AN ABSTRACT OF THE DISSERTATION OF

Wei Zhang for the degree of Doctor of Philosophy in Chemistry presented on April 24, 2006.

Title: Synthetic Studies toward the Total Synthesis of Amphidinolide B_1

Abstract approved: _____

Rich G. Carter

Amphidinolide B_1 is one of the most potent cytotoxic compounds in the amphidinolide family. Its bioactivity and intriguing structure has drawn attention from synthetic chemists. Although numerous synthetic efforts toward the total synthesis of amphidinolide B_1 have been published, it still remains an unconquered synthetic target.

One of the unique structural features of amphidinolide B_1 is the C_{13}-C_{15} highly substituted diene. While most other synthetic groups tried to apply palladium or copper-mediated cross coupling methodologies to form this functionality, we elaborated this subtle moiety with a novel $TiCl_4$-mediated Fleming-type coupling and subsequent dehydration sequence. Our convergent strategy featured a highly diastereoselective aldol condensation of western aldehyde 104 and eastern ketone 105. This result is in stark contrast to prior

efforts using similar approaches. The macrocyclic ring was established *via* a spontaneous intramolecular Wadsworth-Emmons olefination with excellent yield and stereoselectivity. A novel approach toward the formation of the unusual allyl epoxide moiety was affected with an oxidative elimination of the selenide species 416 to give the allyl epoxide 417 as a single isomer. The only challenge remaining in this total synthesis is two deprotection steps. After extensive experimentation, we discovered that the PMB protection group had to be removed before the macrolactonization and the incorporation of the allyl epoxide functionality. After deprotection of the PMB ether, a global desilylation will complete the total synthesis of amphidinolide B_1.

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Synthetic Studies toward the Total Synthesis of Amphidinolide B_1

by

Wei Zhang

A DISSERTATION

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Doctor of Philosophy

Presented April 24, 2006

Commencement June 2006

Doctor of Philosophy dissertation of Wei Zhang presented on April 24, 2006

APPROVED:

Major Professor, representing Chemistry

Chair of the Department of Chemistry

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Wei Zhang, Author

ACKNOWLEDGEMENTS

I would like to thank Professor Rich G. Carter for the support, guidance, inspiration and friendship that he extended throughout my graduate career. I would also like to thank the members of the Carter group, both past and present for their friendship and all kinds of help.

I thank Alex Yokochi for his X-ray crystallographic expertise, Roger Kohnert for his advice and guidance with NMR spectroscopy and Jeff Morre for his efforts with MS spectroscopy.

I would like to thanks National Institute of Health and the Chemistry Department of Oregon State University for financial support.

I would also thank my wife Shuhong Liu and my parent Yanti Zhang and Tiying Zhang, whose love and support have been so important to my career.

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Synthetic Studies toward the Total Synthesis of Amphidinolide B_1

GENERAL INTRODUCTION

As one of the most potent cytotoxic compounds of amphidinolide family, amphidinolide B_1 was isolated from a culture of *amphidinium* genus free-swimming dinoflagellate.[1] In addition to its intriguing bioactivity, amphidinolide B_1 has some attractive structural features including a C_{13}-C_{15} highly substituted diene, an unusual allyl epoxide moiety, nine stereocenters and 26-membered macrolactone skeleton. Although numerous synthetic efforts toward the total synthesis of amphidinolide B_1 have been published, it remains an unconquered target.

In our synthetic study, many useful protocols have been developed. To establish the C_{13}-C_{15} diene, we applied a novel Fleming-type coupling and subsequent dehydration sequence. A highly diastereoselective chelation-controlled aldol between aldehyde **104** and ketone **105** was affected to form C_{18} stereocenter as a single isomer. The macrocycle skeleton was established *via* a spontaneous intramolecular Wadsworth-Emmons olefination in an excellent yield and stereoselectivity. A novel sequence of selenide incorporation and oxidative elimination of selenide **416** provided the unusual allyl epoxide **417** as a single isomer. The only challenge remains in this total synthesis is two deprotection steps.

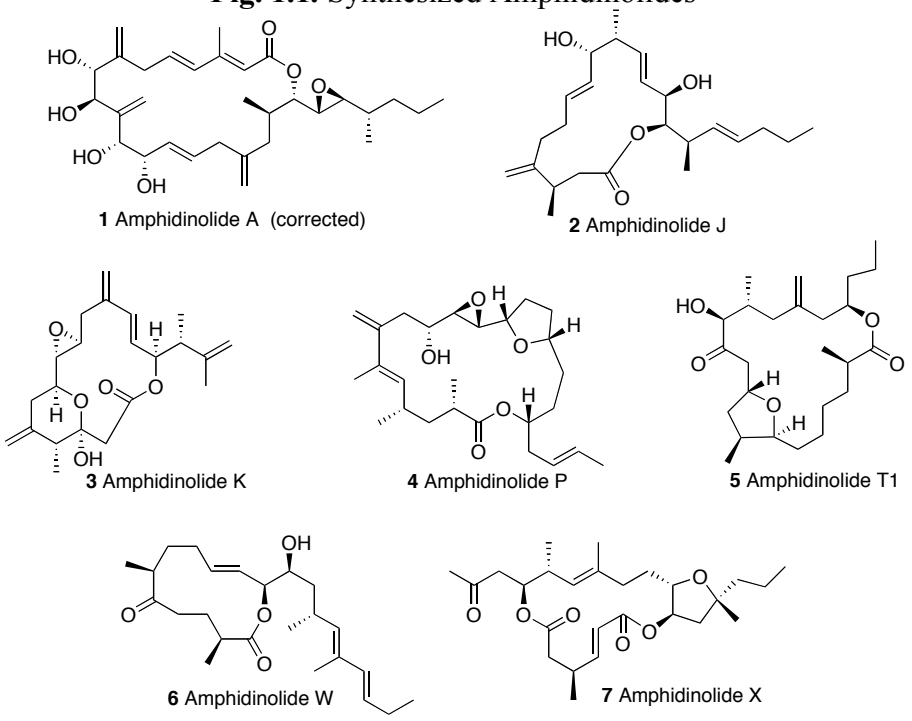
Chapter I. Background of Amphidinolide B_1

1.1. Introduction

For the past two decades, increasing attention has been focused on marine microorganisms, which have been a prolific source of compounds with novel structural features and appealing biological activities.[2] Often, symbiotic microorganisms such as microalgae in marine invertebrates have proved to be hopeful sources of potential bioactive substances.[3] Koboyashi and his co-workers isolated a series of novel marolides with potent cytotoxicity from cultures of the dinoflagellate *Amphidinium* sp., a type of symbiotic microalgae, in the mid 1980s. First isolated from the inner tissue of the Okinawan flatworm *Amphiscolops* sp. and then harvested from unialgae cultures cultivated on large-scale in a laboratory, these macrolides have demonstrated potent antineoplastic activity against a series of cancer cell lines in human bodies.[4]

To date, Kobayashi and co-workers have disclosed numerous spectroscopic studies of the ever-expanding amphidinolide family of novel polyene polyol-based macrolactones. More importantly, they have proved that most of amphidinolides have potent cytotoxicity.[5] In accord with the abundant discovery of these structurally intriguing macrolides, total syntheses of various members of amphidinolide family, such as amphidinolide A,[6] K,[7] P,[8] J,[9] R,[10] T1-T5[11] W,[12]and X[13] have been reported.

Fig. 1.1. Synthesized Amphidinolides

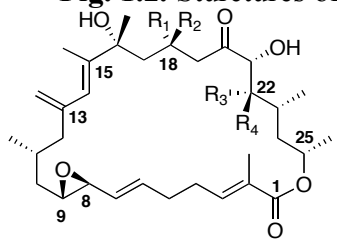


1.2. Isolation and Bioactivity of Amphidinolide B_{1-5}

Amphidinolide B_1, B_2 and B_3 were isolated from the *amphidinium* genus free-swimming dinoflagellate, which was originally collected at Brewers Beach, St. Thomas, US Virgin Island. The relative stereochemistry of amphidinolide B_1 was determined by a single crystal X-ray diffraction analysis.[1] The absolute stereochemistry was established by synthetic degradation study.[14] Sharing similar structural features, amphidinolide B_1, B_2 and B_3 exhibited potent cytotoxcity with impressive IC_{50} activity against a series of cancer cell lines: L1210 Murine leukemia cell line (0.14 ng/mL), human colon tumor HCT 116 cell line (0.12 ng/mL), and KB cancer cell line (4.2 ng/mL). In addition to the

cytotoxicity, amphidinolide B_1 was also applied as a tool for physiological and biological studies.[15]

Fig. 1.2. Sturctures of Amphidinolide B_1, B_2 and B_3



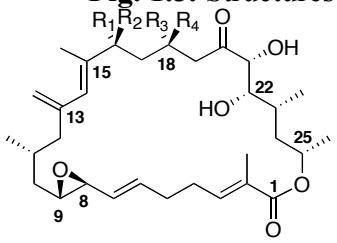
8 Amphidinolide B_1: $R_1 = R_3 = OH$, $R_2 = R_4 = H$

9 Amphidinolide B_2: $R_2 = R_3 = OH$, $R_1 = R_4 = H$

10 Amphidinolide B_3: $R_1 = R_4 = OH$, $R_2 = R_3 = H$

Recently, amphidinolide B_4 and B_5 were isolated from the dinoflagelllate *amphidinium* sp., which was harvested from a marine acoel flatworm *amphiscolops* sp. obtained from Ma'eda Cape, Okinawa. The relative chemistry of amphidinolide B_4 and B_5 were established by careful analyses of NMR spectrometry and detailed comparison of the ^{13}C NMR data of B_4 and B_5 with those of amphidinolide B_1, H_1, H_2 and H_3. Amphidinolide B_4 and B_5 showed potent cytotoxicity against a couple of cancer cell lines with excellent IC50 activity: murine lymphoma L1210 (0.12 ng/mL and 1.4 ng/mL, respectively), human epidermoid carcinoma KB cells (1.0 ng/mL and 4.0 ng/mL, respectively).[16]

Fig. 1.3. Structures of Amphidinolide B_4 and B_5



11 Amphidinolide B_4: $R_1 = R_4 = H$, $R_2 = R_3 = OH$

12 Amphidinolide B_5: $R_2 = R_3 = H$, $R_1 = R_4 = OH$

1.3. Previous Synthetic Studies toward the Total Synthesis Amphidinolide B_1

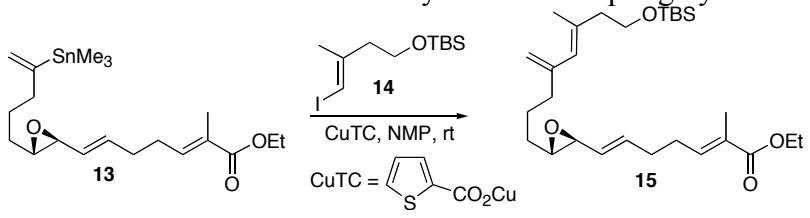
In addition to the potent cytotoxicity exhibited by amphidinolide B_1, the intriguing architectural structure, including a highly substituted C_{13}-C_{15} diene, an unusual allyl epoxide motif, 9 stereocenters and a 26-membered macrolactone, makes it an attractive synthetic target. Since the first synthetic efforts toward the total synthesis of amphidinolide B_1 published in 1997 by Lee and co-workers, numerous laboratories have published in this highly competitive area. Yet, amphidinolide B_1 remains as an unconquered target.

1.3.1. Previous Strategies to Construct (*E*)-1,1,3-trisubstituted C_{13}-C_{15} Diene

As the construction of the C_{13}-C_{15} diene is concerned, one possible strategy would be using palladium or copper catalyzed coupling reactions. Specifically, Stille reaction is one of the most frequently applied methods for the coupling of olefinic sp^2 centers, but the sterically hindered diene as presented in amphidinolide B_1 is one of the fields without being fully explored with this methodology.[17] Indeed, many early synthetic efforts toward amphidinolide B_1 adopted this method. For example, Pattenden and co-workers attempted to construct the 26-membered macrocycle by intramolecular Stille coupling in a late synthetic stage.[18] A model study was firstly applied to address a potential complication caused by the sensitivity of allyl epoxide, on which competitive reactions might occur in the presence of transition metals.

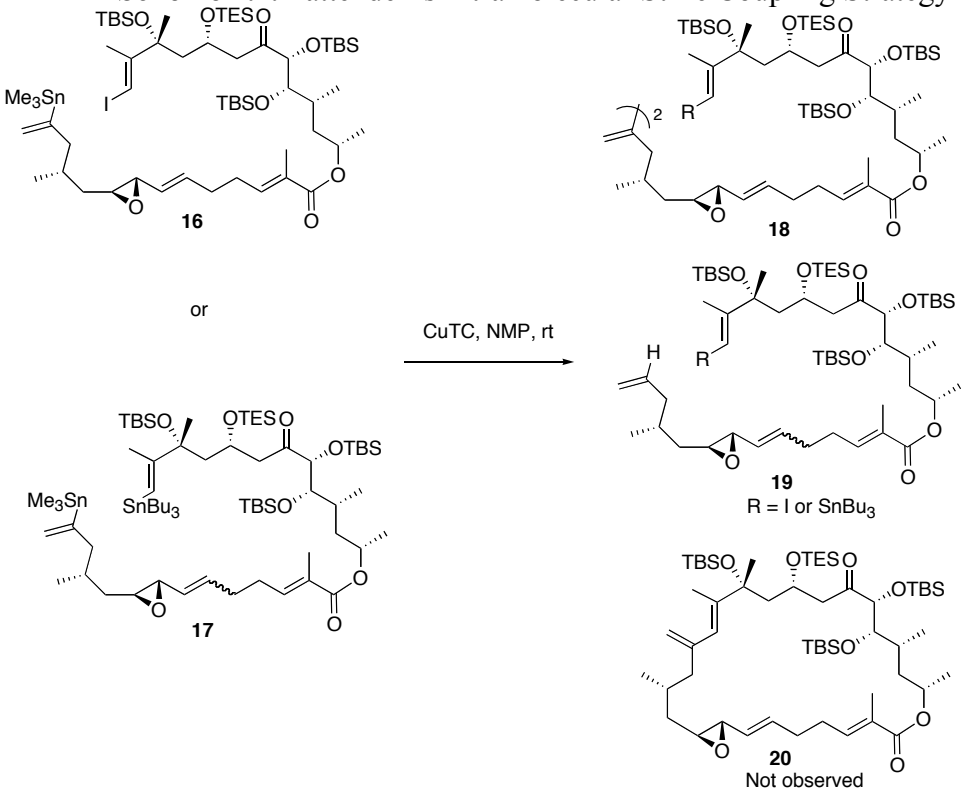
Mediated by copper(I)-thiophene-2-carboxylate (CuTC), the model study showed the intermolecular coupling was a success (Scheme 1.1).

Scheme 1.1. Successful Model Study of Stille Coupling by Pattenden



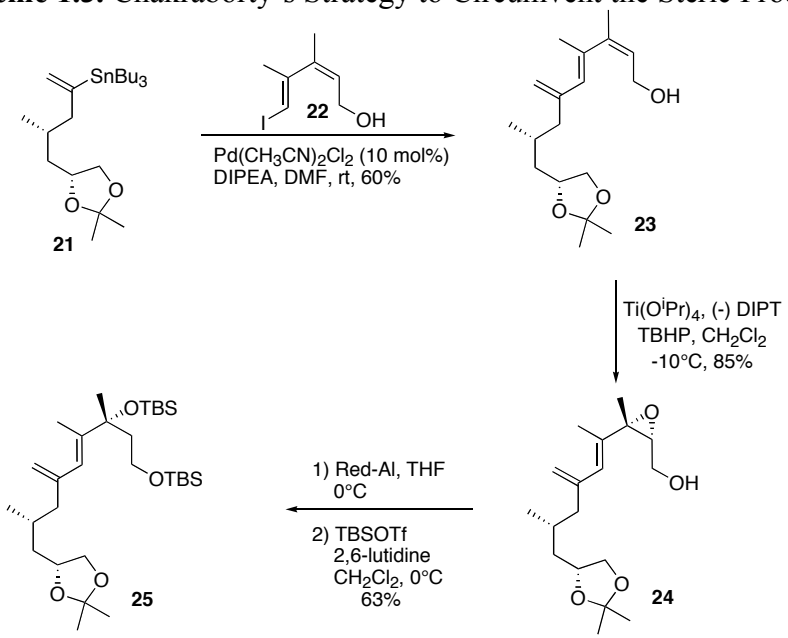
Unfortunately, the intramolecular coupling between the vinyl iodide and vinyl stannane failed using the same reaction conditions. Instead of obtaining the expected macrolactone **20**, a dimer **18** resulting from vinylstannane-vinylstannane coupling, and a smaller amount of destannylation product **19** were observed. In order to solve the problem that might have been caused by the steric hindrance imparted by TBS protected tertiary alcohol, a tin-tin coupling precursor was prepared by iodine-tin exchange, as there seems a propensity for vinyl stannanes to undergo tin-tin coupling.[19] Unfortunately, the di-stannane coupling failed to affect the intramolecular sp^2-sp^2 coupling. Again, only a dimer species and a destannylation compound were formed (Scheme 1.2). To date, no update of their research has been reported.

Scheme 1.2. Pattenden's Intramolecular Stille Coupling Strategy



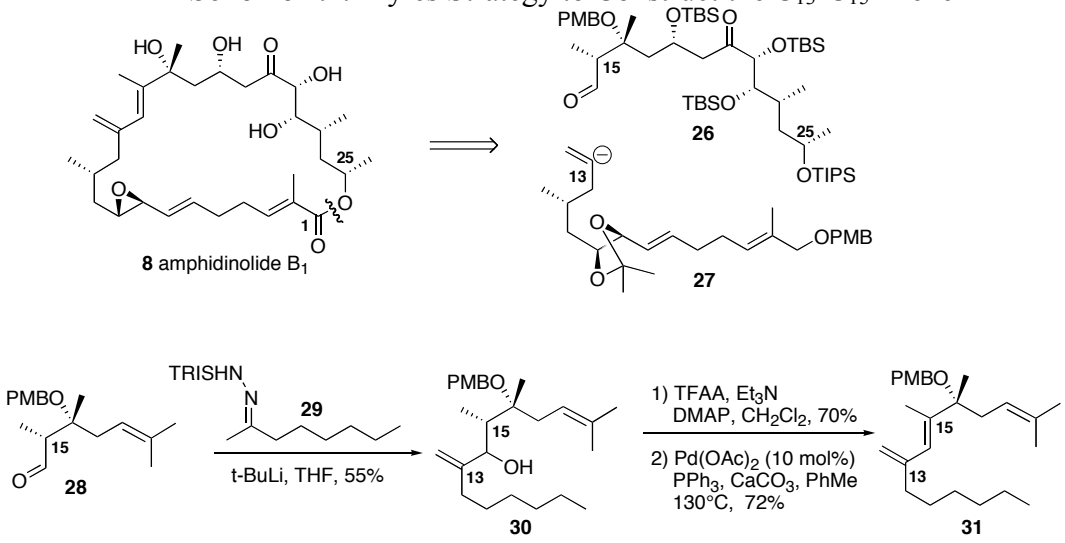
To circumvent the difficulty imparted by the sterically compromised C_{13}-C_{15} diene, Chakraborty and co-workers applied intermolecular Stille coupling reaction to construct the diene **23** without the adjacent quaternary center (Scheme 1.3). Although the strategy of a Sharpless asymmetric epoxidation followed with an epoxide opening reaction was successfully applied to elaborate the highly substituted diene **25**, preparation of the precursor of the Stille coupling alone required 14 steps, which made this strategy inefficient.

Scheme 1.3. Chakraborty's Strategy to Circumvent the Steric Problem



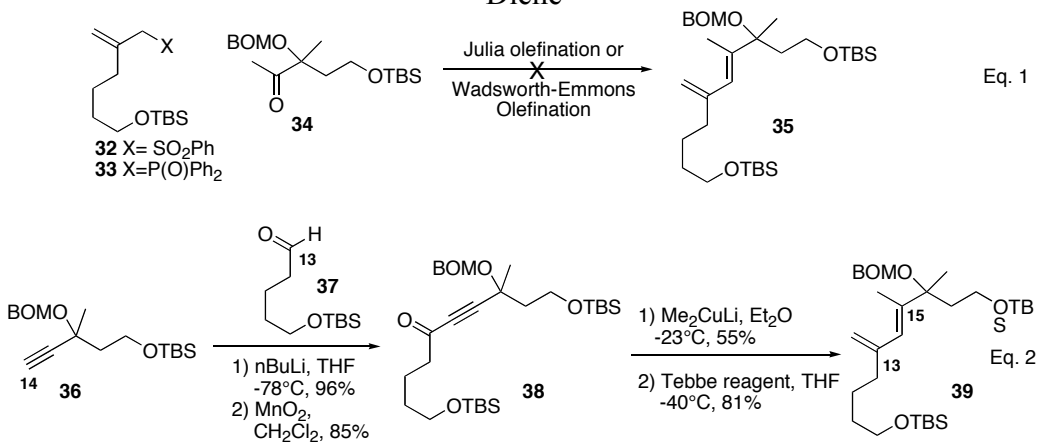
Instead of using Pd or Cu-coupling reactions, Myles and co-workers proposed to construct C_{13}-C_{15} with a nueclophilic addition of vinyl anion to an aldehyde followed with a dehydration reaction mediated by Pd (Scheme 1.4).[20] A model study was firstly carried out to prove the feasibility of this concept. The vinyl anion was generated from the trisylhydrazone of 2-octanone **29**. A Subsequent nucleophilic addition to the aldehyde gave the alcohol **31**. Conversion of the secondary alcohol to the corresponding acetate, followed with a Hauser type elimination in the presence of Pd (0) provided the (E)-1,1,3-trisubstituted diene as a single stereoisomer.[21] To date, there is no update study applying this strategy on the authentic substrates reported.

Scheme 1.4. Myles Strategy to Construct the C_{13}-C_{15} Diene



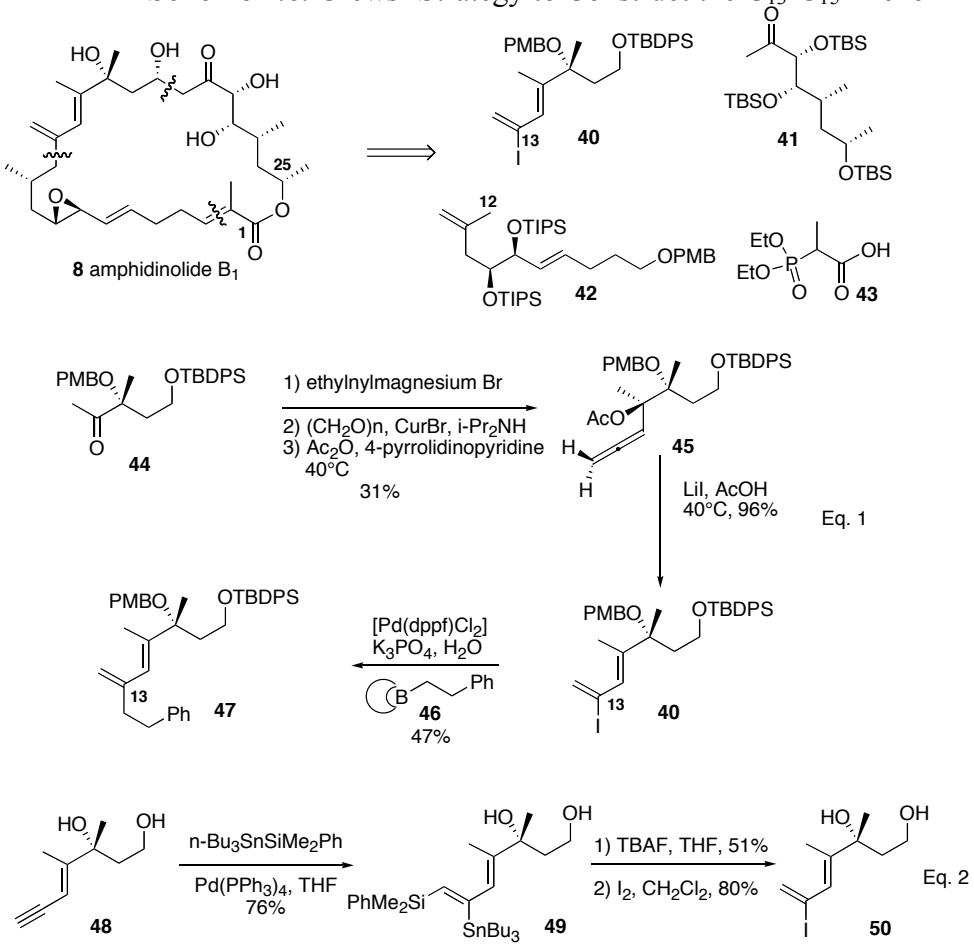
Although most of the previous studies toward the highly substituted diene attempted to build the $C_{13\text{-}14}$ bond, Nishiyama and co-workers chose to form the diene *via* $C_{14\text{-}15}$ bond connection (Scheme 1.5).[22] Unfortunately, this approach proved ineffective (Eq. 1). An alternative route was described involving a disconnection between the $C_{13\text{-}14}$ bond (Eq. 2). They disclosed a racemic synthetic study toward the formation of a non-fully functionalized (E)-1,1,3-trisubstituted diene by nucleophilic addtion of a lithiated alkyne to an aldehyde, followed with cuprate addition and Tebbe olefination.

Scheme 1.5. Nishiyama's Racemic Strategy to Elaborate the C_{13}-C_{15} Diene



Recently, Crews and co-workers reported an approach using iodide-mediated S_N2' reaction to access a 1,3-diene iodide substrate **40** (Scheme 1.6).[23] Subsequently, this iodide **40** was subjected to Suzuki-Miyaura coupling condition[24] to construct the C_{12}-C_{13} bond. A model study was carried out to established the feasibility of the Suzuki-Miyaura reaction (Eq. 1). The 1,3-dienyl iodide **50** could also derived from enyne substrate by silylstannylation of alkyne employing n-Bu_3SnMe_2Ph/$Pd(PPh_3)_4$, followed with desilylation with TBAF and iodination (Eq. 2).[25]

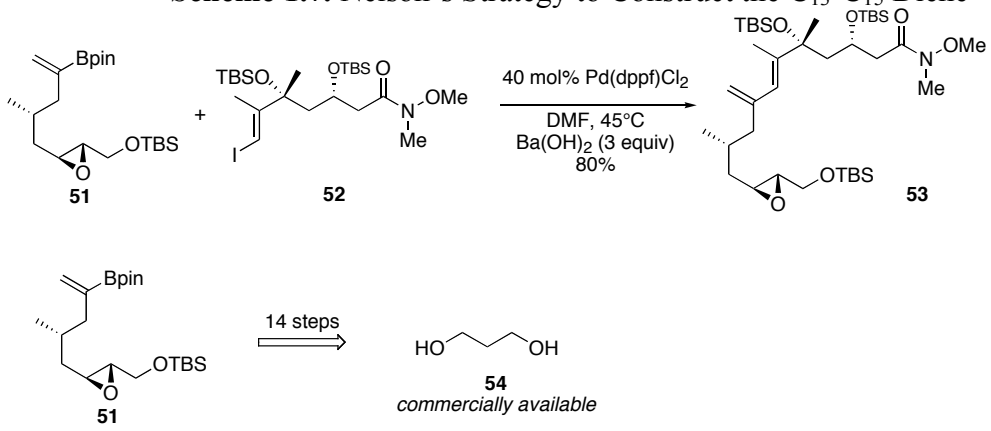
Scheme 1.6. Crews' Strategy to Construct the C_{13}-C_{15} Diene



Very recently, Nelson and co-workers successfully installed the trisubstituted diene unit by applying Suzuki cross-coupling (Scheme 1.7).[26] It is the first successful example of using Pd cross-coupling to access to the fully functionalized diene. This approach requires 40 mol% Pd catalyst and an elevated temperature. Also, it is not trivial to prepare the precursors of the Pd coupling, the vinylborane **51** alone requires 14 steps from the commercially available 1,3-propanediol **54**.[27] In addition, this route will apparently end up

applying Julia-type coupling to elaborate the allyl epoxide moiety, which will be similar to the syntheses reported by Pattenden and Lee.

Scheme 1.7. Nelson's Strategy to Construct the C_{13}-C_{15} Diene



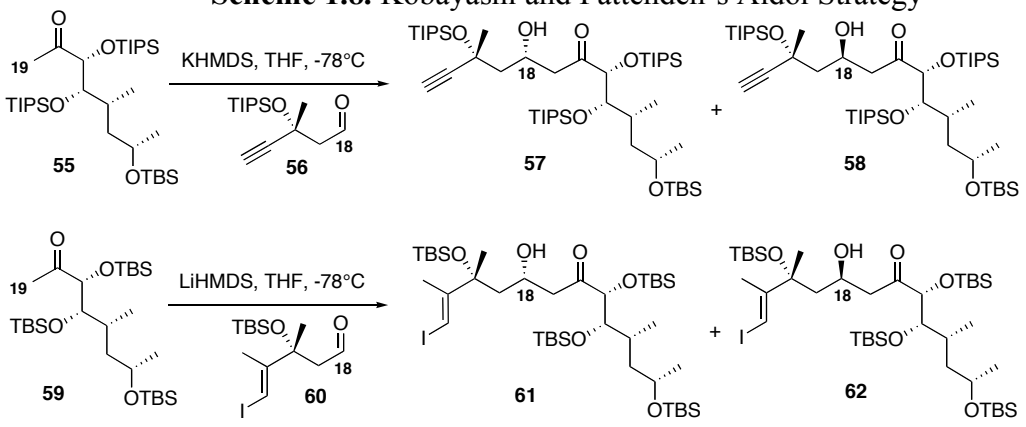
In summary, one of the most intriguing problems related to the total synthesis of amphidinolide is formation of the highly substituted C_{13}-C_{15} diene. To the date we initiated our synthetic study in 2000, there was no efficient strategy has address this important issue. Stille coupling reaction was not readily feasible to this sterically compromised situation. In addition, the preparation of precursors for Stille or Suzuki coupling reactions was not trivial. In our synthetic study, we needed to discover an efficient and novel method applicable to the synthesis of the fully functionalized C_{13}-C_{15} diene.

1.3.2. Previous Strategies to Construct the C_{18} Stereocenter and the Preparation of the Top C_{14}-C_{26} Fragment of Amphidinolide B_1

The strategy to establish the C_{18} stereocenter is another important issue. In a convergent approach toward the top part of the molecule, one possible disconnection would be between C_{18}-C_{19} sigma bond. This bond in the forward

direction would be accessible *via* an aldol condensation reaction. Kobayashi and Pattenden applied an aldol strategy to construct the C_{18} stereocenter and unite two subunits to give the top C_{14}-C_{26} fragment (Scheme 1.8).[18,28] In both cases, similar methyl ketones and aldehydes were used. Also, the enolates were generated using similar bases, NaHMDS or KHMDS. In both cases, an unsatisfactory 3:2 diastereoselectivity with a comparatively poor overall yield was observed. A more detailed mechanistic rationale for this transformation will be discussed in Chapter 4.1.

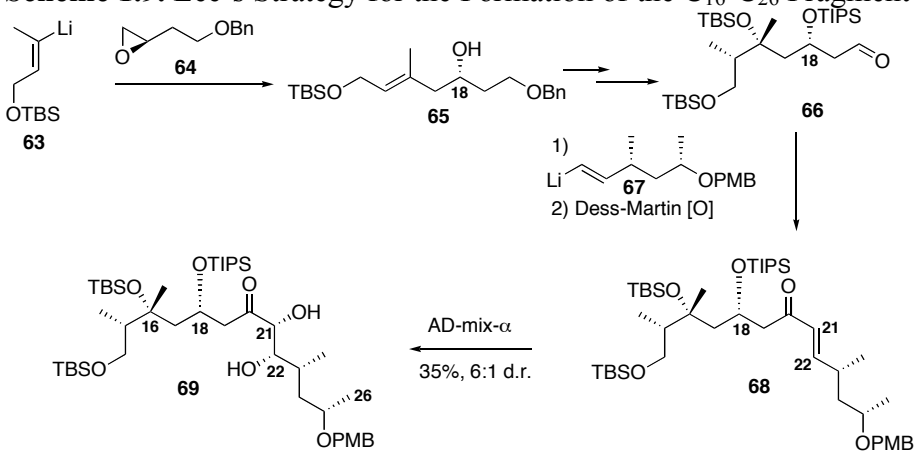
Scheme 1.8. Kobayashi and Pattenden's Aldol Strategy



Most of other approaches obtained the C_{18} stereocenter from commercially available chiral substrates. For example, Lee and co-workers furnished the C_{18} stereocenter by epoxide opening of a derivative from (*R*)-1,2-epoxybutanol **64** (Scheme 1.9). Subsequently, functional group manipulations led to an aldehyde species **66**. Coupling between the aldehyde **66** and the vinyl lithium **67** followed with a Dess-Martin oxidation give the corresponding enone

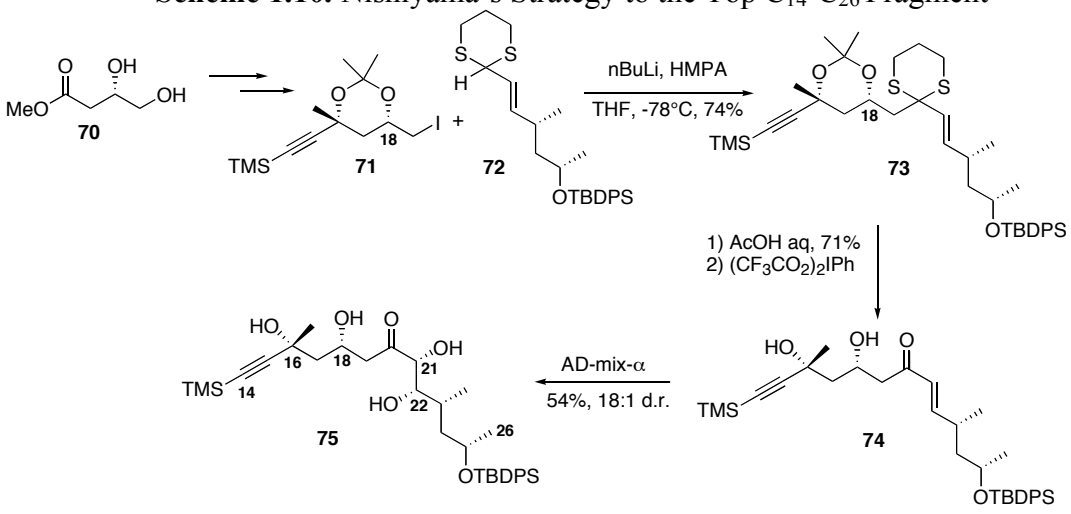
68. Sharlpess asymmetric dihydroxylation provided the fully functionalized C_{16}-C_{26} fragment.[29]

Scheme 1.9. Lee's Strategy for the Formation of the C_{16}-C_{26} Fragment



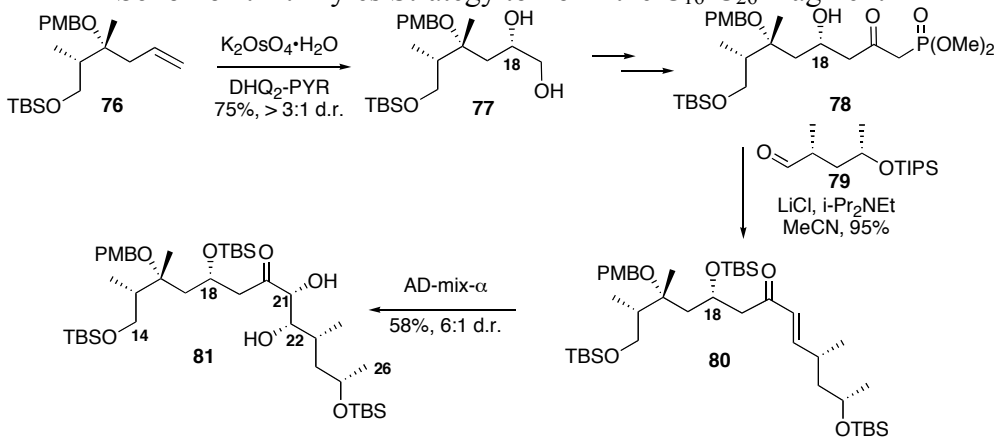
Nishiyama and co-workers also obtained the C_{18} stereocenter from a commercially available compound, 1,2-epoxybutanol (Scheme 1.10).[30] Functional group manipulations led to an iodo-species **71**. An umpolung featured alkylation of dithiane **72** and a subsequent Sharpless asymmetric dihydroxylation were executed to provide the C_{16}-C_{26} fragment of amphdinolide B_1.

