scheme 3.13. EDC Coupling of the Building Block Acid and the Amine

Following the same procedure as described above, 16 different inhibitors (**3.116-3.131**) were synthesized.

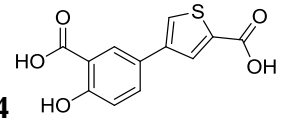
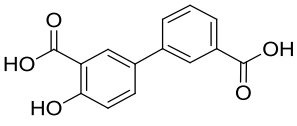
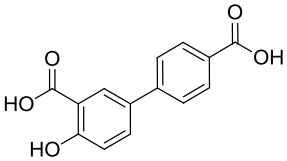
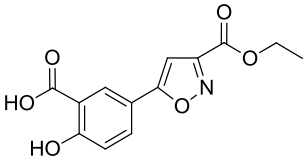
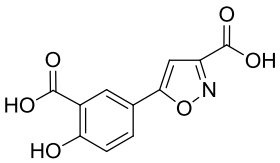
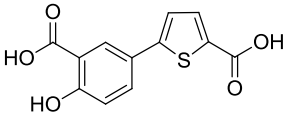
All the salicylic building blocks (fully or partially deprotected form) and inhibitors were tested against different phosphatase enzymes, YopH, PTP1B, and SHP2-D2C, CD45, VHR (only in selected cases).

3.4.5. Inhibitory activity studies

3.4.5.1. Inhibitory potencies of fully deprotected building block acids

Among six different building blocks tested, building block **3.74** containing 3-carboxyl-5-aryl substituted thiophene showed mild activity against different PTPs (Table 3.4). However, there was no selectivity between bacterial YopH and mammalian PTP1B.

Table 3.4. Structure and IC_{50} values Building Block Acids

	IC_{50} value (μM)	
Structure	**YopH**	**PTP1B**
 **3.74**	**280±9**	**220±20**
 **3.75**	>200	>200
 **3.76**	>200	>200
 **3.72**	No Inh at 500 µM	
 **3.77**	No Inh at 500 µM	
 **3.73**	No Inh at 500 µM	

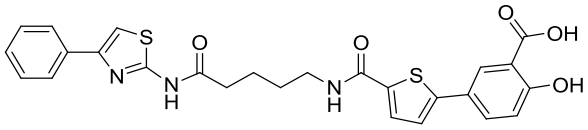
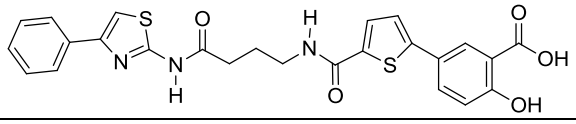
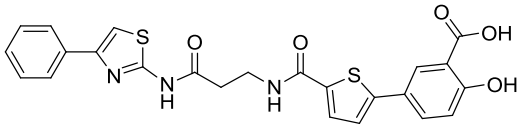
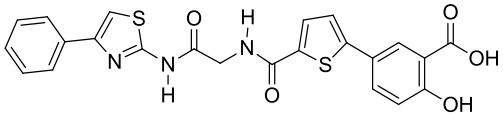
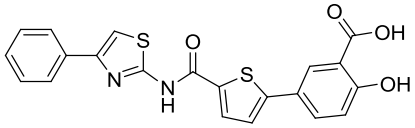
3.4.5.2. Inhibitory potencies of inhibitors

In an effort to study the structure activity relationship (SAR) study, we synthesized inhibitors varying different parameters. The heterocyclic building block, linker length, and amine were carried one at a time.

3.4.5.2.1. Variation in chain length (n = 0 to 4), constant amine and building block

The linker chain length was varied from 0 to 4 keeping the building block and amine the same (Table 3.5). Inhibitor **3.119** with one carbon linker showed very good inhibitory activity (in low micromolar range) against both bacterial YopH and mammalian PTP1B proteins. This inhibitor, however, was not selective between YopH and PTP1B. The inhibitor containing four carbons linker **3.116** also showed good activity, but it was more active towards PTP1B than YopH. Other inhibitors showed weak activity towards these proteins.

Table 3.5. Structures and IC_{50} Values of Inhibitors with Different Chain Length

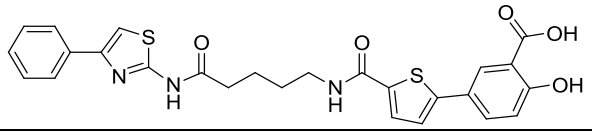
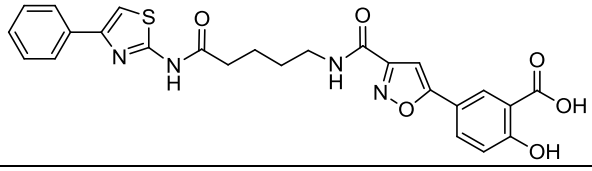
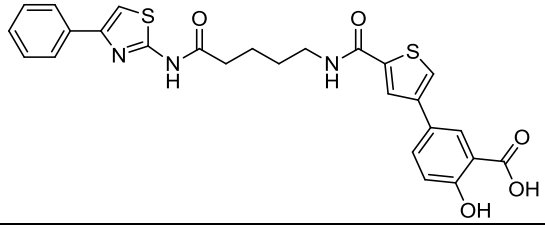
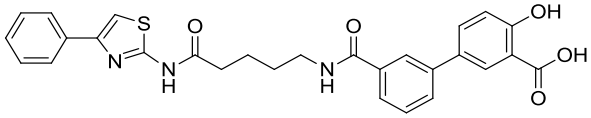
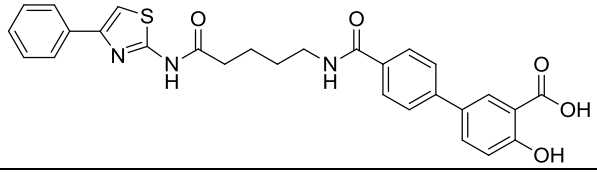
	IC_{50} value (μM)	
Structure	**YopH**	**PTP1B**
3.116 	**11.1±0.8**	**6.9±0.7**
3.117 	>200	>200
3.118 	>50	>50
3.119 	**5.0±0.2**	**4.5±0.1**
3.120 	>200	>200

3.4.5.2.2. Variation in building block acid, constant amine and chain length

With the exception of **3.124,** all inhibitors with different building blocks and the same linker (n=4) and amine were active to some extent against both proteins (Table 3.6). The inhibitor with 2,5-disubstituted thiophene containing building block **3.116** was about four and five times more active against YopH and PTP1B, respectively than the inhibitor with 2,4-disubstituted thiophene derivative **3.122.** Isoxazole derivative **3.121** also showed some potency but, it was about 2 times more active towards PTP1B.

Interestingly, the compound in which the five-membered heterocycle was replaced with an aromatic hydrocarbon maintained activity against both types of proteins tested. For example, inhibitor **3.123** with 1,3-disubstituted benzene showed IC_{50} value of 22.2 and 30.8 μM against YopH and PTP1B proteins, respectively.

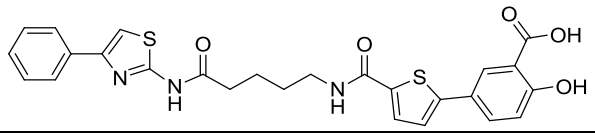
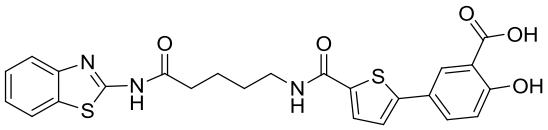
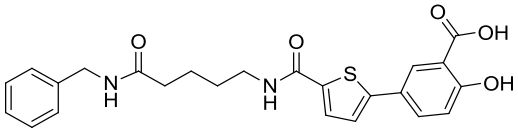
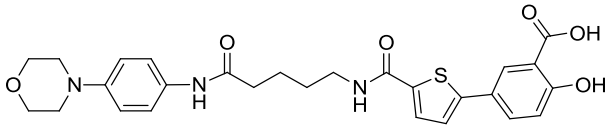
Table 3.6. Structures and IC_{50} Values of Inhibitors with Different Building Blocks

	IC_{50} value (μM)	
Structure	**YopH**	**PTP1B**
3.116 	**11.1±0.8**	**6.9±0.7**
3.121 	**23±0.4**	**12.2±0.3**
3.122 	44.2±14.9	31.8±4.6
3.123 	22.2±0.7	30.8±1.0
3.124 	>50	>50

3.4.5.2.3. Variation in amines, constant carbon chain and building block acid

Among the four different amines tested, 2-amino-4-phenylthiazole containing inhibitor **3.116** showed best activity against YopH and PTP1B proteins with respectable IC_{50} values (Table 3.7).

Table 3.7. Structures and IC_{50} Values of Inhibitors with Different amines

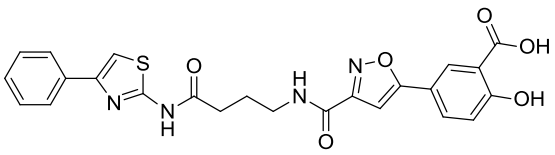
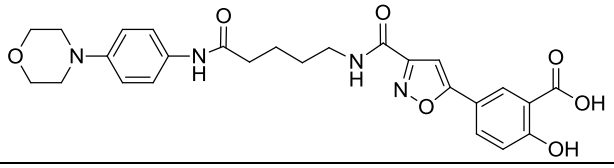
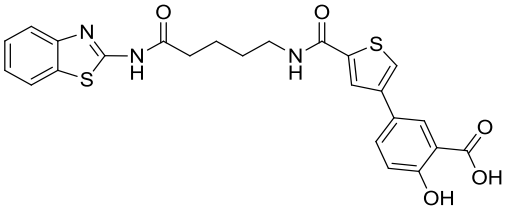
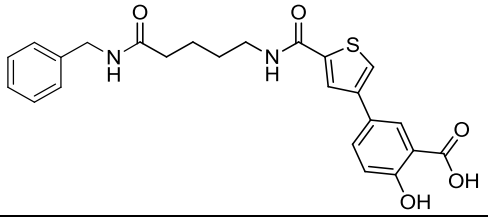
	IC_{50} value(μM)	
Structure	**YopH**	**PTP1B**
3.116 	**11.1±0.8**	**6.9±0.7**
3.125 	>20	>20
3.126 	>200	>200
3.127 	>200	>200

3.4.5.2.4. Miscellaneous Inhibitors (random synthesis)

Some inhibitors synthesized by the random combination of building block, amine and linker length also showed modest activity against YopH and PTP1B (Table 3.8). It was interesting to observe that inhibitor **3.129** with 4-morpholino-phenylamine, 4-carbon chain and isoxazole containing building block was 5 times more potent for bacterial

YopH than mammalian PTP1B which might be a good starting point for the selective inhibitor synthesis between YopH and PTP1B proteins.

Table 3.8. Structures and IC_{50} Values of Randomly Synthesized Inhibitors

	IC_{50} value (μM	
Structure	**YopH**	**PTP1B**
3.128 	**66±1**	**38±3**
3.129 	**63±1**	**310±40**
3. 130 	**39.5±1.9**	**31.8±1.7**
3.131 	>50	**40.9±7.9**

3.4.5.2.5. Inhibitory activity of inhibitors against YopH and few mammalian proteins

A few compounds were tested against different mammalian PTPs (SHP2-D2C, CD45, and VHR) all of which showed activity to some extent (Table 3.9). In fact, inhibitors **3.116, 3.121** and **3.128** were active in low micromolar range against all mammalian

proteins tested. Inhibitors **3.116, 3.121** and **3.128** were about 1.3 to 6 times more active towards the mammalian proteins than bacterial YopH. The fully deprotected building block **3.74** was also mildly active against the mammalian proteins with about 2 to 5 times more activity than bacterial YopH.

Table 3.9. The IC_{50} Values of Inhibitors Against YopH and Few Mammalian PTPs

	IC_{50} value (μM)				
Inhibitor	**YopH**	**PTP1B**	**SHP2-D2C**	**CD45**	**VHR**
3.74	280±9	220±20	66±2	150±20	142±6
3.116	11.1±0.8	6.9±0.7	4.4±0.3	6.2±0.1	7.5±0.7
3.121	23±0.4	12.2±0.3	4.1±0.1	8.4±0.3	5.3±0.2
3.128	66±1	38±3	23±2	52±3	32±3
3.129	63±1	310±40	76±5	45±5	137±4

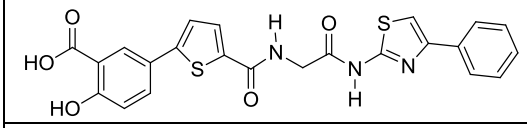
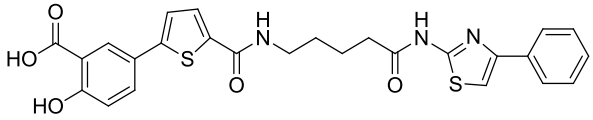
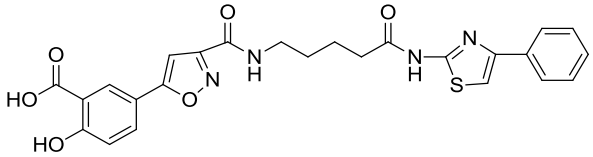
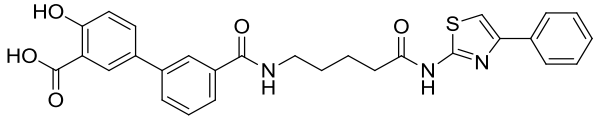
3.4.5.3. Summary of inhibitory activities

Inhibitor **3.119** containing the 2,5-disubstituted thiophene containing building block, one carbon linker and 4-phenyl-thiophene derivative as side chain was the most potent inhibitor synthesized (Table 3.10). The four carbon linker derivative of this inhibitor **3.116** also showed very good activity against PTPs tested. On the other hand, inhibitor **3.122** with different orientation of the heterocycle (2,4-disubstituted thiophene) compared to **3.116** displayed 8 times less activity against YopH.

Inhibitors **3.121** and **3.123** containing an isoxazole heterocycle and an aromatic ring (instead of a heterocycle) were also active towards both proteins in micro-molar range. Among the four different amines (present in the side chain) tested, only 2-amino-4-phenylthiazole containing inhibitors were broadly active, suggesting it to be a necessary

moiety for the activity. Also, inhibitor **3.129** with 4-morpholino-phenyl amine was five times selective for bacterial YopH protein than mammalian PTP1B.

Table 3.10. Structures and IC_{50} Values of the Most Potent Inhibitors

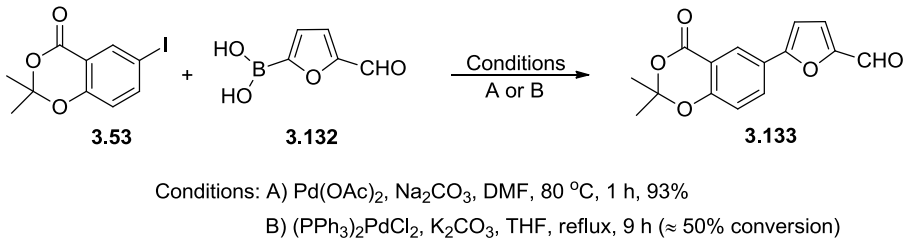
	IC_{50} value (μM)	
Structure	**YopH**	**PTP1B**
3.119 	**5.0±0.2**	**4.5±0.1**
3.116 	**11.1±0.8**	**6.9±0.7**
3.121 	**23±0.4**	**12.2±0.3**
3.123 	**22.2±0.7**	**30.8±1.0**

3.4.6. Expanding the scope of Suzuki coupling towards building block synthesis

As discussed earlier in section **3.4.1.3**, many building block acids were synthesized in one step by the Suzuki coupling of acetonide protected iodosalicylic acid **3.53** with corresponding boronic acids. In order to expand the utility of Suzuki coupling for the rapid synthesis of YopH and other phosphatase inhibitors, some other reactions were explored.