Scheme 1.10. Nishiyama's Strategy to the Top C_{14}-C_{26} Fragment



Myles and co-workers established the C_{18} stereocenter using a Sharpless dihydroxylation in a poor diastereoselectivity (Scheme 1.11).[19] Subsequently, a series of functional group manipulations provided a ketophosphonate species **78**. A Wadsworth-Emmons olefination was applied to couple the keto-phosphonate subunit with an aldehyde **79**, followed with another Sharpless asymmetric dihydroxylation to establish the C_{14}-C_{26} fragment **81**.

Scheme 1.11. Myles Strategy to Form the C_{16}-C_{26} Fragment

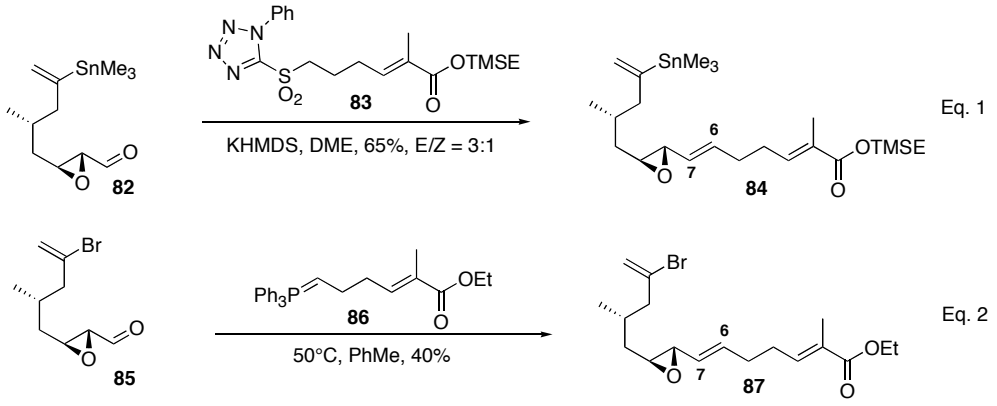


In summary, most of efforts by other laboratories have included a convergent synthetic route to the C_{14}-C_{26} fragment. The plan to set up the C_{18} stereocenter influenced the strategy to construct this top subunit. Sharpless asymmetric dihydroxylation was a frequently used method to establish the C_{21}-C_{22} diol. Due to the steric hinderance and unfavorable electronic state, Sharpless asymmetric dihydroxylation suffers from elongated reaction time, low yield and comparatively poor diastereoselectivity.

1.3.3. Previous Strategies to Elaborate the Allyl epoxide Motif

Among the previous studies, only Pattenden and Lee addressed the preparation of the unusual allyl epoxide moiety (Scheme 1.12). Both applied Sharpless asymmetric epoxidation protocol to furnish the expoxide moiety and followed with the oxidation of the alcohol and subsequent olefination. In Pattenden's approach,[18] modified Julia coupling provided an unsatisfactory 3:1 of E/Z selectivity (Eq. 1). Lee's strategy required comparatively harsh conditions (50°C for Wittig olefination) and only provided 40% yield.[31] It should be noted that the E/Z selectivity was not reported in this case (Eq. 2).

Scheme 1.12. Previous Works on the Construction of the Allyl epoxide Motif



1.4. Conclusion

Although many synthetic studies toward the total synthesis of amphidinolide B_1 had been reported by the date we initiated our research study, the question of how to efficiently prepare the highly substituted diene had not been successfully addressed. Since all of the prior studies included a convergent approach and similar C_{14}-C_{26} subunits, some of strategies inevitably overlapped. For example, there are three approaches using a Sharpless asymmetric dihydroxylation to elaborate C_{21}-C_{22} diol. Among all the prior works, only Pattenden's work was close to the completion of the total synthesis. He also constructed the allyl epoxide moiety, albeit in a poor E/Z selectivity. Unsolved problems included an efficient strategy to construct the C_{13}-C_{15} diene, a novel approach to elaborate the C_{18}-C_{26} extremely functionalized fragment, a feasible method getting access the allyl epoxide motif, a successful method to

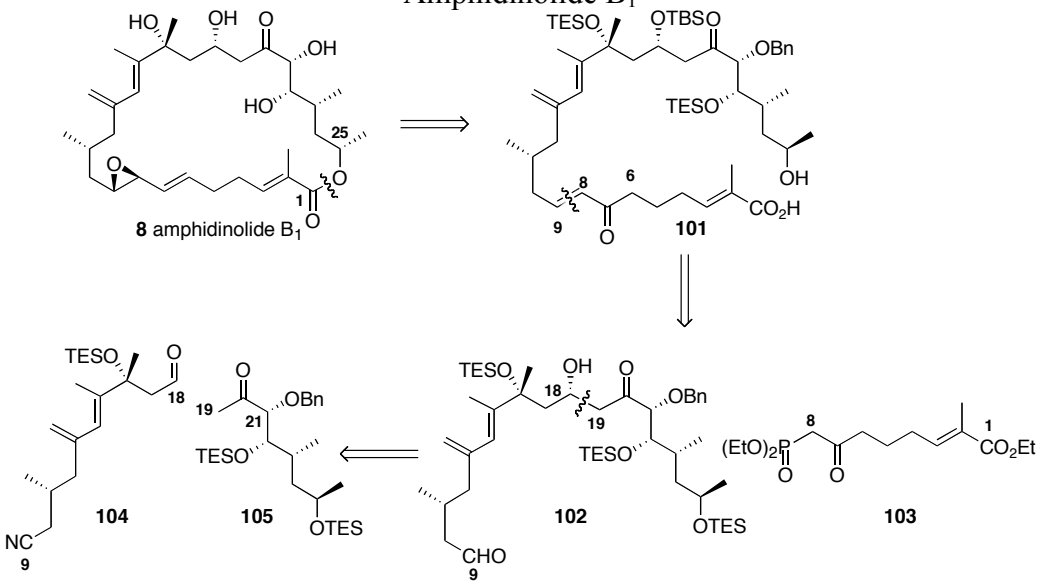
form the macrolactone core structure and most importantly, a completed total synthesis of amphidinolide B_1.

Chapter II. Preparation of the Western Aldehyde

2.1 Retrosynthetic Analysis

An original retrosynthetic analysis started from the disconnection of the ester linkage to provide the carboxylic acid species **101** (Scheme 2.1). Further disconnection of the C_8-C_9 olefinic bond led to the northern aldehyde **102** and the southern ketophosphonate subunit **103**. In the northern part, the C_{18}-C_{19} bond could be constructed by an aldol condensation. In this way, the northern part can be further divided into an eastern subunit, a methyl ketone **105** and a western subunit, an aldehyde **104**. The synthetic study started with the preparation of the western aldehyde **104**.

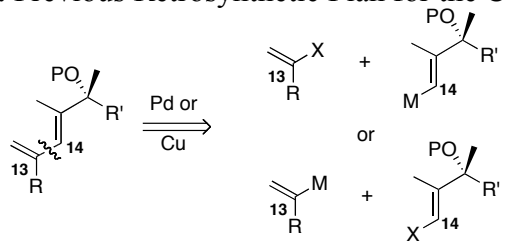
Scheme 2.1. Retrosynthetic Plan toward the Total Synthesis of Amphidinolide B_1



2.2. Construction of the Highly Substituted Diene

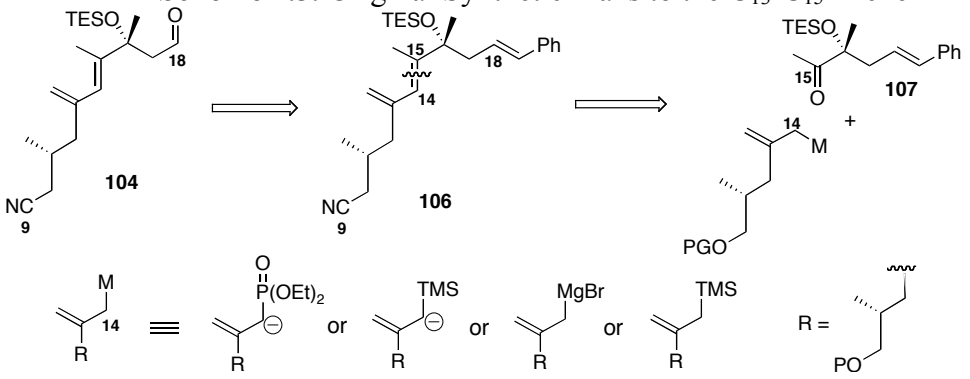
One of the most important issues related to the preparation of the western aldehyde **104** was the construction of the sterically hindered diene moiety. As discussed in the introduction part, most of the prior works chose the disconnection between the C_{13}-C_{14} bond. The palladium or copper catalyzed coupling reaction could be applied to either one of the combinations of the vinyl halogen and the vinyl metal species (Scheme 2.2).

Scheme 2.2. Previous Retrosynthetic Plan for the C_{13}-C_{15} Diene



Based on the failed efforts reported by Pattenden and co-workers[32] and potential inefficiency caused by the preparation of Pd cross-coupling precursors, we proposed to disconnect the C_{14}-C_{15} bond. In this way, two subunits will be reasonably deduced as a methyl ketone and a nucleophilic allyl subunit. The latter subunit could be reduced to an allyl phosphonate anion,[33] allyl silane anion,[34] allyl Grignard reagent[35] or an allyl silane (Scheme 2.3).[36] We chose to explore the Wadsworth-Emmons olefination first.

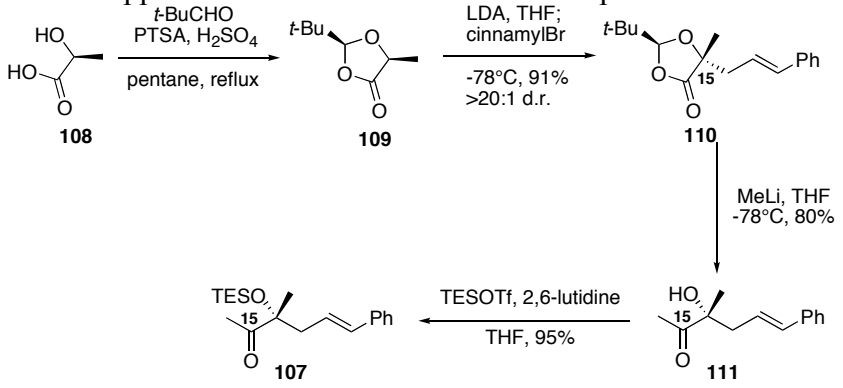
Scheme 2.3. Original Synthetic Plans to the C_{13}-C_{15} Diene



2.2.1. Preparation of the Methyl Ketone Subunit 107

Our synthetic study started from the preparation of the methyl ketone subunit **107** (Scheme 2.4). Acetalization of the commercially available (*L*)-lactic acid with pivaldehyde provided the acetal lactone **109**. Seebach alkylation[37] of the lactone with cinnamyl bromide led to the tertiary alkoxy moiety **110** in 91% yield and greater than 20:1 dr. Subsequent treatment of the alkylation product with methyl lithium yielded the methyl ketone **111** with a free tertiary hydoxyl group. Silylation of the newly generated alcohol provided the methyl ketone subunit **107**.

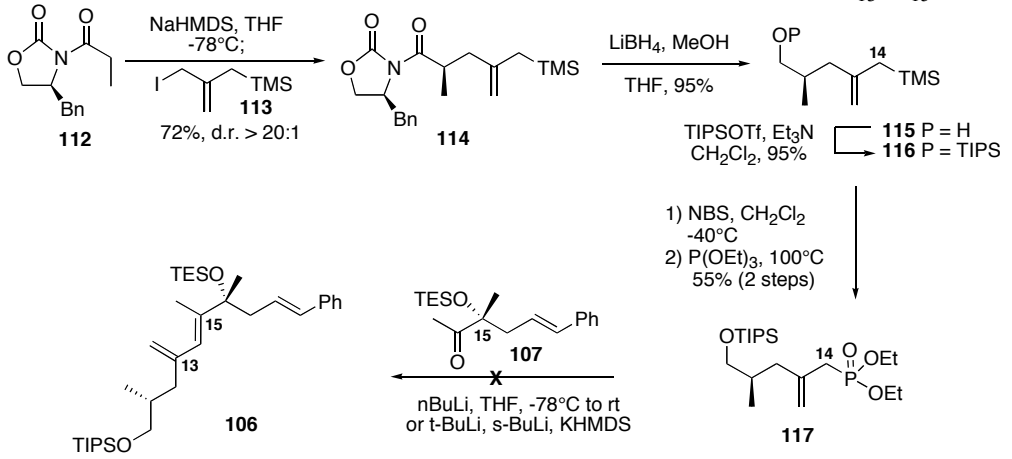
Scheme 2.4. Application of Seebach Protocol to Prepare the Ketone Subunit



2.2.2. Application of Horner-Wadsworth-Emmons Olefination to Form the C_{14}-C_{15} Bond

With one of the subunits ready, the other precursor of Horner-Wadsworth-Emmons Olefination was prepared starting from commercially available Evans' auxiliary (Scheme 2.5). Alkylation with the readily available iodide species **113** (made from the corresponding commercially available allyl chloride using Finkelstein reaction[38]), led to the alkylated product **114**. Reductive cleavage of the Evans' auxiliary and subsequent silyl protection gave allyl silane **116**. Upon treatment with NBS and heating with $P(OEt)_3$ in a sealed tube, the phosphonate precursor **117** was synthesized with a reasonable overall yield. However, enolization of phosphonate with *t*-BuLi, *s*-BuLi or KHMDS failed to initiate Wadsworth-Emmons olefination to generate the expected diene **106**.

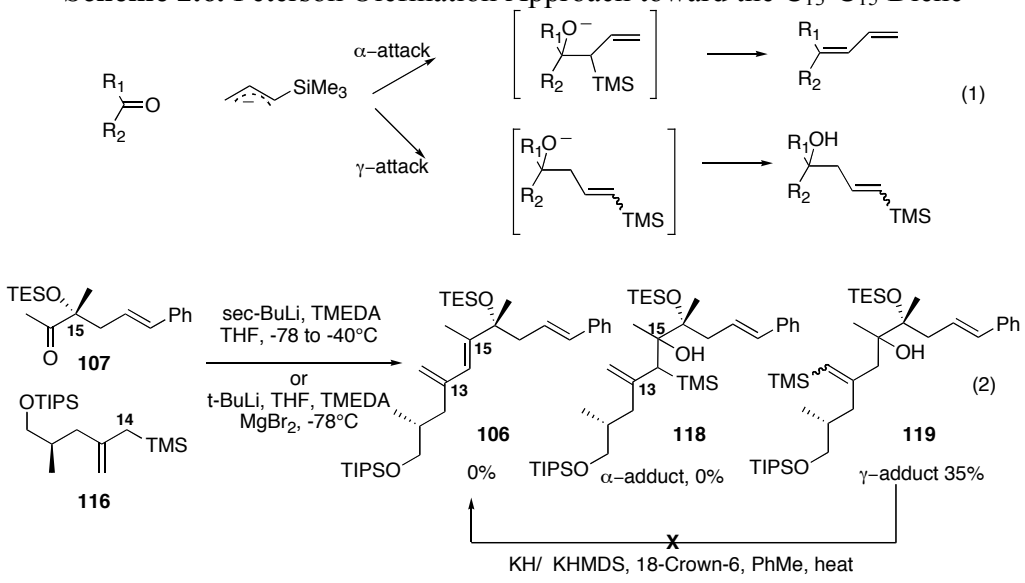
Scheme 2.5. Wadsworth-Emmons Olefination Plan to the C_{13}-C_{15} Diene



2.2.3. Application of Peterson Olefination to Form the C_{13}-C_{15} Diene

Peterson olefination was an alternative method to access to the diene motif (Scheme 2.6). In general, the allyl trimethylsilyl anion can react to ketone in either α-attack to generate an β-alkoxysilane, or γ-attack resulting a δ-hydroxy vinylsilane.[39] The β-alkoxysilane can undergo a Peterson olefination reaction to furnish a diene. Following a Magnus' protocol,[40] *sec*-butyllithium was applied to deprotonate the allyl trimethylsilane **116**, but subsequent addition of the methyl ketone **107** gave the γ-adduct in a poor yield. None of expected diene or β-alkoxysilane was observed. In a modified procedure, *in situ* generated $MgBr_2$ was added in order to encourage the formation of the α-adduct,[41] but also failed to show any promising results. Finally, attempts to turn the γ-adduct into the β-alkoxysilane or diene *via* a [1,3]-sigmatropic rearrangement reaction were also not productive.[42]

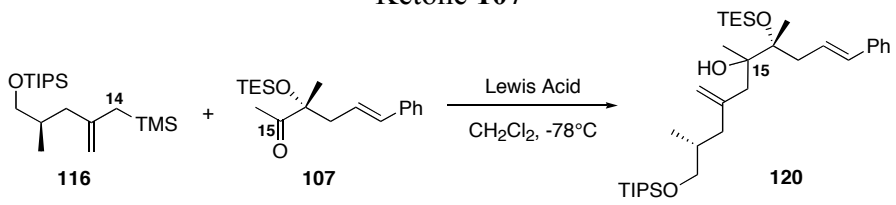
Scheme 2.6. Peterson Olefination Approach toward the C_{13}-C_{15} Diene



2.2.4. Fleming Coupling to Elaborate the C_{13}-C_{15} Diene

Since nucleophilic addition of the allyltrimethylsilane anion to the ketone failed to build the C_{14}-C_{15} bond, another rational alternate would be using Fleming-type coupling between the allyl silane species **116** and the carbonyl substrate **107**. After screening a series of Lewis acids in an order of increasing Lewis acidity, we discovered that freshly distilled $TiCl_4$ was the most effective Lewis acid for this transformation generating a 60~65% yield in an inconsequential 6:1 dr at C_{15} quaternary center (Chart 2.1).

Chart 2.1. Fleming-Type Coupling of the Allysilane **116** and the Ketone **107**



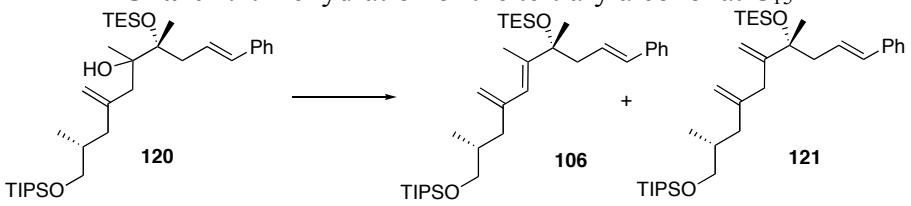
Entry	*Lewis acid*	*Yield*
1	TMSOTf	N.R.
2	BF_3•OEt_2	N.R.
3	Me_2AlCl	N.R.
4	$AlMe_3$	N.R.
5	$SnCl_4$	N.R.
6	$TiCl_4$/$Ti(OiPr)_4$	N.R.
7	$TiCl_4$	25~40%
8	$TiCl_4$*	60~65%

* $TiCl_4$ was freshly distilled over Cu powder under a reduced pressure provided by an asparatus pump.

2.2.5. Dehydration of the C_{15} Tertiary Alcohol

With the C_{14}-C_{15} bond formed, the next goal was to synthesize the C_{13}-C_{15} diene *via* dehydration. After a systematic screening, a dehydration protocol using pyridine and $SOCl_2$ was chosen for its high conversion rate and amiable features (Chart 2.2). We also discovered that the dehydration conditions using pyridine and $SOCl_2$ exhibited a solvent effect. While non-polar solvents, such as PhMe, Et_2O or cyclohexane, tended to improve the ratio between the conjugated diene **106** and unconjugated diene **121**; polar solvents, for example CH_2Cl_2, CH_3CN and THF, lowered the ratio. It was also discovered that lowered temperature also helped to increase the ratio. To date, the best result was obtained using PhMe as a solvent at –78°C to give 99% overall yield of the dehydration products containing a single stereoisomer of the conjugated diene **106**, which was contaminated by the unconjugated diene **121** in a ratio of 2.2:1.

Chart 2.2. Dehydration of the tertiary alcohol at C_{15}



Conditions	*Temp °C*	*Overall Yield %*	**106 : 121**
Pyridine, MsCl	0 to rt	0	N/A
Pyridine, $POCl_3$	rt to 110 °C	0	N/A
2,6-lutidine, Tf_2O	0 to rt	0	N/A
Pyridine, $SOCl_2$	-78	99	2.2:1*
Burgess Reagent	0	80	1:1
Martin's Reagent	50	30	1:1

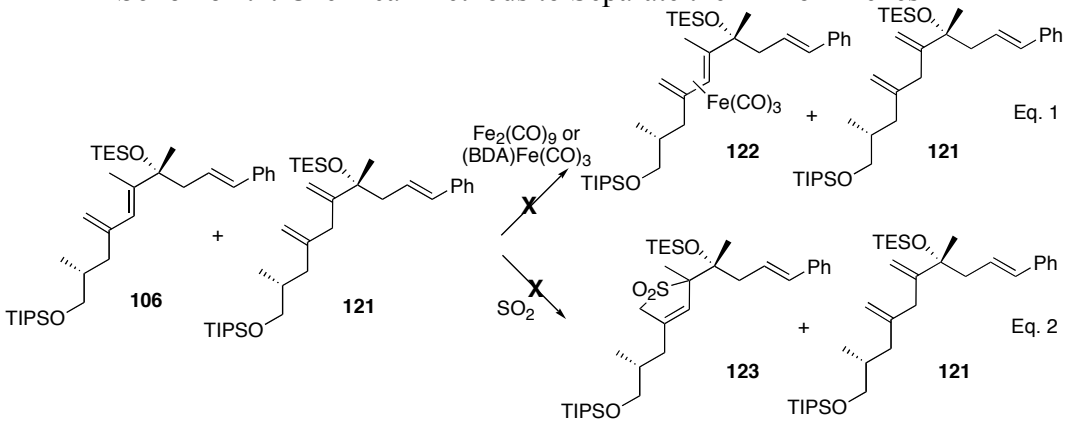
* The reaction was carried out in PhMe.

2.2.6. Separation of the Conjugated and Unconjugated Dienes

After successfully synthesizing the diene, the priority shifted to the separation between the conjugated and unconjugated dienes. Since conventional SiO_2 chromatography and $AgNO_3$-doped SiO_2 chromatography failed to give good separation due to the close R_f exhibited by the two dienes, one of the alternates would be using the different chemical property between the conjugated and unconjugated dienes to separate them. One of the options was to apply transition metal substrate, for example $Fe_2(CO)_9$,[43] to coordinate the conjugated diene without affect the unconjugated diene (Scheme 2.7, Eq. 1).

It would be ideal considering not only the polarity change after the coordination that might grant an efficient separation, but also the conjugated diene can be protected in a form of an iron complex. Unfortunately, all attempts to access the tricarbonyliron complex using either $Fe_2(CO)_9$ or $(BDA)Fe(CO)_3$[44] failed. The failure might due to the hindrance imparted by the adjacent quaternary center.

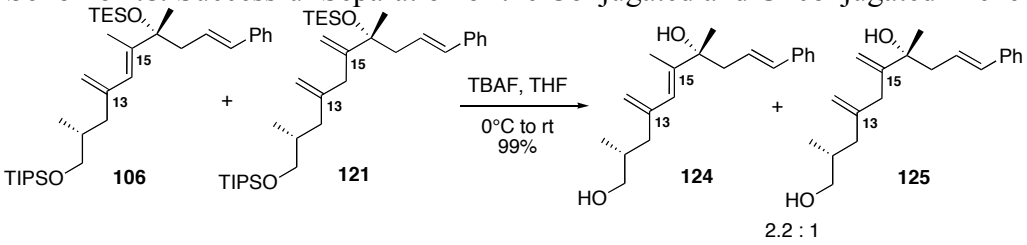
Scheme 2.7. Chemical Methods to Separate the Mix of Dienes



Another option would be formation of the cyclic sulfone *via* bubbling of SO_2 into the mixture of dienes. The uncojugated diene **121** would remain intact and the conjugated diene **106** should form a cyclic sulfone (Scheme 2.7, Eq. 2).[45] The conjugated diene **106** also should be recovered readily from the sulfone upon heating. Unfortunately, the conjugated diene **106** decomposed upon the treatment of SO_2, while the intact unconjugated diene **121** could be isolated cleanly. The failure might be caused by the sensitivity exhibited by the conjugated diene toward acidic conditions.

After many isolation efforts, the mixture of conjugated and unconjugated diene proved to be separable by a normal phase HPLC (Scheme 2.8).[46] For logistical ease in the separation procedure, the TIPS and TES silyl ether protecting groups were removed by TBAF to generate a mixture of two diols **124** and **125**. These diols are comparatively easier to separat by conventional SiO_2 chromatography.

Scheme 2.8. Successful Separation of the Conjugated and Unconjugated Diene

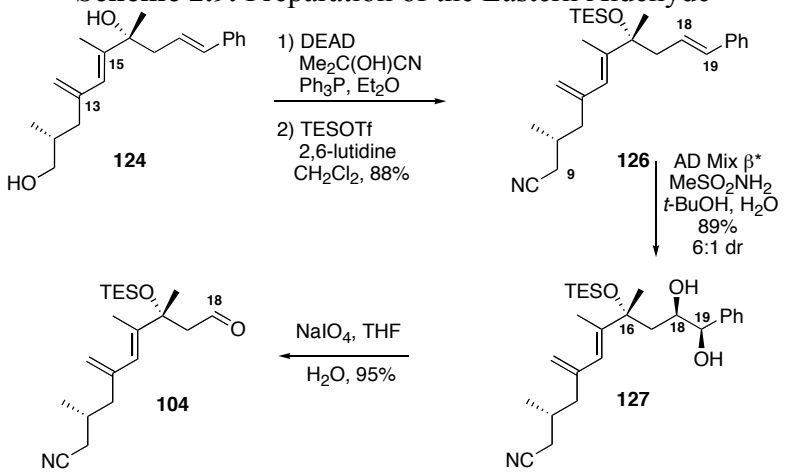


2.3. Selectively Functionalize C_{18}-C_{19} Olefinic Bond and Formation of the Western Aldehyde 104

Once the diene **124** was prepared, functional group manipulations led to the western aldehyde **104** (Scheme 2.9). First, a Mitsunobu-type incorporation of a nitrile group at C_9 and a subsequent silyl ether protection led to the nitrile substrate **126**.[47] In order to obtain the western aldehyde, a selective functionalization of the C_{18}-C_{19} olefinic bond had to be achieved in the presence of C_{13}-C_{15} conjugated diene. A modified conditions of Sharpless asymmetric dihydroxylation with AD mix β [48] exclusively provided regioselectively dihydroxylated product **127** as a mixture of 6:1 dr on C_{18}-C_{19} diols. The selectivity for the C_{18}-C_{19} alkene over the C_{13}-C_{15} diene was

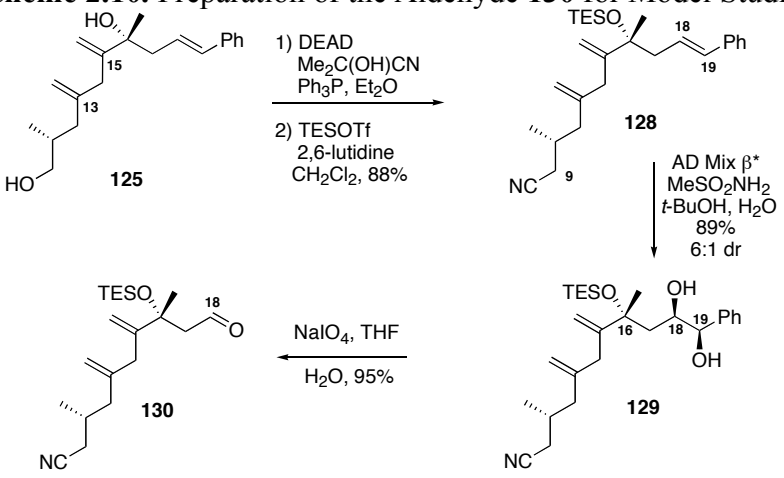
attributed to a beneficial π–stacking interaction between the neighboring aromatic ring and the corresponding aromatic moieties in Sharpless ligand.[49] A racemic dihydroxylation conditions using OsO_4 and NMO generated a complex mixture. AD mix α also proved to be a poor reagent for this transformation. With the diol in hand, a subsequent oxidative cleavage of the diol with $NaIO_4$ provided the western subunit **104**.

Scheme 2.9. Preparation of the Eastern Aldehyde



In a parallel route, the unconjugated diene **125** was treated with the same procedure, so that it could be used as an advanced model in the later studies (Scheme 2.10). Interestingly, dihydroxylation of the unconjugated diene **128** with AD mix β was again regioselective for the C_{18}-C_{19} alkene; however, no diastereoselectivity was observed in the dihydroxylation. Again, a subsequent oxidative cleavage of the diol provided the corresponding aldehyde **130**, which would be applied as a model substrate in the future studies.

Scheme 2.10. Preparation of the Aldehyde **130** for Model Studies

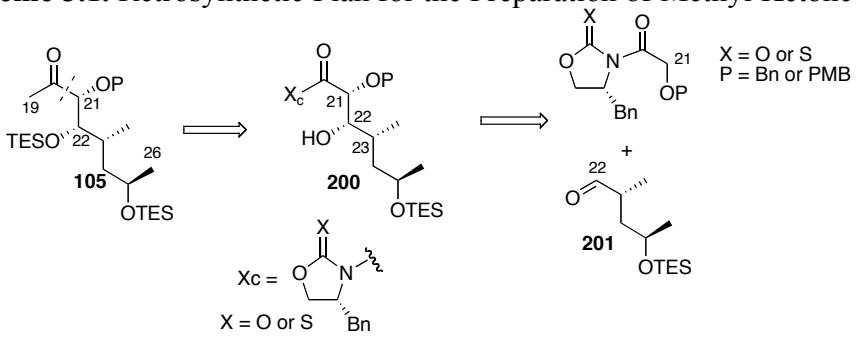


Chapter III. Preparation of the Eastern Methyl Ketone

3.1. Retrosynthetic Plan for the Preparation of Methyl Ketone 105

With the western fragment **104** in hand, our next goal was to prepare the eastern methyl ketone **105**. Retrosynthetic analysis showed that **105** could be derived from intermediate **200** (Scheme 3.1). The C_{21}-C_{22} bond of **200** would be constructed by aldol reaction from the oxazolidinone or oxazolidinethione auxiliary species and the aldehyde **201**.

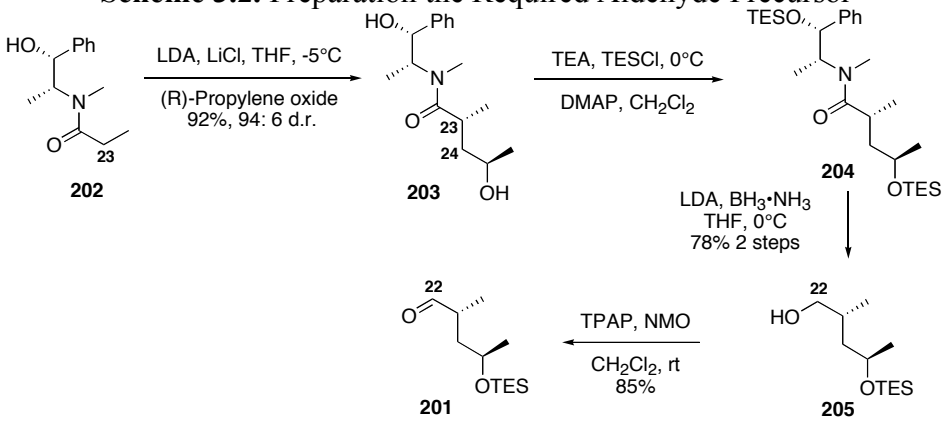
Scheme 3.1. Retrosynthetic Plan for the Preparation of Methyl Ketone **105**



3.2. Preparation of the Aldehyde 201

The required aldehyde **201** was synthesized in four steps from commercially available Myers auxiliary **202** (Scheme 3.2). The Myers alkylation protocol[50] with the commercially available (*R*)-propylene oxide provided the $C_{23,24}$-coupled product **203** in 94:6 d.r.[51] A Subsequent TES protection followed by a reduction with BH_3•NH_3/LDA and Ley oxidation[52] yielded the desired aldehyde **201**.

Scheme 3.2. Preparation the Required Aldehyde Precursor



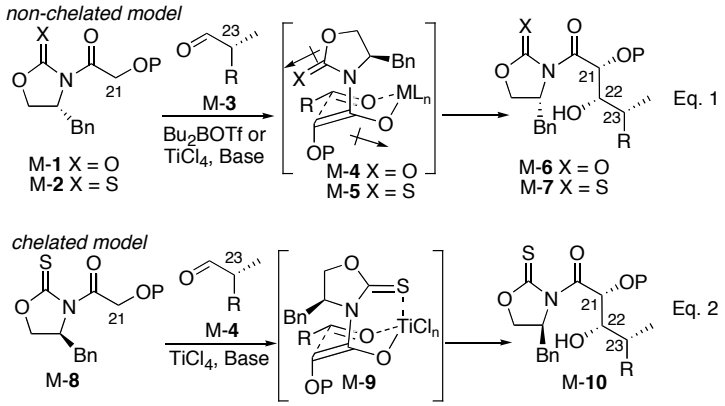
3.3. Titanium-Mediated Aldol Reaction to Form C_{21}-C_{22} Bond

3.3.1. General Introduction of Titanium-Mediated Aldol Reaction

With the required aldehyde **201** ready, our nearst goal was to explore the aldol reaction to connect the C_{21}-C_{22} bond. Some of the general knowledge about Evans' and Crimmins' adol reaction would be necessary at this point. The so-called "Evans-syn" aldol reactions with chiral oxazolidniones using dibutylboron triflate and the appropriate amine base have become the standard by which new asymmetric and diastereoselective reactions are judged against[53] (Scheme 3.3). The recently developed titanium-mediated oxazolidinethione aldol reaction, from the Crimmins laboratory, has been shown to provide comparable levels of selectivity on the wide range of systems.[54] There are several advantages to the Crimmins' aldol methodology (e.g., relative ease of auxiliary cleavage and use of the logistically easier titanium enolates). One particularly attractive attribute is the flexibility imparted by Crimmins' chelated and nonchelated models depending on the amount of $TiCl_4$ and amine base

(normally (-)-sparteine) that is added. This modification provides access to both the Evans-*syn* product *via* the nonchelated model (Eq. 1) and the non-Evans-s*yn* adduct *via* the chelated model (Eq. 2).

Scheme 3.3. Generalized Examples of Crimmins' and Evans' Aldol Adducts

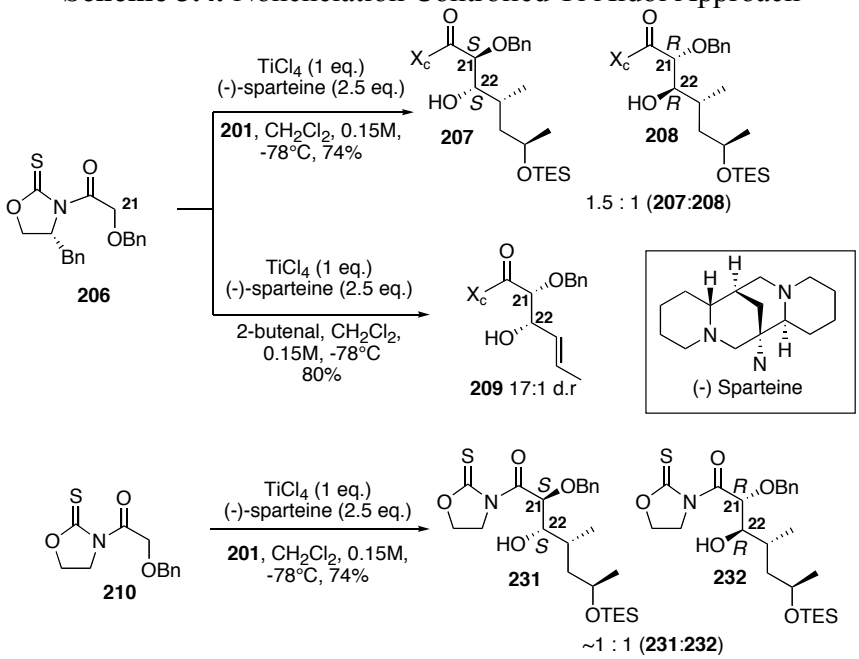


3.3.2. Application of Non-Chelation Controlled Ti-Aldol Conditions

Exploration into the aldol reaction commenced with the known oxazolidinethione auxiliary **206**[55] (Scheme 3.4). Treatment with the prescribed conditions for obtaining non-chelation or "Evans-*syn*" aldol adducts [$TiCl_4$ (1.0 equiv.), (-)-sparteine (2.5 equiv.)] provided two diastereomeric aldol adducts **207** and **208** in a 1.5:1 ratio. Unlike as predicted in the Crimmins' models for this transformation, *none* of the expected Evans-*syn* adduct was observed. Instead, the *anti* adducts **207** (H_{21}-H_{22} J = 9.3 Hz) and **208** (H_{21}-H_{22} J = 8.4 Hz)[56] were isolated in nearly equal amounts.[57] The addition of additives such as NMP or alternate bases (e.g. TMEDA) did not affect the observed stereochemical outcome.[58] Thwarted by this unexpected result, we turned to an

achiral aldehyde (2-butenal) to ensure the protocol was performing as expected. Aldol reaction under the identical conditions [$TiCl_4$ (1.0 equiv.), (-)-sparteine (2.5 equiv.)] provided solely the expected Evans-*syn* adduct **209** (H_{21}-H_{22} J = 3.3 Hz) in a 17:1 ratio. One possible explanation would be a mismatched relationship between the directing effect of the auxiliary and the inherit stereochemical preference of the aldehyde. To this end, the experiment was conducted with the achiral auxiliary **210**; however, equal amounts of the two previously observed stereochemistries (21*S*, 22*S* and 21*R*, 22*R*) were again the only observable products.

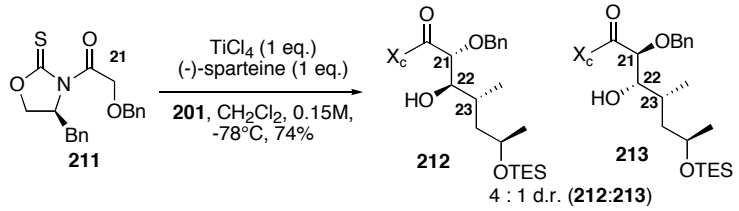
Scheme 3.4. Nonchelation Controlled Ti Aldol Approach



3.3.3. Application of Chelation Controlled Ti-Aldol Conditions

Given that the non-chelation approach provided none of the desired *syn* adduct, the complementary chelation aldol would appear to be the next logical step (Scheme 3.5). Using the enantiomeric oxazolidinethione auxiliary **211**, treatment under the chelation conditions [$TiCl_4$ (2 equiv.), (-)-sparteine (1 equiv.)] proceeded poorly and in low yield. Crimmins has also reported that the use of less $TiCl_4$ [(1 equiv.), (-)-sparteine (1 equiv.)] proceeds *via* the chelated model.[43] Treatment using these conditions provided some improvement in the selectivity of the transformation, yielding a more respectable 4:1 ratio of products (**212:213)** (**212**: H_{21}-H_{22} J = 8.8 Hz; **213**: H_{21}-H_{22} J = 9.2 Hz). It is important to note that despite the expected directing effect of the auxiliary (e.g. **206** should give the same absolute configuration at C_{21}, C_{22} under non-chelation conditions as enantiomeric auxiliary **211** gives under chelation conditions), the major product **212** from the chelation-controlled conditions using **211** contained the 21*R*, 22*R* stereochemistry of the minor product **208** from the non-chelation conditions with **206**. Alcohol **212** is synthetically useful as it possesses the correct *anti, anti* C_{21}-C_{23} stereochemistry for amphidinolide B_3. It became apparent at this juncture that the titanium-based aldol were unable to provide the necessary stereochemical relationship for amphidinolides B_1 and B_2.

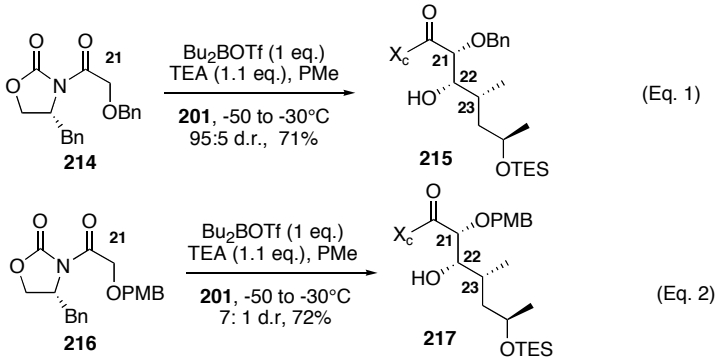
Scheme 3.5. Chelation Controlled Ti Aldol Reaction



3.4. Application of Borane Aldol to Form the C_{21}-C_{22} Bond

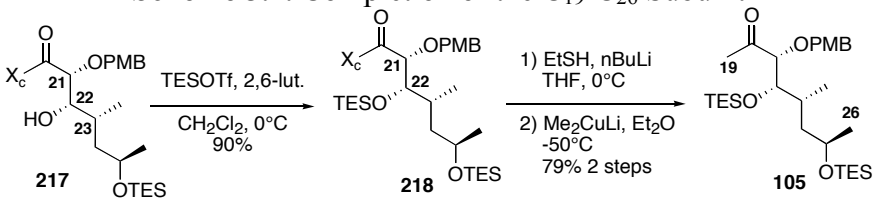
Since titanium-mediated aldol reaction failed to elaborate the *syn*-aldol adducts we needed, borane-mediated aldol was the next alternate we should pursue. We were gratified to observe that use of the auxiliary **214**[59] under boron-mediated conditions did yield the desired Evans-*syn* adduct **215** (H_{21}-H_{22} J = 2.1 Hz) in a 95:5 *syn:syn* and *syn:anti* ratio (72% isolated yield of **215**) (Scheme 3.6, Eq. 1). *To the best of our knowledge, these results represent the first reported examples of the stereochemical divergence between the titanium-mediated oxazolidinethiones and boron-mediated oxazolidinones.* Considering benzyl deprotection of the C_{21} alcohol might be problematic at a late stage, a PMB group was applied instead. Interestingly, the selectivity was decreased to 7:1 d.r. with comparable yield (Scheme 3.6, Eq. 2).

Scheme 3.6. Borane Mediated Aldol



Completion of the C_{19}-C_{26} subunit of amphidinolide B_1 was accomplished in three steps. Silylation using TESOTf provided the bissilylated compound **218**. Conversion to the thioester using LiSEt followed by cuprate coupling gave the methyl ketone **105** (Scheme 3.7).[60]

Scheme 3.7. Completion of the C_{19}-C_{26} Subunit

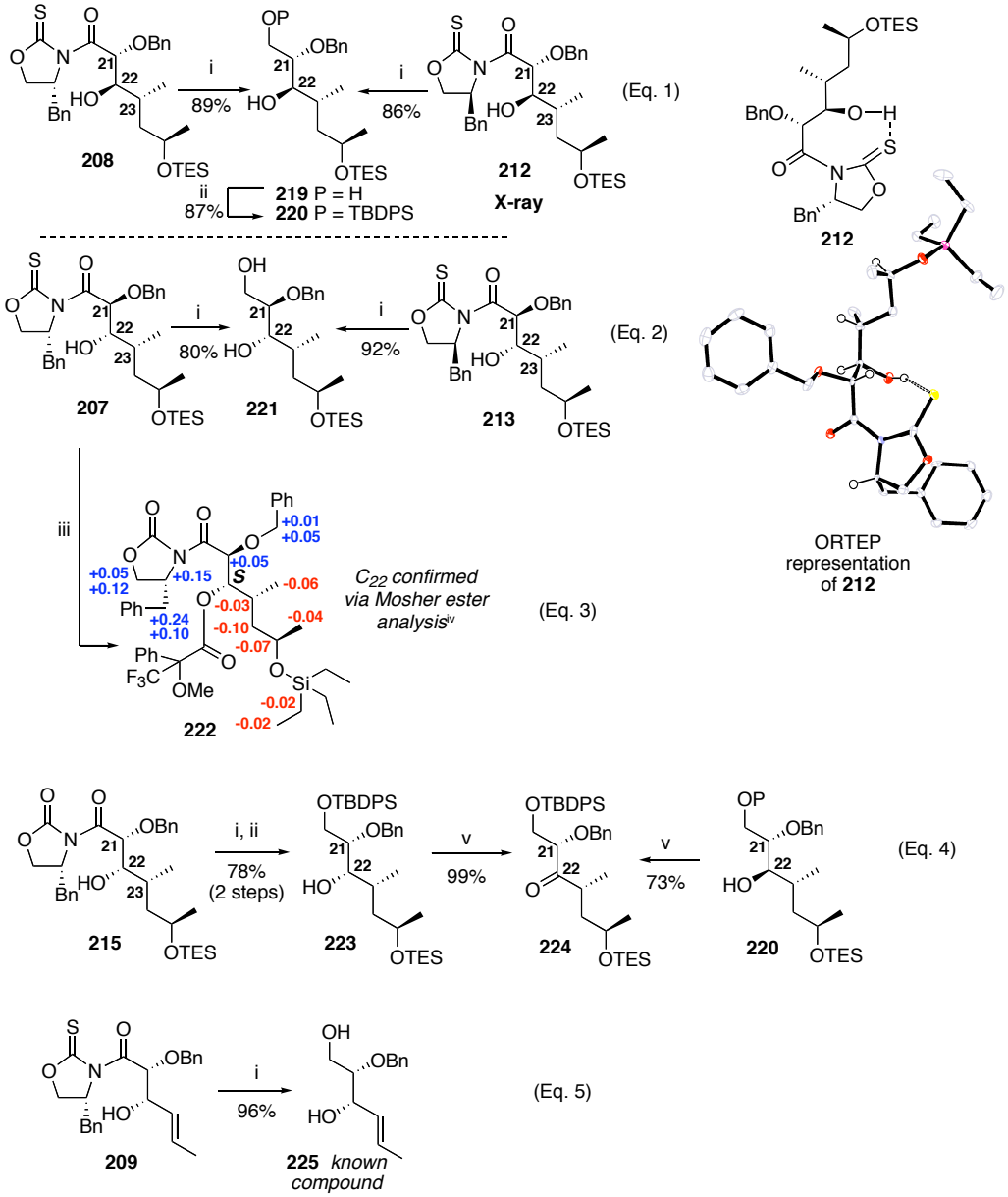


3.5. Confirmation of Absolute Stereochemistry of Aldol Adducts

Stereochemical assignment of the aldol products **207**-**209**, **212**-**213** and **215** was accomplished *via* a series of degradation experiments and X-ray crystallographic analysis of **212** (Scheme 3.8). Reductive removal of the auxiliaries from adducts **208** and **212** yielded an identical diol **219** (Eq. 1), thereby confirming **208** vis-à-vis X-ray structure **212**. An analogous path was followed for adducts **207** and **213** to yield the diol **221** (Eq. 2). The stereochemistry of **215** was confirmed *via* conversion to the TBDPS ether **223** and correlation with the TBDPS ether **220** through TPAP oxidation to the ketone **224** (Eq. 4). This degradation also indirectly established one of the two unknown stereocenters of **207** and **213** as 21*S* by assignment of both aldol adducts **212** and **215** as the 21*R* configuration. The 22*S* configuration was confirmed by Mosher ester analysis of **222** (Eq. 3).[61] Finally, the

stereochemistry of **209** was confirmed by reduction to a known compound **225**. (Eq. 5)[62]

Scheme 3.8. Confrimation of Absolute Stereochemistry of Aldol Adducts



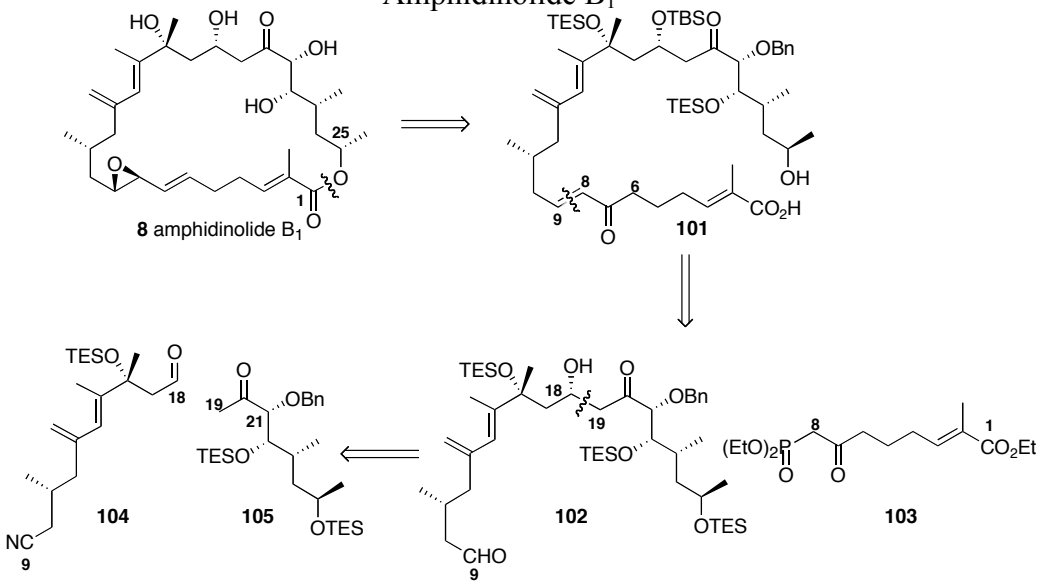
Scheme 3.8. i. $LiBH_4$, MeOH, THF, 0°C to r.t.; ii. TBDPSCl, imid., DMAP, CH_2Cl_2, 0°C to r.t.; iii. (*R*) / (*S*) Mosher acid chloride, DMAP, CH_2Cl_2; iv. Difference in ppm [(*S*)-Mosher Ester – (*R*)-Mosher ester, $CDCl_3$, 400 MHz NMR] shown on structure **222**; v. TPAP, CH_2Cl_2, mol. sieves.

Chapter IV. Synthetic Effort toward the Macrocycle Core Structure of Amphidinolide B_1

4.1. Synthesis of Northern C_9-C_{26} Fragment 102

After the completion of synthesizing both the diene fragment **104** and the methyl ketone **105**, our focus shifted toward the completion of the northen fragment **102** of amphidinolide B_1 (Scheme 4.1). According to our original plan, an aldol reaction will be applied to unite **104** and **105** to generate the northern fragment **102**.

Scheme 4.1. Review the Retrosynthetic Plan toward the Total Synthesis of Amphidinolide B_1

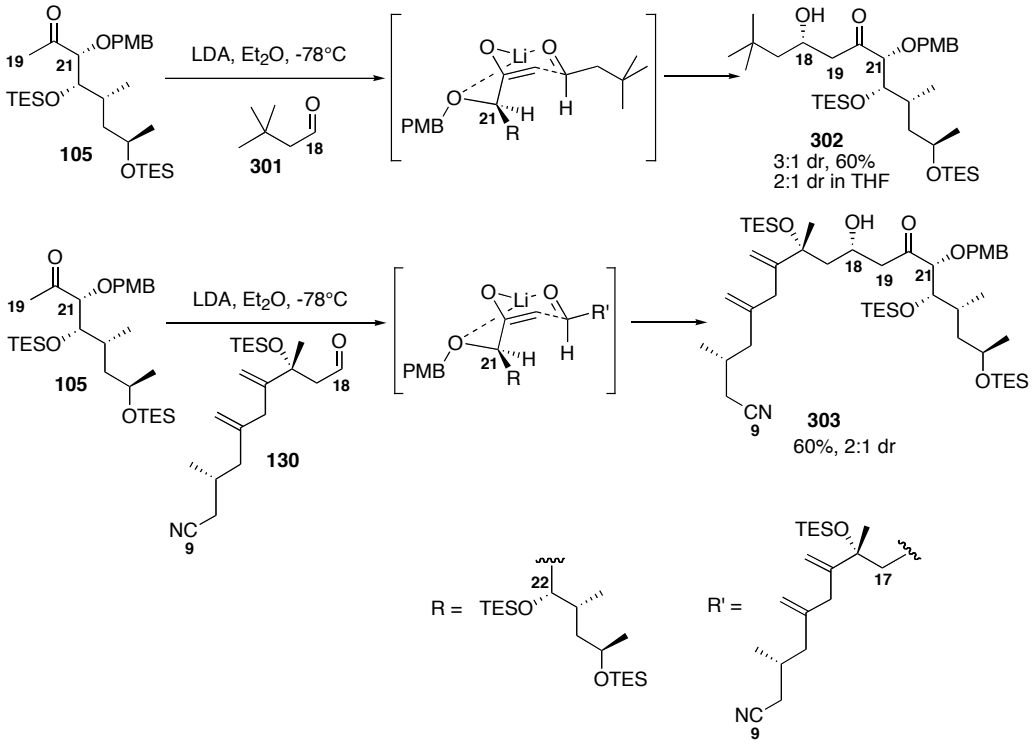


As described in the introduction part (Chapter 1.3.2), there were two synthetic studies had applied a similar aldol condensation strategy to form the C_{18}-C_{19} bond. In both cases, poor selectivity (~3:2 d.r.) was obtained at C_{18} stereocenter (see Scheme 1.8). Two common features can be observed in these

two example: (1) aldehydes without fully functionalized C_{13}-C_{15} conjugated diene motif, (2) silyl ether protecting groups (which generally were considered to prevent chelation[63]) applied to protect the α-hydroxyl group on the methyl ketone. On the contrary, we believed α-chelation would improve the diastereoselectivity as showed in scheme 4.2.

In order to test the validity of this proposal, a model study was initiated first. A commercially available aldehyde **301** with a β-quaternary center was applied in a chelation-controled aldol (Scheme 4.2). Using LDA as a base in a solvent of ether, the aldol reaction was successfully carried out to generate 60% isolated yield and 3:1 d.r. This result had shown one fold improvement on diastereoselectivity in comparison with the previously reported efforts. Interestingly, the diastereoselectivity decreased to 2:1 when the reaction was carried out in a solvent of THF. Subsequently, we applied the identical conditions to the advanced model substrate **130** containing an unconjugated diene moiety. Interestingly, upon this substrate, the aldol reaction produced a 60% isolated yield but in a slightly reduced level of selectivity (2:1 dr).

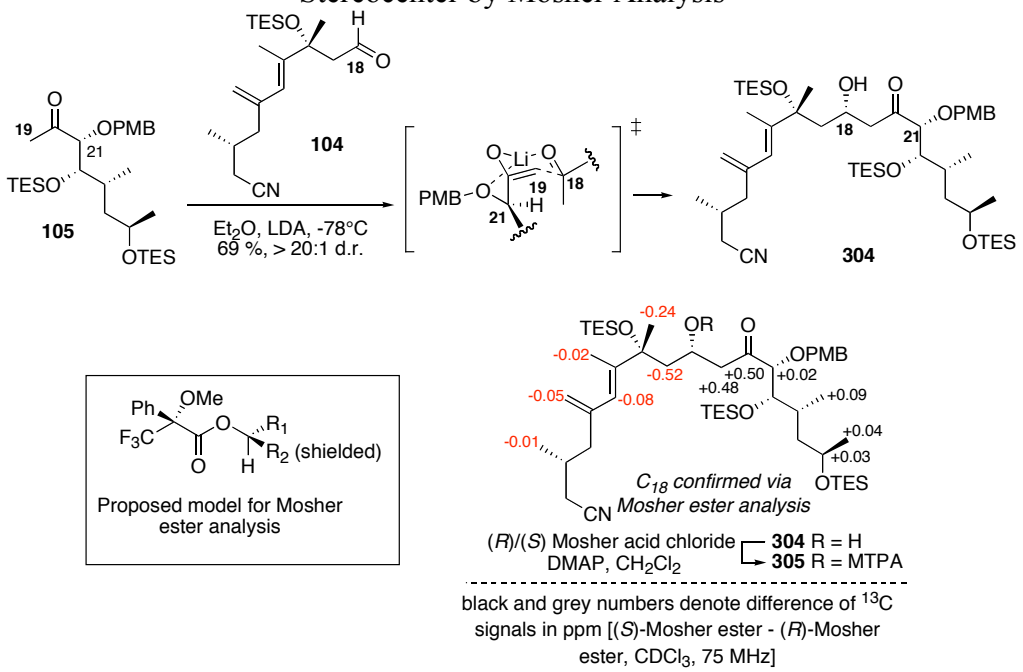
Scheme 4.2. Model Studies of Chelation-controlled Aldol



Fortunately, use of the desired substrate **104** generated highly improved results (Scheme 4.3). The chelation-controled aldol condensation of the lithium enolate derived from the methyl ketone **105** with the aldehyde **104** provided the coupled material **304** in 69% yield as a *single* diastereomer. This result is in stark contrast to works by Pattenden's and Kobayashi's laboratories in which poor selectivity (~ 3:2 d.r.) was observed using enolates derived from LDA, NaHMDS or KHMDS.[18,28] The absolute stereochemistry of C_{18} was confirmed by Mosher ester analysis. One possible explanation for the significant improvement of diastereoselectivity could be that increase allyl strain is introducted by the C_{13}-C_{15} conjugated diene. This congestion causes the

neighboring C_{16} stereocenter to adopt a conformation which is complementary to directing effect of the C_{21} PMB ether.

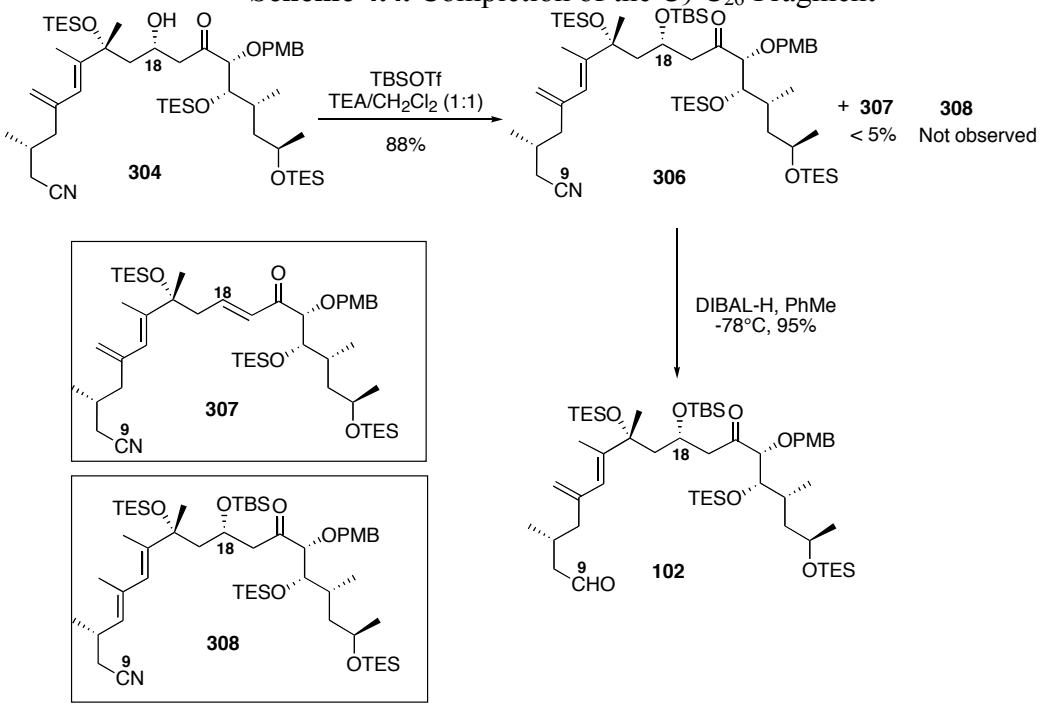
Scheme 4.3. Chelation-controled Aldol and Confirmation of the C_{18} Stereocenter by Mosher Analysis



Subsequential silyl protection at C_{18} initially proved problematic with traditional conditions such as using 1.2 equivalent of 2,6-lutidine and 1.0 equivalent of TBSOTf. Under these conditions, *β*-elimination product **307** (~20%) and isomerized diene product **308** (~10%) were observed. After considerable experimentation, a large excess of triethylamine was applied to solve this problem (Scheme 4.4).[64] Under these conditions, the elimination product **307** was less than 5% based on NMR analysis and no isomerization product **308** observed. Next, a selective reduction of the C_9 nitrile in the presence of the electronically more reactive C_{20} ketone was achieved with

DIBAL-H in toluene at -78°C with an 95% yield. In this way, the complete northern C_9-C_{26} fragment **102** was achieved.

Scheme 4.4. Completion of the C_9-C_{26} Fragment

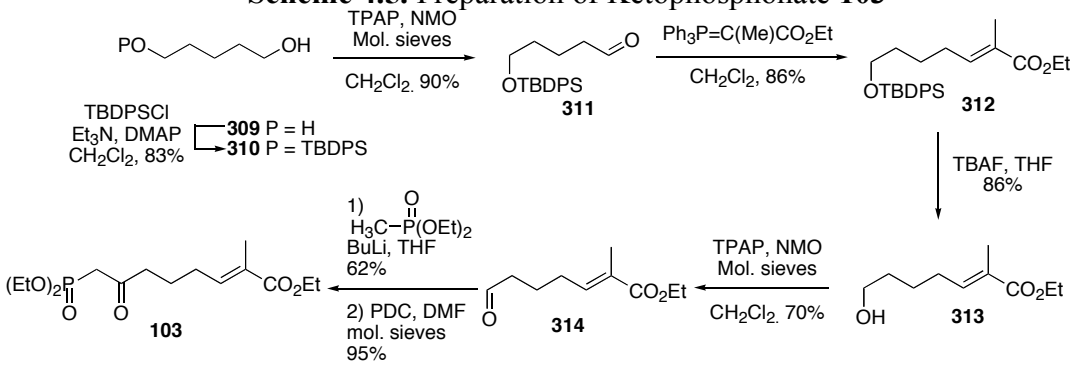


4.2. Construction of the Entire Carbon Backbone of Amphidinolide B_1 and Model Study for Epoxide Functionality

After preparation of the northern subunit **102**, the southern C_1-C_8 fragment ketophosphonate **103** was readily available from the commercially available 1,5-pentadiol **309** in 8 steps (Scheme 4.5). First, a selective silyl ether protection of the commercially available 1,5-pentadiol gave **310**, Ley oxidation and Wittig olefination gave the unsaturated ester **312** as a single stereo isomer. Desilylation and Ley oxidation yielded the aldehyde **314**. Nucleophilic attack

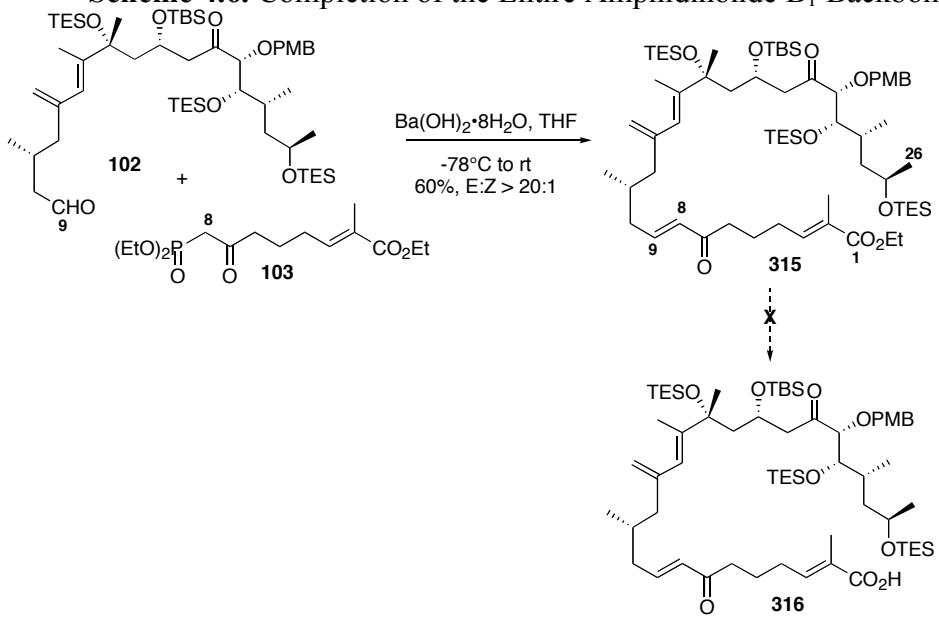
with a lithiated phosphonate, followed with an oxidation reaction gave the ketophosphonate **103**.