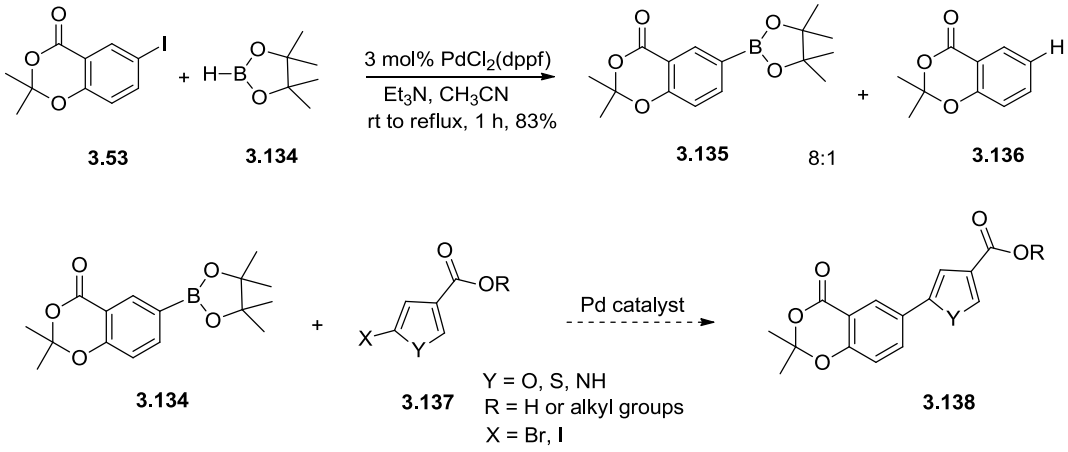
Palladium catalyzed coupling of acetonide protected iodosalicylic acid **3.53** with 5-formylfuran-2-boronic acid **3.132** was carried out (Scheme 3.14). Palladium acetate was

found to be efficient among the different palladium sources used.[35] The aldehyde **3.133** can be converted to the acid ready for coupling by treating with silver nitrate and aqueous water.[37]



Scheme 3.14. Suzuki Coupling of Iodide **3.53** with Boronic Acid

Alternatively, the iodide **3.53** was converted to its boronate ester **3.135** by treating with pinacolborane **3.134** in the presence of palladium catalyst (Scheme 3.15).[38] The boronate ester derivative **3.135** can potentially be coupled to a wide variety of commercially available halides **3.137** to synthesize various building blocks **3.138**.



Scheme 3.15. Palladium Catalyzed Coupling of Iodide with Pinacol Boronic Acid

3.5. Summary

1) Yersinia pestis is the pathogenic bacteria causing human diseases ranging from gastrointestinal syndromes to bubonic plague. Although the plague has long been considered as eradicated, it can re-emerge under suitable environmental conditions. The available antibiotics can be ineffective as bacteria can develop multi-drug resistant strain. Furthermore, the pathogen can be misused as a biological weapon in warfare.

2) Y. Pestis contains a virulence protein known as YopH. This is similar to protein tyrosine phosphatase of human beings. Upon injection into the human body, YopH can dephosphorylate many proteins, affects the signal transduction network within the body reducing immune response. Specific molecules can act against the YopH protein and inhibit its virulence activity.

3) Many inhibitors are known but all have some limitations: low activity, little selectivity between YopH and human phosphatase proteins, cumbersome synthesis, etc.

4) In order to synthesize active YopH inhibitors rapidly, we designed and synthesized a number of inhibitors (bidentate ligands). Most of these inhibitors were synthesized in 6-9 steps form commercially available starting materials. Many of these compounds showed very good potency (in low micromolar range) against phosphatases (YopH and PTP1B).

5) A rapid method for synthesizing heterocyclic building blocks (a part of phosphatase inhibitors) was developed. Palladium catalyzed Suzuki coupling of acetonide protected iodosalicylic acid and commercially available boronic acids were employed. Alternatively, the boronate ester, synthesized from iodosalicylic acid, can also be coupled to various easily available halides following the same chemistry.

3.6. General Experimental

Glassware used for all experiments were oven-dried and all reactions were carried out under argon atmosphere unless otherwise mentioned. All reaction solvents were purified prior to use: CH_2Cl_2, MeOH, MeCN were dried by distillation over calcium hydride and THF over sodium-benzophenone ketyl. Reagent grade DMF was obtained from Sigma-Aldrich and used without further purification.

Proton (^1H) NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra at 75 MHz. Proton NMR spectra were referenced to residual $CDCl_3$ (7.27 ppm) and ^{13}C {^1H} NMR spectra were referenced to the center line of $CDCl_3$ (77.23 ppm). Crystal structure(s) were determined on a Bruker Apex- II CCD single crystal diffractometer. Optical rotations were measured on a polarimeter using a glass cell with 2 mL capacity and 10 cm path length. Infrared spectra were recorded on FTIR instrument using NaCl plates (liquids, oils) or using an ATR attachment (solids).

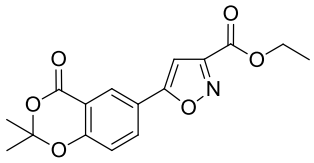
General procedure for the EDC-coupling: To a stirred solution of carboxylic acid (1.0 equiv.) and HOBt (1.5 to 2.0 equiv.) in DMF under argon at room temperature (rt) was added EDC.HCl (1.5 to 2.0 equiv.) and amine (1.2 equiv.) sequentially. The resulting mixture was stirred at room temperature (unless otherwise specified) for 26-48 hour (TLC monitoring). The solvent was removed in *vacuo* and the residue was dissolved EtOAc. The EtOAc layer was washed with 5 % HCl (2X), saturated aq. $NaHCO_3$ solution (2X) and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated and the crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) or recrystallized with EtOAc and hexanes.

General procedure for the Boc removal: To a stirred solution of boc-protected amine in dry CH_2Cl_2 (2 mL/mmol) was added trifluoroacetic acid (TFA) (2 mL/mmol) and stirred for 1 to 4 h at rt (TLC monitoring). The solvent was evaporated, EtOAc was added and neutralized with aq. solution of $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and the crude product was used without further purification (or purified by column chromatography, SiO_2, hexanes:EtOAc). [Note: In some cases, while washing with brine, solids came out from the solution which was filtered. From NMR, this was known to be the product and was used without further purification].

General procedure for the acetonide removal: A solution of acetonide protected salicylic acid in TFA and water (9:1) was stirred for 22-24 h at rt. After that, the solvent was evaporated, cold water was added in the crude solid and stirred for 10 minutes. The reaction mixture was filtered and the solid product was dried in *vacuo*. In all cases, NMR in DMSO-D_6 showed only the product peaks.

General procedure for the Suzuki coupling: To a stirred solution of iodide (1.0 equiv.) in dry DMF at rt. was added $Pd(OAc)_2$ (5 mol%), Na_2CO_3 (2.0 equiv.), and boronic acid (1.2-1.5 equiv.) sequentially and the resulting solution was heated to 80 ^oC. After 1-4 h, the reaction mixture was cooled to rt. and the solvent was evaporated (Wherever necessary, 5-10 mL EtOAc was added in the crude reaction mixture and acidified with 1M HCl (pH 0-1). Layers were separated and organic layer was evaporated). The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc).

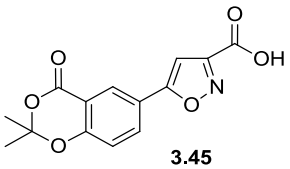
Building blocks:



3.56

Ethyl-5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)isoxazole-3-carboxylate (3.56): Acetylene **3.54** (0.700 g, 3.46 mmol), chloro-oxime **3.55** (1.575 g, 10.39 mmol), and Et_3N (1.4 mL, 10.0 mmol) were reacted in THF (65 mL) following the literature procedure[32] described to give product **3.56** as a colorless solid (0.750 g, 68%).

IR (neat, NaCl) 3135, 2988, 1749, 1711, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.39 (1H, d, *J* = 2.2 Hz), 8.02 (1H, dd, *J* = 2.2, 8.6 Hz), 7.11 (1H, d, *J* = 8.6 Hz), 6.93 (1H, s), 4.48 (2H, q, *J* = 7.1 Hz), 1.78 (6H, s), 1.45 (3H, t, *J* = 7.1 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 170.0, 160.3, 160.0, 157.7, 157.3, 133.7, 127.7, 121.8, 118.6, 114.2, 107.3, 100.2, 62.5, 26.1, 14.3; HRMS (FAB, MH^+) calcd for $C_{16}H_{16}NO_6$: 318.0977. Found 318.0970.

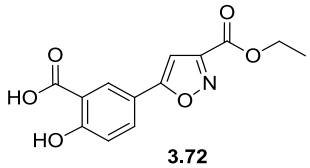


3.45

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)isoxazole-3-carboxylic acid (3.45): To a stirred solution of ester **3.56** (0.020 g, 0.063 mmol) in THF (0.5 mL) was added water (0.5 mL) and the reaction mixture was cooled to 0 ^oC using an ice bath. Lithium hydroxide (2.0 mg, 0.083 mmol) was added and the mixture was stirred for 15 minutes at 0 ^oC when the TLC analysis showed the reaction was complete. EtOAc (5 mL) was added to the reaction mixture and it was acidified (pH 0-1) by 1M HCl solution. The

layers were partitioned, the aq. layer was extracted with EtOAc (5 mL, 5X) and the combined organic layers were washed with brine. After drying over anhydrous Na_2SO_4, the organic layer was concentrated in *vacuo*. The crude product **3.45** (0.018 g, quantitative yield) was used for the next step without further purification. [Note: Large scale reactions needed longer reaction time and produced a mixture of mono- and dicarboxylic acids (acetonide removal). Extraction of the crude mixture with chloroform separated the mono and dicarboxylic acids.]

^{1}H NMR ($CDCl_3$): δ 8.43 (1H, d, *J* = 2.0 Hz), 8.04 (1H, dd, *J* = 2.2, 8.6 Hz), 7.14 (1H, d, *J* = 8.6 Hz), 7.00 (1H, s), 1.80 (6H, s); ^{13}C {^{1}H} NMR (MeOD-D_4): δ 171.3, 162.4, 161.7, 159.2, 159.0, 135.2, 128.0, 123.1, 119.9, 115.4, 108.6, 101.5, 26.0.

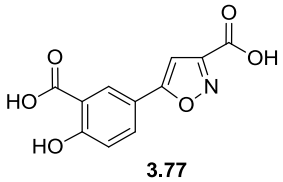


3.72

5-(3-(ethoxycarbonyl)isoxazol-5-yl)-2-hydroxybenzoic acid (3.72): To a stirred solution of ester **3.56** (0.100 g, 0.315 mmol) in TFA (0.90 mL) at rt. was added water (0.10 mL) and stirred at that temperature for 18 h (off white solids came out of the solution). Solvent evaporated, cold water (2 mL) was added to the crude solid, stirred for 10 minutes and filtered. Proton NMR of crude showed the product and unreacted starting material (about 12%). Purification by column chromatography (SiO_2, hexanes:EtOAc) gave product **3.72** as a colorless solid (0.06 g, 69% or 90% based on recovered starting material).

IR (neat, NaCl) 3135, 2500-3400 (broad), 1722, 1688, 1614 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 8.25 (1H, d, *J* = 2.2 Hz), 8.03 (1H, dd, *J* = 2.3, 8.7 Hz), 7.34 (1H, s), 7.10 (1H, d, *J* =

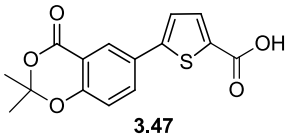
8.7 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 1.32 (3H, t, *J* = 7.1 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.3, 170.5, 163.0, 159.7, 157.1, 133.1, 128.1, 118.7, 117.7, 114.3, 99.9, 62.2, 14.2.



3.77

5-(3-carboxy-4-hydroxyphenyl)isoxazole-3-carboxylic acid (3.77): Acetonide protected ester **3.56** (0.079 g, 0.25 mmol) and LiOH (0.030 g, 1.25 mmol) were reacted in THF (1 mL) and water (1 mL) for 16 h following the procedure described above for compound **3.45** to obtain fully hydrolyzed acid **3.77** as a colorless solid (0.072 g, quant. crude yield).

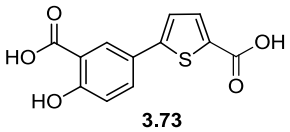
IR (neat, NaCl) 3400-2500 (broad), 3127, 1738, 1680, 1645, 1610 cm^{-1}; ^{1}H NMR (MeOD-D_4): δ 8.38 (1H, d, *J* = 2.2 Hz), 8.01 (1H, dd, *J* = 2.3, 8.7 Hz), 7.11 (1H, d, *J* = 8.7 Hz), 7.08 (1H, s); ^{13}C {^{1}H} NMR (MeOD-D_4): δ 172.8, 172.2, 165.0, 162.5, 159.0, 133.9, 129.3, 119.5, 119.4, 114.6, 100.2.



3.47

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)thiophene-2-carboxylic acid (3.47): Iodide **3.53** (0.121 g, 0.400 mmol), $Pd(OAc)_2$ (0.004 g, 0.020 mmol), Na_2CO_3 (0.085 g, 0.800 mmol), and boronic acid **3.67** (0.103 g, 0.600 mmol) were reacted in DMF (5 mL) following the general procedure for Suzuki coupling to obtain **3.47** as a pale yellow solid (0.095 g, 78%).

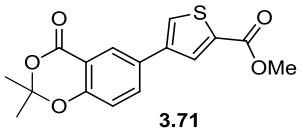
IR (neat, NaCl) 3400-2400 (broad), 1740, 1670, 1605 cm^{-1}; ^{1}H NMR (MeOD-D_4): δ 8.16 (1H, d, *J* = 2.2 Hz), 7.83 (1H, dd, *J* = 2.3, 8.6 Hz), 7.71 (1H, d, *J* = 3.9 Hz), 7.28 (1H, d, *J* = 3.9 Hz), 7.03 (1H, d, *J* = 8.6 Hz), 1.74 (6H, s); ^{13}C {1H} NMR (MeOD-D_4): δ 165.5, 162.7, 157.5, 150.3, 136.0, 135.7, 134.8, 130.1, 128.1, 125.4, 119.6, 115.1, 108.4, 26.9.



3.73

5-(3-carboxy-4-hydroxyphenyl)thiophene-2-carboxylic acid (3.73): Compound **3.47 (**0.034 g, 0.112 mmol) was reacted with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.73** as a colorless solid (0.019 g, 64%).

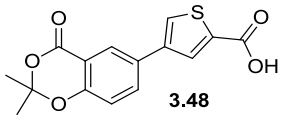
IR (neat, NaCl) 3400-2400 (broad), 1657, 1620 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 8.06 (1H, s), 7.90 (1H, d, *J* = 8.6 Hz), 7.70 (1H, d, *J* = 3.7 Hz), 7.50 (1H, d, *J* = 3.7 Hz), 7.07 (1H, d, *J* = 8.6 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 162.7, 161.5, 148.8, 1134.4, 133.9, 132.4, 127.3, 124.2, 123.9, 118.3.



3.71

Methyl-4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)thiophene-2-carboxylate (3.71): Iodide **3.53** (0.121 g, 0.400 mmol), $Pd(OAc)_2$ (0.004 g, 0.020 mmol), Na_2CO_3 (0.085 g, 0.800 mmol), and boronic acid **3.70** (0.089 g, 0.480 mmol) were reacted in dry DMF (5 mL) following the general procedure for Suzuki coupling to obtain **3.71** as a pale yellow solid (0.110 g, 87%).