Scheme 4.5. Preparation of Ketophosphonate **103**



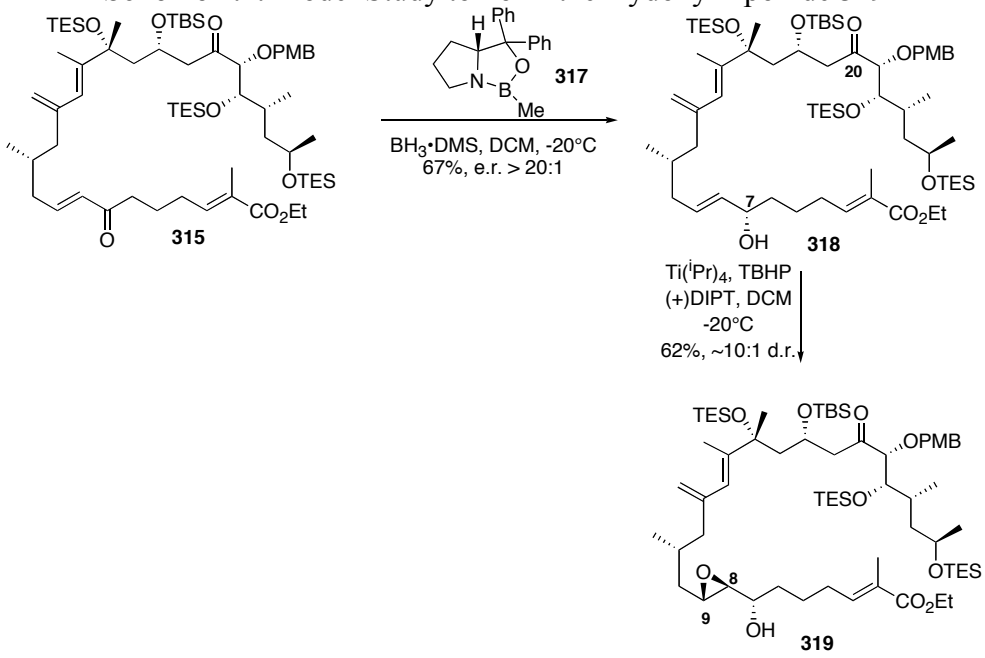
With both southern and northern fragments ready, our goal was turned to the coupling of **102** and **103** *via* Wadsworth-Emmons olefination (Scheme 4.6). After testing a series of conditions (including Masamune-Roush conditions [65] with LiCl/DBU and KHMDS/THF conditions), Paterson's conditions[66] with $Ba(OH)_2$ was determined to be the most effective way to form the C_8-C_9 olefinic bond. The enone **315** was accomplished as a single olefin isomer with a fully functionalized entire carbon backbone of amphidinolide B_1. With ester **315** in hand, a series of hydrolysis conditions were screened, including $LiOH/THF/H_2O$, $NaOH/^iPrOH/H_2O$ at either ambient or elevated temperature.[60] Unfortunately, none of these conditions yielded the expected acid **316**. Decomposition was consistently observed upon forcing conditions.

Scheme 4.6. Completion of the Entire Amphidinolide B_1 Backbone



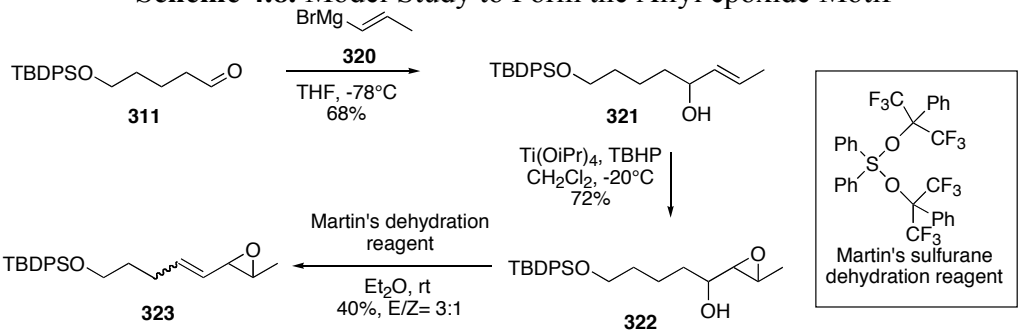
Although free carboxylic acid **316** was not able to be obtained from **315**, **315** still can be useful for a model study to test the feasibility of our proposal of elaborating the α,β-unsaturated epoxide functionality. In a model study (Scheme 4.7), a regioselective and diastereoselective reduction of the enone carbonyl using (*R*)-2-methyl-CBS-oxazaborolidine **317**[67] led to the alcohol **318** as a single diastereoisomer. A subsequent Sharpless asymmetric epoxidation with (+)-DIPT and $Ti(O^iPr)_4$ provided the epoxide **319** in a ratio of 10:1 d.r.[68]

Scheme 4.7. Model Study to Form the Hydoxyl Epoxide **319**



In a separate model study, dehydration of hydroxyl epoxide motif was tested (Scheme 4.8). Firstly, the hydroxyl epoxide **322** was prepared in two steps from the previously made aldehyde **311**. A commercially available Grignard reagent **320** was added to the aldehyde **311** to give the allylic alcohol **321**. Next, a racemic epoxidation of the alcohol **321** with $Ti(O^iPr)_4$ and TBHP yielded the hydroxyl epoxide **322**. With model substrate **322** in hand, dehydration with Martin's sulfurane reagent generated allyl epoxide **323** in 3:1 E/Z selectivity and a modest yield. These results should lay the foundation for the ultimate incorporation of these functionalities after the closure of the macrocyclic ring.

Scheme 4.8. Model Study to Form the Allyl epoxide Motif



4.3. Efforts to Construct the Macrocyclic Ring

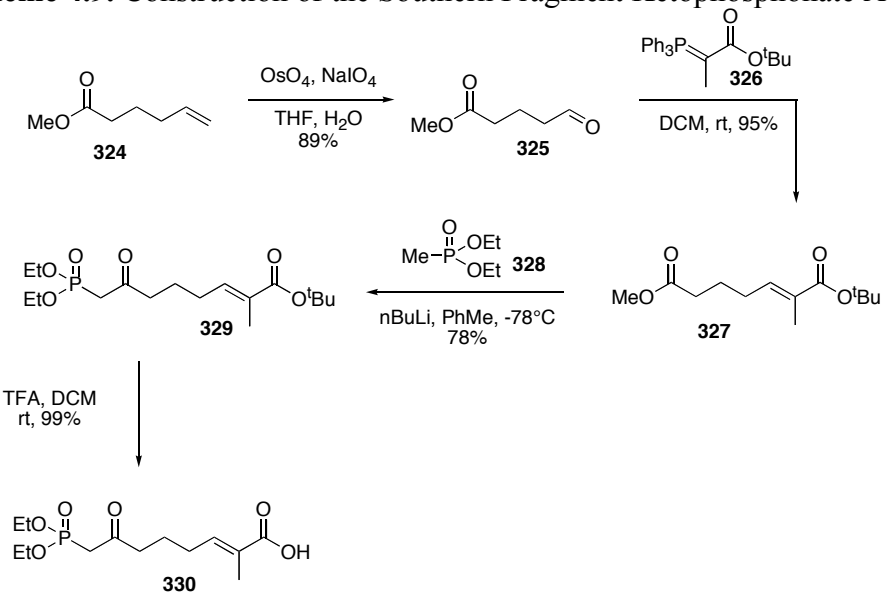
After the successful model studies of elaborating the allyl epoxide moiety, our goal returned to the construction of the macrocycle core structure of amphidinolide B_1. Since the acid **316** was not available from **315**, one of the options would be directly coupling the aldehyde **103** with a ketophosphonate substrate **330** (Scheme 4.9) containing a free acid motif. If the olefination coupling were to succeed, a subsequent selective desilylation would render a suitable precursor for Mitsunobu macrolactonization.

4.3.1. Construction of the Southern Fragment Ketophosphonate Acid

Preparation of the southern fragment ketophosphonate acid **330** started from the commercially available methyl 5-hexanoic acid **324** in 4 steps (Scheme 4.9). An oxidative cleavage of the double bond yielded the aldehyde **325**. Next, Wittig reaction led to the diester **327** in a good yield.[69] A selective nucleophilic addition of the lithiated diethyl methyl phosphonate generated the

methyl ester **329**. A subsequent acidic hydrolysis of *t*-butyl ester gave ketophosphonate acid **330.**

Scheme 4.9. Construction of the Southern Fragment Ketophosphonate Acid

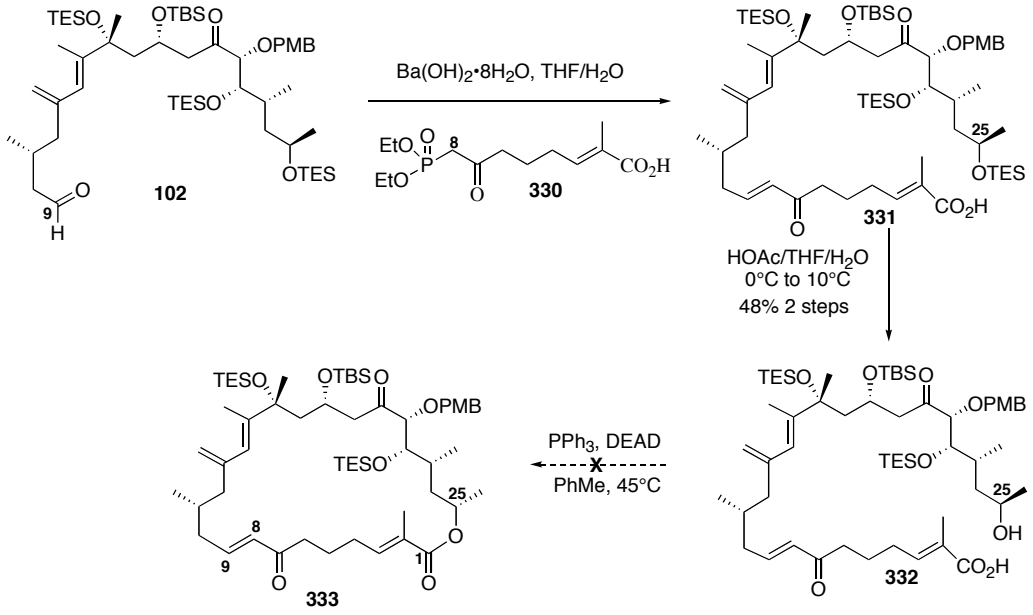


4.3.2. Intramolecular Mitsunobu Approach to the Macrocycle

Once the ketophosphonate acid **330** was obtained, the $Ba(OH)_2$ olefination conditions was applied to couple the aldehyde **102** with ketone phosphonate acid **330** to afford the acid **331** (Scheme 4.10). Next, the acid **331** was *in situ* treated with a pre-mixed solution of HOAc/THF/H_2O (8:8:1) [70]at 0°C to selectively desilylate at C_{25} to generate the secoacid **332**. Next, a range of intramolecular Mitsunobu cyclization conditions were screened, including slow addition of the substrate into the premixed PPh_3 and DEAD, adding PPh_3 and DEAD portion-wise, and slowly adding substrate at elevated temperatures. [71] Unfortunately, the acid **331** consistently failed to undergo macrocyclization.

The failure might due to the unexpected steric hindrance of the C_{25} alcohol as well as α–methyl substituted acid.

Scheme 4.10. Efforts to From the Macrolactone

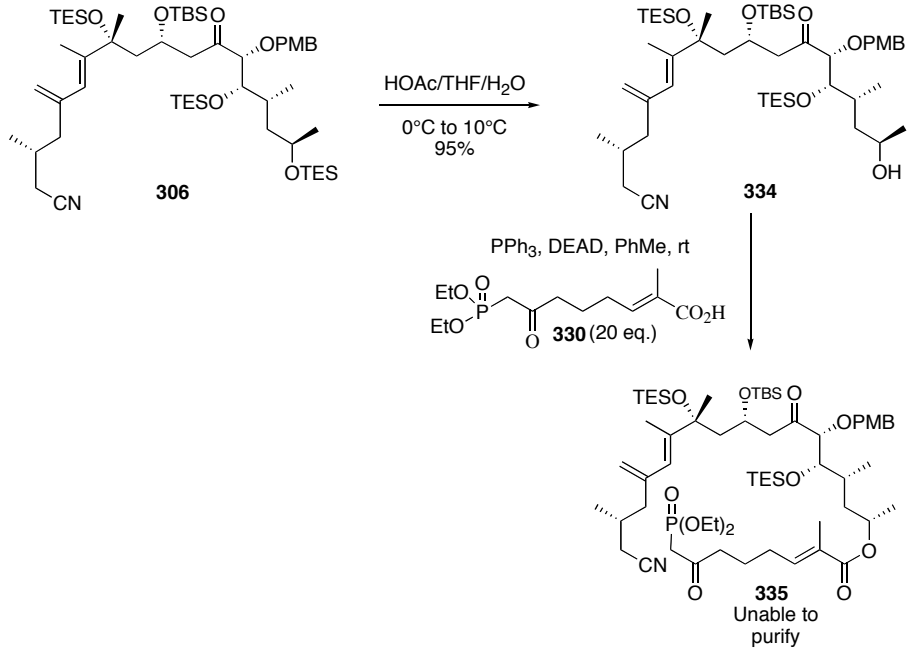


4.3.3. Intramolecular Wadsworth-Emmons Olefination toward the Macrocycle

In order to avoid the unfavorable steric hindrance on both C_{25} alcohol and α–methyl substituted C_1 acid, one logical alternative would be closing the macrocyclic ring with intramolecular Wadsworth-Emmons olefination [72] (Scheme 4.11). Started from a selective deprotection of the less hindered TES ether on the previously prepared **306**, followed by *intermolecular* Mitsunobu-type esterification [73] with a large excess of acid **330** produced the ketophosphonate **335**. Unfortunately, purification of the ketophosphonate was complicated by the presence of a large excess of the coupling reagents. To

date, isolation of the significant amount of ketophosphonate **335** through this route has not proven logistically feasible.

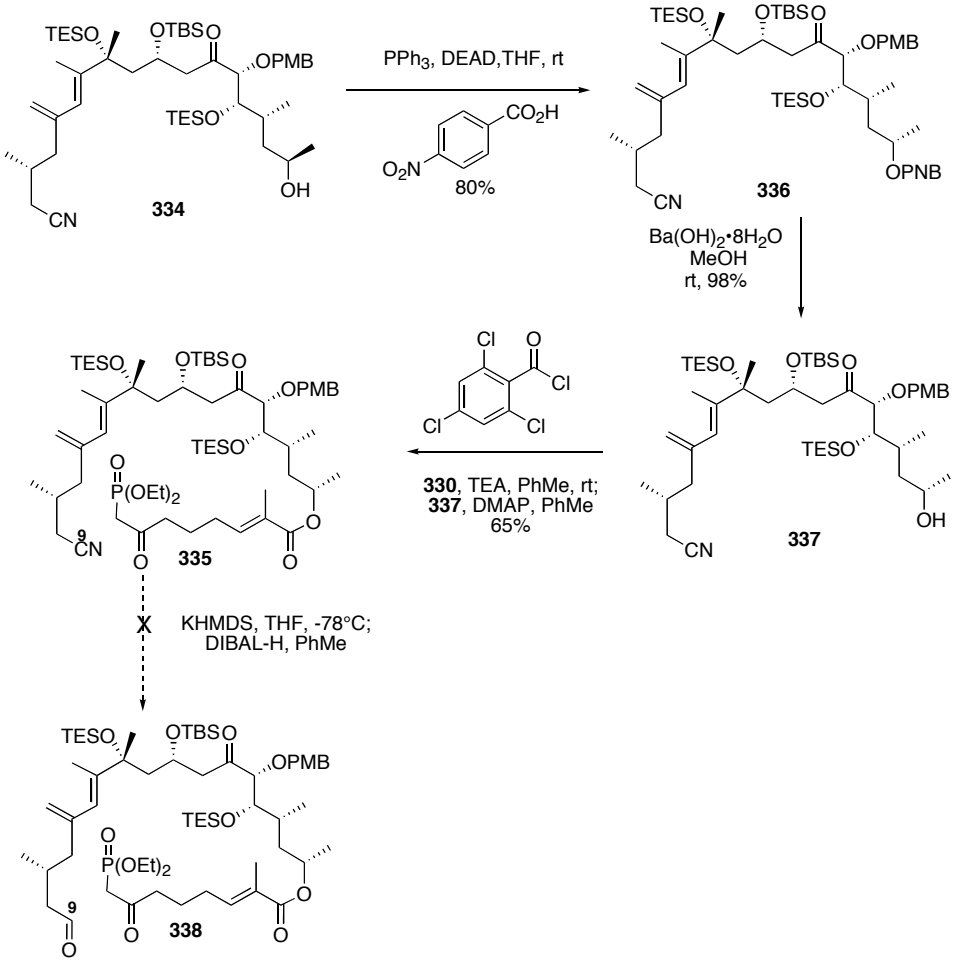
Scheme 4.11. Mitsunobu-type Esterfication to Make the Intramolecular Wadsworth-Emmons Precursor



In order to circumvent the isolation problem, we decided to reverse the stereocenter on C_{25} alcohol, followed with a Yamaguchi-type esterification to obtain the ketophosphonate **338** (Scheme 4.12). Inversion of the C_{25} alcohol of the previously prepared substrate **334** was achieved with Mitsunobu inversion using *p*-nitro-benzoic acid, followed with hydrolysis removal of PNB group to give the C_{25} epimer alcohol **337**. Next, Yamaguchi esterification[74] was successfully applied to give the ketophosphonate **335** with a decent yield. Finally, selective reduction of the C_9 nitrile was required in the presence of the ketophosphonate. Ketophosphonate was pretreated with KHMDS in order to

mask the ketophosphonate functionality as its enolized form. Unfortunately, treatment of this intermediate with DIBAL-H led to a complex mixture of products.

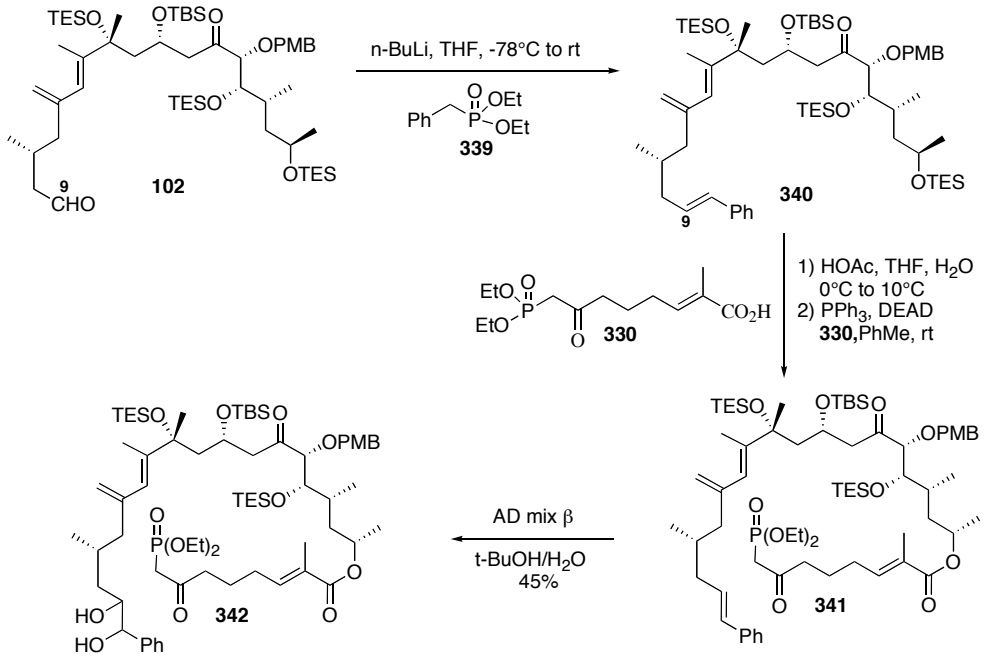
Scheme 4.12. Yamaguchi-type Esterification to Make the Intramolecular Wadsworth-Emmons Precursor



Based on our previous success with regiochemically-directed olefinic cleavage (See Scheme 2.9), we proposed to protect the aldehyde **102** as its styrene derivative (Scheme 4.13). The aldehyde could be revealed by sequential selective dihydoxylation and oxidative cleavage. The aldehyde **102**

was transferred into its styrene derivative by Wadsthworth-Emmones olefination with an unoptimized 40% yield as a single isomer. Next, a sequential treatment of selective desilylation and Mitsunobu esterification provided **341** in an unoptimized 30% yield based on a NMR spectroscopic estimation (the ester **341** was contaminated with an unseparable impurity). Unfortunately, the impurity compromised the subsequent asymmetric dihydroxylation step. Once the ester **341** was purified by HPLC, the dihydroxylated product could be obtained in an unoptimized 45% yield. Although this route was promising, we needed a more efficient approach to construct the macrocyclic ring.

Scheme 4.13. Protect the C_9 Aldehyde as Its Styrene Derivative

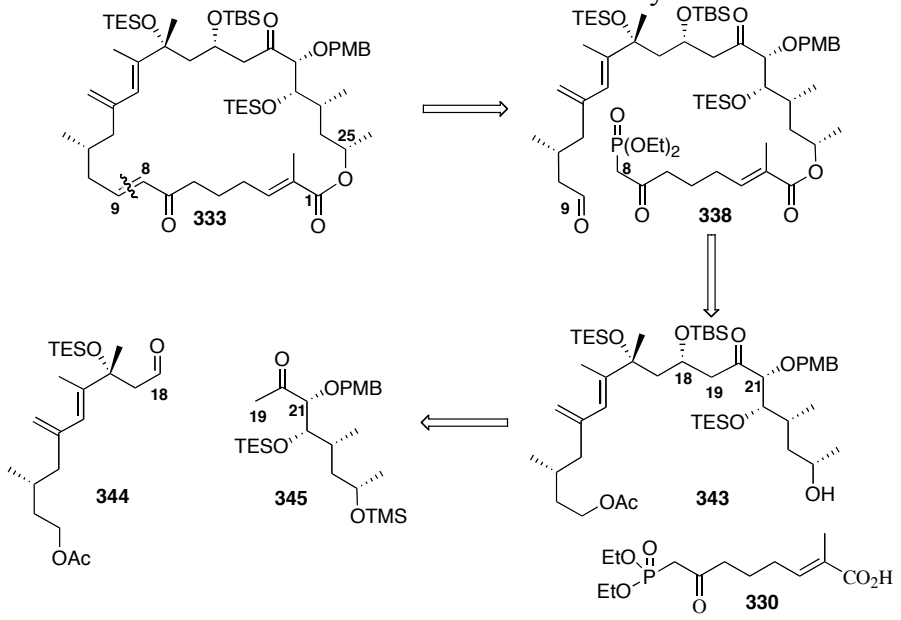


4.4. Completion of the Macrocyclic Ring of Amphidinolide B_1

4.4.1. Reconsideration of the Retrosynthetic Plan

After all the previous synthetic studies and efforts toward the macrocyclic core structure of amphidinolide B_1, we proposed a modified approach (Scheme 4.14). The macrocycle **333** would be obtained from the aldehyde **338** *via* an intramolecular Wadsworth-Emmons olefination. The aldehyde **338** would be derived *via* a Yamaguchi esterfication coupling between the northern fragment **343** and the previously prepared ketophosphonate acid **330**. The northern fragment would be constructed again by a chelation-controled aldol (2nd generation aldol) between the methyl ketone **345** and the aldehyde **344**.

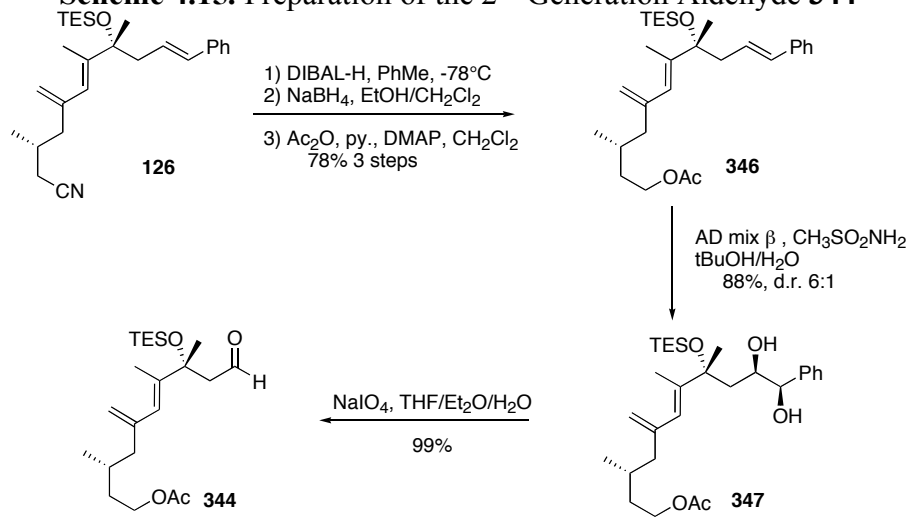
Scheme 4.14. Reconsideration of the Retrosynthetic Plan



4.4.2. Preparation of precursors for the 2nd Generation Aldol

Preparation of the 2nd generation aldehyde **344** started from the previously synthesized nitrile species **126.** A sequential reduction with DIBAL-H and $NaBH_4$ gave a corresponding primary alcohol. The newly obtained alcohol was protected as an acetate derivative **346** (Scheme 4.15). Again, Sharpless asymmetric dihydroxylation provided the regio-selectively dihydroxylated product **347** in a 88% yield in an inconsequential 6:1 d.r. The diol **347** was oxidatively cleaved to yield the 2nd generation aldehyde **344**.

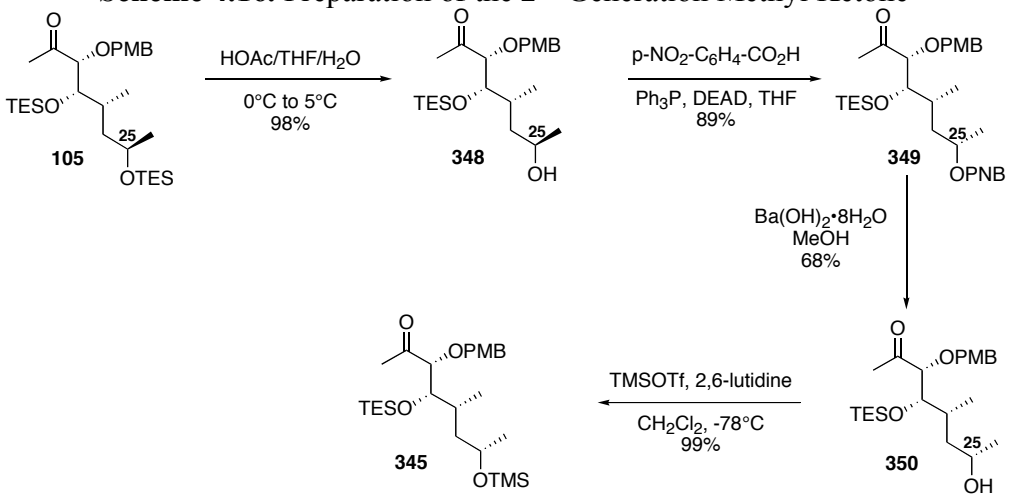
Scheme 4.15. Preparation of the 2nd Generation Aldehyde **344**



Preparation of the 2nd generation methyl ketone **345** was accomplished in 4 steps from the previously obtained methyl ketone **105**[75] (Scheme 4.16). The less hindered C_{25}-TES group was removed by a treatment with a premixed AcOH/THF/H_2O solution to yield an alcohol **348**. The stereochemistry at C_{25} was reversed according to Mitsunobu protocol with *p*-NO_2-benzonic acid.

Subsequent cleavage of the PNB group and reprotection of the C_{25} alcohol yielded **345**.

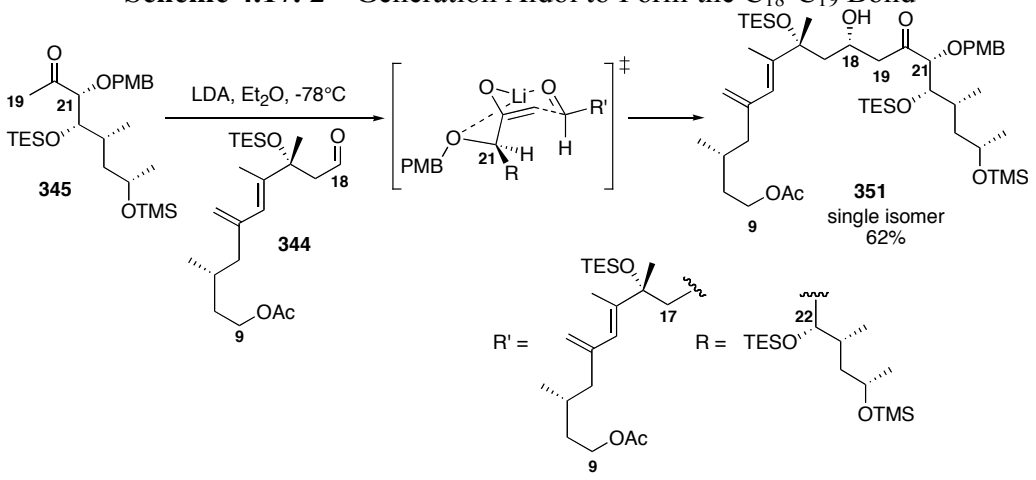
Scheme 4.16. Preparation of the 2nd Generation Methyl Ketone



4.4.3. Formation of 351 with 2nd Generation Aldol

With both aldol precursors ready, the northern fragment **351** was constructed by a 2nd generation aldol condensation (Scheme 4.17). Again, the excellent diastereoselectivity was attributed, in part, to a chelation-controlled chair-like transition state.[76] We were gratified to discover that the acetate group did not interfere with the aldol condesation.

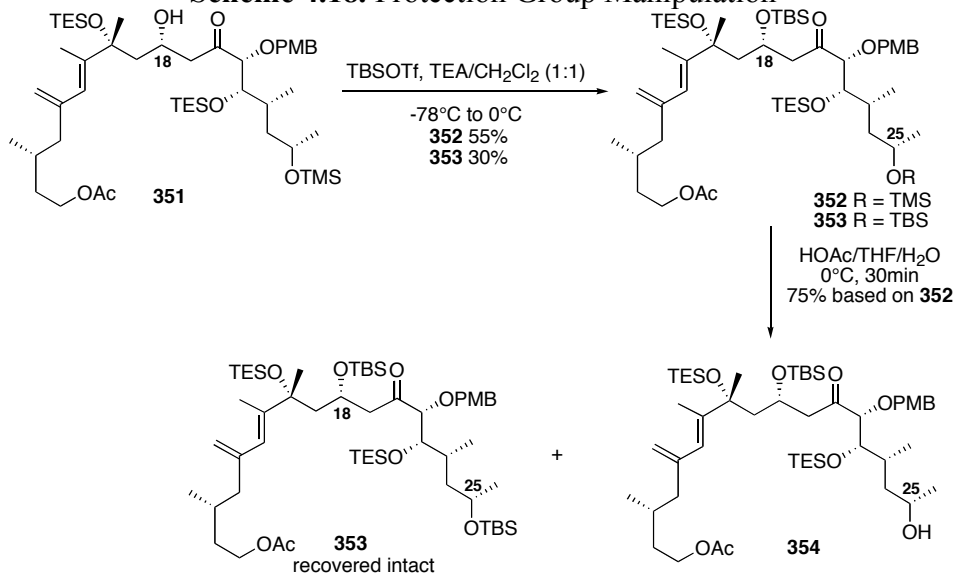
Scheme 4.17. 2nd Generation Aldol to Form the C_{18}-C_{19} Bond



4.4.4. Completion of the Macrocyclic Ring of Amphidinolide B_1

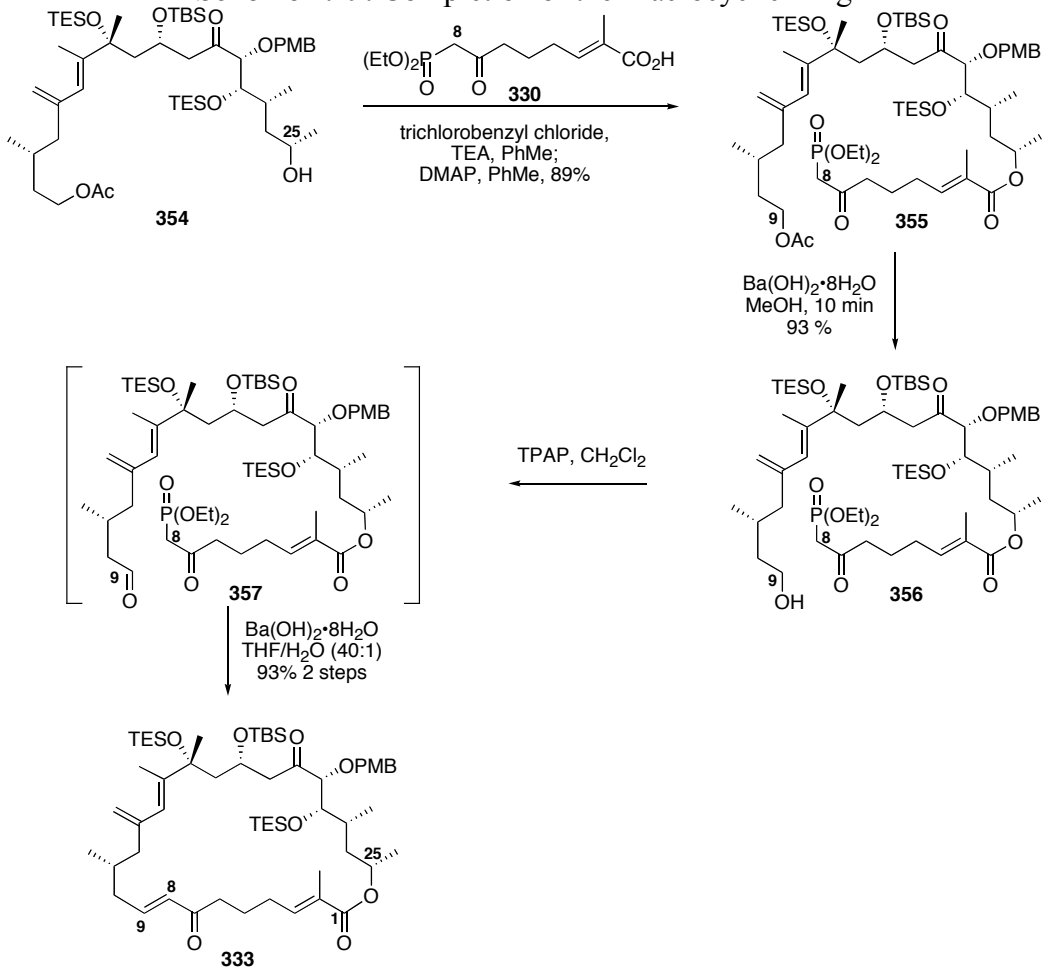
With the successful 2nd generation aldol reaction accomplished, functional group manipulation was subsequently required (Scheme 4.18). Initially, the C_{18} hydroxyl group was protected as its TBS silyl ether using the previously modified conditions (See Scheme 4.5). Unfortunately, we discovered that a significant amount of C_{25} TMS ether was replaced by a TBS ether under these conditions. This C_{25} TBS ether could not be removed with the established conditions using HOAc/THF/H_2O. A solution to this problem will be presented in Chapter 5.4.

Scheme 4.18. Protection Group Manipulation



With alcohol **354** in hand, the synthetic goal shifted to the preparation of the entire carbon backbone of amphidinolide B_1 and closure of the macrolactone (Scheme 4.19). Again, a Yamaguchi-type esterification was applied to form the ester linkage with an excellent yield of the ester **355**. A facile deprotection of the acetate of C_9 alcohol was affected with $Ba(OH)_8 \bullet 8H_2O$ to yield the compound **356**. Next, the alcohol **356** was treated with stoichiometric TPAP to form the expected aldehyde **357**, which proved to be highly reactive as even attempted removal of TPAP *via* a chromatographic filtration led to a significant loss of material. Upon careful analysis of the reaction, a spontaneous intramolecular Wadsworth-Emmons olefination of a significant amount of the aldehyde was observed to provide the desired macrocycle **355**. The reaction could be driven to completion by the addition of $Ba(OH)_2$ in THF/H_2O with 93% yield over 2 steps.

Scheme 4.19. Completion of the Macrocyclic Ring

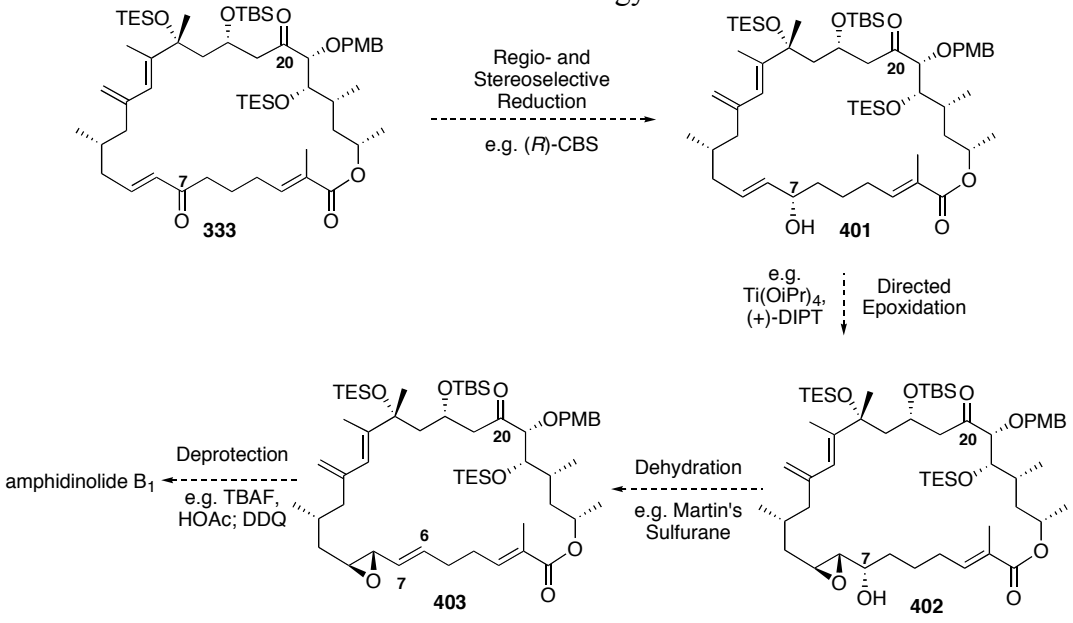


Chapter V. The End Game of the Total Synthesis

5.1. Overview of the Strategy for the Construction of Allyl epoxide Motif

Once the macrocycle of amphidinolide B_1 was accomplished, our goal was focused on the final functional group manipulation necessary to synthesize amphidinolide B_1. Based on our successful model study (see Scheme 4.7), we planned to use (*R*)-CBS reduction to both regioselectively and asymmetrically reduce the less hindered C_7 ketone in the presence of C_{20} ketone. Next, a directed Sharpless asymmetric dihydroxylation will provide a hydroxyl epoxide precursor **402**. Subsequent dehydration of the C_7 alcohol would furnish the required allyl epoxide product **402**. Finally, global deprotection would complete the total synthesis of amphidinolide B_1 (Scheme 5.1).

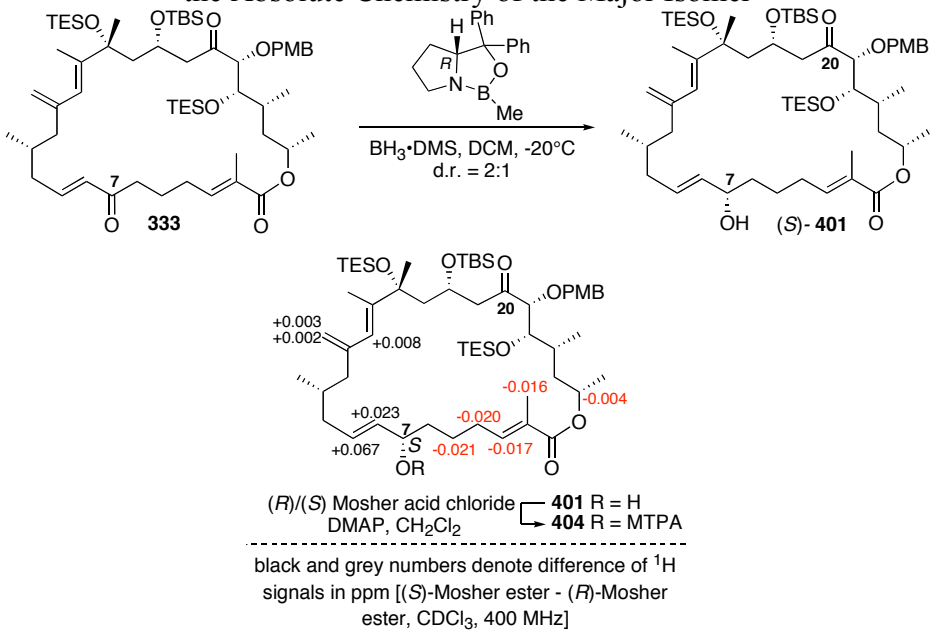
Scheme 5.1. Overview of the Strategy for the End Game



5.2. Unsuccessful Application of the Model Study Conditions onto the Real Substrates

Although (*R*)-CBS reduction[77] worked well on the acyclic model system (See Scheme 4.7), it gave a poor diastereoselectivity (2:1 d.r.) on the cyclic substrate **333** (Scheme 5.2). The major isomer was the expected (*S*)-alcohol, which was confirmed by Mosher ester analysis. The poor diastereoselectivity might due to a mismatched relationship between the (*R*)-CBS reagent and the confirmational effects exhibited by the macrolactone.

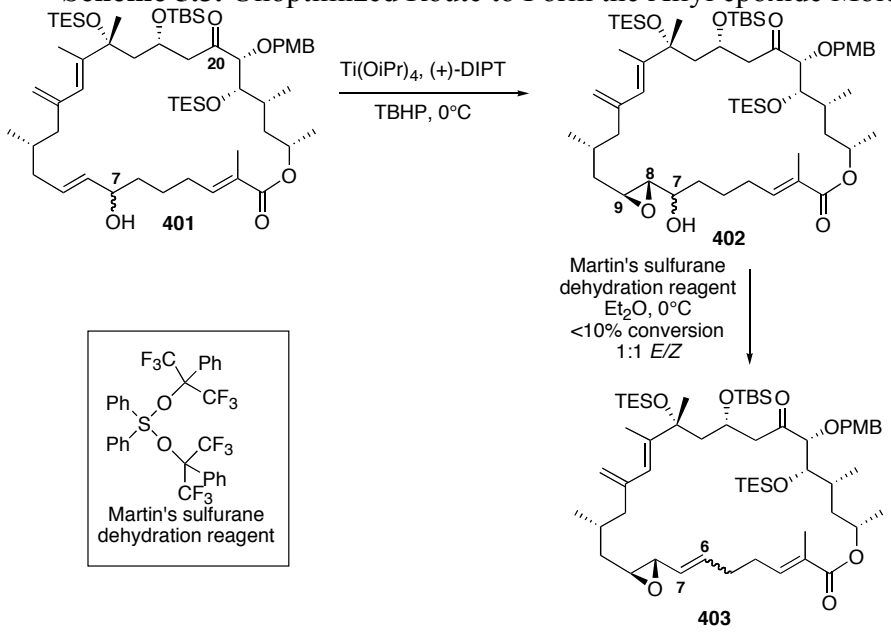
Scheme 5.2. (*R*)-CBS Reduction and Mosher Ester Analysis to Confirm the Absolute Chemistry of the Major Isomer



After the absolute stereochemistry of the major isomer was confirmed, the fact that only HPLC can provide a clean separation of two epimeric alcohols urged us to submit the mixture to the Sharpless asymmetric epoxidation (Scheme 5.3). Gratifyingly, only a single $C_{8\text{-}9}$ epoxide diastereoisomer was

observed. It should be noted that the major isomer (*S*)-**401** could be transferred into allylic epoxide at -20°C within 2 hours; while the minor (*R*)-**401** required overnight at 0°C. This phenomenon suggested that although (*R*)-**401** was a mismatched case for the directed epoxidation conditions, a complete reagent-controlled epoxidation was able to provide a single isomer of the $C_{8\text{-}9}$ epoxide. With the hydroxyl epoxide **402** in hand, dehydration conditions were screened. Although the model study on the acyclic system achieved 3:1 *E/Z* selectivity of the alkene obtained by dehydration with Martin's sulfurane dehyration reagent (see Scheme 4.8), little reaction occurred on the substrate **402** in a poor 1:1 *E/Z* selectivity.

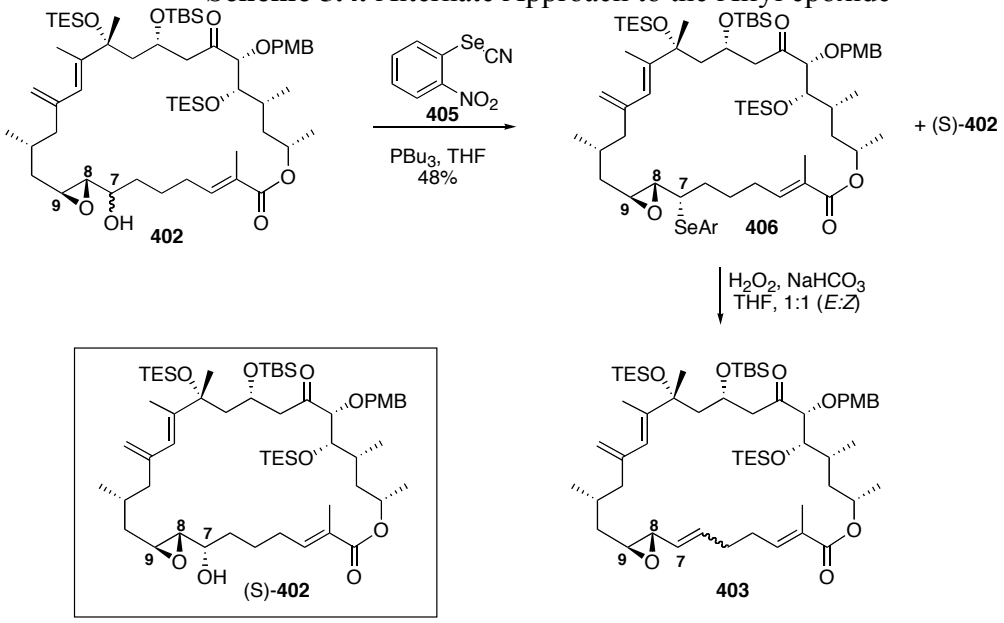
Scheme 5.3. Unoptimized Route to Form the Allyl epoxide Moiety



The poor yield of the dehydration with Martin's sulfurane reagent forced us to consider an alternate method to form the alkene. One option would

be incorporation of a selenide followed with an oxidative elimination to generate allyl epoxide functionality (Scheme 5.4). Upon a treatment with a large excess of *o*-nitrophenylselenium nitrile **405** (20 equivalent) and PBu_3, only the *minor C_7 epimer* (*R*)-**402** was transformed into the corresponding selenide **406**. The (*S*)-alcohol **402** was recovered intact. The selenide **406** was subsequently submitted to an oxidative conditions using H_2O_2 to yield the allyl epoxide with 1:1 *E/Z* selectivity with a modest 35% yield.

Scheme 5.4. Alternate Approach to the Allyl epoxide

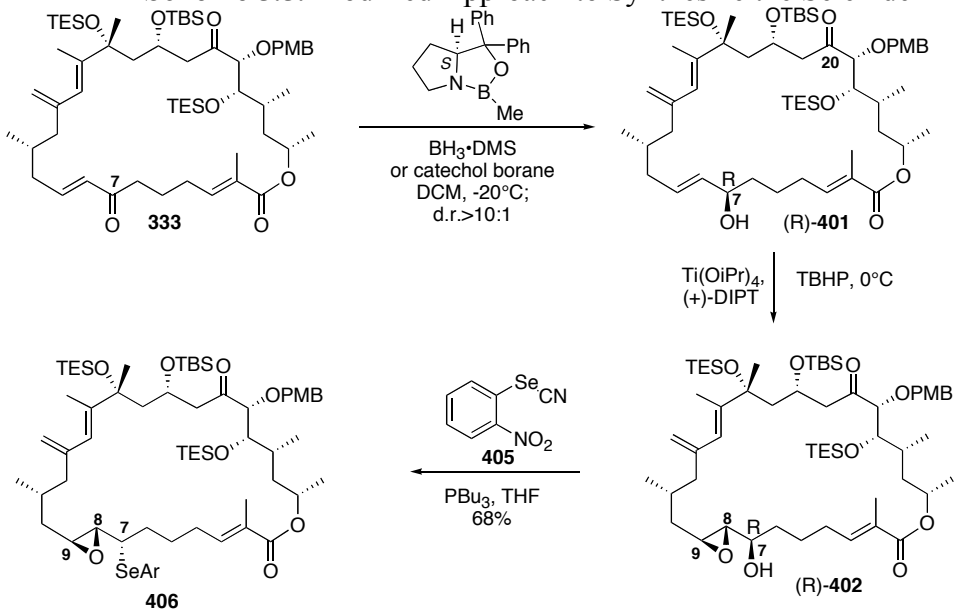


5.3. Modified Approach to Synthesize Selenide Compound 406

The unsuccessful application of the model study conditions to the real substrate system reminded us of the significance of conformational effects. In addition, it was unacceptable that only one of the minor alcohol (*R*)-**402** could be converted into selenide. Our strategy had to be changed accordingly to

address these problems. Considering (*R*)-CBS reduction was a mismatched case on the cyclic substrate, the use of the (*S*)-CBS reagent would appear to be a logical experiment to perform (Scheme 5.5). Indeed, (*S*)-CBS reduction provided the expected alcohol (*R*)-**401** with a significantly improved diastereoselectivity (greater than 10:1 d.r.) with a 72% overall yield using either BH_3•DMS or catechol borane. It should be noted that the major product from (*S*)-CBS reduction was the minor one in (*R*)-CBS reduction. Subsequent titanium-catalyzed epoxidation [78] of the $C_{8,9}$ olefine provided a single diastereoisomer with 60% yield. Again, this ligand-controlled epoxidation was sluggish, requiring a prolonged reaction time and elevated temperature, but the transformation proceeded cleanly to give the epoxide (*R*)-**402**. Next, incorporation of the selenide was established to yield **406** in a 68% yield.

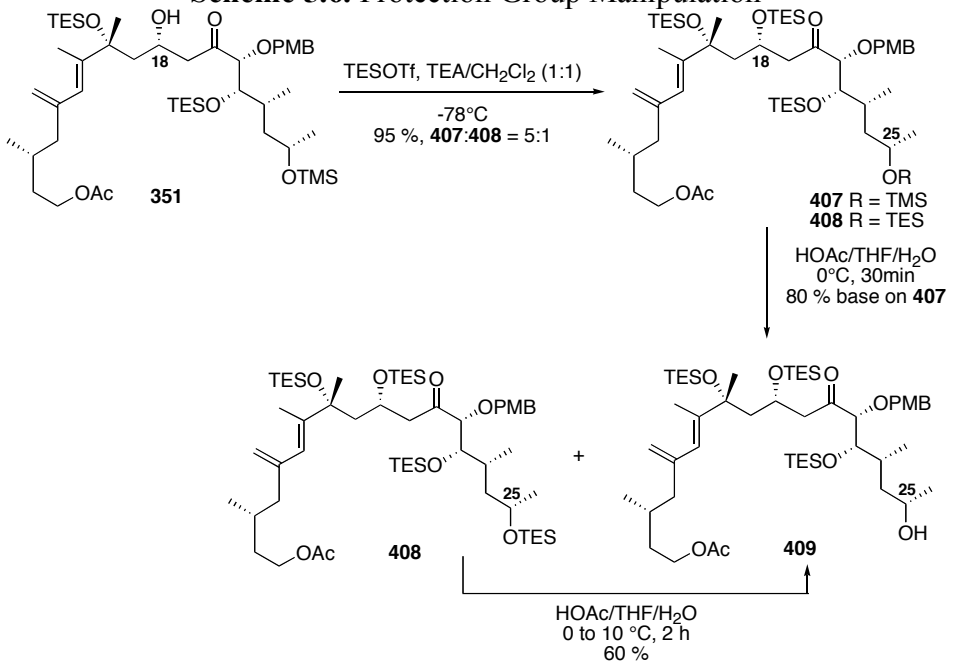
Scheme 5.5. Modified Approach to Synthesize the Selenide



5.4. Protection Group Manipulation and End Games of the Total Synthesis

In order to make the pipeline sequence more efficient, we turned back to optimize some steps. One problematic step was the silyl protection of 2nd generation aldol product (see Scheme 4.18). Since TBS silyl ether protection required a higher temperature for the stericly hindered alcohol at C_{18}, we proposed to apply less bulky TES ether (Scheme 5.6). We gladly discovered that TES silyl ether **407** could be formed at -78°C with only a minor amount of TMS replacement. Furthermore, the TES silyl ether at C_{25} could be selectively removed in the presence of C_{18} TES group to yield **409**.

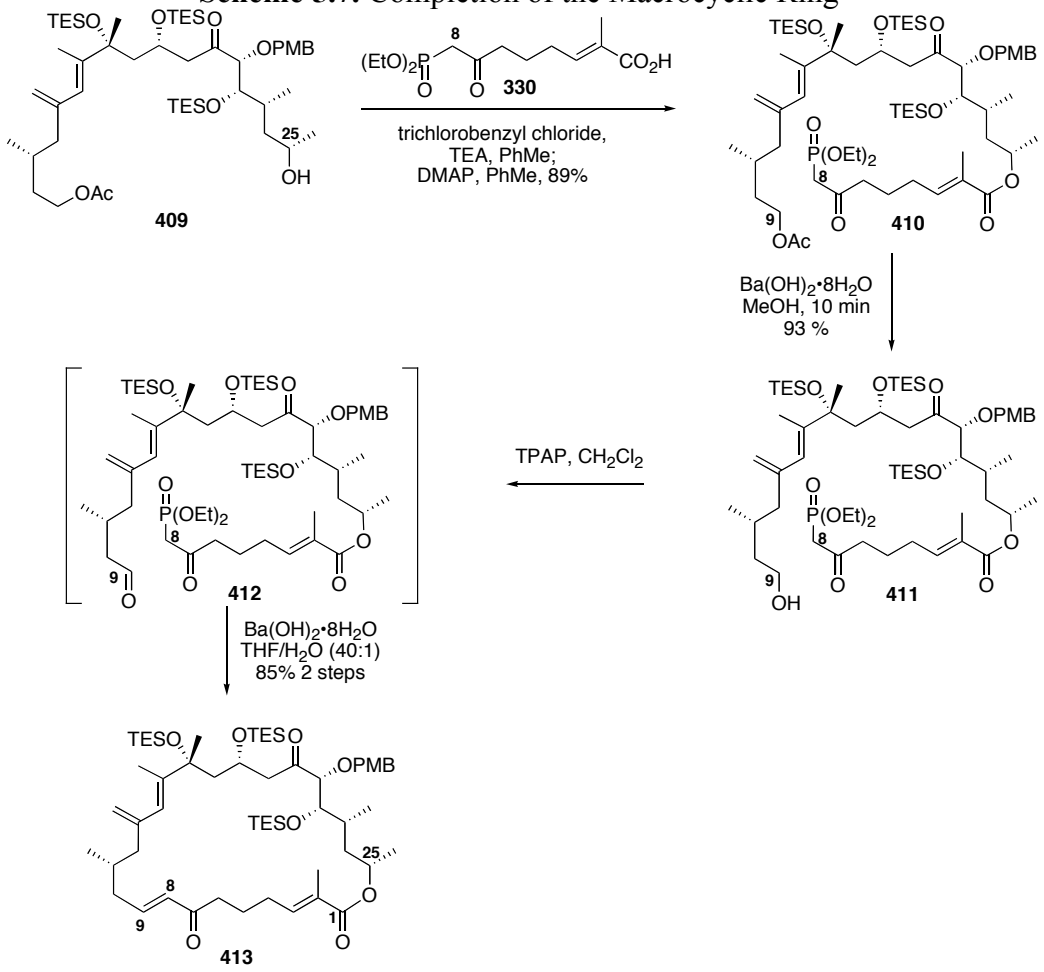
Scheme 5.6. Protection Group Manipulation



With an improved protocol developed, subsequent Yamuguchi esterification provided the ester **410**. Deprotection of acetate, followed with

TPAP oxidation yielded the aldehyde. Again, the spontaneous cyclization of the aldehyde was pushed to completion by adding $Ba(OH)_2 \cdot H_2O$ in THF/H_2O to generate the macrolactone **413** in an excellent overall yield (85% over two steps).

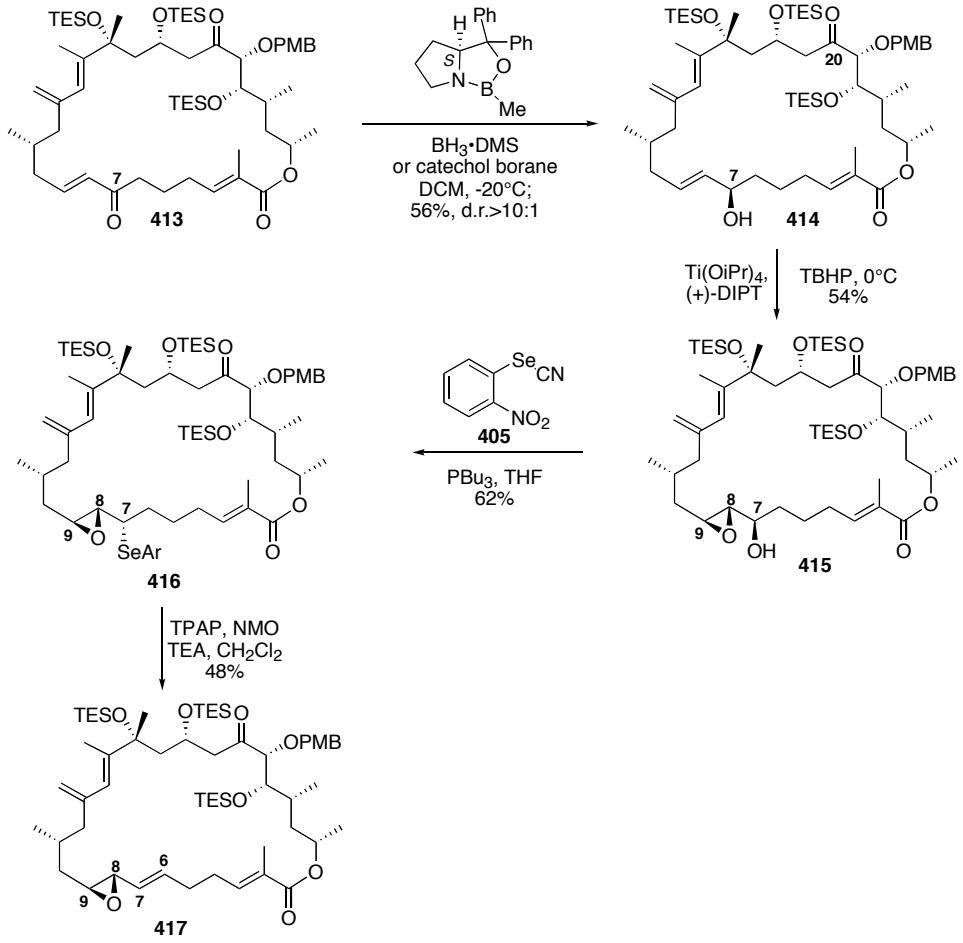
Scheme 5.7. Completion of the Macrocyclic Ring



After obtaining the macrolactone **413**, (*S*)-CBS reduction was applied to generate the allylic alcohol **414** with an excellent diastereoselectivity (Scheme 5.8). Subsequent titanium-mediated epoxidation induced a single isomer of the

epoxide species **415**, which was converted to selenide **416** successfully. Gratifyingly, elimination of the selenide species was accomplished using TPAP/NMO conditions [79] buffered with triethylamine to yield a single stereoisomer of allyl epoxide **417**, which contains all the functionalities of the natural product.

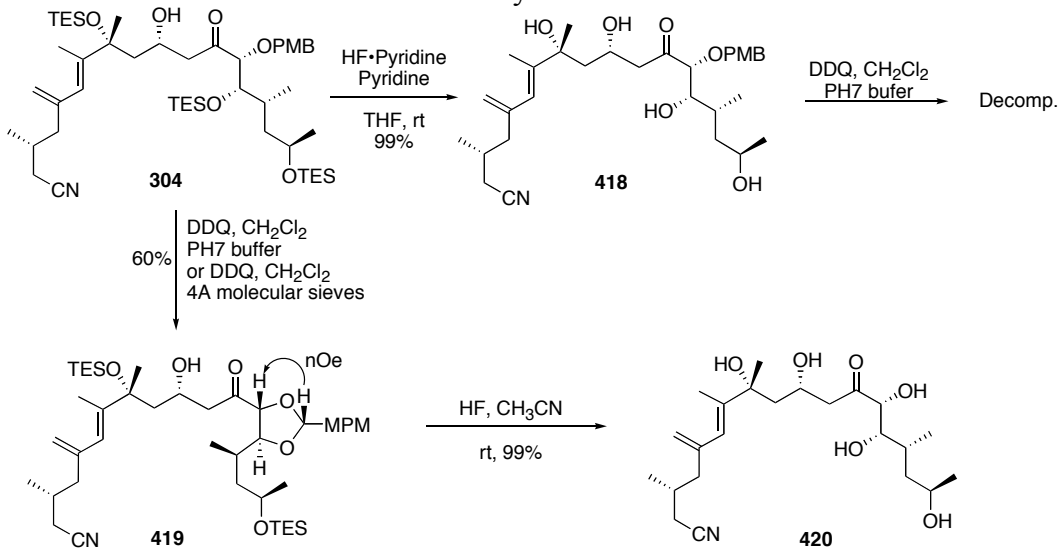
Scheme 5.8. Accomplishment of the Fully Functionalized Amphidinolide B_1 Structure



5.5. Synthetic Studies of Deprotection

With fully functionalized product **417** in hand, two deprotection steps remain as the final challenge of this total synthesis. Due to a limit amount of **417**, some model studies were first explored (Scheme 5.9). A previously synthesized compound **304** was chosen to test deprotection of PMB group and global desilylation. HF•pyridine was applied onto **304** to successfully provide the universally desilylated product **418**, which, however, decomposed upon the treatment of DDQ even in the presence of PH7 buffer. Once the order of deprotection was changed, treated **304** with DDQ in the presence buffer first, an unexpected acetal **419** was obtained as a single epimer.[80] The stereochemistry was determined by nOe analysis. The formation of acetal was attributed to the participation of the neighboring TES protected alcohol. In order to improve the yield of acetal, molecular sieves was added into an anhydrous CH_2Cl_2 solution during the DDQ deprotection of **304**, the yield indeed was improved from 40% to 60%. The acetal was subsequently treated with HF/CH_3CN[81] at ambient temperature to provide the globally desilylated alcohol **420**.

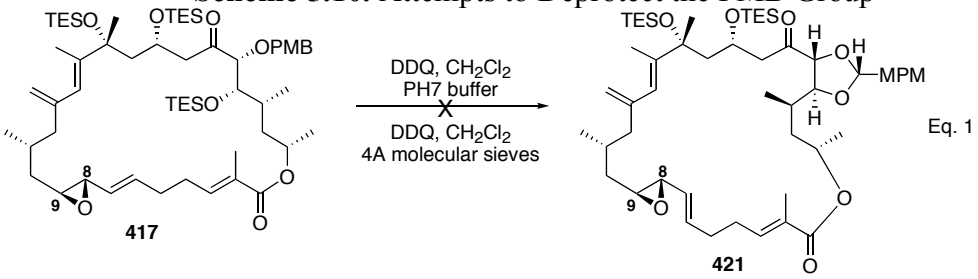
Scheme 5.9. Model Deprotection Studies of PMB Ether and Global Desilylation



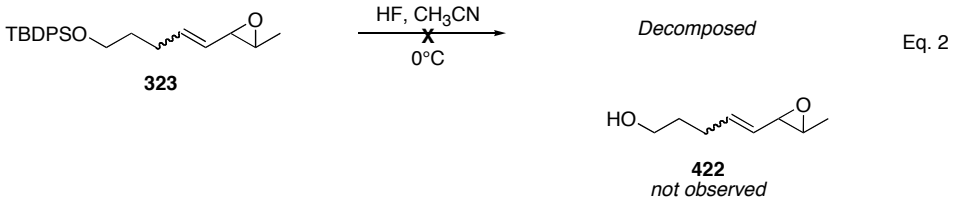
Equipped with the information obtained from model studies, we initiated the final exploration of this total synthesis. Unfortunately, once the conditions were applied to the real substrate **417**, no expected product was observed (Scheme 5.10, Eq. 1). The starting material decomposed rapidly upon the treatment either under anhydrous conditions or a PH7 buffered solutions. One possible speculation was that the rigid conformation of the macrolactone prevented the formation of the expected acetal **421**. In addition, the unusual allyl epoxide moiety might be sensitive to the oxidative conditions. Also, another model study showed that allyl epoxide was fragile in the presence of HF/CH_3CN (Scheme 5.10, Eq. 2). The previously synthesized allyl epoxide substrate **323** was decomposed upon the treatment of HF/CH_3CN conditions.

These unfortunate results forced us to consider removing the PMB group prior to the cyclization and incorporation of the allyl epoxide moiety.