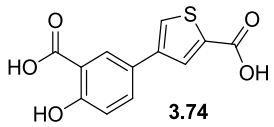
IR (neat, NaCl) 3104, 2949, 1730, 1703, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.14 (1H, d, *J* = 2.3 Hz), 8.02 (1H, d, *J* = 1.6 Hz), 7.75 (1H, dd, *J* = 2.3, 8.5 Hz), 7.62 (1H, d, *J* = 1.6 Hz), 7.00 (1H, d, *J* = 8.5 Hz), 3.90 (3H, s), 1.74 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 162.6, 161.1, 155.6, 141.0, 134.8, 134.3, 131.8, 129.9, 127.1, 127.0, 118.1, 114.0, 106.8, 52.5, 26.0; HRMS (FAB, MNa) calcd for $C_{16}H_{14}O_5Na$: 314.0460. Found 314.0463.



3.48

4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)thiophene-2-carboxylic acid (3.48): To a stirred solution of ester **3.71** (0.032 g, 0.100 mmol) in dry DMF (1 mL) at rt was added anhydrous LiCl (0.006 g, 0.150 mmol) in one portion and refluxed for 18 h. The reaction mixture was the cooled to rt and acidified with 1M HCl (0-1 pH). The product was extracted with EtOAc (5 mL, 5X), the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by column chromatography (SiO_2, hexanes:EtOAc) to obtain **3.48** as a colorless solid (0.029 g, 97%).

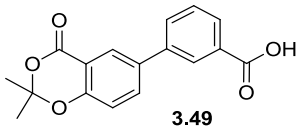
IR (neat, NaCl) 3400-2300 (broad), 1752, 1674, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.04 (1H, d, *J* = 2.3 Hz), 7.95 (1H, d, *J* = 1.6 Hz), 7.83 (1H, dd, *J* = 2.4, 8.6 Hz), 7.83 (1H, d, *J* = 1.7 Hz), 6.97 (1H, d, *J* = 8.6 Hz), 1.63 (6H, s); ^{13}C NMR {^{1}H} ($CDCl_3$): δ 165.2, 162.7, 157.0, 142.3, 137.1, 135.9, 132.7, 131.6, 128.8, 127.7, 119.3, 115.2, 108.2, 26.01. HRMS (FAB, MH^+) calcd for $C_{15}H_{13}O_5S$: 305.0484. Found 305.0490.



3.74

4-(3-carboxy-4-hydroxyphenyl)thiophene-2-carboxylic acid (3.74): Compound **3.48** (0.026 g, 0.085 mmol), TFA (0.90 mL) and water (0.10 mL) were reacted following the general procedure for acetonide removal to afford the product **3.74** as a colorless solid (0.015 g, 68%).

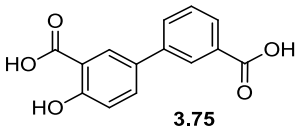
IR (neat, NaCl) 3400-2400 (broad), 1657, 1620 cm^{-1}; ^{1}H NMR (MeOD-D_4): δ 8.14 (1H, s), 8.09 (1H, s), 8.06 (1H, s), 7.92 (1H, d, *J* = 8.5 Hz), 7.02 (1H, d, *J* = 8.6 Hz); ^{13}C NMR {^{1}H} ($CDCl_3$): δ 171.4, 162.9, 160.5, 140.9, 135.5, 133.4, 131.0, 127.4, 126.9, 125.7, 117.9, 117.8.



3.49

3-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)benzoic acid (3.49): Iodide **3.53** (0.760 g, 2.50 mmol), $Pd(OAc)_2$ (0.028 g, 0.125 mmol), Na_2CO_3 (0.530 g, 5.00 mmol), and boronic acid **3.68** (0.622 g, 3.75 mmol) were reacted in dry DMF (25 mL) following the general procedure for Suzuki coupling to obtain **3.49** as a colorless solid (0.595 g, 80%).

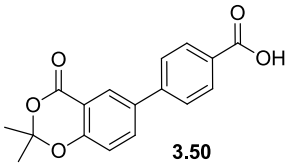
IR (neat, NaCl) 3400-2400 (broad), 1734, 1676 cm^{-1}; ^{1}H NMR (DMSO-D_6) δ 8.19 (1H, s), 8.11 (1H, s), 8.06 (1H, d, *J* = 8.5 Hz), 7.96 (2H, d, *J* = 7.3 Hz), 7.62 (1H, t, *J* = 7.7 Hz), 7.26 (1H, d, *J* = 8.5 Hz), 1.74 (6H, s); ^{13}C NMR (DMSO-D_6) δ 167.8, 160.8, 155.9, 139.3, 136.1, 134.8, 132.3, 131.6, 130.2, 129.2, 127.8, 127.6, 118.9, 114.2, 107.4, 26.0; HRMS (FAB, MH^+) calcd for $C_{17}H_{15}O_5$: 299.0919. Found 299.0927.



3.75

4-hydroxy-[1,1'-biphenyl]-3,3'-dicarboxylic acid (3.75): Compound **3.49** (0.060 g, 0.200 mmol), TFA (0.90 mL) and water (0.10 mL) were reacted following the general procedure for acetonide removal to afford **3.75** as a colorless solid (0.048 g, 92%).

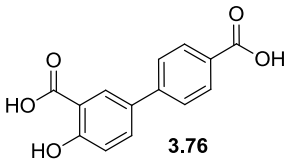
IR (neat, NaCl) 3500-2400 (broad), 1680, 1579 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 11.36 (1H, broad s), 8.13 (1H, s), 8.06 (1H, s), 7.92 (2H, d, *J* = 7.5 Hz), 7.89 (1H, d, *J* = 8.1 Hz), 7.59 (1H, d, *J* = 7.7 Hz), 7.09 (1H, d, *J* = 8.6 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.2, 167.9, 161.6, 140.0, 134.6, 132.2, 131.3, 131.0, 130.1, 128.8, 128.6, 127.4, 118.7, 114.3.



3.50

4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)benzoic acid (3.50): Iodide **3.53** (0.152 g, 0.500 mmol), $Pd(OAc)_2$ (0.006 g, 0.027 mmol), Na_2CO_3 (0.106 g, 1.000 mmol), and boronic acid **3.69** (0.099 g, 0.600 mmol) were reacted in dry DMF (5 mL) following the general procedure for Suzuki coupling to obtain **3.50** as a colorless solid (0.085 g, 57%).

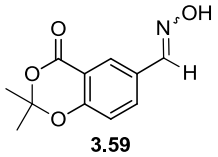
IR (neat, NaCl) 3400-2400 (broad), 1734, 1676 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 8.22 (1H, d, *J* = 2.3 Hz), 8.13 (2H, d, *J* = 8.4 Hz), 7.98 (1H, dd, *J* = 2.3, 8.6 Hz), 7.74 (2H, d, *J* = 8.4 Hz), 7.18 (1H, d, *J* = 8.6 Hz), 1.79 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 167.7, 160.7, 156.2, 143.0, 136.2, 134.5, 130.8, 130.5, 127.8, 127.3, 118.9, 114.2, 107.4, 26.0.



3.76

4-hydroxy-[1,1'-biphenyl]-3,4'-dicarboxylic acid (3.76): Compound **3.50** (0.060 g, 0.200 mmol), TFA (0.90 mL) and water (0.10 mL) were reacted following the general procedure for acetonide removal to afford **3.76** as a colorless solid (0.044 g, 82%).

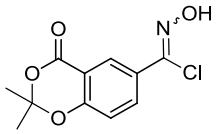
IR (neat, NaCl) 3500-2400 (broad), 1680, 1579 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 11.39 (1H, brd s), 8.12 (1H, s), 8.00 (2H, d, *J* = 8.2 Hz), 7.93 (1H, d, *J* = 8.7 Hz), 7.77 (2H, d, *J* = 8.2 Hz), 7.10 (1H, d, *J* = 8.6 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 167.1, 161.2, 143.0, 134.0, 130.0, 129.1, 128.4, 126.2, 118.0.



3.59

2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxine-6-carbaldehyde oxime (3.59): Aldehyde **3.58** (1.03 g, 5.00 mmol), hydroxyl amine hydrochloride (0.695 g, 10.0 mmol), and pyridine (1.05 mL, 13.0 mmol) were reacted in EtOH (25 mL) following the procedure described below for compound **3.64** to produce oxime **3.59** as a colorless solid (1.00 g, 90%).

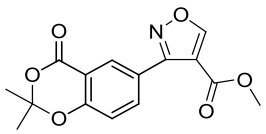
IR (neat, NaCl) 3297, 2992, 2942, 1730, 1626 cm-^{1}; ^{1}H NMR ($CDCl_3$): δ 8.13 (1H, s), 8.10 (1H, d, *J* = 2.1 Hz), 7.88 (1H, dd, *J* = 2.2, 8.6 Hz), 7.01 (1H, d, *J* = 8.6 Hz), 1.76 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 160.8, 157.3, 148.6, 134.2, 129.1, 127.2, 118.2, 113.8, 107.0, 26.0; HRMS (FAB, M^+) calcd for $C_{11}H_{11}NO_4$: 221.0688. Found 221.0688.



3.60

N-hydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxine-6-carbimidoyl chloride (3.60): Oxime **3.59** (0.221 g, 1.00 mmol) and *N*-chlorosuccinimide (NCS) (0.147 g, 1.10 mmol) were reacted in dry DMF (2 mL) following the literature procedure**Error! ookmark not defined.** described to obtain **3.60** as a colorless solid (0.170 g, 67%).

^{1}H NMR ($CDCl_3$): (Mixture of cis and trans isomers) δ 8.72 (1H, s), 8.44 (1H, d, *J* = 2.3 Hz), 8.13 (1H, d, *J* = 2.1 Hz), 8.05 (1H, dd, *J* = 2.3, 8.7 Hz), 7.68 (1H, dd, *J* = 2.2, 8.6 Hz), 7.05 (1H, d, *J* = 8.6 Hz), 7.00 (1H, d, *J* = 8.8 Hz), 1.76 (6H, s), 1.75 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 160.7, 159.5, 157.6, 139.5, 137.9, 134.8, 134.0, 129.0, 127.7, 119.0, 117.7, 114.4, 113.4, 108.2, 107.6, 107.1, 26.00, 25.98; HRMS (FAB, MH^+) calcd for $C_{11}H_{11}NClO_4$: 256.0377. Found 256.0385.

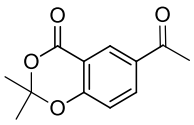


3.61

methyl 3-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)isoxazole-4-carboxylate (3.61): Chlorooxime **3.60** (0.170 g, 0.666 mmol), methyl propiolate (0.18 mL, 2.00 mmol), and Et_3N (0.28 mL, 2.00 mmol) were reacted in dry THF (22 mL) following the literature procedure described**Error! Bookmark not defined.** to give **3.61** as a olorless solid (0.020 g, 10%).

IR (neat, NaCl) 3123, 2942, 1742, 1715, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.35 (1H, d, *J* = 2.2 Hz), 8.16 (1H, dd, *J* = 2.2, 8.6 Hz), 7.29 (1H, d, *J* = 1.2 Hz), 7.12 (1H, d, *J* = 8.6 Hz),

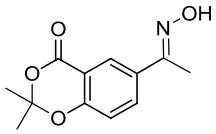
4.03 (3H, s), 1.80 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 161.6, 161.2, 160.5, 157.8, 157.2, 134.7, 128.5, 123.0, 118.6, 114.0, 107.3, 107.2, 53.2, 26.1; HRMS (FAB, MNa^+) calcd for $C_{15}H_{13}NO_6Na$: 326.0641. Found 326.0633.



3.63

6-acetyl-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (3.63): To an ice-cold solution of 5-acetyl salicylic acid **3.62** (0.5 g) in TFA (4 mL) were added trifluoroacetic anhydride (2.5 mL) and acetone (0.5 mL), sequentially. The mixture was slowly warmed to rt, stirred for an hour and refluxed at 100 ^{o}C for 22 h. The reaction mixture was the cooled to rt and concentrated in *vacuo*. Ethyl acetate (10 mL) was added followed by the saturated aq. $NaHCO_3$ with constant shaking to neutralize the reaction mixture (till the bubbling seized). The layers separated and the aq. layer was extracted with EtOAc (10 mL, 3X). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. Column chromatography (SiO_2, hexanes:EtOAc) of the crude solids obtained **3.63** as a colorless solid (0.430 g, 71%).

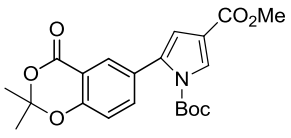
IR (neat, NaCl) 3004, 2990, 1739, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.45 (1H, d, *J* = 2.1 Hz), 8.14 (1H, dd, *J* = 2.2, 8.7 Hz), 6.99 (1H, d, *J* = 8.7 Hz), 2.54 (3H, s), 1.70 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 195.6, 160.2, 159.4, 136.0, 131.9, 130.7, 117.8, 112.8, 107.0, 26.4, 25.8; HRMS (FAB, MH^+) calcd for $C_{12}H_{13}O_4$: 221.0814. Found 221.0811.



3.64

(E)-6-(1-(hydroxyimino)ethyl)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (3.64): To a stirred solution of ketone **3.63** (2.20 g, 10.0 mmol) in dry EtOH (50 mL) at rt was added hydroxylamine hydrochloride ($NH_2OH.HCl$) (1.39 g, 20.0 mmol), and pyridine (2.10 mL, 26.0 mmol) drop wise, and the reaction mixture was refluxed at 80 ^oC for 22 h. The solvent was evaporated, water (50 mL) and EtOAc (50 mL) were added, the layers separated and the aq. layer was extracted with EtOAc (20 mL, 3X). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude solids were purified by column chromatography (SiO_2, hexanes:EtOAc) to obtain product **3.64** as a colorless solid (2.15 g, 91%).

IR (neat, NaCl) 3500, 2915, 1691 cm-^{1}; ^{1}H NMR ($CDCl_3$): δ 8.98 (1H broad s), 8.08 (1H, d, *J* = 2.2 Hz), 7.85 (1H, dd, *J* = 2.3, 8.7 Hz), 6.90 (1H, d, *J* = 8.7 Hz), 2.22 (3H, s), 1.67 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 161.1, 156.8, 154.6, 134.0, 131.4, 127.6, 117.7, 113.3, 106.9, 25.9, 12.2; HRMS (FAB, MH^+) calcd for $C_{12}H_{13}NO_4$: 235.0845. Found 235.0843.



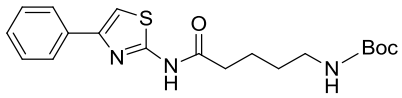
3.66

1-*tert*-butyl 3-methyl 5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-1H-pyrrole-1,3-dicarboxylate (3.66): Oxime **3.64** (0.117 g, 0.500 mmol), DABCO (0.006 g, 0.050 mmol), methyl propiolate (44 μL, 0.500 mmol), boc-anhydride (0.218 g, 1.00

mmol), DMAP (0.006 g, 0.050 mmol), and Et_3N (70 μL, 0.500 mmol) were reacted in toluene (1.0 mL) following the literature procedure[34] described to produce boc-protected pyrrol **3.66** as a colorless liquid (0.026 g, 13%).

IR (neat, NaCl) 2992, 1734, 1709 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.03 (1H, d, *J* = 2.2 Hz), 7.64 (1H, dd, *J* = 2.2, 8.5 Hz), 6.99 (1H, d, *J* = 8.7 Hz), 6.91 (1H, d, *J* = 3.7 Hz), 6.21 (1H, d, *J* = 3.7 Hz), 3.86 (3H, s), 1.76 (6H, s), 1.48 (9H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 160.7, 160.5, 155.9, 149.4, 137.4, 137.0, 129.7, 126.5, 125.0, 118.2, 117.2, 113.2, 110.9, 106.7, 86.0, 51.8, 27.3, 25.9; HRMS (FAB, MNa^+) calcd for $C_{21}H_{23}NO_7Na$: 424.1372. Found 424.1378.

Amines and their precursors:

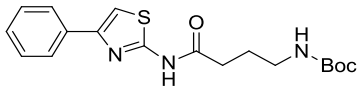


3.86

***tert*-Butyl (5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)carbamate (3.86):** EDC.HCl (1.150 g, 6.00 mmol), HOBt (0.811 g, 6.00 mmol), amine **3.77** (0.529 g, 3.00 mmol), and acid **3.85** (0.717 g, 3.30 mmol) were reacted in dry DMF (9 mL) following the general procedure for EDC coupling to afford **3.86** as a colorless solid (0.810 g, 72%).

IR (neat, NaCl) 3387, 3145, 2933, 1703, 1679, 1550 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.97 (1H, brd s), 7.81 (2H, dd, *J* = 1.4, 8.5 Hz), 7.43 (2H, dt, *J* = 1.4, 8.4 Hz), 7.37 (1H, tt, *J* = 1.4, 8.5 Hz), 7.13 (1H, s), 4.60 (1H, brd s), 3.08 (2H, app q, *J* = 6.4 Hz), 2.24 (2H, t, *J* = 7.4 Hz), 1.61 (2H, quin, *J* = 7.4 Hz), 1.46 (9H, s), 1.38 (2H, quin, *J* = 6.9 Hz); ^{13}C {^1H} NMR ($CDCl_3$): δ 171.5, 159.8, 156.0, 149.4, 134.5, 128.9, 128.2, 126.3, 107.9, 79.1,

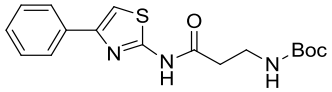
39.9, 35.1, 29.3, 28.5, 21.9; HRMS (FAB, MNa^+) calcd for $C_{19}H_{25}N_3O_3SNa$: 398.1514. Found 398.1503.



3.87

***tert*-Butyl (4-oxo-4-((4-phenylthiazol-2-yl)amino)butyl)carbamate (3.87):** EDC.HCl (0.502 g, 2.62 mmol), HOBt (0.354 g, 2.62 mmol), acid **3.84** (0.356 g, 1.75 mmol), and amine **3.78** (0.370 g, 2.10 mmol) were reacted in dry DMF (9 mL) following the general procedure of EDC coupling to afford **3.87** as a colorless solid (0.350 g, 46%).

IR (neat, NaCl) 3387, 3145, 2933, 1703, 1679, 1550 cm^{-1}; ^1H NMR (DMSO-D_6): δ 12.23 (1H, s), 7.89 (2H, d, *J* = 7.1 Hz), 7.59 (1H, s), 7.44 (2H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 6.85 (1H, t, *J* = 5.5 Hz), 2.96 (2H, app q, *J* = 6.7 Hz), 2.45 (2H, t, *J* = 7.4 Hz), 1.72 (2H, quin, *J* = 7.1 Hz), 1.37 (9H, s); ^{13}C NMR {^1H} (DMSO-D_6): δ 171.2, 157.9, 155.6, 148.7, 134.3, 128.7, 127.7, 125.6, 107.8, 77.5, 38.6, 32.3, 28.2, 25.0.

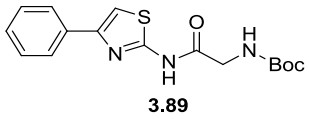


3.88

***tert*-Butyl (3-oxo-3-((4-phenylthiazol-2-yl)amino)propyl)carbamate (3.88):** EDC.HCl (1.92 g, 10.01 mmol), HOBt (1.35 g, 10.00 mmol), acid **3.83** (1.13 g, 5.97 mmol), and amine **3.78** (0.881 g, 5.00 mmol) were reacted in dry DMF (15 mL) following the general procedure of EDC coupling to afford **3.88** as a colorless solid (1.55 g, 89%).

IR (neat, NaCl) 3250, 3193, 2980, 1699, 1549 cm-^{1}; ^1H NMR (MeOD-D_4): δ 7.89-7.92 (2H, m), 7.37-7.43 (2H, m), 7.36 (1H, s), 7.27-7.33 (1H, m), 3.42-3.47 (2H, m), 2.69 (2H, t, *J* = 6.6 Hz), 1.44 (9H, s); ^{13}C {^1H} NMR (MeOD-D_4): δ 171.8, 159.4, 158.5, 151.3,

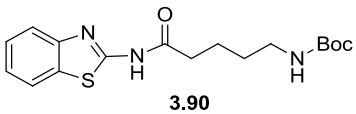
136.1, 129.7, 128.9, 127.2, 108.6, 80.4, 37.6, 37.2, 28.8; HRMS (FAB, MNa^+) calcd for $C_{17}H_{21}N_3O_3SNa$: 370.1201. Found 370.1207.



3.89

***tert*-Butyl (2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)carbamate (3.89):** EDC.HCl (1.92 g, 10.01 mmol), HOBt (1.35 g, 10.00 mmol), acid **3.82** (1.05 g, 5.99 mmol), and amine **3.78** (0.881 g, 5.00 mmol) were reacted in dry DMF (15 mL) following the general procedure for EDC coupling to afford **3.89** as a colorless solid (1.35 g, 81%).

IR (neat, NaCl) 3428, 3397, 3227, 3096, 2976, 1703, 1657 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.5 (1H, brd s), 7.78-7.81 (2H, m), 7.38-7.43 (2H, m), 7.33-7.36 (1H, m),7.15 (1H, s), 5.22 (1H, broad s), 3.98 (2H, brd s), 1.47 (9H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 168.1, 157.8, 156.3, 150.2, 134.6, 129.0, 128.4, 126.4, 108.3, 81.2, 44.6, 28.5; HRMS (FAB, MNa^+) calcd for $C_{16}H_{19}N_3O_3SNa$: 356.1045. Found 356.1052.

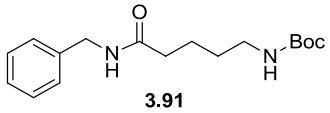


3.90

***tert*-Butyl (5-(benzo[d]thiazol-2-ylamino)-5-oxopentyl)carbamate (3.90):** EDC.HCl (1.15 g, 6.00 mmol), HOBt (0.811 g, 6.00 mmol), acid **3.85** (0.869 g, 4.00 mmol), and amine **3.79** (0.721 g, 4.80 mmol) were reacted in dry DMF (12 mL) following the general procedure for EDC coupling to afford **3.90** as a colorless solid after recrystallization (1.120 g, 80%).

IR (neat, NaCl) 3358, 3203, 2978, 2925, 1683, 1610, 1520 cm-^{1}; ^1H NMR ($CDCl_3$): δ 11.20 (1H, brd s), 7.83 (1H, dd, *J* = 0.6, 7.9 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.44 (1H, dt, *J*

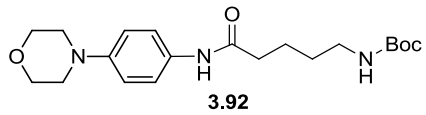
= 1.2, 7.4 Hz), 7.32 (1H, dt, *J* = 1.0, 8.0 Hz), 4.59 (1H, brd s), 3.12 (2H, app q, *J* = 6.6 Hz), 2.52 (2H, t, *J* = 7.4 Hz), 1.74 (2H, quin, *J* = 7.3 Hz), 1.52 (2H, quin, *J* = 7.4 Hz), 1.44 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.9, 159.7, 156.3, 148.1, 132.1, 126.5, 124.1, 121.8, 120.5, 79.5, 40.0, 36.0, 29.7, 28.6, 22.3; HRMS (FAB, MH^+) calcd for $C_{17}H_{24}N_3O_3S$: 350.1538. Found 350.1549.



3.91

***tert*-Butyl (5-(benzylamino)-5-oxopentyl)carbamate (3.91):** EDC.HCl (0.863 g, 4.50 mmol), HOBt (0.608 g, 4.50 mmol), acid **3.85** (0.651 g, 3.00 mmol), and amine **3.80** (0.39 mL, 3.60 mmol) were reacted in dry DMF (9 mL) following the general procedure of EDC coupling to afford **3.91** as a colorless solid (0.680 g, 74%).

IR (neat, NaCl) 3317, 2974, 2929, 1695, 1642, 1504 cm-^{1}; ^{1}H NMR ($CDCl_3$): δ 7.27-7.37 (5H, m), 5.91 (1H, brd s), 4.61 (1H, brd s), 4.44 (2H, d, *J* = 5.7 Hz), 3.14 (2H, app q, *J* = 6.5 Hz), 2.26 (2H, t, *J* = 7.3 Hz), 1.71 (2H, quin, *J* = 7.5 Hz), 1.53 (2H, quin, *J* = 7.0 Hz), 1.42 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.9, 156.4, 138.6, 129.0, 128.1, 127.7, 79.4, 43.9, 40.0, 36.2, 29.8, 28.6, 22.9; HRMS (FAB, MH^+) calcd for $C_{17}H_{27}N_2O_3$: 307.2022. Found 307.2017.

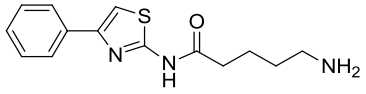


3.92

***tert*-Butyl (5-((4-morpholinophenyl)amino)-5-oxopentyl)carbamate (3.92):** To a stirred solution of amine **3.81** (0.535 g, 3.00 mmol) in dry CH_2Cl_2 (9 mL) at rt was added DMAP (0.073 g, 0.60 mmol) and pyridine (0.73 mL, 9.00 mmol)., and the reaction

mixture was stirred for 5 minutes before adding acid **3.85** (0.782 g, 3.6 mmol). The reaction mixture was then cooled to 0 ^{o}C (ice bath), stirred for 15 minutes, DCC (1.24 g, 6.00 mmol) was added and stirred at 0 ^{o}C temperature for an additional 1 h. The reaction mixture was then warmed up to rt and stirred for additional 22 h. Water (5 mL) was added, filtered and the residue was washed with EtOAc. The crude solid was purified by column chromatography (SiO_2, hexanes:EtOAc) to afford product **3.92** as a colorless solid (0.700, 60%, contains some DCC urea).

IR (neat, NaCl) 3355, 3272, 2975, 1670, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$): (contains some DCC urea) δ 7.69 (1H, brd s), 7.42 (2H, d, *J* = 8.9 Hz), 6.85 (2H, d, *J* = 8.9 Hz), 4.73 (1H, brd s), 3.85 (4H, t, *J* = 4.6 Hz), 3.13 (2H, app q, *J* = 6.4 Hz), 3.08 (4H, t, *J* = 4.7 Hz), 2.35 (2H, t, *J* = 7.3 Hz), 1.70 (2H, app quin, *J* = 7.3 Hz), 1.54 (2H, app quin, *J* = 6.9 Hz), 1.43 (9H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.4, 156.4, 148.1, 131.2, 121.5, 116.3, 79.3, 67.0, 49.9, 39.8, 36.7, 34.0, 29.6, 28.5.

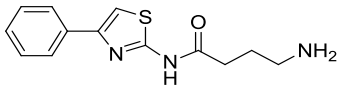


3.93

5-amino-N-(4-phenylthiazol-2-yl)pentanamide (3.93): Boc-amine **3.86** (0.660 g, 1.76 mmol) and TFA/CH_2Cl_2 (3 mL each) were reacted following the general procedure for boc removal to produce **3.93** as a colorless solid (0.365 g, 75%).

IR (neat, NaCl) 3500-2600 (broad), 3387, 1687, 1527 cm^{-1}; ^{1}H NMR (MeOD-D_4): δ 7.66 (2H, d, *J* = 7.1Hz), 7.04-7.18 (4H, m), 2.76 (2H, t, *J* = 7.2 Hz), 2.35 (2H, t, *J* = 6.8 Hz), 1.52-1.61 (4H, m); ^{13}C {^{1}H} NMR (MeOD-D_4): δ 173.2, 159.3, 151.3, 136.0, 129.7,

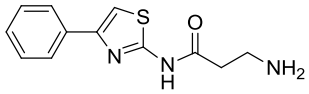
129.0, 127.1, 108.6, 40.5, 35.8, 28.1, 23.1; HRMS (FAB, MH^+) calcd for $C_{14}H_{18}N_3OS$: 276.1171. Found 276.1172.



3.94

4-amino-N-(4-phenylthiazol-2-yl)butanamide (3.94): Boc-amine **3.87** (0.200 g, 0.548 mmol) and TFA/CH_2Cl_2 (1 mL each) were reacted following the general procedure of boc removal to produce **3.94** as a colorless solid (0.105 g, 72%).

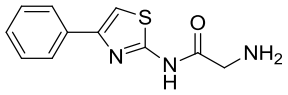
IR (neat, NaCl) 3500-2500 (broad), 1679, 1664, 1537 cm^{-1}; ^1H NMR (MeOD-D_4) δ 7.91 (2H, d, *J* = 7.4 Hz), 7.40 (2H, t, *J* = 7.6 Hz), 7.38 (1H, s), 7.31 (1H, t, *J* = 7.5 Hz), 3.07 (2H, t, *J* = 7.6 Hz), 2.67 (2H, t, *J* = 7.0 Hz), 2.06 (2H, quin, *J* = 7.1 Hz); ^{13}C NMR (MeOD-D_4) δ 171.0, 158.1, 150.1, 134.7, 128.5, 127.8, 125.9, 107.4, 39.1, 31.9, 22.6; HRMS (FAB, MNa^+) calcd for $C_{13}H_{15}N_3OSNa$: 284.0833. Found 284.0839.



3.95

3-amino-N-(4-phenylthiazol-2-yl)propanamide (3.95): Boc-amine **3.88** (0.868 g, 2.50 mmol) and TFA/CH_2Cl_2 (5 mL each) were reacted following the general procedure for boc removal to produce **3.95** as a colorless solid (0.510 g, 82%).

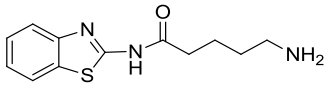
IR (neat, NaCl) 3400-2400 (broad), 1676, 1537 cm-^{1}; ^1H NMR (MeOD-D_4): δ 7.88-7.91 (2H, m), 7.36-7.41 (2H, m), 7.38 (1H, s), 7.27-7.32 (1H, m), 3.31-3.33 (2H, m), 2.91 (2H, t, *J* = 6.3 Hz); ^{13}C {^1H} NMR (MeOD-D_4): δ 170.9, 159.3, 151.2, 136.0, 129.7, 128.9, 127.1, 108.7, 36.8, 35.4; HRMS (FAB, MH^+) calcd for $C_{12}H_{14}N_3OS$: 248.0857. Found 248.0861.



3.96

2-amino-N-(4-phenylthiazol-2-yl)acetamide (3.96): Boc-amine **3.89** (0.833 g, 2.50 mmol) and TFA/CH_2Cl_2 (5 mL each) were reacted following the general procedure for boc removal to produce **3.96** as a colorless solid (0.495 g, 85%).

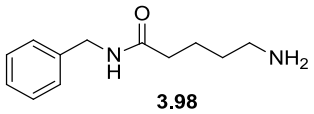
IR (neat, NaCl) 3366, 3200, 3092, 1676, 1545 cm-^{1}; ^{1}H NMR (MeOD-D_4): δ 7.85-7.88 (2H, m), 7.34-7.40 (2H, m), 7.36 (1H, s), 7.25-7.31 (1H, m), 3.70 (2H, brd s); ^{13}C {^{1}H} NMR (MeOD-D_4): δ 169.3, 157.9, 150.1, 134.7, 128.5, 127.8, 125.9, 107.6, 42.7; HRMS (FAB, MNa^+) calcd for $C_{11}H_{11}N_3OSNa$: 256.0521. Found 256.0525.



3.97

5-amino-N-(benzo[d]thiazol-2-yl)pentanamide (3.97): Boc-amine **3.90** (0.314 g, 0.90 mmol) and TFA/CH_2Cl_2 (2 mL each) were reacted following the general procedure for boc removal to produce **3.97** as a colorless solid (0.175 g, 78%).