Scheme 5.10. Attempts to Deprotect the PMB Group



Eq. 1



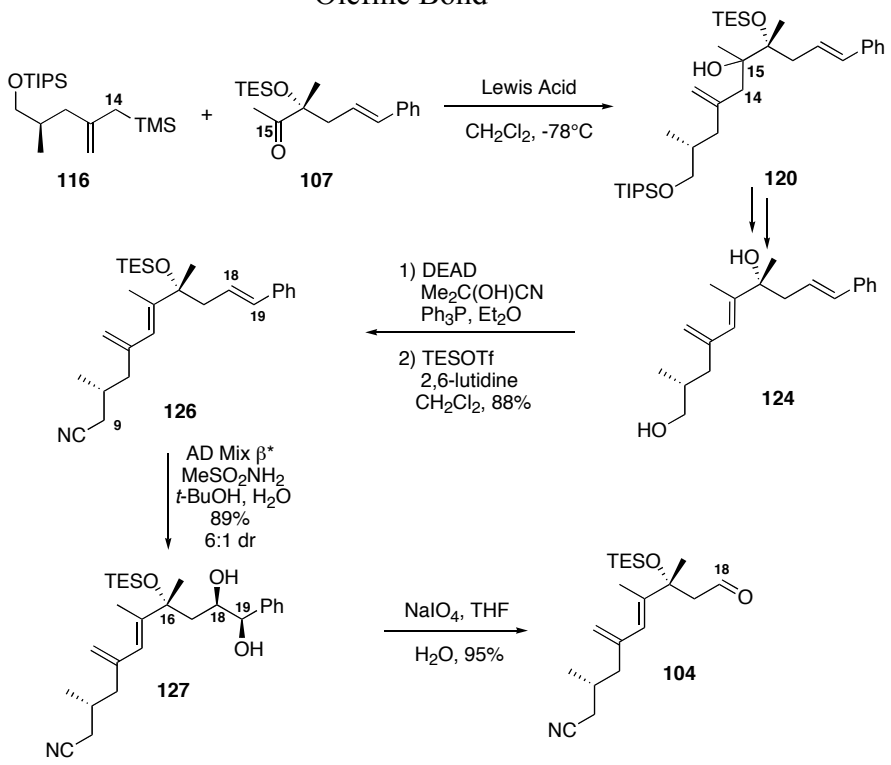
Eq. 2

Chapter VI. Conclusion and Future Work

6.1. General Conclusion

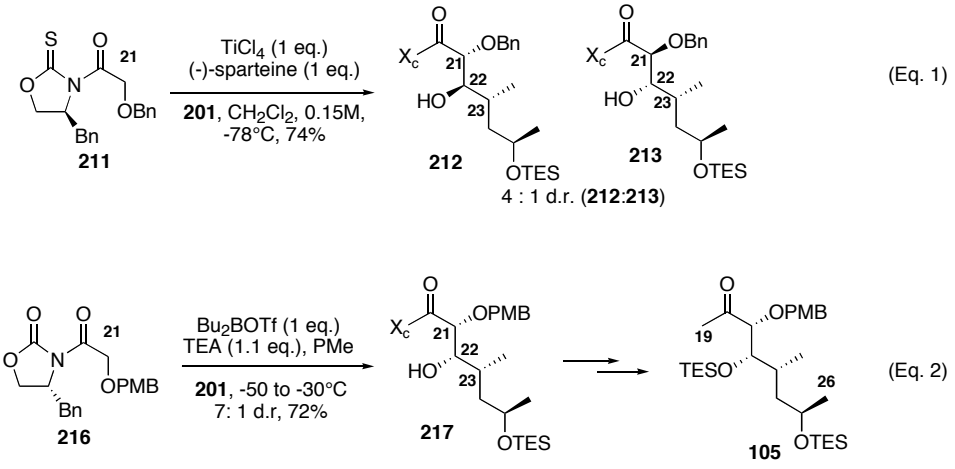
During the course of our synthetic efforts toward amphidinolide B_1, we developed several important protocols. A novel Fleming-type coupling mediated by freshly distilled $TiCl_4$ was applied successfully to form C_{14}-C_{15} bond of **120**. A subsequent dehydration yielded the highly substituted C_{13}-C_{15} diene motif of **124**. A regiospecific Sharpless asymmetric dihydroxylation selectively functionalized the C_{18}-C_{19} olefin bond in the presence of the conjugated diene and the western aldehyde **104** was obtained by oxidative cleavage of the diol **127** (Scheme 6.1)**.**

Scheme 6.1. Formation of Diene and Selective Oxidative Cleavage C_{18}-C_{19} Olefine Bond



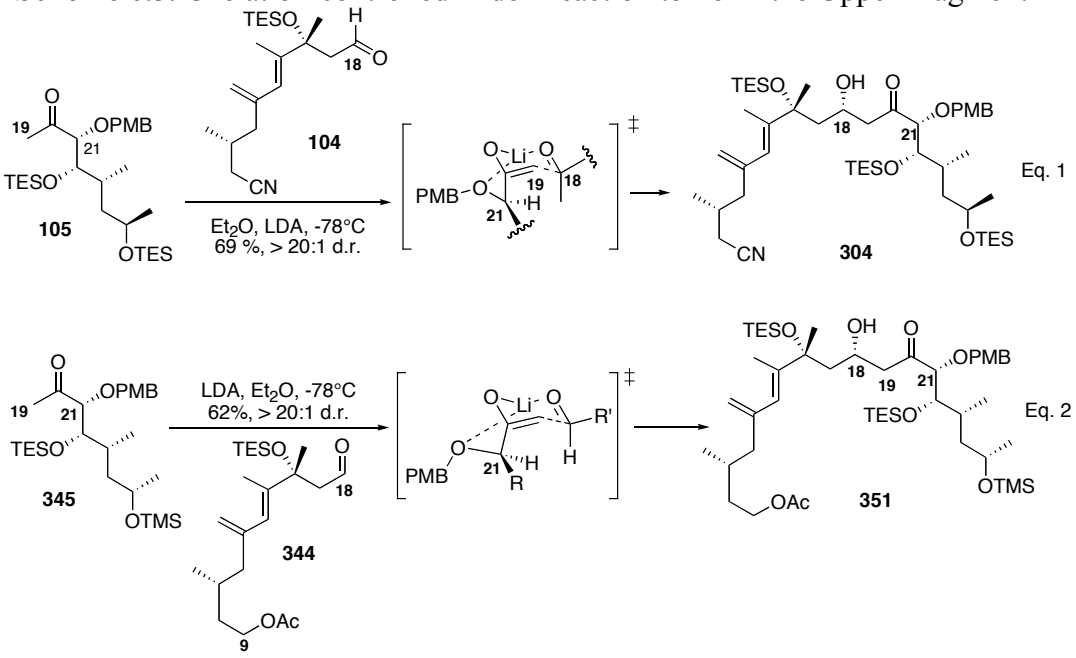
In the preparative study of eastern subunit **105**, borane-mediated aldol reaction provided the required *syn*,*syn* C_{21}-C_{23} stereochemistry for amphidinolide B_1 (Scheme 6.2). Different from its counterpart, titanium-mediated aldol only generated *anti*, *anti* C_{21}-C_{23} stereochemistry. The *anti*-aldol product **212** obtained *via* titanium-mediated aldol is synthetically useful as it possesses the correct *anti*, *anti* C_{21}-C_{23} stereochemistry for amphidinolide B_3.

Scheme 6.2. Titanium-mediated Aldol and Borane-mediated Aldol



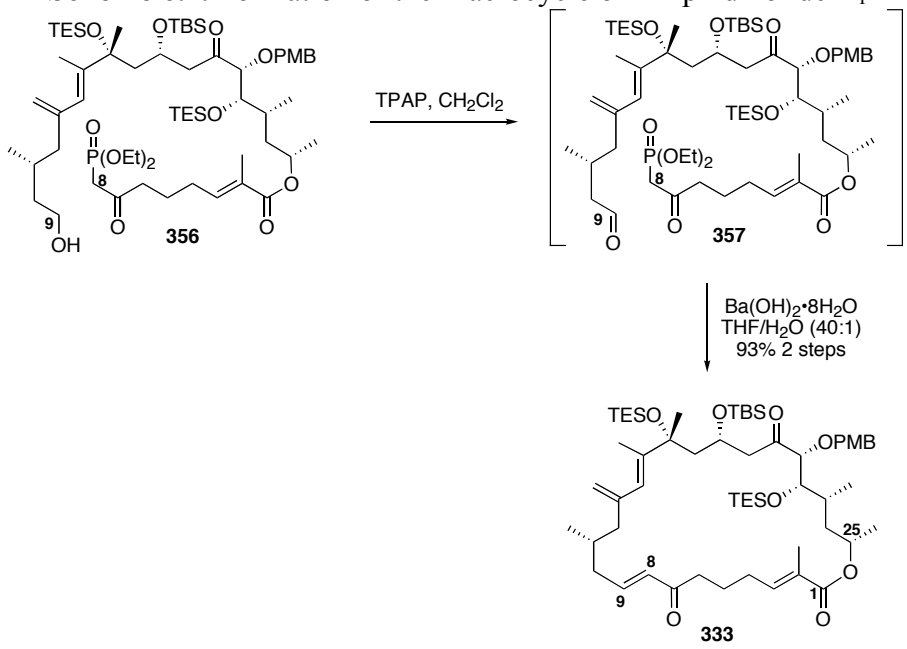
The northern fragment of amphidinolide B_1 was synthesized by uniting the western aldehyde **104** with the eastern methyl ketone **105** by a chelation-controlled aldol reaction (Scheme 6.3, Eq. 1). In stark contrast to the prior synthetic efforts, a single isomer at C_{18} stereocenter was achieved. Based on the need of strategic optimization, 2nd generation aldol was successfully designed and executed (Eq. 2).

Scheme 6.3. Chelation-controlled Aldol Reaction to Form the Upper Fragment



After failed macrolactonization *via* the C_1-C_{25} ester linkage, synthetic efforts shifted to preparing the macrocycle *via* an intramolecular Wadsworth-Emmons olefination (Scheme 6.4). A series of synthetic endeavors, including the successful development of 2nd generation aldol, facilitated the formation of the aldehyde precursor **357** of intramolecular Wadsworth-Emmons reaction. With the aldehyde **357** in hand, a spontaneous intramolecular Wadsworth-Emmons olefination occurred to yield the macrolactone **333**. This transformation could be driven to completion by the addition of $Ba(OH)_2$ to give an excellent 93% yield of the macrolactone **333**.

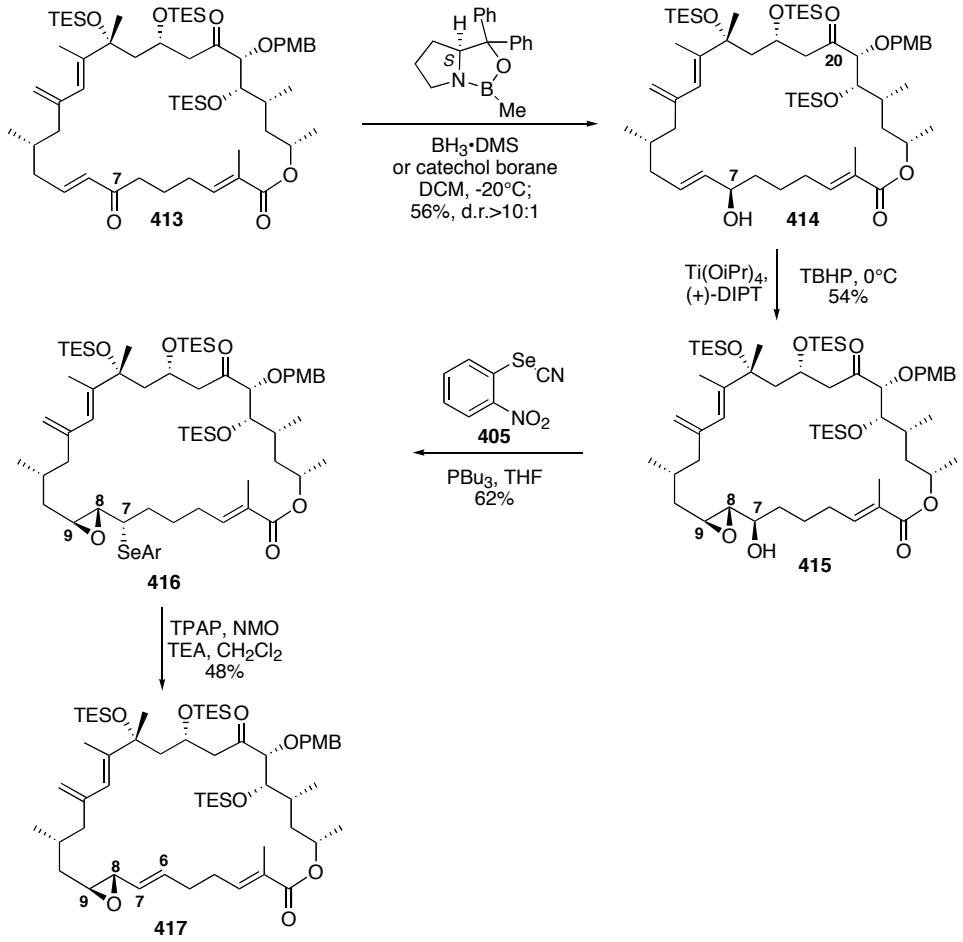
Scheme 6.4. Formation of the Macrocycle of Amphidinolide B_1



After the successful establishment of the macrocycle **417**, selective reduction of C_7 ketone became top priority. Considering (*R*)-CBS reduction was a mismatch case on cyclic substrate (See Scheme 5.2), the alternate (*S*)-CBS reduction would be a logical experiment to perform. Indeed, (*S*)-CBS reduction proved to be a matched case yielding the allylic alcohol **414** with an excellent stereoselectivity (Scheme 6.5). Next, we were gratified to observe that although the subsequent titanium-mediated epoxidation was mismatched case requiring elevated temperature and elongated reaction time, a complete reagent-controlled epoxidation was achieved to yield the epoxide **414** as a single isomer. Subsequently, incorporation of selenide was accomplished to generate the compound **416** and a modified elimination conditions successfully provided the allyl epoxide **417** as a single isomer. With the fully functionalized

product **417** in hand, the only challenge remained in this total synthesis is two deprotection steps.

Scheme 6.5. Accomplishment of the Fully Functionalized Amphidinolide B_1 Structure

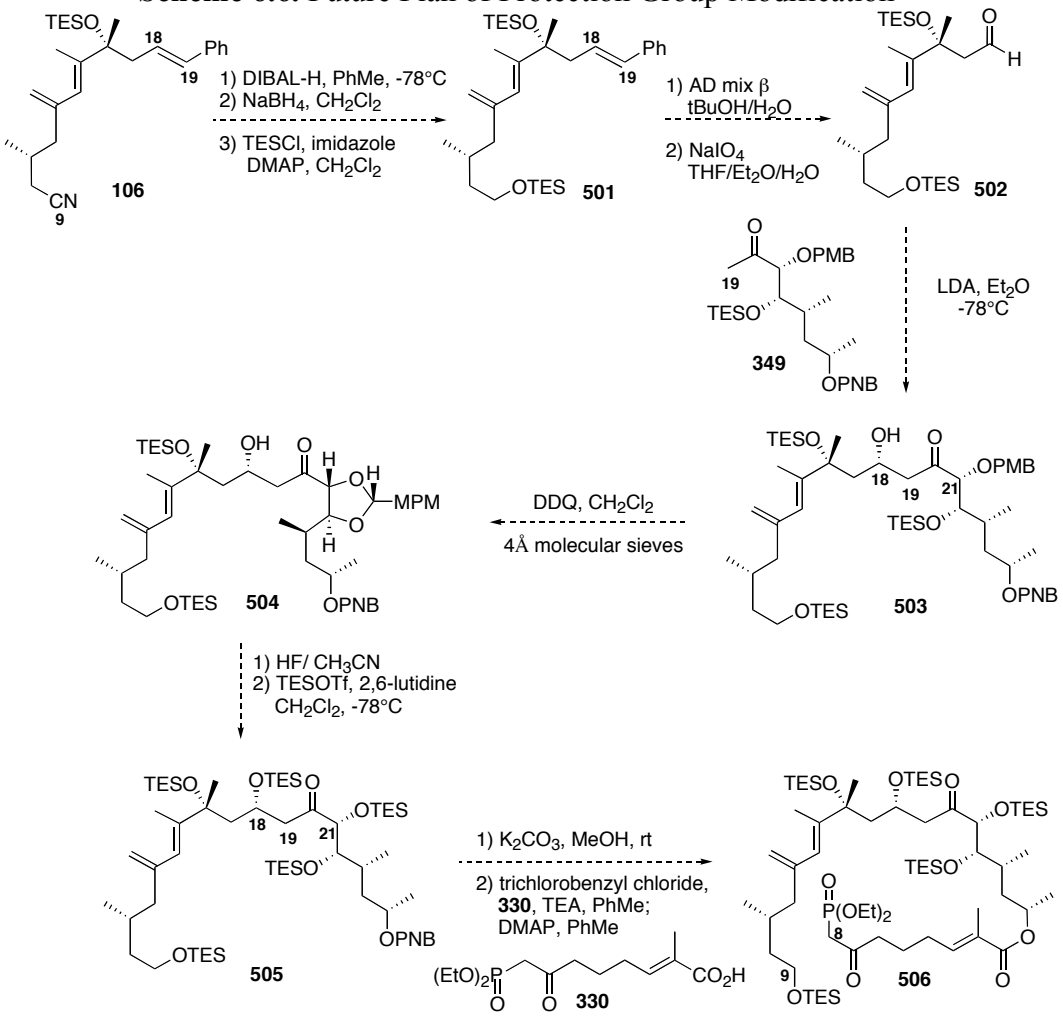


6.2. Proposed Future Work

In order to complete the total synthesis, the synthetic strategy has to be modified. Protection group manipulation will start from the previously prepared compound **106** (Scheme 6.6). A sequential DIBAL-H and $NaBH_4$ reduction of the C_9 nitrile and subsequent TES ether protection will yield

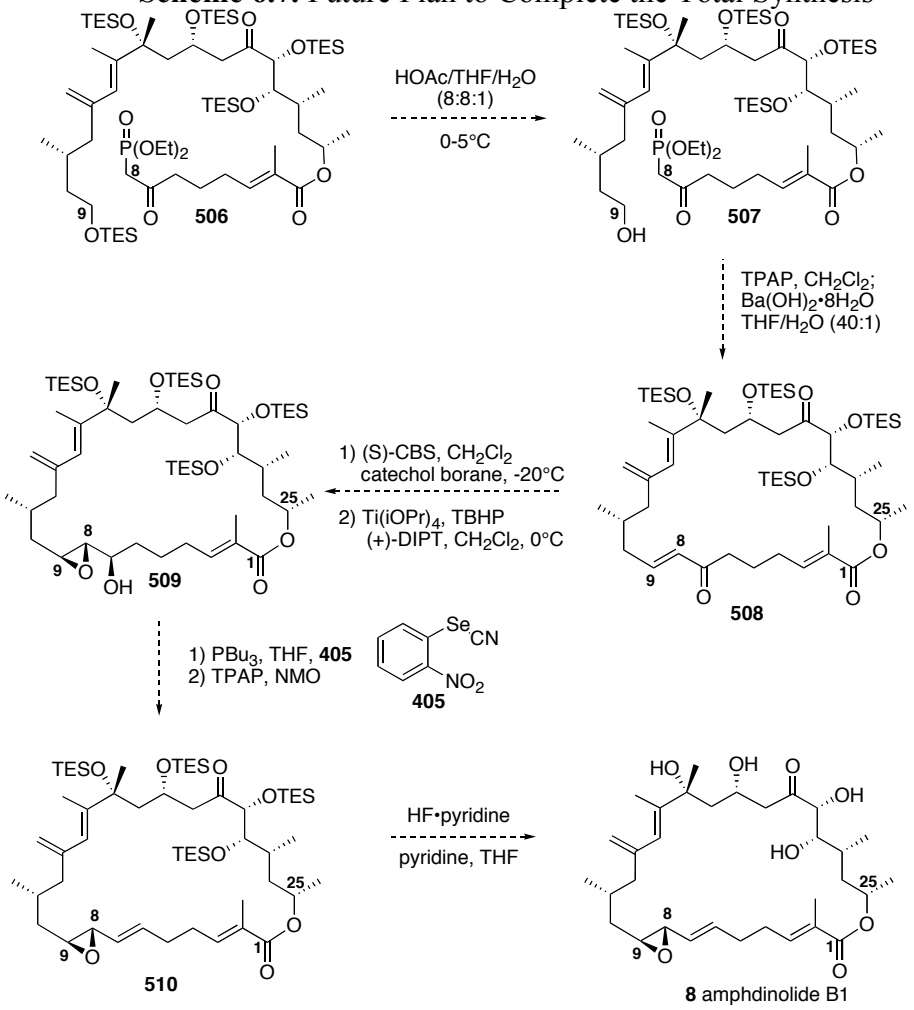
substrate **501**. Regioselective Sharpless asymmetric dihydroxylation and oxidative cleavage of the newly generated diol will lead to the aldehyde **502**. Chelation-controlled aldol condensation between aldehyde **502** and a previously prepared ketone **349** will form the alcohol **503**. Based on our previous synthetic study (see Scheme 5.9), treatment of **503** with DDQ will yield the cyclic acetal **504**. Cleavage of the acetal with HF/CH_3CN followed with TES ether protection will give **505**. Removal of PNB and subsequent Yamaguchi esterification will produce the ketophosphonate **506**.

Scheme 6.6. Future Plan of Protection Group Modification



With ester **506** in hand, selective removal of the primary TES ether will be affected by well applied conditions, using HOAc/THF/H_2O (8:8:1) at 0~5°C, to give a free alcohol **507** (Scheme 6.7). The following steps can use the previously developed conditions (see Scheme 5.7 & 5.8). Oxidation of the alcohol **507** will initiate the spontaneous macrolactonization, which can be driven to completion by adding $Ba(OH)_2$•$8H_2O$, to yield macrocycle **508**. (*S*)-CBS reduction will provide a corresponding allylic alcohol and a subsequent titanium-mediated epoxidation will form the epoxide **509**. Incorporation of selenide and sequential oxidative elimination will furnish the allyl epoxide **510**. At last, the total synthesis will be accomplished by a global deprotection using HF•pyridine conditions.

Scheme 6.7. Future Plan to Complete the Total Synthesis



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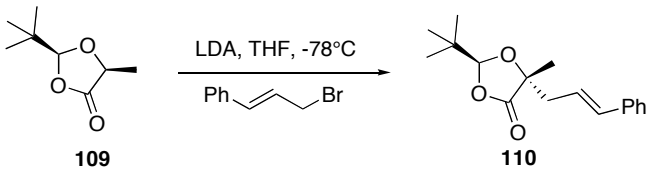
Chapter VII. Experimentals and Supporting Information

General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^{1}H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to trimethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to trimethylsilane and referenced internally to the residually protonated solvent. Optical rotations were recorded using a sodium lamp at 589 nm in $CHCl_3$.

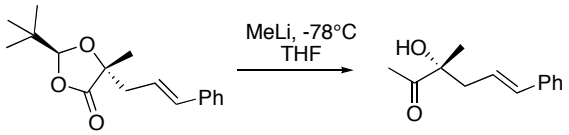
Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel.

Air and / or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a atmosphere of argon, in glassware dried in an oven at 120°C or by a bunsen flame, then cooled under argon. Solvents and commercial reagents were purified *via* Glass Contour® Solvent Purification Systems (SPS), in accord with Perrin and Armarego[82] or used without further purification.



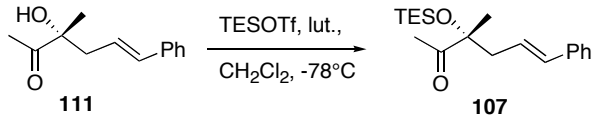
Lactone **110**: To a solution of diisopropyl amine (1.67 g, 2.3 mL, 16.5 mmol) in THF (7.6 mL) at –78°C added *n*-BuLi (6.6 mL, 16.5 mmol, 2.5 M in hexanes) dropwise. After 10 min, the white slurry was warmed to –10°C for 30 min. Then, the solution was cooled back to –78°C and another 58 mL THF was added slowly to the above solution. Next, a solution of Seebach lactone[37] **109** (2.37 g, 15.0 mmol) in THF (15 mL) was added dropwise to the above solution. After 20 min, a solution of cinnamyl bromide (4.43 g, 3.33 mL, 22.5 mmol) in THF (10 mL) was added dropwise. After 30 min, the reaction was warmed slowly to –10°C over 2 h. After 5 min, the reaction was quenched with sat. aq. NH_4Cl (30 mL) and warmed to r.t. After 10 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-10% EtOAc / hexanes, to give **110** (3.74 g, 13.7 mmol, 91%) as a white solid: $[\alpha]_D^{23}$ +45.5° (c 1.21, $CHCl_3$); IR (thin film) 3027, 2963, 1796, 1484, 1173, 1138, 970, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.42 (m, 5H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.23 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.24 (s, 1H), 2.72 (dd, *J* = 6.0, 10.8 Hz, 1H), 2.62 (dd, *J* = 6.0, 10.8 Hz, 1H), 1.51 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

175.5, 137.1, 135.3, 128.8, 127.9, 126.5, 122.4, 108.9, 80.2, 40.3, 34.8, 23.5, 23.1; HRMS (FAB+) calcd. for $C_{17}H_{23}O_3$ (M+H) 275.1647, found 275.1650.

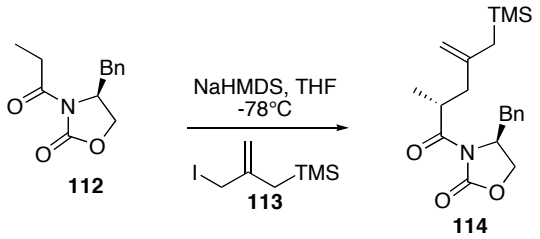


110 **111**

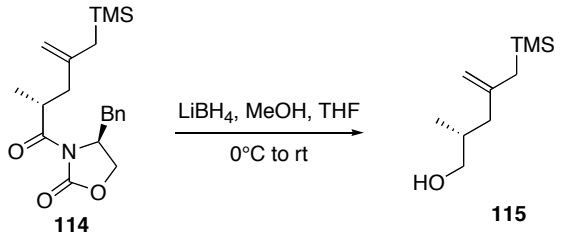
Methyl ketone **111**: To a solution of lactone acetal **110** (1.37 g, 5.0 mmol) in THF (100 mL) at –78°C was added MeLi (4.64 mL, 5.6 mmol, 1.2 M in Et_2O) *via* syringe pump. After 15 min, the resulted solution was warmed to r.t. After additional 10 min, the solvent was concentrated *in vacuo*, diluted with Et_2O (50 mL), filtrated through a plug of Celite® and concentrated again *in vacuo*. The yellow oil was purified by chromatography over silica gel, eluting with 10-30% EtOAc / hexanes, to give **111** (0.78 g, 3.85 mmol, 77%) as a colorless oil: $[\alpha]_D^{23}$ -9.8° (c 0.89, $CHCl_3$); IR (thin film) 3472 (br), 3026, 2974, 2933, 1709, 1494, 1449, 1356, 1157, 1120, 969, 749, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.34 (m, 5H), 6.46 (d, J = 15.9 Hz, 1H), 6.15 (dt, J = 15.9, 7.2 Hz, 1H), 3.84 (s, 1H), 2.62 (dd, J = 1.2, 7.2 Hz, 2H), 2.25 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 137.1, 133.9, 128.7, 127.7, 126.5, 123.8, 79.1, 43.3, 25.3, 24.2 HRMS (FAB+) calcd. for $C_{13}H_{17}O_2$ (M+H) 205.1229, found 205.1225.



Ketone **107**: To a solution of ketone **111** (340 mg, 1.66 mmol) in THF (8.3 mL) at -78°C was added 2,6-lutidine (0.27 g, 0.29 mL, 2.49 mmol). After 5 min, TESOTf (0.53 g, 0.45 mL, 1.99 mmol) was added. After 30 min, the reaction was warmed to r.t. After 5 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL). After 10 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 15 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-6% EtOAc / hexanes, to give **107** (448 mg, 1.41 mmol, 88%) as a colorless oil: $[\alpha]_D^{23}$ +0.7° (c 0.70, $CHCl_3$); IR (thin film) 3027, 2955, 2916, 2876, 1718, 1457, 1415, 1350, 1239, 1166, 1131, 1016, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.33 (m, 5H), 6.38 (d, J = 15.9 Hz, 1H), 6.09-6.20 (m, 1H), 2.40-2.63 (m, 2H), 2.21 (s, 3H), 1.38 (s, 3H), 1.01 (t, J = 7.5 Hz, 9H), 0.68 (q, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 137.8, 133.6, 128.9, 127.6, 126.5, 125.1, 83.0, 45.2, 26.2, 25.4, 7.6, 7.1; HRMS (FAB+) calcd. for $C_{19}H_{31}O_2Si$ (M+H) 319.2093, found 319.2094.

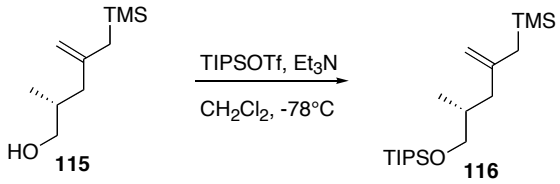


Allylsilane **114**: To a solution of NaHMDS (5.6 mL, 5.6 mmol, 1.0 M in THF) at –78°C was added a solution of imide **112** (1.09 g, 4.67 mmol) in THF (4.6 mL). After 20 min, a solution of allyl iodide **113**[83] (3.6 g, 14 mmol) in THF (3 mL) was added *via* cannula. After 10 min, the reaction was warmed slowly to 10 °C over 4 h and quenched with sat. aq. NH_4Cl (25 mL). After 10 min at r.t., the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 4-15% EtOAc / hexanes, to give **114** (1.46 g, 4.06 mmol, 87%) as a colorless oil: $[\alpha]_D^{23}$ +30.6° (c 0.66, $CHCl_3$); IR (thin film) 2954, 1780, 1699, 1632, 1454, 1385, 1349, 1246, 1207, 1101, 851, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H), 4.66-4.69 (m, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 4.14-4.19 (m, 2H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.26 (dd, *J* = 3.3, 13.2 Hz, 1H), 2.71 (dd, *J* = 3.9, 13.2 Hz, 1H), 2.52 (dd, *J* = 7.5, 14.4 Hz, 1H), 2.04 (dd, *J* = 7.5, 14.4 Hz, 1H), 1.59 (d, *J* = 3.6 Hz, 2H), 1.17 (d, *J* = 6.9 Hz), 0.04 (s. 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 153.5, 145.1, 135.8, 129.9, 129.3, 127.7, 109.7, 66.3, 55.7, 42.6, 38.4, 36.2, 26.8, 17.4, -1.0; HRMS (FAB+) calcd. for $C_{20}H_{30}NO_3Si$ (M+H) 360.1995, found 360.1989.

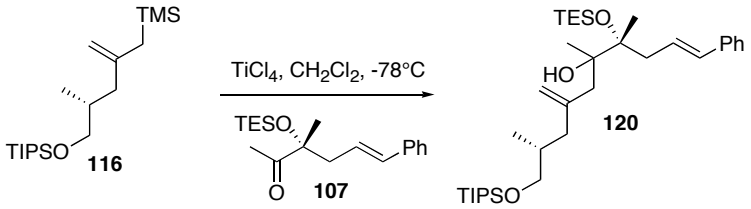


114 **115**

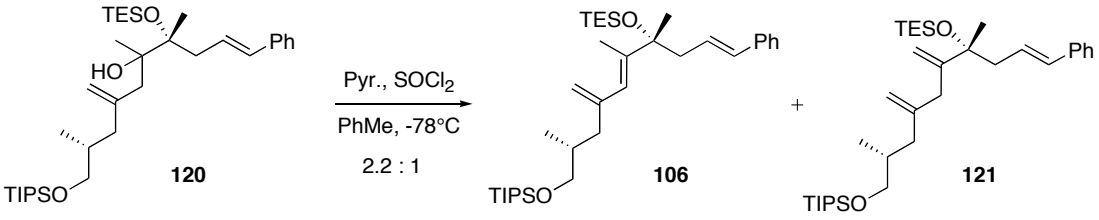
Allylsilane **115**: To a solution of **114** (1.88 g, 5.23 mmol) in THF (35 mL) at 0°C was added sequentially MeOH (0.20 g, 0.25 mL, 6.28 mmol) followed by $LiBH_4$ (3.14 mL, 6.28 mmol, 2.0 M in THF). After 2 h at 0°C, the reaction was warmed to r.t. After 2 h, the reaction was quenched with sat. aq. sodium tartrate (25 mL). After stirring for 20 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15-25% Et_2O / pentane, to give **115** (0.96 g, 5.18 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ (+) 9.4° (c 0.84, $CHCl_3$); IR (thin film) 3337 (br), 3072, 2954, 2916, 1631, 1455, 1419, 1248, 1036, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5,60 (d, *J* = 15.6 Hz, 2H), 3.44-3.52 (m, 2H), 2.03-2.10 (m, 1H), 1.77-1.89 (m, 2H), 1.54 (s, 2H), 1.41 (t, OH), 0.91 (d, *J* = 6.3 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 109.2, 68.7, 43.1, 34.2, 26.7, 17.2, -0.9; HRMS (FAB+) calcd. for $C_{10}H_{23}OSi$ (M+H) 187.1440, found 186.1447



Allylsilane **116**: To a solution of alcohol **115** (308 mg, 1.65 mmol) in CH_2Cl_2 at –78°C was added sequentially Et_3N (0.25 g, 0.34 mL, 2.48 mmol) and TIPSOTf (607 mg, 0.53 mL, 1.98 mmol). After 20 min, the reaction was warmed to r.t. After 5 min, the reaction was quenched with sat. aq. NH_4Cl (25 mL). After 5 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1% EtOAc / hexanes, to give **116** (560 mg, 1.64 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ -4.9° (c 0.98, $CHCl_3$); IR (thin film) 3072, 2944, 2866, 1631, 1463, 1387, 1248, 1103, 1068, 878, 849, 796, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57-4.58 (m, 1H), 4.54 (s, 1H), 3.47-3.51 (m, 2H), 2.18 (dd, *J* = 5.4, 13.8, 1H), 1.78-1.82 (m, 1H), 1.63-1.71 (m, 1H), 1.51 (s, 2H), 1.04-1.08 (m, 21H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 108.8, 68.9, 42.7, 34.6, 26.7, 18.5, 17.0, 12.4, -0.9; HRMS (FAB+) calcd. for $C_{19}H_{42}OSi_2$ (M+) 342.2774, found 342.2772.

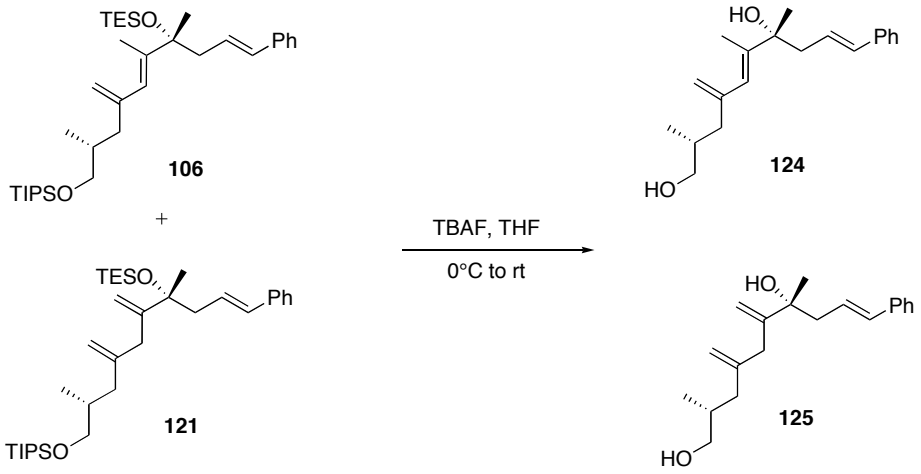


Tertiary alcohol **120**: To a solution of allylsilane **116** (214 mg, 0.62 mmol) and ketone **107** (96 mg, 0.3 mmol) in CH_2Cl_2 (3.0 mL) at –78°C was added freshly distilled $TiCl_4$ (117.6 mg, 70 μL, 0.62 mmol) *via* micro-syringe dropwise. After 15 min, the dark red solution was quenched with sat. aq. K_2CO_3 (5 mL) and warmed to r.t. immediately. After 20 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 0.5-2% EtOAc / hexanes, to give **120** (382 mg, 0.19 mmol, 65%) as a colorless oil of a mixture of isomers (d.r. = 6:1). The major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.39 (m, 5H), 6.35-6.44 (m, 2H), 4.93 (s, 1H), 4.84 (s, 1H), 3.57-3.61 (m, 1H), 3.43-3.48 (m, 1H), 2.55-2.60 (m, 2H), 2.35-2.40 (m, 1H), 2.31 (dd, J = 5.7, 10.8, 1H), 2.16 (d, J = 9.9 Hz, 1H), 2.03 (dd, J = 5.7, 10.8 Hz, 1H), 1.85-1.88 (m, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 1.08-1.10 (m, 21H), 0.99 (t, J = 6.0 Hz, 9H), 0.94 (d, J = 5.1 Hz, 3 H), 0.70 (q, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 138.0, 132.5, 128.9, 127.9, 127.4, 126.4, 115.4, 81.9, 77.7, 68.6, 43.3, 42.2, 42.1, 34.8, 23.1, 21.3, 18.5, 17.5, 12.4, 7.7, 7.4; HRMS (FAB+) calcd. for $C_{35}H_{64}O_3Si_2$ (M+) 588.4394, found 588.4382.