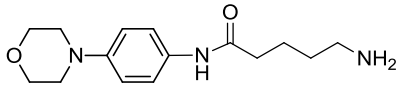
IR (neat, NaCl) 3362, 3252, 3203, 2937, 1695, 1597 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 7.97 (1H, d, *J* = 7.7 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.43 (1H, t, *J* = 7.2 Hz), 7.30 (1H, t, *J* = 7.3 Hz), 2.77 (2H, t, *J* = 6.4 Hz), 2.54 (2H, t, *J* = 6.5 Hz), 1.61-1.68 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.7, 158.5, 149.2, 132.1, 126.7, 124.1, 122.3, 121.1, 39.1, 35.2, 27.2, 22.2; HRMS (FAB, MH^+) calcd for $C_{12}H_{16}N_3OS$: 250.1014. Found 250.1008.



3.98

5-amino-N-benzylpentanamide (3.98): Boc-amine **3.91** (0.520 g, 1.70 mmol) and TFA/CH_2Cl_2 (3.5 mL each) were reacted following the general procedure for boc removal to give the crude product. The highly polar product remained in the aqueous layer while the reaction mixture was neutralized with saturated aq. $NaHCO_3$ solution. Therefore, the aq. layer was evaporated to obtain off-white solid, which was extracted with EtOAc (10 mL, 3X) to produce **3.98.** The product was used for the next step without further purification.

^{1}H NMR (MeOD-D_4): δ 7.20-7.32 (5H, m), 4.37 (2H, d, *J* = 5.7 Hz), 2.85 (2H, broad s), 2.29 (2H, t, *J* = 6.7 Hz), 1.62-1.171 (4H, m) (also contains ethyl acetate peaks).



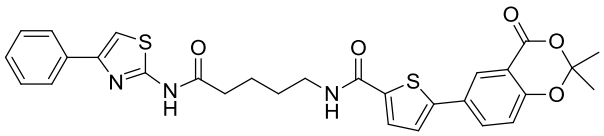
3.99

5-amino-N-(4-morpholinophenyl)pentanamide (3.99): Boc-amine **3.92** (0.430 g, 1.14 mmol) and TFA/CH_2Cl_2 (2 mL each) were reacted following the general procedure of boc removal to give the product **3.99**. The highly polar product remained in the aqueous layer while the reaction mixture was neutralized with aq. $NaHCO_3$ solution. Therefore, the aq. layer was evaporated and the remaining thick liquid was used without any purification for the further reaction.

IR (neat, NaCl) 3305, 3027, 2970, 1657, 1510 cm^{-1}; ^{1}H NMR (MeOD-D_4): δ 7.36 (2H, d, *J* = 9.1 Hz), 6.84 (2H, d, *J* = 9.1 Hz), 3.74 (4H, t, *J* = 4.7 Hz), 3.01 (4H, t, *J* = 4.8 Hz), 2.89 (2H, t, *J* = 6.9 Hz), 2.35 (2H, t, *J* = 6.6 Hz), 1.60-1.71 (4H, m); ^{13}C {^{1}H} NMR

(MeOD-D_4): δ 173.5, 149.7, 132.6, 122.6, 117.4, 68.0, 51.1, 40.4, 36.8, 28.1, 23.5; HRMS (FAB, MNa) calcd for $C_{15}H_{23}N_3O_2Na$: 300.1688. Found 300.1689.

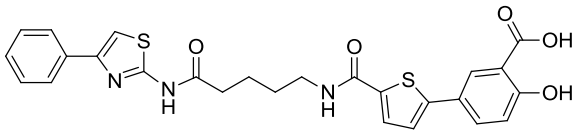
Inhibitors and their precursors:



3.100

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)thiophene-2-carboxamide (3.100): EDC.HCl (0.366 g, 1.908 mmol), HOBt (0.258 g, 1.908 mmol), acid **3.47** (0.290 g, 0.954 mmol), and amine **3.93** (0.315 g, 1.145 mmol) were reacted in dry DMF (6 mL) following the general procedure for EDC coupling to afford **3.100** as a colorless solid (0.180 g, 34%).

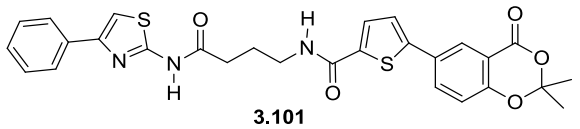
IR (neat, NaCl) 3427, 3252, 2913, 1756, 1687, 1625, 1540 cm^{-1}; ^1H NMR (DMSO-D_6): δ 12.24 (1H, s), 8.59 (1H, t, *J* = 5.5 Hz), 8.07 (1H, d, *J* = 2.2 Hz), 8.00 (1H, dd, *J* = 2.3, 8.6 Hz), 7.88 (2H, d, *J* = 7.3 Hz), 7.73 (1H, d, *J* = 3.9 Hz), 7.57 (1H, s), 7.55 (1H, d, *J* = 3.9 Hz), 7.42 (2H, t, *J* = 7.3 Hz), 7.31 (1H, t, *J* = 7.2 Hz), 7.19 (1H, d, *J* = 8.6 Hz), 3.28 (2H, app q, *J* = 6.3 Hz), 2.51 (2H, t, *J* = 6.4 Hz), 1.68 (6H, s), 1.54-1.66 (4H, m); ^{13}C {^1H} NMR (DMSO-D_6): δ 171.5, 160.8, 159.9, 157.8, 155.2, 148.7, 145.1, 139.3, 134.2, 134.1, 129.0, 128.7, 128.2, 127.7, 125.6, 125.5, 124.7, 118.4, 113.5, 107.8, 106.8, 34.5, 28.6, 25.2 (2C), 22.2, 21.0; HRMS (FAB, MNa^+) calcd for $C_{29}H_{27}N_3O_5S_2Na$: 584.1290. Found 584.1308.



3.116

2-hydroxy-5-(5-((5-oxo-5-((4-phenylthiazol-2-l)amino)pentyl)carbamoyl) thiophen-2-yl)benzoic acid: Compound **3.100** (0.090 g, 0.160 mmol) was reacted with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.116** as a yellow solid (0.055 g, 66%).

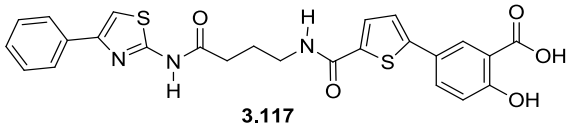
IR (neat, NaCl) 3309, 3300-2300 (broad), 1715, 1679, 1617, 1552 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.25 (1H, s), 8.51 (1H, t, *J* = 5.5 Hz), 8.04 (1H, d, *J* = 2.3 Hz), 7.89 (2H, d, *J* = 7.4 Hz), 7.86 (1H, dd, *J* = 2.3, 8.6 Hz), 7.71 (1H, d, *J* = 3.9 Hz), 7.60 (1H, s), 7.44 (1H, d, *J* = 4.0 Hz), 7.42 (2H, d, *J* = 7.8 Hz), 7.34 (1H, t, *J* = 7.3 Hz), 7.05 (1H, d, *J* = 8.7 Hz), 3.27 (2H, app q, *J* = 6.5 Hz), 2.51 (2H, t, *J* = 5.8 Hz), 1.66-1.69 (2H, m), 1.55-1.58 (2H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.5, 171.3, 161.0, 160.8, 157.9, 148.7, 146.2, 138.4, 134.3, 132.8, 129.0, 128.7, 127.7, 127.0, 125.6, 124.6, 123.6, 118.2, 113.6, 107.9, 39.0, 34.6, 28.7, 22.3; HRMS (FAB, MH^+) calcd for $C_{26}H_{24}N_3O_5S_2$: 522.1157. Found 522.1158.



3.101

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(4-oxo-4-((4-phenylthiazol-2-yl)amino)butyl)thiophene-2-carboxamide (3.101): EDC.HCl (0.057 g, 0.300 mmol), HOBt (0.040 g, 0.300 mmol), acid **3.47** (0.061 g, 0.200 mmol), and amine **3.94** (0.079 g, 0.300 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.101** as a colorless solid (0.072 g, 66%).

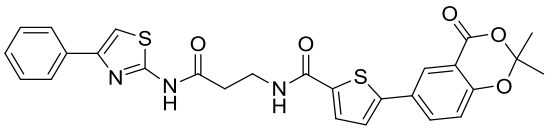
IR (neat, NaCl) 3355, 3196, 2930, 1749, 1668, 1614 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.59 (1H, t, *J* = 5.5 Hz), 8.09 (1H, d, *J* = 2.4 Hz), 8.02 (1H, dd, *J* = 2.4, 8.6 Hz), 7.89 (1H, d, *J* = 7.2 Hz), 7.75 (1H, d, *J* = 3.9 Hz), 7.61 (1H, s), 7.59 (1H, d, *J* = 3.9 Hz), 7.43 (2H, t, *J* = 7.3 Hz), 7.31 (1H, t, *J* = 7.3 Hz), 7.22 (1H, d, *J* = 8.6 Hz), 3.31 (2H, app q, *J* = 6.3 Hz), 2.55 (2H, t, *J* = 7.3 Hz), 1.90 (2H, quin, *J* = 7.0 Hz), 1.74 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.2, 160.8, 159.8, 157.8, 155.2, 148.7, 145.1, 139.3, 134.3, 134.1, 129.1, 128.7, 128.2, 127.7, 125.6, 125.5, 124.7, 118.4, 113.5, 107.8, 106.8, 38.6, 32.3, 25.3 (2C), 24.6; HRMS (FAB, MH^+) calcd for $C_{28}H_{26}N_3O_5S_2$: 548.1314. Found 548.1298.



3.117

2-hydroxy-5-(5-((4-oxo-4-((4-phenylthiazol-2-yl)amino)butyl)carbamoyl) thiophen-2-yl)benzoic acid (3.117): Compound **3.101** (0.045 g, 0.082 mmol) was reacted with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.117** as a yellow solid (0.036 g, 86%).

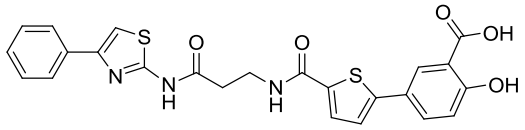
IR (neat, NaCl) 3301, 2961, 2915, 1688, 1626, 1560 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.55 (1H, brd s), 8.04 (1H, brd s), 7.84-7.90 (3H, m), 7.72 (1H, d, *J* = 3.5 Hz), 7.60 (1H, s), 7.45 (1H, d, *J* = 3.4 Hz), 7.41 (2H, d, *J* = 7.5 Hz), 7.31 (1H, t, *J* = 7.1 Hz), 7.04 (1H, d, *J* = 8.6 Hz), 3.31 (2H, under HOD peak), 2.54 (2H, t, *J* = 6.5 Hz), 1.86-1.90 (2H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.9 (2C), 161.8, 161.7, 158.6, 149.4, 147.0, 139.0, 135.0, 133.5, 129.8, 129.4, 128.4, 127.7, 126.3, 125.3, 124.2, 118.9, 114.4, 108.6, 39.2, 33.1, 25.4; HRMS (FAB, MH^+) calcd for $C_{25}H_{21}N_3O_5S_2Na$: 530.0820. Found 530.0809.



3.102

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(3-oxo-3-((4-phenylthiazol-2-yl)amino)propyl)thiophene-2-carboxamide (3.102): EDC.HCl (0.077 g, 0.400 mmol), HOBt (0.054 g, 0.400 mmol), acid **3.47** (0.061 g, 0.200 mmol), and amine **3.95** (0.059 g, 0.240 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.102** as a colorless solid (0.047 g, 44%).

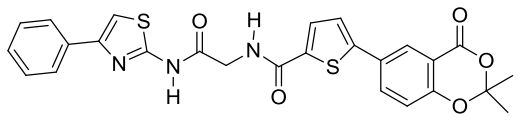
IR (neat, NaCl) 3350, 3188, 2930, 1749, 1668, 1612 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.36 (1H, s), 8.75 (1H, t, *J* = 5.4 Hz), 8.09 (1H, d, *J* = 2.3 Hz), 8.03 (1H, dd, *J* = 2.4, 8.6 Hz), 7.90 (2H, d, *J* = 7.2 Hz), 7.76 (1H, d, *J* = 4.0 Hz), 7.63 (1H, s), 7.59 (1H, d, *J* = 3.9 Hz), 7.43 (2H, t, *J* = 7.3 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 7.22 (1H, d, *J* = 8.6 Hz), 3.59 (2H, app q, *J* = 6.3 Hz), 2.78 (2H, t, *J* = 6.7 Hz), 1.73 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 169.8, 161.0, 159.8, 157.8, 155.3, 148.7, 145.3, 139.1, 134.3, 134.2, 129.3, 128.7, 128.2, 127.8, 125.6, 125.6, 124.8, 118.4, 113.6, 107.9, 106.8, 35.4, 35.0, 25.3 (2C).



3.118

2-hydroxy-5-(5-((3-oxo-3-((4-phenylthiazol-2-yl)amino)propyl)carbamoyl) thiophen-2-yl)benzoic acid (3.118): Compound **3.102** (0.035 g, 0.066 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.118** as a yellow solid (0.026 g, 81%).

IR (neat, NaCl) 3500-2500 (broad), 1672, 1606, 1552 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.35 (1H, s), 8.69 (1H, t, *J* = 5.1 Hz), 8.04 (1H, brd s), 7.89 (2H, d, *J* = 7.6 Hz), 7.87 (1H, d, *J* = 8.6 Hz), 7.73 (1H, d, *J* = 3.7 Hz), 7.62 (1H, s), 7.45 (1H, d, *J* = 3.9 Hz), 7.42 (2H, d, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 7.05 (1H, d, *J* = 8.6 Hz), 3.58 (2H, app q, *J* = 5.9 Hz), 2.78 (2H, t, *J* = 6.6); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 170.5 (2C), 161.8 (2C), 158.5, 149.5, 147.1, 138.8, 135.0, 133.5, 130.0, 129.4, 128.5, 127.7, 126.4, 125.3, 124.3, 118.9, 108.7, 36.0, 35.8; HRMS (FAB, MH^{+}) calcd for $C_{24}H_{20}N_3O_5S_2$: 494.0844. Found 494.0830.

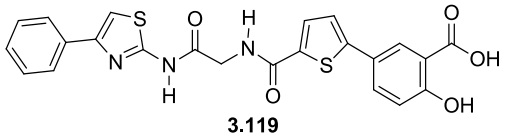


3.103

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)thiophene-2-carboxamide (3.103): EDC.HCl (0.057 g, 0.300 mmol), HOBt (0.040 g, 0.300 mmol), acid **3.47** (0.061 g, 0.200 mmol), and amine **3.96** (0.056 g, 0.240 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.103** as a colorless solid (0.086 g, 83%).

IR (neat, NaCl) 3405, 3193, 3065, 2988, 1745, 1691, 1637 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.50 (1H, s), 9.07 (1H, t, *J* = 5.5 Hz), 8.12 (1H, d, *J* = 1.9 Hz), 8.06 (1H, dd, *J* = 1.9, 8.6 Hz), 7.92 (2H, d, *J* = 7.6 Hz), 7.85 (1H, d, *J* = 3.8 Hz), 7.66 (2H, s), 7.45 (2H, t, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.1 Hz), 7.24 (1H, t, *J* = 8.6 Hz), 4.21 (2H, d, *J* = 5.5 Hz), 1.74 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 168.9, 162.2, 160.6, 158.5, 156.1, 149.6, 146.4, 139.1, 135.0 (2C), 130.6, 129.5, 128.9, 128.6, 126.4 (2C), 125.6, 119.2, 114.3, 108.9, 107.6,

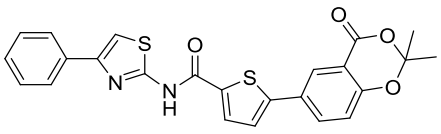
43.1, 26.0 (2C); HRMS (FAB, MH^+) calcd for $C_{26}H_{22}N_3O_5S_2$: 520.1001. Found 520.1010.



3.119

2-hydroxy-5-(5-((2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)carbamoyl) thiophen-2-yl)benzoic acid (3.119): Compound **3.103** (0.060 g, 0.116 mmol) was reacted with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.119** as a yellow solid (0.047 g, 85%).

IR (neat, NaCl) 3400-2400 (broad), 1695, 1641, 1591 cm^{-1}; ^1H NMR (DMSO-D_6): δ 12.48 (1H, s), 9.00 (1H, brd s), 8.08 (1H, brd s), 7.90-7.93 (3H, m), 7.83 (1H, s), 7.65 (1H, s), 7.52 (1H, d, *J* = 3.1 Hz), 7.45 (2H, t, *J* = 7.1 Hz), 7.34 (1H, t, *J* = 7.0 Hz), 7.07 (1H, d, *J* = 8.5 Hz), 4.21 (2H, under HOD peak); ^{13}C {^1H} NMR (DMSO-D_6): δ 171.9, 169.0, 162.2, 161.8, 158.4, 149.6, 147.5, 138.0, 135.0, 133.6, 130.6, 129.4, 128.5, 127.8, 126.4, 125.2, 124.4, 118.9, 114.4, 108.8, 43.1; HRMS (FAB, MNa) calcd for $C_{23}H_{17}N_3O_5S_2Na$: 502.0507. Found 502.0491.

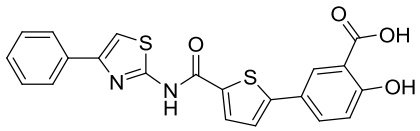


3.104

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(4-phenylthiazol-2-yl)thiophene-2-carboxamide (3.104): EDC.HCl (0.043 g, 0.225 mmol), HOBt (0.030 g, 0.225 mmol), acid **3.47** (0.046 g, 0.150 mmol), and amine **3.78** (0.040 g, 0.225 mmol)

were reacted in dry DMF (1 mL) following the general procedure for EDC coupling to afford **3.104** as a yellow solid (0.043 g, 62%).

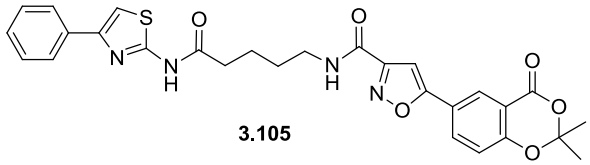
IR (neat, NaCl) 3405, 3193, 3065, 1745, 1691, 1637 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.94 (1H, s), 8.30 (1H, d, *J* = 4.0 Hz), 8.16 (1H, d, *J* = 2.3 Hz), 8.09 (1H, dd, *J* = 2.4, 8.6 Hz), 7.96 (2H, d, *J* = 7.2 Hz), 7.72 (1H, d, *J* = 4.0 Hz), 7.71 (1H, s), 7.46 (2H, t, *J* = 7.2 Hz), 7.35 (1H, t, *J* = 7.3 Hz), 7.25 (1H, t, *J* = 8.6 Hz), 1.74 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 160.5, 160.1, 158.8, 156.4, 149.9, 148.7, 136.9, 135.2, 135.0, 132.9, 129.5, 128.6, 128.5, 126.7, 126.5, 126.2, 119.2, 114.3, 109.4, 107.6, 26.0.



3.120

2-hydroxy-5-(5-((4-phenylthiazol-2-yl)carbamoyl)thiophen-2-yl)benzoic acid (3.120): Compound **3.104** (0.030 g, 0.065 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.120** as a yellow solid (0.023 g, 84%).

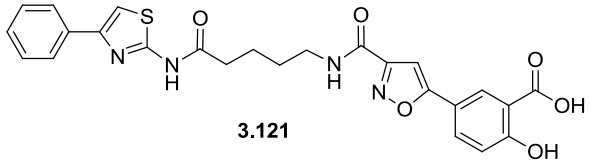
IR (neat, NaCl) 3500-2500 (broad), 1664, 1614, 1556 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.90 (1H, s), 8.29 (1H, d, *J* = 3.3 Hz), 8.11 (1H, broad s), 7.93-7.98 (3H, m), 7.70 (1H, broad s), 7.60 (1H, d, *J* = 3.0 Hz), 7.46 (2H, t, *J* = 7.2 Hz), 7.35 (1H, t, *J* = 7.2 Hz), 7.09 (1H, d, *J* = 8.6 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.9, 162.2, 160.2, 158.9, 150.0, 149.8, 135.8, 135.0, 133.7, 132.9, 129.5, 128.5, 128.1, 126.5, 125.0, 124.8, 119.0, 114.7, 109.4.



3.105

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)isoxazole-3-carboxamide (3.105): EDC.HCl (0.332 g, 1.73 mmol), HOBt (0.234 g, 1.73 mmol), acid **3.45** (0.250 g, 0.865 mmol), and amine **3.93** (0.262 g, 0.951 mmol) were reacted in dry DMF (3 mL) following the general procedure for EDC coupling to afford **3.105** as a colorless solid (0.190 g, 40%).

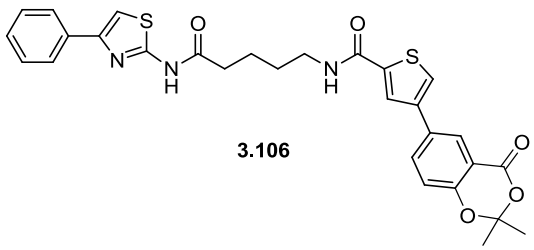
IR (neat, NaCl) 3409, 3119, 2934, 1740, 1690, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 11.43 (1H, s), 8.38 (1H, d, *J* = 2.1 Hz), 7.91 (1H, dd, *J* = 2.2, 8.6 Hz), 7.79 (2H, d, *J* = 7.0 Hz), 7.41 (2H, t, *J* = 6.9 Hz), 7.36 (1H, t, *J* = 7.1 Hz), 7.13 (1H, s), 7.04 (1H, d, *J* = 8.6 Hz), 7.01 (1H, s), 3.39 (2H, app q, *J* = 6.6 Hz), 2.22 (2H, t, *J* = 7.2 Hz), 1.77 (6H, s), 1.66 (2H, app quin, *J* = 7.5 Hz), 1.48 (2H, app quin, *J* = 6.8 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 171.3, 169.9, 160.3, 159.7, 159.4, 159.1, 157.6, 149.6, 134.4, 133.8, 129.1, 128.4, 127.5, 126.5, 121.9, 118.5, 114.1, 108.1, 107.2, 99.4, 39.0, 35.3, 28.8, 26.0, 22.2; HRMS (FAB, MH^+) calcd for $C_{28}H_{27}N_4O_6S$: 547.1651. Found 547.1641.



3.121

2-hydroxy-5-(3-((5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)carbamoyl) isoxazol-5-yl)benzoic acid (3.121): Compound **3.105** (0.065 g, 0.120 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.121** as a colorless solid (0.035 g, 58%).

IR (neat, NaCl) 3347, 3119, 3300-2500 (broad), 2934, 1695, 1676, 1620 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.22 (1H, s), 8.82 (1H, t, *J* = 5.7 Hz), 8.24 (1H, d, *J* = 2.2 Hz), 8.02 (1H, dd, *J* = 2.2, 8.7 Hz), 7.86 (2H, d, *J* = 7.3 Hz), 7.56 (1H, s), 7.41 (2H, t, *J* = 7.3 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 7.22 (1H, s), 7.10 (1H, d, *J* = 8.7 Hz), 3.28 (2H, app q, *J* = 6.4 Hz), 2.48 (2H, t, *J* = 7.2 Hz), 1.56-1.68 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.9, 171.3, 169.9, 163.0, 160.1, 158.9, 158.3, 149.1, 134.6, 133.3, 129.1, 128.2, 128.0, 126.0, 118.8, 118.1, 108.2, 99.1, 38.9, 34.9, 28.7, 22.6; HRMS (FAB, MH^{+}) calcd for $C_{25}H_{23}N_4O_6S$: 507.1338. Found 507.1336.

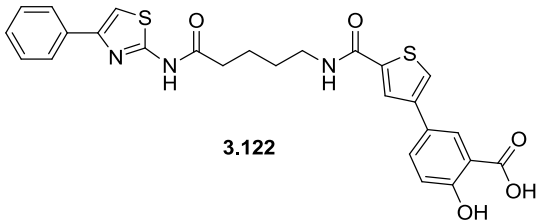


3.106

4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)thiophene-2-carboxamide (3.106): EDC.HCl (0.192 g, 1.00 mmol), HOBt (0.135 g, 1.00 mmol), acid **3.48** (0.152 g, 0.500 mmol), and amine **3.93** (0.165 g, 0.600 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.106** as a colorless solid (0.112 g, 40%).

IR (neat, NaCl) 3413, 3250, 3212, 2951, 1742, 1680, 1622, 1541 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.26 (1H, s), 8.58 (1H, t, *J* = 5.1 Hz), 8.29 (1H, s), 8.15 (2H, d, *J* = 5.0 Hz), 8.05 (1H, d, *J* = 8.6 Hz), 7.89 (2H, d, *J* = 7.8 Hz), 7.60 (1H, s), 7.43 (2H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 7.23 (1H, d, *J* = 8.5 Hz), 3.30 (2H, app q, *J* = 6.7 Hz), 2.50 (2H, under solvent peaks), 1.73 (6H, s), 1.68 (2H, app quin, *J* = 7.1 Hz), 1.58 (2H, app quin, *J* = 7.0 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.2, 161.5, 160.9, 158.6, 155.4, 149.4, 141.9,

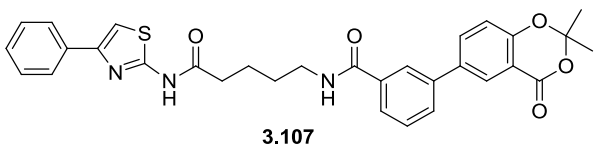
140.4, 135.1, 135.0, 130.5, 129.4, 128.4, 126.8, 126.4, 126.3, 126.2, 118.8, 114.1, 108.6, 107.4, 41.0, 35.3, 29.4, 26.0, 23.0; HRMS (FAB, MH^+) calcd for $C_{29}H_{28}N_3O_5S_2$: 562.1470. Found 562.1466.



3.122

2-hydroxy-5-(5-((5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)carbamoyl) thiophen-3-yl)benzoic acid (3.122): Compound **3.106** (0.042 g, 0.075 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.122** as a purple solid (0.035 g, 90%).

IR (neat, NaCl), 3400-2500 (broad), 3305, 2938, 1680, 1622, 1606, 1552 cm^{-1}; ^1H NMR (DMSO-D_6): δ 12.30 (1H, s), 8.64 (1H, brd s), 8.24 (1H, s), 8.11 (1H, brd d, *J* = 7.8 Hz), 8.04 (1H, s), 7.94 (2H, d, *J* = 7.2 Hz), 7.91 (1H, s), 7.64 (1H, s), 7.48 (2H, t, *J* = 7.2 Hz), 7.37 (1H, t, *J* = 7.2 Hz), 7.13 (1H, brd d, *J* = 6.0 Hz), 3.28 (2H, app q, *J* = 6.4 Hz), 2.48 (2H, t, *J* = 7.2 Hz), 1.56-1.68 (4H, m); ^{13}C NMR {^1H} (DMSO-D_6): δ 172.1, 161.6, 158.6, 149.4, 141.7, 141.2, 135.0, 133.8, 129.4, 128.4, 128.1, 126.9, 126.7, 126.3, 124.9, 118.8, 108.6, 39.4, 35.3, 29.4, 23.0; HRMS (FAB, MH^+) calcd for $C_{26}H_{24}N_3O_5S_2$: 522.1157. Found 522.1157.

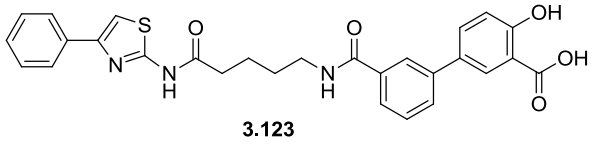


3.107

3-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)benzamide (3.107): EDC.HCl (0.153 g, 0.800 mmol), HOBt (0.108 g,

0.800 mmol), acid **3.49** (0.119 g, 0.400 mmol), and amine **3.93** (0.165 g, 0.600 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.107** as a colorless solid (0.095 g, 43%).

IR (neat, NaCl) 3320, 2946, 1749, 1703, 1626, 1541 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.68 (1H, t, *J* = 5.4 Hz), 8.20 (1H, d, *J* = 2.1 Hz), 8.15 (1H, s), 8.08 (1H, dd, *J* = 2.1, 8.5 Hz), 7.82-7.91 (4H, m), 7.61 (1H, s), 7.57 (2H, t, *J* = 7.8 Hz), 7.43 (1H, t, *J* = 7.6 Hz), 7.32 (1H, t, *J* = 7.0 Hz), 6.27 (1H, d, *J* = 8.6 Hz), 3.33 (2H, under HOD peak), 2.50 (2H, under solvent peak), 1.74 (6H, s), 1.59-1.70 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.2, 166.5, 160.9, 158.6, 155.8, 149.4, 139.0, 136.2, 136.1, 135.2, 135.0, 129.9, 129.8, 129.4, 128.5, 127.7, 127.5, 126.4, 125.7, 118.8, 114.2, 108.6, 107.4, 39.2, 35.3, 29.4, 26.0, 23.0; HRMS (FAB, MH^+) calcd for $C_{31}H_{30}N_3O_5S$: 556.1906. Found 556.1902.

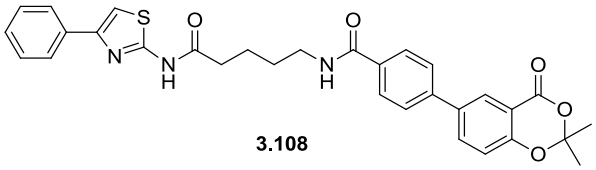


3.123

4-hydroxy-3'-((5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)carbamoyl)-[1,1'-biphenyl]-3-carboxylic acid (3.123): Compound **3.107** (0.050 g, 0.090 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.123** as a yellow solid (0.035 g, 75%).

IR (neat, NaCl) 3550-2400 (broad), 3505, 3266, 2938, 1634, 1595, 1576 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.65 (1H, t, *J* = 5.3 Hz), 8.08-8.12 (2H, m), 7.85-7.95 (3H, m), 7.80 (2H, d, *J* = 8.5 Hz), 7.61 (1H, s), 7.53 (1H, t, *J* = 7.7 Hz), 7.43 (2H, t, *J* = 7.1 Hz), 7.32 (1H, t, *J* = 7.2 Hz), 7.10 (1H, d, *J* = 8.5 Hz), 3.43 (2H, under HOD peak), 2.50 (2H, under solvent peak), 1.59-1.69 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.7,

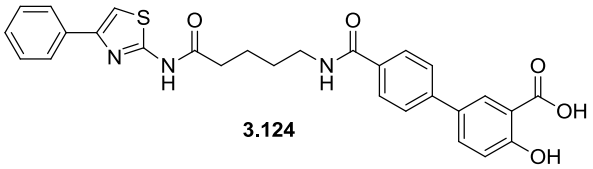
171.5, 165.9, 160.8, 157.9, 148.7, 139.0, 135.2, 134.3, 134.0, 130.7, 129.0, 128.7, 128.1, 127.7, 126.0, 125.6, 124.7, 117.9, 113.4, 107.8, 38.6, 34.6, 28.7, 22.3; HRMS (FAB, MNa) calcd for $C_{28}H_{25}N_3O_5SNa$: 538.1412. Found 538.1403.



3.108

4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)benzamide (3.108): EDC.HCl (0.096 g, 0.500 mmol), HOBt (0.067 g, 0.500 mmol), acid **3.50** (0.075 g, 0.250 mmol), and amine **3.93** (0.103 g, 0.375 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.108** as a colorless solid (0.085 g, 61%).