Dienes **106** and **121**: To a solution of **120** (118 mg, 0.20 mmol) in PhMe (5.0 mL) at –78°C was added sequentially pyridine (79.0 mg, 0.08 mL, 1.0 mmol) and $SOCl_2$ (71.4 mg, 44 μL, 0.60 mmol) *via* micro-syringe. After 30 min, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and warmed to r.t. After 20 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 0.5-1% EtOAc / hexanes, to give mixture of **106** and **121** (114 mg, 0.20 mmol, 99%, 2.2:1 ratio) was separable by HPLC as colorless oil. Conjugate diene **106**: $[\alpha]_D^{23}$ -43.2° (c 0.1, $CHCl_3$); IR (thin film) 2954, 2866, 1640, 1459, 1156, 1119, 1013, 882, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.34 (m, 5H), 6.35 (d, *J* = 12.0 Hz, 1H), 6.18 (dt, J = 12.0, 5.4 Hz, 1H), 5.89 (s, 1H), 5.01 (s, 1H), 4.82 (s, 1H), 3.44 (d, *J* = 4.2 Hz, 2H), 2.48-2.50 (m, 2H), 2.35 (dd, *J* = 3.6, 9.9 Hz, 1H), 1.84 (d, *J* = 0.9 Hz, 3H), 1.82 (dd, *J* = 3.6, 9.9 Hz, 1H), 1.66-1.72 (m, 1H), 1.46 (s, 3H), 1.07-1.09 (m, 21H), 1.00 (t, *J* = 5.7 Hz, 9H), 0.78 (d, *J* = 5.6 Hz, 3H), 0.64 (q, *J* = 5.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 142.8, 138.3, 131.9, 128.8, 127.4, 127.2, 126.3, 125.5, 114.5, 78.7, 68.6, 46.3, 42.6, 34.9, 27.2, 18.5, 16.7, 15.0, 12.4, 7.6, 7.2; HRMS (FAB+) calcd. for $C_{35}H_{62}O_2Si_2$ (M+) 570.4288, found 570.4277.

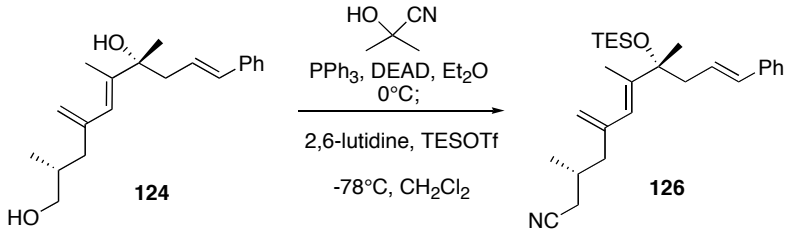
Unconjugated diene **121**: $[\alpha]_D^{23}$ -1.3° (c 1.74, $CHCl_3$); IR (thin film) 3026, 2942, 2865, 1643, 1495, 1462, 1381, 1241, 1097, 1012, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.36 (m, 5H), 6.38 (d, *J* = 12.0 Hz, 1H), 6.16-6.20 (m, 1H), 5.16 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.88 (s, 1H), 3.55-3.59 (m, 1H), 3.44-3.47 (m, 1H), 2.84 (s, 2H), 2.47-2.50 (m, 2H), 2.25 (dd, *J* = 3.6, 9.9 Hz, 1H), 1.74-1.85 (m, 2H), 1.43 (s, 3H), 1.08-1.10 (m, 21H), 1.00 (t, *J* = 6.0 Hz, 9H), 0.92 (d, J = 4.8 Hz, 3H), 0.64 (q, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 146.7, 138.3, 132.2, 128.9, 127.5, 127.2, 126.4, 113.9, 111.1, 78.3, 68.8, 46.4, 39.8, 38.8, 34.6, 27.5, 18.5, 17.2, 12.4, 7.6, 7.3.



Diols **124** and **125**: To a mixture of **106** and **121** (75 mg, 0.13 mmol) in THF (0.1 mL) at 0°C was added TBAF (0.6 mL, 1.0 M in THF). After 10 min, the reaction was warmed to r.t. After 1 h, the reaction was quenched with sat. aq. NH_4Cl (3 mL). After 10 min the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by

chromatography over silica gel, eluting with 20% EtOAc / hexanes, to give diol **124** (20 mg, 0.069 mmol, 61%) as a white foam: $[\alpha]_D^{23}$ -4.9° (c 0.98, $CHCl_3$); IR (thin film) 3373 (br), 3026, 2955, 2925, 2870, 1722, 1627, 1448, 1373, 1032, 966, 897, 741, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.38 (m, 5H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.12-6.20 (m, 1H), 5.97 (s, 1H), 5.07 (s, 1H), 4.86 (s, 1H), 3.28-3.40 (m, 2H), 2.66 (dd, *J* = 7.2, 14.0 Hz, 1H), 2.46 (dd, *J* = 8.0, 14.0 Hz, 1H), 2.26 (dd, *J* = 5.6, 13.6 Hz, 1H), 1.89 (s, 3H), 1.84-1.88 (m, 1H), 1.61-1.66 (m, 1H), 1.42 (s, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 142.9, 137.7, 133.8, 129.0, 127.8, 126.5, 125.9, 125.1, 115.2, 76.0, 68.5, 44.4, 42.5, 34.9, 28.1, 16.6, 15.4; HRMS (ES+) calcd. for $C_{20}H_{28}O_2Na$ (M+Na) 323.1987, found 323.1996.

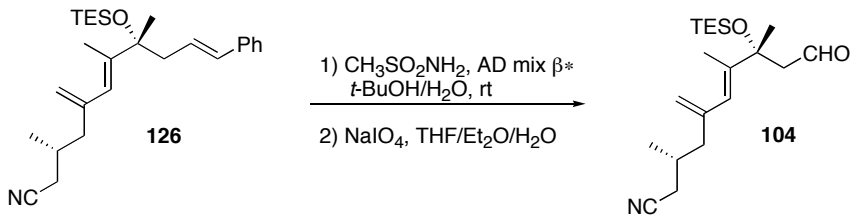
Diol **125:** is colorless oil**:** $[\alpha]_D^{23}$ +7.6° (c 1.21, $CHCl_3$); IR (thin film) 3373, 3081, 3026, 2957, 2926, 2870, 1724, 1644, 1496, 1449, 1373, 1112, 1034, 967, 900, 739, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23-7.39 (m, 5H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.16-6.23 (m, 1H), 5.23 (s, 1H), 4.96 (s, 3H), 3.48-3.52 (m, 2H), 2.85-2.96 (m, 2H), 2.62-2.66 (m, 1H), 2.48-2.52 (m, 1H), 2.18-2.24 (m, 1H), 1.86-1.93 (m, 2H), 1.40 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 146.9, 137.7, 134.3, 128.9, 127.7, 126.6, 125.7, 114.3, 111.8, 75.7, 68.6, 45.0, 40.1, 39.2, 34.3, 28.2, 17.1; HRMS (ES+) calcd. for $C_{20}H_{28}O_2Na$ (M+Na) 323.1987, found 323.1989.



Nitrile **126**: To a solution of **124** (98 mg, 0.33 mmol) in Et_2O (1.6 mL) at 0°C was added sequentially PPh_3 (342 mg, 1.3 mmol) and DEAD (0.24 mL, 1.3 mmol, 40% w/w in PhMe). After 15 min, acetone cyanohydrin (70.0 mg, 74.5 μL, 0.82 mmol) was added dropwise. After 5 min, the reaction was warmed to r.t. After 6 h, the reaction was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10% EtOAc / hexanes, to give a corresponding nitrile intermediate (80 mg, 0.26 mmol, 81%) as a colorless oil: $[\alpha]_D^{23}$ +7.8° (c 0.99, $CHCl_3$); IR (neat) 3479 (br), 2962, 2927, 2246, 1733, 1496, 1456, 1420, 1381, 1105, 968, 902, 743, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.37 (m, 5H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.12-6.18 (m, 1H), 5.95 (s, 1H), 5.12 (s, 1H), 4.92 (s, 1H), 2.66 (dd, *J* = 7.2, 14.0 Hz, 1H), 2.48 (dd, *J* = 7.2, 14.0 Hz, 1H), 2.05-2.20 (m, 4H), 1.88 (s, 3H), 1.76-1.88 (m, 1H), 1.75 (br, 1H), 1.43 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.5, 137.5, 134.0, 129.0, 127.9, 126.5, 125.5, 124.3, 119.1, 116.4, 76.0, 44.8, 44.5, 29.3, 28.1, 24.2, 19.5, 15.5; HRMS (FAB+) calcd. for $C_{21}H_{28}NO$ (M+1) 310.2171, found 310.2144.

To a solution of the above intermeidate (80 mg, 0.26 mmol) in CH_2Cl_2 (1.0 mL) at –78°C was added 2,6-lutidine (111.0 mg, 0.12 mL, 1.04 mmol) and

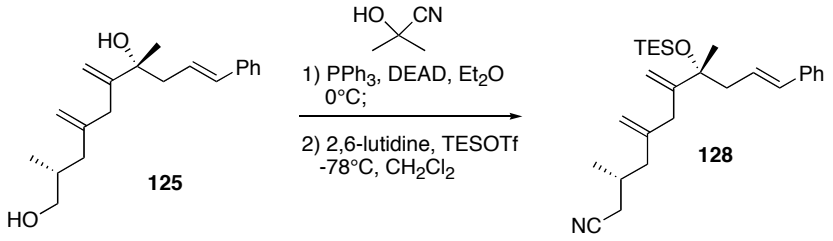
followed by TESOTf (136.9 mg, 0.12 mL, 0.52 mmol). After 30 min, the reaction was warmed to r.t. and quenched with sat. aq. NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1% EtOAc / hexanes, to give nitrile **126** (80 mg, 0.19 mmol, 72%) as a colorless oil: $[\alpha]_D^{23}$ -37.6° (c 0.98, $CHCl_3$); IR (neat) 2957, 2933, 2876, 2240, 1733, 1496, 1457, 1420, 1381, 1160, 1122, 1016, 967, 902, 742, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.33 (m, 5H), 6.33 (d, *J* = 11.7 Hz, 1H), 6.15-6.19 (m, 1H), 5.87 (s, 1H), 5.07 (s, 1H), 4.87 (s, 1H), 2.50 (d, *J* = 5.4 Hz, 2H), 2.15 (dd, *J* = 5.4, 9.9 Hz, 1H), 2.00-2.06 (m, 3H), 1.81 (s, 3H), 1.72-1.79 (m, 1H), 1.47 (s, 3H), 1.02 (t, *J* = 5.7 Hz, 9H), 0.85 (d, *J* = 5.1 Hz, 3H), 0.67 (q, *J* = 5.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.7, 138.1, 131.9, 129.0, 127.4, 127.3, 126.3, 124.6, 119.0, 116.0, 78.8, 46.0, 44.9, 29.3, 27.6, 24.1, 19.4, 15.1, 7.64, 7.26; HRMS (FAB+) calcd. for $C_{27}H_{42}OSiN$ (M+1) 424.3036, found 424.3044.



Aldehyde **104**: To a solution of **126** (75 mg, 0.18 mmol) in *t*-BuOH / H_2O (3 mL, 1:1) was added $MeSO_2NH_2$ (25.6 mg, 0.27 mmol) and AD mix β*[48] (250 mg). After 16 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (3

mL). After 20 min, the mixture was extracted with EtOAc (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% EtOAc / hexanes, to give a mixture of diol isomers (73 mg, d.r. = 6:1, 0.16 mmol, 89%) as a colorless oil. The diol substrate was applied to the next step without further purification.

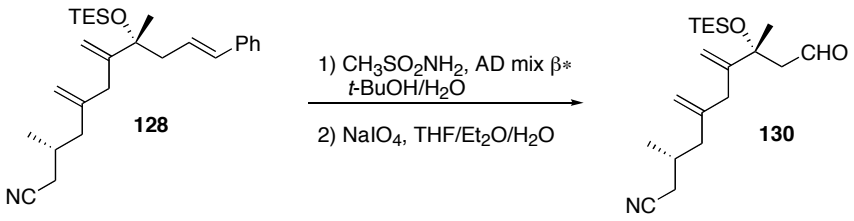
A solution of the mixture described above in THF/Et_2O (2.8 mL, 1:1) was added $NaIO_4$ (304 mg, 1.42 mmol) and H_2O (1.4 mL). After 2 h, the reaction was quenched with sat. aq. NaCl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give aldehyde **104** (54 mg, 0.15 mmol, 96%) as colorless oil: $[\alpha]_D^{23}$ -12.6° (c 1.22, $CHCl_3$); IR (neat) 3081, 2957, 2917, 2876, 2246, 1722, 1628, 1457, 1417, 1381, 1240, 1163, 1126, 1046, 1017, 904, 802, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 3.2 Hz, 1H), 5.99 (s, 1H), 5.10 (s, 1H), 4.89 (s, 1H), 2.61 (dd, *J* = 3.2, 14.8 Hz, 1H), 2.47 (dd, *J* = 2.8, 14.8 Hz, 1H), 2.32 (dd, *J* = 5.2, 16.8 Hz, 1H), 2.15-2.25 (m, 2H), 2.08 (dd, *J* = 7.2, 13.6 Hz, 1H), 1.83-1.92 (m, 1H), 1.80 (s, 3H), 1.47 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 143.2, 142.7, 125.2, 118.9, 116.8, 54.5, 44.8, 30.1, 29.6, 28.3, 24.3, 19.8, 15.2, 7.5, 7.2; HRMS (FAB+) calcd. for $C_{20}H_{36}O_2SiN$ (M+1) 350.2515, found 350.2508.



Nitrile **128**: To a solution of **125** (30 mg, 0.10 mmol) in Et_2O (0.5 mL, 0.2 M) at 0°C was added sequentially PPh_3 (104 mg, 0.4 mmol) and DEAD (72 μL, 0.4 mmol, 40% solution in PhMe). After 15 min, acetone cyanohydrin (21.2 mg, 23.0 μL, 0.25 mmol) was added dropwise. After 5 min, the reaction was warmed to r.t. After 6 h, the reaction was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10% EtOAc / hexanes, to give a corresponding nitrile intermediate (25 mg, 0.08 mmol, 81%) as a colorless oil.

To a solution of the above nitrile (25 mg, 0.08 mmol) in CH_2Cl_2 (0.32 mL, 0.25 M) at –78°C added sequentially 2,6-lutidine (34.3 mg, 37 μL, 0.32 mmol) and TESOTf (42.1 mg, 36 μL, 0.16 mmol). After 30 min, the reaction was warmed to r.t. and quenched with sat. aq. NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1% EtOAc / hexanes, to give **128** (26 mg, 62 μmol, 77%) as a colorless oil: $[\alpha]_D^{23}$ -13.6° (c 0.28, $CHCl_3$); IR (neat) 2957, 2933, 2911, 2875, 2247, 1238, 1157, 1123, 1063, 1005, 967, 905, 742, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17-7.26 (m, 5H), 6.35 (d, J = 15.9 Hz, 1H), 6.08-6.19 (m, 1H), 5.14

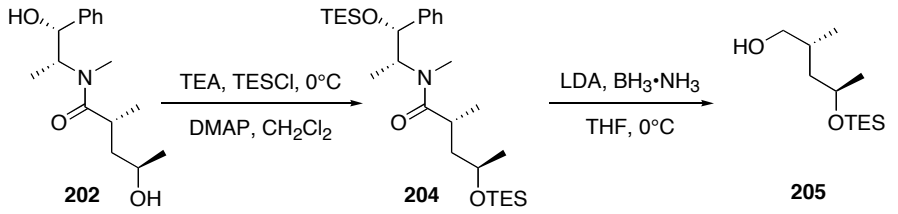
(s, 1H), 4.93 (s, 2H), 4.71 (s, 1H), 2.75-2.85 (m, 2H), 2.46 (dd, J = 0.6, 6.9 Hz, 2H), 2.24-2.32 (m, 1H), 1.97-2.17 (m, 4H), 1.38 (s, 3H), 0.95-1.04 (m, 12H), 0.58-0.68 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 144.9, 138.1, 132.3, 128.9, 127.4, 127.1, 126.4, 119.2, 115.8, 111.1, 78.2, 46.4, 42.3, 38.2, 28.9, 27.7, 24.3, 20.0, 7.6, 7.3.



Aldehyde **130**: To a solution of **128** (26 mg, 62 μmol) in *t*-BuOH / H_2O (1 mL, 1:1) was added $MeSO_2NH_2$ (8.8 mg, 93 μmol) and AD mix β*[Error! Bookmark not defined.,8] (87 mg). After 16 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (3 mL). After 20 min, the mixture was extracted with EtOAc (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% EtOAc / hexanes, to give a mixture of the diol isomers (25.5 mg, d.r. = 1.3:1, 56 μmol, 90%) as a colorless oil. The diol substrate was applied to the next step without further purification.

A solution of the mixture described above in THF/Et_2O (1.24 mL, 1:1) was added $NaIO_4$ (120 mg, 0.56 mmol) and H_2O (0.62 mL). After 2 h, the reaction was quenched with sat. aq. NaCl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*

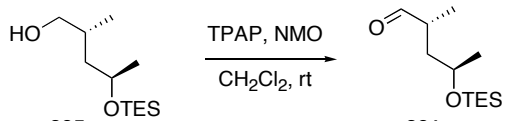
to give aldehyde **130** (18.5 mg, 0.053 mmol, 95%) as colorless oil: $[\alpha]_D^{23}$ -11.4° (c 1.57, $CHCl_3$); IR (neat) 2958, 2915, 2876, 2737, 2246, 1722, 1645, 1457, 1417, 1375, 1239, 1165, 1123, 1045, 1005, 909, 743, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 3.0 Hz, 1H), 5.28 (s, 1H), 4.95 (s, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 2.76 (s, 2H), 2.20-2.62 (m, 5H), 2.02-2.06 (m, 2H), 1.46 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 150.5, 144.3, 119.0, 116.2, 112.6, 54.5, 42.1, 38.4, 28.9, 28.5, 24.3, 24.0, 19.9, 7.5, 7.2.



Alcohol **205**: To a solution of diol **202** (215 mg, 0.77 mmol) in CH_2Cl_2 at 0°C added sequentially TEA (0.32 mL, 2.32 mmol), DMAP (28 mg, 0.23 mmol), and TESCl (0.29 mL, 1.93 mmol). After 2 h at 0°C, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give crude **204** (0.77 mmol) and used without further purification.

To a solution of diisopropyl amine (0.45 mL, 3.2 mmol) in THF (1.9 mL) at –78°C was added *n*-BuLi (1.28 mL, 3.2 mmol, 2.5M in hexanes). After 10 min at –78°C, the solution was warmed to 0°C. After 15 min, BH_3•NH_3

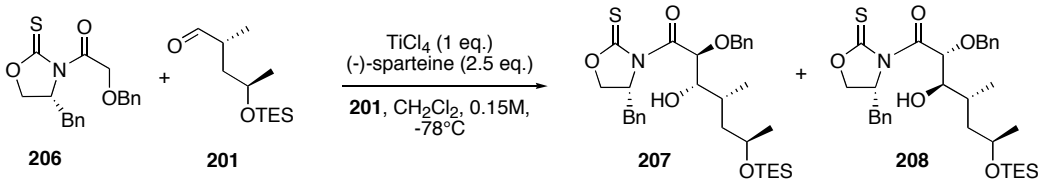
(110 mg, 3.2 mmol) was added at 0°C in one portion. After 15 min at 0°C and 15 min at r.t., the reaction was cooled back to 0°C. A solution of the crude silyl ether product **204** (0.77 mmol) in THF (2.5 mL) was added dropwise. After 2 h at 0°C and 10 h at r.t., the reaction was quenched with sat. aq. NH_4Cl (10 mL) carefully. After 20 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10% EtOAc / hexanes, to give alcohol **205** (140 mg, 0.6 mmol, 78%) as a colorless oil: $[\alpha]_D^{23}$ -9.3° (c 0.87, $CDCl_3$); IR (thin film) 3354 (br), 2956, 2877, 1459, 1415, 1378, 1238, 1132, 1070, 1042, 1016, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01-4.07 (m, 1H), 3.44-3.48 (m, 1H), 3.36-3.40 (m, 1H), 3.21-3.26 (m, 1H), 1.89-1.90 (m, 1H), 1.47-1.51 (m, 2H), 1.20 (d, J = 6.3 Hz, 3H), 0.97 (t, J = 8.1 Hz, 9H), 0.88 (d, J = 6.9 Hz, 3H), 0.62 (q, J = 8.1 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.0, 67.5, 44.8, 32.3, 23.1, 18.6, 7.2, 5.2; HRMS (FAB+) calcd. for $C_{12}H_{29}O_2Si$ (M+1) 233.1937, found 233.1944.



205 **201**

Aldehyde **201**: To a solution of alcohol **205** (170 mg, 0.73 mmol) in CH_2Cl_2 (7.3 mL) at r.t. was added sequentially 4Å MS (0.4 g), NMO (129 mg, 1.1 mmol) and TPAP (13 mg, 36 μmol). After 30 min, the mixture was filtrated through a plug of silicon gel eluting with 30% Et_2O/Pentane (150 mL).

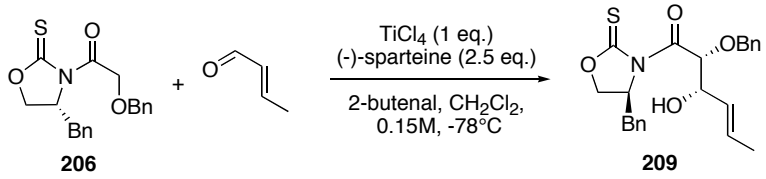
The elute was concentrated *in vacuo* to give aldehyde **201** (143 mg, 0.62 mmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ -27.0° (c 0.47, $CHCl_3$); IR (thin film) 2956, 2936. 2911, 2877, 1727, 1458, 1374, 1114, 1051, 1007, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (t, J = 2.1 Hz, 1H), 3.91-3.97 (m, 1H), 2.50-2.53 (m, 1H), 1.78-1.87 (m, 1H), 1.50-1.59 (m, 1H), 1.18 (d, J = 4.8 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 7.5 Hz, 9H), 0.58 (q, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 66.5, 43.3, 41.3, 24.3, 14.4, 7.2, 5.3; HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 230.1702, found 230.1687.



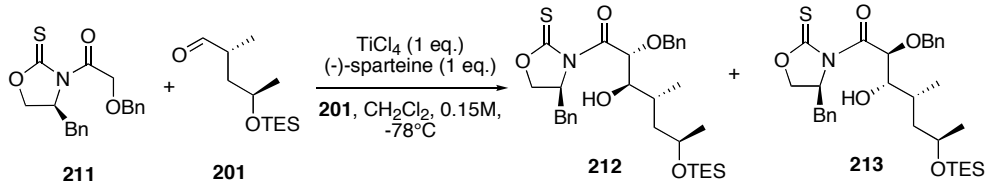
Alcohols **207** and **208**: To a solution of **206** (170 mg, 0.50 mmol) in CH_2Cl_2 (1.5 mL) at –78°C was added sequentially $TiCl_4$ (94.9 mg, 55 μL, 0.50 mmol) and a solution of (-)-sparteine (293.0 mg, 0.29 mL, 1.25 mmol) in CH_2Cl_2 (0.5 mL) dropwise. After 1.5 h, a solution of aldehyde **201** (57 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the solution *via* cannula. After 40 min, the reaction was quenched at –78°C with sat. aq. NH_4Cl (5 mL) and warmed up to r.t. After 10 min, the solution was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-15% EtOAc / hexanes, to give **207** and **208** (dr = 1.5 : 1) (63 mg of **207**, 0.11 mmol, 44%) as a colorless oil.

207: $[\alpha]_D^{23}$ –103.78° (c 3.7, $CHCl_3$); IR (thin film) 3444, 3029, 2959, 2911, 2875, 1709, 1497, 1455, 1367, 1322, 1197, 1161, 1063, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.37 (m, 10H), 6.25 (d, J = 9.3 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.52-4.61 (m, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.22 (dd, J = 1.8, 9.0 Hz, 1H), 3.93-4.04 (m, 3H), 3.18 (dd, J = 3.3, 13.8 Hz, 1H), 2.94 (d, J = 10.2 Hz, 1H), 2.73 (dd, J = 9.6, 13.5 Hz, 1H), 2.18 (ddd, J = 2.1, 6.9, 8.7 Hz, 1H), 1.74-1.58 (m, 1H), 1.57-1.48 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.61 (q, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 175.4, 137.5, 135.4, 129.9, 129.7, 129.4, 128.71, 128.67, 127.8, 77.3, 75.3, 73.9, 71.2, 67.2, 60.7, 44.0, 37.6, 31.6, 24.2, 13.8, 7.4, 5.4; HRMS (FAB+) calcd. for $C_{31}H_{46}NO_5SSi$ (M+1) 572.2866, found 572.2864.

(42 mg of **208**, 0.07 mmol, 30%) as a colorless oil. **208:** $[\alpha]_D^{23}$ –43.96° (c 1.8, $CHCl_3$); IR (thin film) 3484, 3029, 2957, 2932, 2876, 1702, 1497, 1455, 1364, 1325, 1197, 1160, 1061, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.40 (m, 10H), 6.59 (d, J = 8.4 Hz, 1H), 4.62 (s, 2H), 4.20-4.31 (m, 2H), 3.95 (dt, J = 6.3, 18.3 Hz, 1H), 3.64 (s, br 1H), 3.54 (s, br, 1H), 3.18 (dd, J = 3.3, 13.2 Hz, 1H), 2.65 (dd, J = 10.5, 13.5 Hz, 1H), 2.15-2.19 (m, 1H), 1.54-1.64 (m, 2H), 1.17 (d, J = 6.3 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.61 (q, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 175.5, 137.7, 135.8, 129.8, 129.4, 129.0, 128.8, 128.5, 127.8, 78.8, 77.6, 73.2, 71.2, 67.1, 61.3, 41.0, 38.2, 33.3, 24.0, 17.4, 7.3, 5.3; HRMS (FAB+) calcd. for $C_{31}H_{46}NO_5SSi$ (M+1) 572.2866, found 572.2864



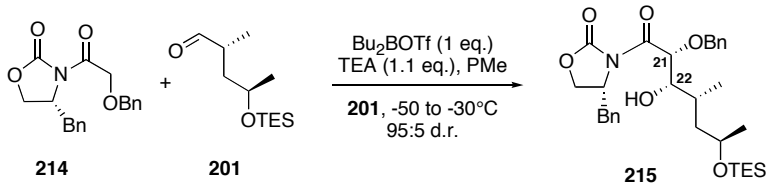
Alcohol **209**: To a solution of auxiliary **206** (34 mg, 0.10 mmol) in CH_2Cl_2 (0.6 mL) at –78°C was added $TiCl_4$ (19.0 mg, 11.1 μL, 0.10 mmol) and (-)-sparteine (58.7 mg, 60.1 μL, 0.25 mmol). After 1.5 h, freshly distilled 2-butenal (9.9 mg, 12.9 μL, 0.15 mmol) was added to the solution dropwise. After 30 min, the reaction was quenched at –78°C with sat. aq. NH_4Cl (5 mL) and warmed up to r.t. After 10 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20-40% EtOAc / Hexanes, to give major product **209** (33 mg, 0.08mmol, 80%) as a white solid: $[\alpha]_D^{23}$ +1.42° (c 0.97, $CHCl_3$); IR (thin film) 3446, 3032, 2923, 2854, 1706, 1496, 1454, 1364, 1326, 1197, 1161, 965, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.33 (m, 10H), 6.26 (d, J = 3.3 Hz, 1H), 5.71-5.81 (m, 1H), 5.58-5.65 (m, 1H), 4.80-4.87 (m, 1H), 4.75 (d, J =11.4 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.48 (s, br, 1H), 4.24-4.35 (m, 2H), 3.24 (dd, J = 3.3, 13.2 Hz, 1H), 2.72 (dd, J = 3.3, 13.6 Hz, 1H), 2.52 (br, 1H), 1.70 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 172.0, 137.4, 135.5, 129.9, 129.5, 129.0, 128.9, 128.7, 127.9, 80.0, 74.1, 73.8, 71.3, 61.3, 37.9, 30.1, 18.2; HRMS (FAB+) calcd. for $C_{23}H_{26}NO_4S$ (M+1) 412.1583, found 412.1589.



Alcohols **212** and **213**: To a solution of **211** (230 mg, 0.67 mmol) in CH_2Cl_2 (3.3 mL) at –78°C was added $TiCl_4$ (126.6 mg, 73.8 μL, 0.67 mmol) and a solution of (-)-sparteine (157.2 mg, 0.15 mL, 0.67 mmol) in CH_2Cl_2 (0.7 mL) dropwise. After 1.5 h, a solution of aldehyde **201** (98 mg, 0.43 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the solution *via* cannula. After 40 min, the reaction was quenched at –78°C with sat. aq. NH_4Cl (5 mL) and warmed up to r.t. After 10 min, the solution was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-15% EtOAc / hexanes, to give **212** and **213** (dr = 4: 1) (130 mg of **312**, 0.23 mmol, 53%) as a white solid. **212:** $[\alpha]_D^{23}$ +122.86° (c 0.7, $CHCl_3$); IR (thin film) 3446, 3029, 2958, 2931, 2875, 1707, 1496, 1455, 1387, 1324, 1197, 1086, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.35 (m, 10H), 6.35 (d, J = 8.8 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 4.58-4.59 (m, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.25 (dd, J = 2.4, 9.2 Hz, 1H), 3.99-4.07 (m, 2H), 3.79-3.85 (m, 1H), 3.38 (d, J = 10.4 Hz, 1H), 3.22 (dd, J = 3.6, 13.6 Hz, 1H), 2.73 (dd, J = 9.6, 13.6 Hz, 1H), 2.16-2.21 (m, 1H), 1.72-1.75 (m, 1H), 1.60-1.63 (m, 1H), 1.25 (d, J = 6 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.01 (t, J = 8.4 Hz, 9H), 0.66 (q, J = 8.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 175.1, 137.4, 135.5, 129.9, 129.7, 129.4, 128.72, 128.67,

127.8, 79.2, 76.4, 73.8, 71.1, 67.5, 60.6, 41.0, 37.6, 33.3, 23.9, 17.6, 7.3, 5.4; HRMS (FAB+) calcd. for $C_{31}H_{46}NO_5SSi$ (M+1) 572.2866, found 572.2864.

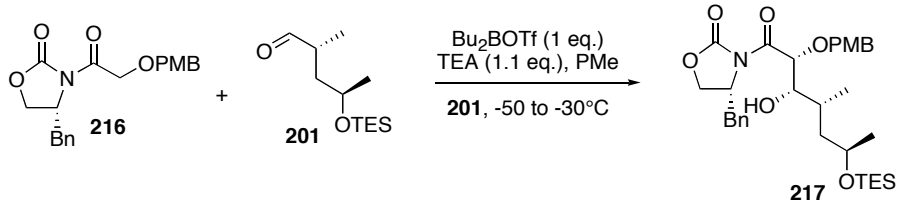
213: $[\alpha]_D^{23}$+38.40° (c 1.25, $CHCl_3$); IR (thin film) 3484, 2958, 2908, 2874, 1705, 1454, 1364, 1322, 1196, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17-7.43 (m, 10H), 6.58 (d, J = 9.2 Hz, 1H), 4.84-4.87 (m, 1H), 4.62-4.67 (m, 2H), 4.26-4.34 (m, 2H), 3.98 (dt, J = 6.0, 17.6 Hz, 1H), 3.84-3.89 (m, 1H), 3.20 (dd, J = 3.3, 13.2 Hz, 1H), 2.74 (d, J = 7.8 Hz, 1H), 2.65 (dd, J = 10.5, 13.2 Hz, 1H), 2.16-2.20 (m, 1H), 1.57-1.65 (m, 1H), 1.45-1.52 (m, 1H), 1.17 (d, J = 6.3 Hz, 3H), 0.93 (t, J = 8.1 Hz, 9H), 0.87 (d, J = 6.9 Hz, 3H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 176.0, 137.7, 135.7, 129.8, 129.4, 129.1, 128.8, 128.5, 127.8, 77.8, 76.2, 73.2, 71.3, 67.2, 61.3, 43.8, 38.3, 31.6, 24.0, 13.4, 7.3, 5.4; HRMS (FAB+) calcd. for $C_{31}H_{46}NO_5SSi$ (M+1) 572.2866, found 572.2864.



214 201 215

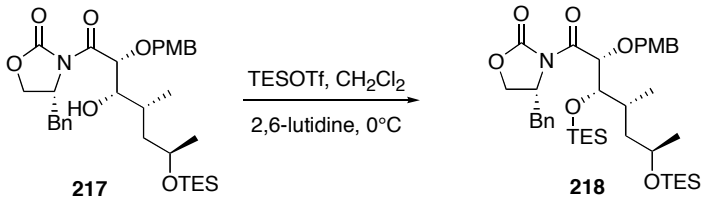
Alcohol **215**: To a solution of imide **214** (49 mg, 0.15 mmol) in PhMe (0.35 mL) at –50°C was sequentially added TEA (17.3 mg, 24.0 μL, 0.17 mmol) and Bu_2BOTf (43.8 mg, 40.2 μL, 0.16 mmol). After 1.5 h, a solution of aldehyde **201** (23 mg, 0.10 mmol) in PhMe (0.15 mL) was transferred dropwise into the reaction *via* cannula. After 40 min, the reaction was allowed to warm

to –30°C within 30 min. After 1 h, the reaction was quenched by sequentially adding pH 7 phosphate buffer (0.5 mL), MeOH (0.5 mL) and THF (0.5 mL). Next, the solution was warmed up to 0°C. After 5 min, 30% aqueous H_2O_2 (0.5 mL) in MeOH (0.5 mL) was added dropwise. After 1 h, the reaction mixture was extracted with EtOAc (3 X 15 mL) and the combined organic layer was diluted with pH 7 phosphate buffer (20 mL). The mixture was concentrated *in vacuo* and the resulted mixture was extracted again with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15-20% EtOAc / hexanes, to give **215** (40 mg, 72 μmol, 72%) as a colorless oil: $[\alpha]_D^{23}$ -1.78° (c 2.34, $CHCl_3$); IR (thin film) 3546 (br), 3029, 2957, 2875, 1782, 1709, 1455, 1357, 1210, 1110, 1051, 1012, 736, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.34 (m, 10H), 5.36 (d, J = 2.1 Hz, 1H), 4.65-4.72 (m, 2H), 4.51 (d, J = 11.1 Hz, 1H), 4.17-4.27 (m, 2H), 3.84-3.90 (m, 1H), 3.59-3.63 (m, 1H), 3.32 (dd, J = 3.0, 13.2 Hz, 1 H), 2.77 (dd, J = 3.9, 13.5 Hz, 1 H), 2.31 (d, J = 9.0 Hz, 1H), 1.74-1.81 (m, 1H), 1.54-1.62 (m, 1H), 1.37-1.47 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.953 (t, J = 8.1 Hz, 9H), 0.59 (q, J = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 153.6, 137.5, 135.6, 129.9, 129.4, 128.9 (2 C overlapped), 128.6, 127.9, 78.8, 76.6, 73.3, 67.4 (2 C overlapped), 56.2, 43.1, 38.2, 34.7, 23.6, 16.2, 7.3, 5.3; HRMS (FAB+) calcd. for $C_{31}H_{46}NO_6Si$ (M+1) 556.3095, found 556.3094.