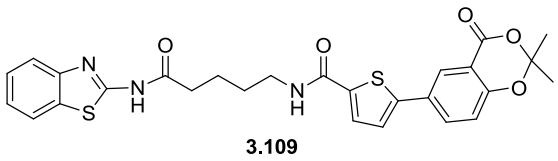
IR (neat, NaCl) 3320, 2946, 1749, 1703, 1626, 1541 cm^{-1}; ^1H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.55 (1H, t, *J* = 5.3 Hz), 8.15 (1H, d, *J* = 2.2 Hz), 8.07 (1H, dd, *J* = 2.3, 8.6 Hz), 7.96 (2H, d, *J* = 8.5 Hz), 7.90 (2H, d, *J* = 7.1 Hz), 7.80 (2H, d, *J* = 8.5 Hz), 7.61 (1H, s), 7.43 (2H, t, *J* = 7.2 Hz), 7.32 (1H, t, *J* = 7.3 Hz), 7.25 (1H, d, *J* = 8.6 Hz), 3.32 (2H, under HOD peak), 2.50 (2H, under solvent peak), 1.74 (6H, s), 1.58-1.69 (4H, m); $^{13}C\{^1H\}$ NMR (DMSO-D_6): δ 172.2, 166.4, 160.8, 158.6, 156.0, 149.4, 141.3, 136.2, 135.0, 134.7, 134.3, 129.5, 128.7, 128.5, 127.6, 127.0, 126.4, 118.8, 114.2, 108.6, 107.4, 39.4, 35.3, 29.4, 26.0, 23.1; HRMS (FAB, MNa) calcd for $C_{31}H_{29}N_3O_5SNa$: 578.1725. Found 578.1718.



3.124

4-hydroxy-4'-((5-oxo-5-((4-phenylthiazol-2-yl)amino)pentyl)carbamoyl)-[1,1'-biphenyl]-3-carboxylic acid (3.124): Compound **3.108** (0.050 g, 0.090 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.124** as a yellow solid (0.040 g, 86%).

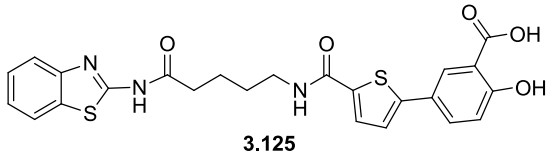
IR (neat, NaCl) 3300-2500, 3284, 2941, 1674, 1634, 1625, 1552 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.27 (1H, s), 8.55 (1H, t, *J* = 5.3 Hz), 8.10 (1H, d, *J* = 2.2 Hz), 7.89-7.95 (5H, m), 7.72 (2H, d, *J* = 8.2 Hz), 7.61 (1H, s), 7.43 (2H, t, *J* = 7.3 Hz), 7.32 (1H, t, *J* = 7.2 Hz), 7.07 (1H, d, *J* = 8.6 Hz), 3.32 (2H, under HOD peak), 2.50 (2H, under solvent peak), 1.58-1.69 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.3 (2C), 166.6, 161.7, 158.6, 149.4, 142.2, 135.0, 134.5, 133.6, 130.8, 129.4, 128.9, 128.6, 128.5, 126.6, 126.3, 118.6, 114.5, 108.6, 38.7, 35.3, 29.3, 23.0; HRMS (FAB, MNa) calcd for $C_{28}H_{25}N_4O_5SNa$: 538.1412. Found 538.1400.



3.109

N-(5-(benzo[d]thiazol-2-ylamino)-5-oxopentyl)-5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)thiophene-2-carboxamide (3.109): EDC.HCl (0.038 g, 0.200 mmol), HOBt (0.027 g, 0.200 mmol), acid **3.47** (0.030 g, 0.100 mmol), and amine **3.97** (0.050 g, 0.200 mmol) were reacted in dry DMF (1 mL) following the general procedure for EDC coupling to afford **3.109** as a colorless solid (0.022 g, 41%).

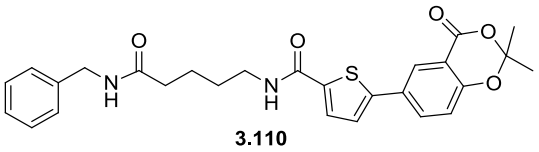
IR (neat, NaCl) 3325, 3203, 2949, 1736, 1699, 1625, 1552 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.36 (1H, s), 8.58 (1H, t, *J* = 5.3 Hz), 8.09 (1H, d, *J* = 2.1 Hz), 8.04 (1H, dd, *J* = 2.2, 8.6 Hz), 7.97 (1H, d, *J* = 7.6 Hz), 7.72-7.76 (2H, m), 7.59 (1H, d, *J* = 3.9 Hz), 7.43 (1H, t, *J* = 7.5 Hz), 7.30 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 8.5 Hz), 3.30 (2H, under HOD peak), 2.50 (2H, under solvent peak), 1.79 (6H, s), 1.57-1.73 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.9, 161.4, 160.5, 158.6, 156.0, 149.2, 145.8, 140.1, 134.9, 132.1, 129.7, 129.0, 126.8, 126.2, 125.5, 124.1, 122.4, 121.2, 119.1, 114.3, 107.6, 39.4, 35.5, 29.4, 26.0, 22.8; HRMS (FAB, MH^+) calcd for $C_{27}H_{26}N_3O_5S_2$: 536.1314. Found 536.1306.



3.125

5-(5-((5-(benzo[d]thiazol-2-ylamino)-5-oxopentyl)carbamoyl)thiophen-2-yl)-2-hydroxybenzoic acid (3.125): Compound **3.109** (0.018 g, 0.033 mmol) was treated with TFA (0.45 mL) and water (0.05 mL) following the general procedure for acetonide removal to afford the product **3.125** as a yellow solid (0.013 g, 79%).

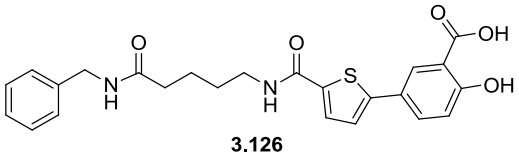
IR (neat, NaCl) 3405, 3320, 3181, 3050, 2940, 1734, 1699, 1626, 1564 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.35 (1H, s), 8.52 (1H, t, *J* = 5.2 Hz), 8.03 (1H, d, *J* = 2.0 Hz), 7.97 (1H, d, *J* = 7.2 Hz), 7.86 (1H, dd, *J* = 2.2, 8.6 Hz), 7.73 (1H, d, *J* = 7.8 Hz), 7.71 (1H, s), 7.46 (1H, s), 7.43 (1H, t, *J* = 7.7 Hz), 7.30 (1H, t, *J* = 7.5 Hz), 7.04 (1H, d, *J* = 8.7 Hz), 3.23 (2H, app q, *J* = 6.4 Hz), 2.55 (2H, t, *J* = 6.8 Hz), 1.57-1.71 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.9, 172.0, 161.8, 161.5, 158.6, 149.2, 146.9, 139.1, 133.4, 132.1, 129.7, 127.7, 126.8, 125.3, 124.2, 124.1, 122.4, 121.1, 118.9, 114.5, 38.9, 35.5, 29.4, 22.8; HRMS (FAB, MH^+) calcd for $C_{24}H_{22}N_3O_5S_2$: 496.1001. Found 496.0996.



3.110

N-(5-(benzylamino)-5-oxopentyl)-5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3] dioxin-6-yl)thiophene-2-carboxamide (3.110): EDC.HCl (0.072 g, 0.375 mmol), HOBt (0.051 g, 0.375 mmol), acid **3.47** (0.076 g, 0.250 mmol), and amine **3.98** (0.077 g, 0.375 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.110** as a colorless solid (0.112 g, 91%).

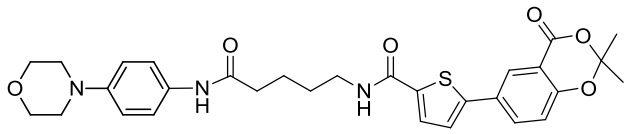
IR (neat, NaCl) 3270, 3077, 2938, 2857, 1738, 1649, 1560 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 8.69 (1H, brd s), 8.41 (1H, t, *J* = 5.8 Hz), 8.08 (1H, s), 8.03 (1H, d, *J* = 9.6 Hz), 7.79 (1H, d, *J* = 3.4 Hz), 7.58 (1H, d, *J* = 3.6 Hz), 7.21-7.33 (6H, m), 4.26 (2H, d, *J* = 5.7 Hz), 3.24 (2H, app q, *J* = 5.6 Hz), 2.17 (2H, t, *J* = 6.8 Hz), 1.72 (6H, s), 1.48-1.52 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.7, 161.4, 160.6, 156.0, 145.7, 140.4, 140.3, 134.9, 129.8, 129.0, 128.96, 127.9, 127.4, 126.2, 125.5, 119.1, 114.3, 107.6, 42.7, 42.5, 35.8, 29.6, 26.0, 23.6; HRMS (FAB, MNa) calcd for $C_{27}H_{28}N_2O_5SNa$: 515.1616. Found 515.1625.



3.126

.**5-(5-((5-(benzylamino)-5-oxopentyl)carbamoyl)thiophen-2-yl)-2-hydroxybenzoic acid (3.126):** Compound **3.110** (0.100 g, 0.203 mmol) was reacted with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.126** as a yellow solid (0.046 g, 50%).

IR (neat, NaCl) 3305, 3077, 2934, 1684, 1622, 1545 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 10.62 (1H, s), 8.50 (1H, brd s), 8.32 (1H, t, *J* = 5.4 Hz), 8.01 (1H, dd, *J* = 1.9, 5.8 Hz), 7.84 (1H, d, *J* = 8.6 Hz), 7.70 (1H, d, *J* = 3.5 Hz), 7.45 (1H, brd s), 7.21-7.32 (4H, m), 7.01 (1H, t, *J* = 9.3 Hz), 4.25 (2H, d, *J* = 5.7 Hz), 3.91 (1H, s), 3.23 (2H, app q, *J* = 5.6 Hz), 2.17 (2H, t, *J* = 6.7 Hz), 1.40-1.65 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): (rotomers present) δ 172.7, 172.0, 169.1, 161.8, 161.51, 164.49, 160.4, 146.9, 146.7, 140.4, 139.2, 139.1, 133.4, 133.3, 129.7, 129.0, 127.9, 127.7, 127.5, 127.4, 125.5, 125.3, 124.3, 124.2, 119.2, 118.9, 114.8, 114.5, 53.3, 42.7, 35.7, 29.6, 23.6; HRMS (FAB, MH^{+}) calcd for $C_{24}H_{25}N_2O_5S$: 453.1484. Found 453.1475.

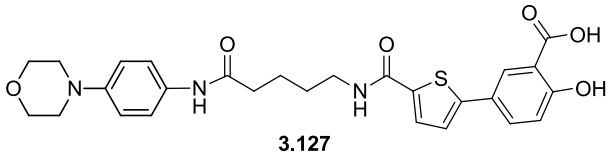


3.111

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-((4-morpholinophenyl) amino)-5-oxopentyl)thiophene-2-carboxamide (3.111): EDC.HCl (0.077 g, 0.400 mmol), HOBt (0.054 g, 0.400 mmol), acid **3.47** (0.061 g, 0.200 mmol), and amine **3.99** (0.111 g, 0.200 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.111** as a purple solid (0.055 g, 49%).

IR (neat, NaCl) 3328, 2953, 1738, 1657, 1610 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 9.78 (1H, s), 8.61 (1H, t, *J* = 5.6 Hz), 8.09 (1H, d, *J* = 2.3 Hz), 8.03 (1H, dd, *J* = 2.3, 8.6 Hz), 7.76 (1H, d, *J* = 3.9 Hz), 7.48 (2H, d, *J* = 8.9 Hz), 7.22 (1H, d, *J* = 8.6 Hz), 6.96 (2H, d, *J* = 8.4 Hz), 3.76 (4H, t, *J* = 4.8 Hz), 3.28 (2H, app q, *J* = 5.9 Hz), 3.07 (4H, app t, *J* = 4.9 Hz), 2.31 (2H, t, *J* = 6.5 Hz), 1.73 (6H, s), 1.56-1.63 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.4, 161.4, 160.6, 156.0, 146.2, 145.8, 140.2, 134.9, 133.5, 129.8, 129.0, 126.2, 125.5,

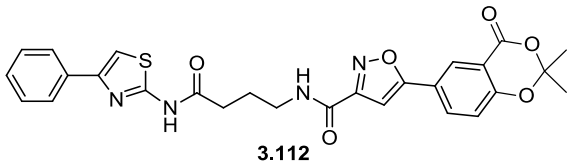
120.8, 119.1, 117.0, 114.2, 107.6, 66.5, 50.4, 39.4, 36.7, 29.5, 26.0, 23.5; HRMS (FAB, MNa) calcd for $C_{30}H_{33}N_3O_6SNa$: 586.1988. Found 586.1985.



3.127

2-hydroxy-5-(5-((5-((4-morpholinophenyl)amino)-5-oxopentyl)carbamoyl) thiophen-2-yl)benzoic acid (3.127): Compound **3.111** (0.035 g, 0.062 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.127** as a purple solid (0.024 g, 75%).

IR (neat, NaCl) 3400-2500 (broad), 3320, 2953, 1702, 1657, 1610 cm^{-1}; ^1H NMR (DMSO-D_6): δ 9.67 (1H, s), 8.50 (1H, s), 8.05 (1H, s), 7.87 (1H, d, *J* = 8.6 Hz), 7.71 (1H, d, *J* = 3.6 Hz), 7.45-7.47 (3H, m), 7.06 (1H, d, *J* = 8.6 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 3.74 (4H, brd s), 3.27 (2H, app q, *J* = 5.8 Hz), 3.05 (4H, brd s), 2.31 (2H, t, *J* = 6.7 Hz), 1.56-1.64 (4H, m); ^{13}C {^1H} NMR (DMSO-D_6): δ 172.0, 171.2, 161.7, 161.5, 147.6, 146.9, 139.1, 133.5, 132.5, 129.7, 127.7, 125.3, 124.2, 120.8, 118.9, 116.2, 114.3, 66.8, 49.8, 39.4, 36.7, 29.6, 23.5; HRMS (FAB, MNa) calcd for $C_{27}H_{28}N_3O_6SNa_2$: 568.1486. Found 568.1486.

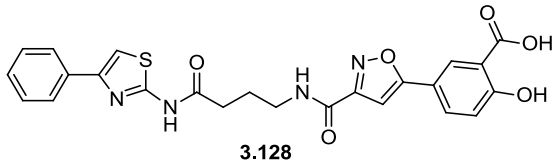


3.112

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(4-oxo-4-((4-phenylthiazol-2-yl)amino)butyl)isoxazole-3-carboxamide (3.112): EDC.HCl (0.107 g, 0.560 mmol), HOBt (0.076 g, 0.560 mmol), acid **3.45** (0.081 g, 0.280 mmol), and amine **3.94** (0.089 g,

0.336 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.112** as a colorless solid (0.100 g, 67%).

IR (neat, NaCl) 3386, 3239, 3208, 1738, 1688, 1641, 1626, 1549 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.24 (1H, s), 8.88 (1H, t, *J* = 5.7 Hz), 8.33 (1H, d, *J* = 2.1 Hz), 8.22 (1H, dd, *J* = 2.1, 8.6 Hz), 7.88 (2H, d, *J* = 7.4 Hz), 7.58 (1H, s), 7.43 (1H, s), 7.42 (2H, t, *J* = 7.8 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 3.34 (2H, app q, *J* = 6.6 Hz), 2.54 (2H, t, *J* = 7.3 Hz), 1.91 (2H, app quin, *J* = 6.8 Hz), 1.74 (6H, s); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.2, 168.7, 159.7, 159.5, 158.4, 157.9, 156.8, 148.7, 134.3, 128.7, 127.7, 126.4, 125.6, 121.4, 118.6, 113.6, 107.9, 107.1, 100.1, 100.0, 38.4, 32.3, 25.34, 25.29, 24.4; HRMS (FAB, MH^{+}) calcd for $C_{27}H_{25}N_4O_6S$: 533.1495. Found 533.1503.

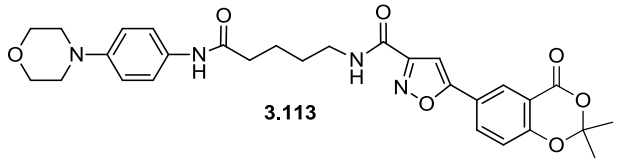


3.128

2-hydroxy-5-(3-((4-oxo-4-((4-phenylthiazol-2-yl)amino)butyl)carbamoyl) isoxazol-5-yl)benzoic acid (3.128): Compound **3.112** (0.055 g, 0.103 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.128** as a yellow solid (0.030 g, 59%).

IR (neat, NaCl) 3347, 3119, 3300-2300 (broad), 1703, 1664 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.25 (1H, s), 8.55 (1H, t, *J* = 5.1 Hz), 8.27 (1H, d, *J* = 1.7 Hz), 8.06 (1H, dd, *J* = 1.8, 8.6 Hz), 7.88 (2H, d, *J* = 7.5 Hz), 7.59 (1H, s), 7.43 (2H, t, *J* = 7.3 Hz), 7.32 (1H, t, *J* = 7.1 Hz), 7.28 (1H, s), 7.13 (1H, d, *J* = 8.7 Hz), 3.32 (2H, app q, *J* = 5.9 Hz), 2.50 (2H, under solvent peak), 1.89 (2H, app quin, *J* = 6.8 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 171.2, 171.1, 169.4, 162.6, 159.7, 158.5, 157.9, 148.7, 134.3, 132.9, 128.7, 127.7, 125.6,

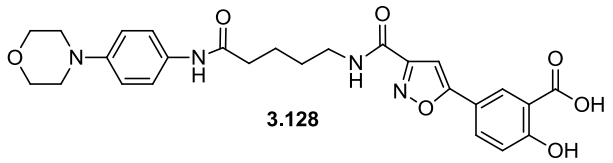
118.5, 117.8, 113.9, 107.9, 98.3, 98.1, 38.3, 32.3, 24.4; HRMS (FAB, MH^+) calcd for $C_{24}H_{21}N_4O_6S$: 493.1181. Found 493.1181.



3.113

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-N-(5-((4-morpholino phenyl)amino)-5-oxopentyl)isoxazole-3-carboxamide (3.113): EDC.HCl (0.146 g, 0.760 mmol), HOBt (0.103 g, 0.760 mmol), acid **3.45** (0.110 g, 0.380 mmol), and amine **3.99** (0.211 g, 0.760 mmol) were reacted in dry DMF (3 mL) following the general procedure for EDC coupling to afford **3.113** as a purple solid (0.090 g, 43%).

IR (neat, NaCl) 3313, 3133, 2945, 1752, 1666, 1625 cm^{-1}; ^1H NMR (DMSO-D_6): δ 9.76 (1H, s), 8.87 (1H, t, *J* = 5.8 Hz), 8.34 (1H, d, *J* = 2.1 Hz), 8.24 (1H, dd, *J* = 2.2, 8.6 Hz), 7.49 (2H, d, *J* = 8.9 Hz), 7.44 (1H, s), 7.33 (1H, d, *J* = 8.7 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 3.76 (4H, t, *J* = 4.3 Hz), 3.29 (2H, app q, *J* = 5.9 Hz), 3.09 (4H, t, *J* = 4.4 Hz), 2.31 (2H, t, *J* = 6.4 Hz), 1.74 (6H, s), 1.49-1.62 (4H, m); ^{13}C {^1H} NMR (DMSO-D_6): δ 171.3, 169.9, 160.5, 160.2, 159.0, 157.6, 146.6, 135.0, 133.3, 127.1, 122.1, 120.9, 119.4, 116.9, 114.3, 107.9, 100.8, 66.6, 50.3, 39.4, 36.6, 29.3, 26.0, 23.4; HRMS (FAB, MNa) calcd for $C_{29}H_{32}N_4O_7Na$: 571.2169. Found 571.2189.

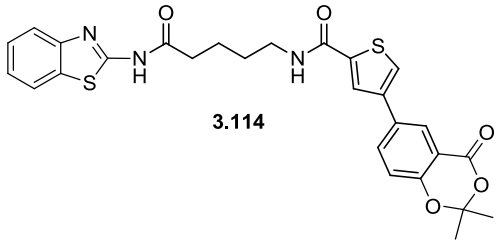


3.128

2-hydroxy-5-(3-((5-((4-morpholinophenyl)amino)-5-oxopentyl)carbamoyl) isoxazol-5-yl)benzoic acid (3.129): Compound **3.113** (0.060 g, 0.110 mmol) was treated with

TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.129** as a purple solid (0.040 g, 71%).

IR (neat, NaCl) 3321, 3300-2400 (broad), 1679, 1589, 1556 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 9.72 (1H, s), 8.83 (1H, t, *J* = 5.2 Hz), 8.28 (1H, s), 8.06 (1H, d, *J* = 8.6 Hz), 7.47 (2H, d, *J* = 8.7 Hz), 7.28 (1H, s), 7.14 (1H, d, *J* = 8.7 Hz), 6.92 (2H, d, *J* = 8.7 Hz), 3.74 (4H, under HOD), 3.28 (2H, app d, *J* = 5.5 Hz), 3.06 (4H, app s), 2.30 (2H, t, *J* = 6.5 Hz), 1.50-1.67 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 1171.8, 171.3, 170.1, 163.3, 160.4, 159.1, 147.0, 133.6, 133.0, 128.4, 120.9, 119.1, 118.5, 116.6, 114.6, 99.5, 66.7, 50.1, 39.3, 36.6, 29.3, 23.4; HRMS (FAB, MNa) calcd for $C_{26}H_{28}N_4O_7Na$: 531.1855. Found 531.1838.

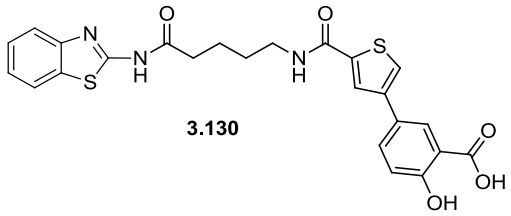


3.114

N-(5-(benzo[d]thiazol-2-ylamino)-5-oxopentyl)-4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)thiophene-2-carboxamide (3.112): EDC.HCl (0.077 g, 0.400 mmol), HOBt (0.054 g, 0.400 mmol), acid **3.47** (0.061 g, 0.200 mmol), and amine **3.96** (0.100 g, 0.400 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.112** as a colorless solid (0.051 g, 47%).

IR (neat, NaCl) 3265, 2917, 1739, 1697, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.03 (1H, d, *J* = 1.9 Hz), 7.78 (1H, s), 7.69 (1H, d, *J* = 7.9 Hz), 7.65 (1H, dd, *J* = 2.0, 8.5 Hz), 7.43 (1H, s), 7.34 (1H, (1H, t, *J* = 7.3 Hz), 7.23 (1H, d, *J* = 7.6 Hz), 6.87 (1H, d, *J* = 8.5 Hz), 6.84 (1H, t, *J* = 6.3 Hz), 3.41 (2H, app q, *J* = 5.8 Hz), 2.54 (2H, t, *J* = 6.8 Hz), 1.77 (2H, app

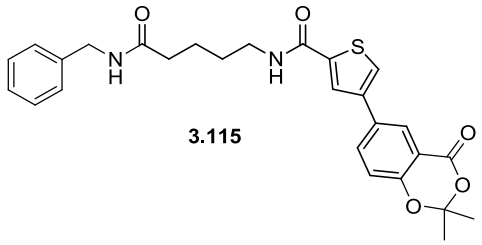
quin, J = 7.2 Hz) 1.65 (6H, s), 1.65 (2H, under methyl peak); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.2, 162.3, 161.3, 155.5, 140.9, 140.5, 134.5, 130.2, 127.1, 126.8, 126.7, 124.8, 124.3, 121.8, 120.5, 118.1, 113.9, 106.9, 39.6, 35.8, 28.9, 26.0, 22.3; HRMS (FAB, MH^+) calcd for $C_{27}H_{26}N_3O_5S_2$: 536.1314. Found 536.1308.



3.130

5-(5-((5-(benzo[d]thiazol-2-ylamino)-5-oxopentyl)carbamoyl)thiophen-3-yl)-2-hydroxybenzoic acid (3.130): Compound **3.114** (0.045 g, 0.084 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.130** as a yellow solid (0.032 g, 77%).

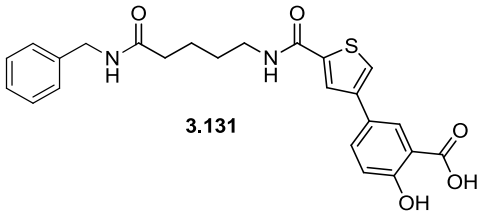
IR (neat, NaCl) 3280, 2913, 1699, 1617, 1556 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 12.33 (1H, s), 8.58 (1H, brd s), 8.20 (1H, s), 8.09 (1H, brd s), 8.00 (1H, s), 7.97 (1H, d, *J* = 7.8 Hz), 7.88 (1H, d, *J* = 8.4 Hz), 7.73 (1H, d, *J* = 7.8 Hz), 7.44 (1H, t, *J* = 7.5 Hz), 7.30 (1H, t, *J* = 7.5 Hz), 7.06 (1H, d, *J* = 8.5 Hz), 3.31 (2H, app q, *J* = 5.9 Hz), 2.56 (2H, t, *J* = 7.0 Hz), 1.71 (2H, app quin, *J* = 7.3 Hz), 1.60 (2H, app quin, *J* = 7.0 Hz); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.9, 161.6, 160.0, 158.6, 149.3, 141.7, 141.2, 133.9, 132.1, 127.9, 126.9, 126.8, 126.7, 125.0, 124.2, 122.4, 121.2, 118.7, 39.4, 35.5, 29.4, 22.8; HRMS (FAB, MH^+) calcd for $C_{24}H_{22}N_3O_5S_2$: 496.1001. Found 496.0986.



3.115

N-(5-(benzylamino)-5-oxopentyl)-4-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3] dioxin-6-yl)thiophene-2-carboxamide (3.115): EDC.HCl (0.086 g, 0.450 mmol), HOBt (0.061 g, 0.450 mmol), acid **3.48** (0.091 g, 0.300 mmol), and amine **3.99** (0.093 g, 0.450 mmol) were reacted in dry DMF (2 mL) following the general procedure for EDC coupling to afford **3.115** as a colorless solid (0.138 g, 93%).

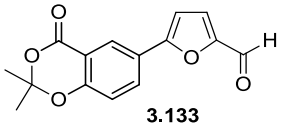
IR (neat, NaCl) 3297, 3077, 2919, 1745, 1618, 1550, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.07 (1H, d, *J* = 2.1 Hz), 7.78 (1H, s), 7.69 (1H, dd, *J* = 2.1, 8.6 Hz), 7.47 (1H, s), 7.15-7.25 (5H, m), 6.92 (1H, d, *J* = 8.5 Hz), 6.03 (1H, broad s), 4.39 (2H, d, *J* = 5.6 Hz), 3.39 (2H, app q, *J* = 5.9 Hz), 2.26 (2H, t, *J* = 6.8 Hz), 1.60-1.75 (4H, m), 1.68 (6H, s); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 173.4, 162.3, 161.3, 155.5, 140.8, 138.5, 134.4, 130.4, 128.9, 128.0, 127.6, 127.0, 126.6, 124.7, 118.1, 113.9, 106.9, 43.8, 39.6, 35.8, 28.8, 26.0, 22.8; HRMS (FAB, MH^+) calcd for $C_{27}H_{29}N_2O_5S$: 493.1797. Found 493.1808.



3.131

5-(5-((5-(benzylamino)-5-oxopentyl)carbamoyl)thiophen-3-yl)-2-hydroxybenzoic acid (3.131): Compound **3.115** (0.074 g, 0.150 mmol) was treated with TFA (0.90 mL) and water (0.10 mL) following the general procedure for acetonide removal to afford the product **3.131** as a yellow solid (0.054 g, 79%).

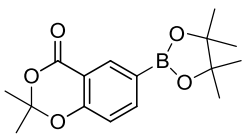
IR (neat, NaCl) 3276, 3080, 2941, 1674, 1634, 1603, 1503 cm^{-1}; ^{1}H NMR (DMSO-D_6): δ 8.61 (1H, s), 8.35 (1H, s), 8.21 (1H, s), 8.10 (1H, s), 8.00 (1H, s), 7.87 (1H, d, *J* = 8.4 Hz), 7.22-7.33 (5H, m), 7.06 (1H, d, *J* = 8.5 Hz), 4.27 (1H, d, *J* = 5.7 Hz), 3.27 (2H, app q, *J* = 5.8 Hz), 2.20 (2H, t, *J* = 6.8 Hz), 1.54-1.61 (4H, m); ^{13}C {^{1}H} NMR (DMSO-D_6): δ 172.7, 161.6, 161.4, 141.7, 141.3, 140.4, 133.7, 129.0, 127.9, 127.4, 126.8, 126.6, 124.8, 116.6, 49.3, 42.7, 35.8, 29.6, 23.6; HRMS (FAB, MNa) calcd for $C_{24}H_{24}N_2O_5SNa$: 475.1304. Found 475.1293.



3.133

5-(2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)furan-2-carbaldehyde (3.133): Iodide **3.53** (0.121 g, 0.400 mmol), boronic acid **3.132** (0.084 g, 0.600 mmol), $Pd(OAc)_2$ (0.004 g, 0.020 mmol), and Na_2CO_3 (0.085 g, 0.800 mmol) were reacted in DMF (5 mL) following the general procedure of Suzuki coupling[35] to produce **3.133** as a colorless solid (0.101 g, 93%).

IR (neat, NaCl) 3119, 2984, 1734, 1657, 1622 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.62 (1H, s), 8.32 (1H, d, *J* = 2.2 Hz), 8.00 (1H, dd, *J* = 2.2, 8.7 Hz), 7.30 (1H, d, *J* = 3.7 Hz), 7.04 (1H, d, *J* = 8.6 Hz), 6.82 (1H, d, *J* = 3.7 Hz), 1.73 (6H, s); ^{13}C {^{1}H} NMR ($CDCl_3$): δ 177.3, 160.5, 157.6, 156.8, 152.2, 133.0, 126.7, 124.2, 123.7, 118.3, 114.0, 107.9, 107.1, 26.0; HRMS (FAB, MNa^{+}) calcd for $C_{15}H_{12}O_5Na$: 295.0583. Found 295.0591.



3.135

2,2-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-benzo[d][1,3] dioxin-4-one (3.135): Iodide **3.53** (0.608 g, 2.00 mmol), pinacolborane **3.134** (0.43 mL, 3.00 mmol), $PdCl_2(dppf).CH_2Cl_2$ (0.049, 0.06 mmol), and Et_3N (0.84 mL) were reacted in acetonitrile (10 mL) following the literature procedure described[38] to obtain **3.135** as a colorless solid (0.450 g, 74%).

IR (neat, NaCl) 3003, 2984, 1738, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.41 (1H, d, *J* = 1.4 Hz), 7.92 (1H, dd, *J* = 1.3, 8.2 Hz), 6.91 (1H, d, *J* = 8.2 Hz), 1.69 (6H, s), 1.29 (12H, s); ^{13}C {^1H} NMR ($CDCl_3$): δ 161.0, 158.3, 142.6, 137.0, 116.6, 113.1, 106.4, 84.2, 25.9, 24.9; HRMS (FAB, MH^+) calcd for $C_{16}H_{21}BO_5$: 305.1560. Found 305.1564.

3.7. References

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