Alcohol **217**: To a solution of imide **216** (107 mg, 0.3 mmol) in PhMe (0.7 mL) at –50°C was sequentially added Et_3N (34.4 mg, 48.2 μL, 0.34 mmol) and Bu_2BOTf (86.0 mg, 80.0 μL, 0.32 mmol). After 1.5 h, a solution of aldehyde **201** (46 mg, 0.20 mmol) in PhMe (0.25 mL) was transferred dropwise into the reaction *via* cannula. After 40 min, the reaction was warmed to –30°C within 30 min. After 1 h, the reaction was quenched with aq. phosphate buffer solution (0.5 mL, pH 7), MeOH (0.5 mL) and THF (0.5 mL). Next, the mixture was warmed up to r.t. A solution of H_2O_2 (0.5 mL, 30% H_2O_2 in H_2O) in MeOH (0.5 mL) was added dropwise. After 1 h, the reaction mixture was extracted with EtOAc (3 X 15 mL) and the combined organic extract was diluted with an aqueous phosphate buffer solution (20 mL, pH 7). The mixture was concentrated *in vacuo* and extracted again with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15-20% EtOAc / hexanes, to give **217** (83 mg, 0.14 mmol, 72%) as a colorless oil: $[\alpha]_D^{23}$ -3.9° (c 0.83, $CHCl_3$); IR (thin film) 3490 (br), 2956, 2875, 1781, 1708, 1612, 1514, 1389, 1248, 1211, 1051, 1012, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.39 (m, 7H), 6.92 (d, J = 8.8 Hz, 2H), 5.36 (d, J = 2.0 Hz, 1H), 4.64-4.72 (m, 1H), 4.64 (d, J

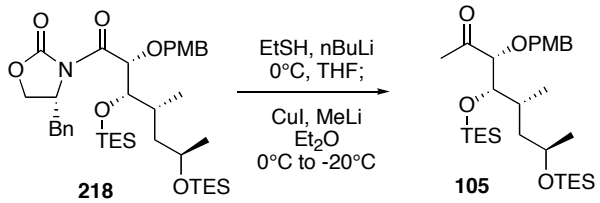
= 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.20-4.29 (m, 2H), 3.84-3.90 (m, 1H), 3.82 (s, 3H), 3.61-3.64 (m, 1H), 3.34 (dd, *J* = 2.8, 13.2 Hz, 1H), 2.78 (dd, *J* = 3.6, 13.5 Hz, 1 H), 2.31 (d, *J* = 10.0 Hz, 1H), 1.74-1.81 (m, 1H), 1.56-1.62 (m, 1H), 1.40-1.48 (m, 1H), 1.15 (d, *J* = 5.6 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 9H), 0.62 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 160.0, 153.6, 135.6, 130.7, 129.8, 129.6, 129.4, 127.8, 114.3, 78.4, 76.6, 73.0, 67.4, 67.3, 56.2, 55.7, 43.1, 38.2, 34.6, 23.6, 16.2, 7.3, 5.3; HRMS (FAB+) calcd. for $C_{32}H_{48}NO_7Si$ (M+1) 586.3200, found 586.3202.



217 **218**

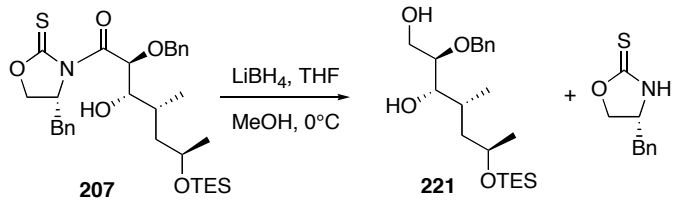
Triethyl silylether **218**: To a solution of alcohol **217** (78 mg, 0.13 mmol) in CH_2Cl_2 (0.3 mL) at 0°C was added sequentially 2,6-lutidine (27.8 mg, 29.8 μL, 0.26 mmol) and TESOTf (68.5 mg, 60.1 μL, 0.26 mmol). After 1 h, the reaction was warmed to r.t. and quenched with sat. aq. NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 4-6% EtOAc / hexanes, to give **218** (84 mg, 0.12 mmol, 90%) as a colorless oil: $[\alpha]_D^{23}$ -33.8° (c 1.9, $CHCl_3$); IR (thin film) 2956, 2911, 2875, 1785. 1704, 1612, 1513, 1456, 1381, 1248, 1082, 1011, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 7H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.25 (d, *J* =

6.0 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.46-4.49 (m, 1H), 4.03-4.12 (m, 3H), 3.73-3.98 (m, 1H), 3.79-3.81 (m, 1H), 3.74 (s, 3H), 3.11 (dd, *J* = 3.0, 13.2 Hz, 1H), 2.40 (dd, *J* = 3.0, 13.5 Hz, 1H), 1.47-1.55 (m, 2H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.87-0.97 (m, 21H), 0.53-0.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 159.9, 153.3, 135.8, 130.6, 130.3, 129.7, 129.4, 127.8, 114.0, 79.6, 77.8, 73.4, 67.6, 66.8, 56.4, 55.6, 44.7, 37.8, 33.9, 24.1, 15.2, 7.5, 7.4, 5.8, 5.4; HRMS (FAB+) calcd. for $C_{38}H_{62}NO_7Si_2$ (M-1) 698.3908, found 698.3890.

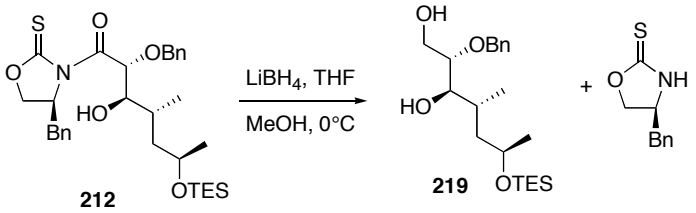


Methyl ketone **105**: To a solution of EtSH (75 mg, 90.2 μL, 1.21 mmol) in THF (9.0 mL) at 0°C was added *n*-BuLi (0.43 mL, 1.07 mmol, 2.5 M in hexane). After 20 min, a solution of **218** (500 mg, 0.714 mmol) in THF (3.0 mL) was transferred *via* cannula dropwise. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL). After 5 min, the mixture was extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by a plug of silica gel, eluting with 10% EtOAc / Hexanes, to give corresponding thioester intermediate (375 mg, 0.68 mmol, 95%) as a colorless oil.

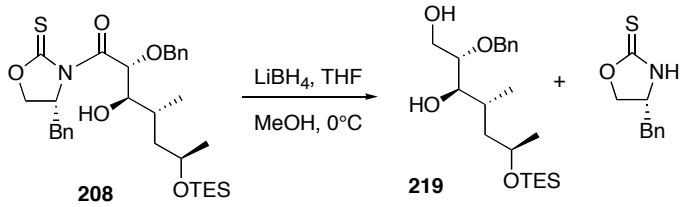
To a suspension of CuI (796 mg, 4.18 mmol) in Et_2O (9.0 mL) at 0°C was added MeLi (5.2 mL, 8.36 mmol, 1.6 M in Et_2O). After 15 min, the colorless solution was cooled to –50°C and a solution of the above thioester intermediate (375 mg, 0.68 mmol) in Et_2O (2.4 mL) was transferred into the reaction dropwise *via* cannula. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (10 mL) at –50°C, warmed to r.t. and extracted with Et_2O (3 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-4% EtOAc / hexanes, to give **105** (326 mg, 0.60 mmol, 89%) as a colorless oil: $[\alpha]_D^{23}$ +31.0° (c 0.80, $CHCl_3$); IR 2956, 2912, 2876, 1716, 1613, 1514, 1457, 1416, 1249, 1172, 1082, 1037, 1007, 820, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.81 (s, 3H), 3.69-3.81 (m, 3H), 2.11 (s, 3H), 1.45-1.48 (m, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.85-0.97 (m, 21H), 0.53-0.61 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 159.8, 130.1, 129.9, 114.1, 88.9, 73.1, 67.4, 55.7, 44.9, 33.5, 27.4, 23.9, 14.3, 7.4, 7.3, 5.7, 5.4; HRMS (FAB+) calcd. for $C_{29}H_{55}O_5Si_2$ (M+1) 539.3588, found 539.3559.



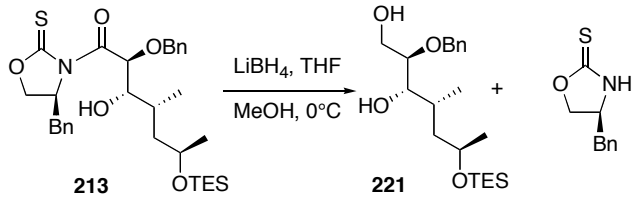
Alcohol **221**: To a solution of **207** (17.6 mg, 31.2 μmol) in THF (0.16 mL) at 0°C added MeOH (2.0 μL, 36.8 μmol) and $LiBH_4$ (20.2 μL, 2.0 M in THF). After 30 min, the reaction was warmed up to r.t. After 30 min, the reaction was quenched with sat. aq. sodium tartarate (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 10-15% EtOAc / hexanes, to give **221** (10.6 mg, 90%) as a colorless oil: $[\alpha]_D^{23}$ –14.0° (c 0.30, $CHCl_3$); IR (thin film) 3400, 2958, 2910, 2876, 1456, 1376, 1237, 1160, 1050, 1028, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.35 (m, 5H), 4.66 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 11.4 mHz, 1H), 3.98 (dt, J = 6.0, 18.0 Hz, 1H), 3.77-3.85 (m, 3H), 3.46-3.51 (m, 1H), 3.09 (br, 1H), 2.59 (br, 1H), 1.99-2.03 (m, 1H), 1.55-1.62 (m, 1H), 1.43-1.54 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H), 0.95 (t, J = 8.1 Hz, 9H), 0.88 (d, J = 6.9 Hz, 3H), 0.61 (q, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.9, 128.4, 128.3, 79.0, 75.7, 72.3, 67.2, 62.5, 43.7, 31.6, 23.6, 14.0, 7.3, 5.4, ;HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 383.2618, found 383.2624.



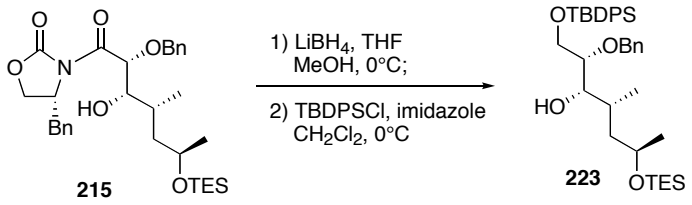
Alcohol **219**: To a solution of **212** (10.6 mg, 20.0 μmol) in THF (0.15 mL) at 0°C added MeOH (1.1 μL, 22.0 μmol) and $LiBH_4$ (11.2 μL, 2.0 M in THF). After 30 min, the reaction was warmed up to r.t. After 30 min, the reaction was quenched with sat. aq. sodium tartarate (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 10-15% EtOAc / hexanes, to give **219** (6.6 mg, 86%) as a colorless oil: $[\alpha]_D^{23}$ –5.0° (c 0.04, $CHCl_3$); IR (thin film) 3409, 2956, 2917, 2849, 1472, 1456, 1237, 1068, 1050, 1012, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 4.62 (dd, J = 3.0, 11.7 Hz, 1H), 4.02 (dt, J = 5.7, 11.4 Hz, 1H), 3.84-3.87 (m, 2H), 3.59-3.63 (m, 1H), 3.51 (dd, J = 4.5, 9.6 Hz, 1H), 2.64 (br, 1H), 1.82-1.92 (m, 1H), 1.51-1.68 (m, 2H), 1.17 (d, J = 6.0 Hz, 3H), 0.94-0.99 (m, 12H), 0.62 (q, J = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.9, 128.3 (2C's), 79.9, 77.6, 71.9, 67.3, 61.7, 42.9, 33.0, 23.9, 17.7, 7.2, 5.3, ;HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 383.2618, found 383.2624.



Alcohol **219**: To a solution of **208** (15 mg, 0.026 mmol) in THF (0.15 mL) at 0°C added MeOH (2.1 μL, 31.9 μmol) and $LiBH_4$ (16.0 μL, 2.0 M in THF). After 30 min, the reaction was warmed up to r.t. After 30 min, the reaction was quenched with sat. aq. sodium tartarate (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 10-15% EtOAc / hexanes, to give **219** (8.6 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ –5.0° (c 0.04, $CHCl_3$); IR (thin film) 3409, 2956, 2917, 2849, 1472, 1456, 1237, 1068, 1050, 1012, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5H), 4.62 (dd, J = 3.0, 11.7 Hz, 1H), 4.02 (dt, J = 5.7, 11.4 Hz, 1H), 3.84-3.87 (m, 2H), 3.59-3.63 (m, 1H), 3.51 (dd, J = 4.5, 9.6 Hz, 1H), 2.64 (br, 1H), 1.82-1.92 (m, 1H), 1.51-1.68 (m, 2H), 1.17 (d, J = 6.0 Hz, 3H), 0.94-0.99 (m, 12H), 0.62 (q, J = 8.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.9, 128.3 (2C's), 79.9, 77.6, 71.9, 67.3, 61.7, 42.9, 33.0, 23.9, 17.7, 7.2, 5.3, ;HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 383.2618, found 383.2624.



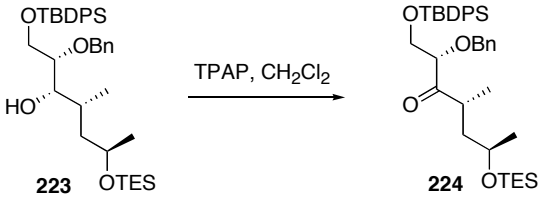
Alcohol **221**: To a solution of **213** (37 mg, 65 μmol) in THF (0.32 mL) at 0°C added MeOH (3.2 μL, 78.0 μmol) and $LiBH_4$ (40.1 μL, 2.0 M in THF). After 30 min, the reaction was warmed up to r.t. After 30 min, the reaction was quenched with sat. aq. sodium tartarate (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 10-15% EtOAc / hexanes, to give **221** (22.0 mg, 92%) as a colorless oil: $[\alpha]_D^{23}$ –14.0° (c 0.30, $CHCl_3$); IR (thin film) 3400, 2958, 2910, 2876, 1456, 1376, 1237, 1160, 1050, 1028, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.35 (m, 5H), 4.66 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 11.4 mHz, 1H), 3.98 (dt, J = 6.0, 18.0 Hz, 1H), 3.77-3.85 (m, 3H), 3.46-3.51 (m, 1H), 3.09 (br, 1H), 2.59 (br, 1H), 1.99-2.03 (m, 1H), 1.55-1.62 (m, 1H), 1.43-1.54 (m, 1H), 1.18 (d, J = 6.0 Hz, 3H), 0.95 (t, J = 8.1 Hz, 9H), 0.88 (d, J = 6.9 Hz, 3H), 0.61 (q, J = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.9, 128.4, 128.3, 79.0, 75.7, 72.3, 67.2, 62.5, 43.7, 31.6, 23.6, 14.0, 7.3, 5.4, ;HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 383.2618, found 383.2624.



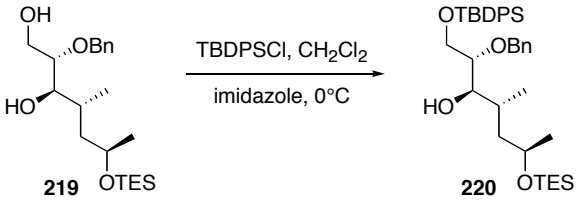
Alcohol **223**: To a solution of **215** (21 mg, 37 μmol) in THF (0.2 mL) at 0°C added MeOH (2.3 μL, 44 μmol), and $LiBH_4$ (22.2 μL, 44 μmol). After 2 h, the reaction was quenched with sat. aq. sodium tartarate (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*. Without further purification, the crude mixture with evans' auxiliary was applied directly to the next step.

To a solution of mixture from the previous step in CH_2Cl_2 (0.2 mL) at 0°C was sequentially added imidazole (3.1 mg, 44 μmol), DMAP (2.5 mg, 11 μmol) and TBDPSCl (14.3 μL, 44 μmol). After 20 min, the reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 2-4% EtOAc / hexanes, to give **223** (18 mg, 78% over 2 steps) as a colorless oil: $[\alpha]_D^{23}$ +20.0° (c 1.16, $CHCl_3$); IR (thin film) 3445, 3070, 2957, 2931, 2875, 1471, 1456, 1427, 1113, 1059, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.76 (m, 15H), 4.79 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 11.2 Hz, 1H), 3.84-3.94 (m, 3H), 3.61 (dd, J = 4.8, 10.0 Hz, 1H), 3.49-3.53 (m, 1H), 2.51 (d, J = 5.2 Hz, 1H), 1.68-1.75 (m, 1H), 1.54-1.59 (m, 1H), 1.43-1.48 (m, 1H), 1.15 (d, J = 6.0 Hz, 1H), 1.11 (s, 9H), 0.91-0.98 (m, 12H), 0.60 (q, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

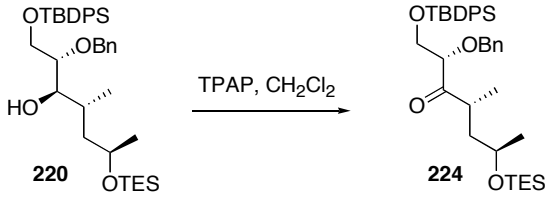
δ 138.7, 136.1, 135.6, 135.2, 133.7, 133.5, 130.2, 130.0, 128.8, 128.7, 128.25, 128.20, 80.9, 74.7, 73.5, 67.1, 64.6, 44.4, 32.8, 27.3, 24.0, 19.6, 14.9, 7.3, 5.4; HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 621.3795, found 621.3794.



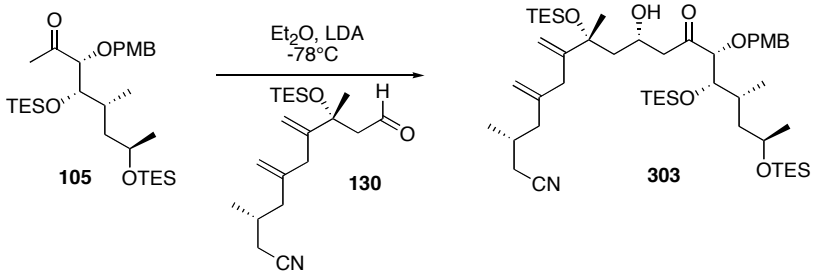
Ketone **224**: To a solution of **223** (4.0 mg, 6 μmol) in CH_2Cl_2 at r.t. was added TPAP (3.0 mg, 8 μmol). After 20 min, the reaction mixture was filtrated through a plug of silicon gel eluted with 20% EtOAc / Hexanes. The elute was concentrated *in vacuo* to give the ketone **224** (3.8 mg, 6 μmol) as a colorless oil: $[\alpha]_D^{23}$ –11.59° (c 0.88, $CHCl_3$); IR (thin film) 3445, 3070, 2957, 2931, 2875, 1471, 1456, 1427, 1113, 1059, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.71 (m, 15H), 4.72 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.09 (t, J = 4.0 Hz, 1H), 3.97-4.00 (m, 2H), 3.85 (dt, J = 6.0, 18.4 Hz, 1H), 3.17-3.22 (m, 1H), 1.87-1.92 (m, 1H), 1.42-1.47 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.8 Hz, 1H), 0.94 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 138.4, 136.10, 136.06, 134.8, 133.55, 133.48, 130.5, 130.4, 128.8, 128.1, 128.0, 85.44, 73.0, 67.3, 64.6, 42.4, 39.0, 27.1, 24.1, 19.6, 17.1, 7.3, 5.3; HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 619.3561, found 619.3593.



Alcohol **220**: To a solution of **219** (14 mg, 37 μmol) in CH_2Cl_2 (0.2 mL) at 0°C was sequentially added imidazole (3.1 mg, 44 μmol), DMAP (2.0 mg, 0.011 mmol) and TBDPSCl (14.4 μL, 44 μmol). After 20 min, the reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-4% EtOAc / hexanes, to give **220** (20 mg, 87%) as a colorless oil: $[\alpha]_D^{23}$ +9.3° (c 1.30, $CHCl_3$); IR (thin film) 3440, 3070, 2957, 2931, 2876, 1547, 1471, 1427, 1113, 1069, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.76 (m, 15H), 4.66 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 3.93-4.00 (m, 3H), 3.58-3.64 (m, 2H), 3.05 (d, J = 3.6 Hz, 1H), 1.78-1.85 (m, 1H), 1.63-1.70 (m, 1H), 1.47-1.52 (m, 1H), 1.13 (d, J = 5.6 Hz, 3H), 1.10 (s, 9H), 0.98 (t, J = 8.0 Hz, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.62 (q, J = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 136.1, 135.6, 135.2, 133.57, 133.53, 130.2, 130.1, 128.7, 128.20, 128.15, 127.9, 80.4, 77.2, 72.6, 67.7, 64.5, 42.2, 32.6, 27.3, 24.0, 19.6, 17.5, 7.3, 5.4; HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 621.3795, found 621.3794.

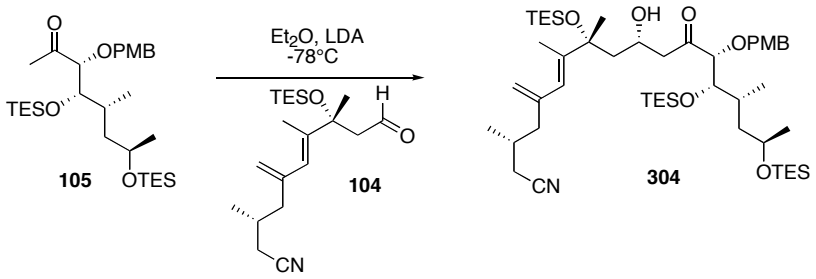


Ketone **224**: To a solution of **220** (5.2 mg, 8 μmol) in CH_2Cl_2 (0.2 mL) at r.t. was added TPAP (4.0 mg, 9 μmol). After 20 min, the reaction mixture was filtrated through a plug of silicon gel eluted with 20% EtOAc / Hexanes. The elute was concentrated *in vacuo* to give the ketone **224** (3.8 mg, 6 μmol) as a colorless oil: $[\alpha]_D^{23}$ –11.59° (c 0.88, $CHCl_3$); IR (thin film) 3445, 3070, 2957, 2931, 2875, 1471, 1456, 1427, 1113, 1059, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.71 (m, 15H), 4.72 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.09 (t, J = 4.0 Hz, 1H), 3.97-4.00 (m, 2H), 3.85 (dt, J = 6.0, 18.4 Hz, 1H), 3.17-3.22 (m, 1H), 1.87-1.92 (m, 1H), 1.42-1.47 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.8 Hz, 1H), 0.94 (t, J = 8.0 Hz, 9H), 0.56 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 138.4, 136.10, 136.06, 134.8, 133.55, 133.48, 130.5, 130.4, 128.8, 128.1, 128.0, 85.44, 73.0, 67.3, 64.6, 42.4, 39.0, 27.1, 24.1, 19.6, 17.1, 7.3, 5.3; HRMS (FAB+) calcd. for $C_{12}H_{26}O_2Si$ (M+) 619.3561, found 619.3593.



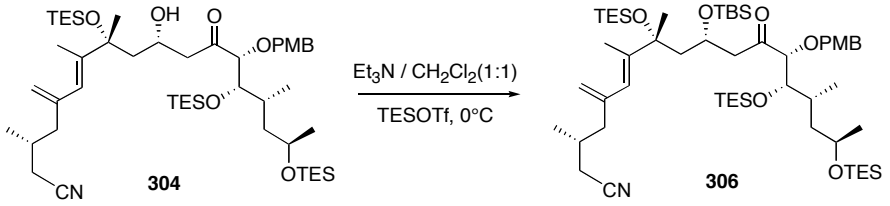
Alcohol **303**: To a solution of **105** (43 mg, 80 μmol) in Et_2O (0.40 mL) at –78°C was added LDA (90.2 μL, 1.0 M in THF). After 20 min, a pre-cooled (-78°C) solution of **130** (18.5, 53 μmol) in Et_2O (0.24 mL) was transferred in one portion *via* cannula at –78°C. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting carefully with 5% EtOAc / hexanes, to give **303** as a colorless oil (major isomer 18.0 mg, 20 μmol, 40%): $[\alpha]_D^{23}$ +25.0° (c 0.48°, $CHCl_3$); IR (neat) 3519, 2955, 2911, 2875, 1714, 1604, 1515, 1457, 1415, 1379, 1249, 1172, 1120, 1085, 1037, 1004, 906. 805, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.24 (s, 1H), 4.95 (s, 1H), 4.92 (s, 1H), 4.84 (s, 1H), 4.47 (d, J = 11.1 Hz, 1H), 4.28-4.36 (m, 2H), 3.90 (s, 3H), 3.73-3.80 (m, 3H), 3.49 (d, J = 1.5 Hz, 1H), 2.88 (dd, J = 7.5, 17.7 Hz, 1H), 2.70-2.82 (m, 2H), 1.99-2.46 (m, 6H), 1.81 (dd, J = 5.7, 14.4 Hz, 1H), 1.36-1.53 (m, 7H), 1.08 (d, J = 5.7 Hz, 3H), 1.06 (d, J = 5.7 Hz, 3H), 0.84-0.99 (m, 30H), 0.51-0.61 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 159.7, 152.0, 144.6, 130.0, 119.0, 116.0, 114.0, 111.9, 88.5, 78.9, 77.6, 72.8, 67.3, 65.1, 55.7, 48.7, 47.1, 45.1, 42.4, 38.2, 33.6, 28.9, 27.2,

24.3, 23.7, 19.9, 13.9, 7.6, 7.4, 7.3, 7.1, 5.7, 5.3; HRMS (ES+) calcd. for $C_{49}H_{89}O_7Si_3NNa$ (M+Na) 910.5845, found 910.5883.



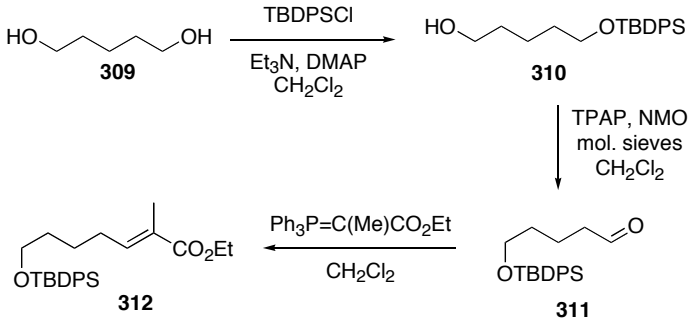
Alcohol **304**: To a solution of **105** (73 mg, 0.14 mmol) in Et_2O (0.7 mL) at –78°C was added LDA[84] (0.15 mL, 1.0 M in THF). After 20 min, a pre-cooled (-78°C) solution of **104** (31.5 mg, 0.09 mmol) in Et_2O (0.4 mL) was transferred in one portion *via* cannula at –78°C. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / hexanes, to give **304** (55 mg, 0.06 mmol, 69%) as a colorless oil: $[\alpha]_D^{23}$ +21.3° (c 0.60, $CHCl_3$); IR (neat) 3496, 2955, 2911, 2876, 1715, 1614, 1515, 1457, 1418, 1379, 1249, 1086, 1036, 1008, 903, 807, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 5.09 (s, 1H), 4.89 (s, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.33-4.36 (m, 2H), 3.80 (s, 3H), 3.76-3.80 (m, 3H), 3.61 (s, 1H), 2.95 (dd, *J* = 7.2, 18.0 Hz, 1H), 2.05-2.40 (m, 6H), 1.88-1.95 (m, 1H), 1.81 (s, 3H), 1.52 (s, 3H), 1.37-1.52 (m, 5H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.83-0.98 (m, 30H), 0.51-0.67 (m, 18H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 159.7, 144.8, 143.2, 130.1, 124.3, 118.9, 116.7, 114.1, 88.5, 79.7, 72.9, 67.3, 65.1, 55.7, 48.4, 47.2, 45.1, 44.9, 33.5, 29.6, 26.7, 24.3, 23.6, 19.8, 15.2, 13.9, 7.5, 7.4, 7.3, 7.0, 5.7, 5.4; HRMS (FAB+) calcd. for $C_{49}H_{90}O_7Si_3N$ (M+1) 888.6025, found 888.6052.



Silylether **306**: To a solution of **304** (55 mg, 60 μmol) in CH_2Cl_2 (0.15 mL) at r.t. was added Et_3N (0.15 mL). The solution was then cooled to –78°C. After 5 min, TESOTf (65.8 mg, 60.4 μL, 0.25 mmol) was added dropwise. After 5 min, the reaction was warmed to r.t. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3% EtOAc / Hexanes, to give **306** (53 mg, 53 μmol, 88%) as a colorless oil: $[\alpha]_D^{23}$ +35.1° (c 0.50, $CHCl_3$); IR (neat) 2954, 2928, 2876, 1714, 1615, 1515, 1458, 1381, 1250, 1167, 1125, 1065, 1006, 987, 835, 776, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.80 (s, 1H), 5.07 (s, 1H), 4.89 (s, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.21-4.25 (m, 2H), 3.81 (s, 3H), 3.64-3.81 (m, 3H), 3.17 (dd, *J* = 9.3, 18.0 Hz, 1H), 2.58 (dd, *J* = 2.7, 17.7 Hz, 1H), 2.38 (dd, *J* = 4.5, 16.8 Hz, 1H), 2.19 (dd, *J* = 6.9, 16.8 Hz, 1H), 2.05-2.10 (m,

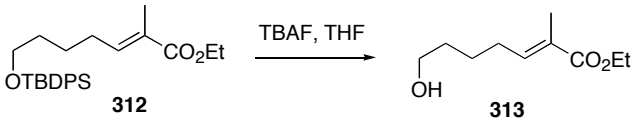
2H), 1.86-1.94 (m, 2H), 1.79 (s, 3H), 1.66-1.79 (m, 1H), 1.58-1.62 (m, 1H), 1.40 (s, 3H), 1.28-1.35 (m, 2H), 1.07 (d, J = 6.3 Hz, 3H), 1.05 (d, J = 5.4 Hz, 3H), 0.86-0.97 (m, 30H), 0.78 (s, 9H), 0.50-0.65 (m, 18H), 0.05 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 159.5, 143.6, 143.1, 130.3, 129.9, 124.9, 119.0, 116.6, 113.9, 89.1, 77.3, 72.3, 67.2, 66.1, 55.6, 49.7, 46.4, 45.5, 44.7, 33.7, 29.4, 29.0, 26.3, 24.3, 23.5, 19.7, 18.4, 15.4, 12.9, 7.7, 7.4, 7.3, 5.7, 5.3, -3.7, -4.2; HRMS (FAB+) calcd. for $C_{55}H_{104}O_7Si_4N$ (M+1) 1002.6890, found 1002.6923.



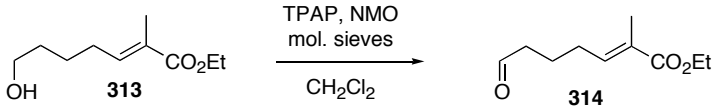
Ester 312: To a stirred solution of 1,5-pentanediol **309** (1.01 g, 1.02 mL, 9.70 mmol) in CH_2Cl_2 (25 mL) at r.t. was added sequentially Et_3N (356 mg, 0.45 mL, 3.52 mmol) and DMAP (13 mg, 0.11 mmol). After 5 min, TBDPSCl (880 mg, 0.84 mL, 3.20 mmol) was added dropwise over 5 min. After 12 h, the reaction was quenched with saturated aqueous NH_4Cl (30 mL), extracted with Et_2O (3 x 20 mL) and the dried ($MgSO_4$) extract was concentrated *in vacuo* to give alcohol **310** (783 mg, 2.30 mmol, 76%) as a clear oil.

To a stirred solution of alcohol **310** (422.6 mg, 1.23 mmol) and powdered 4 Å molecular sieves (approx. 1 g) in CH_2Cl_2 (5 mL) at r.t. was added sequentially TPAP (21.7 mg, 0.06 mmol) and NMO (216.8 mg, 1.85 mmol). After 1 h, the reaction was filtered through a small plug of silica gel, eluting with 20% EtOAc/hexane, to give **311** (310.3 mg, 0.91 mmol, 74%) as a clear oil.

To a stirred solution of aldehyde **311** (216 mg, 0.63 mmol) in CH_2Cl_2 (2 ml) at r.t. was added (carbethoxyethylidene)triphenylphosphorane (367 mg, 0.95 mmol). After 2.5 h, the reaction was concentrated *in vacuo* and purified by flash chromatography, eluting with 4%-10% EtOAc/hexane, to give **312** (223 mg, 0.53 mmol, 84%) as a clear oil: IR (neat) 3070, 2934, 2858, 1710, 1651, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 1.5, 5.9 Hz, 4H), 7.35-7.46 (m, 6H), 6.75 (dt, J = 1.2, 6.1 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.67 (t, J = 5.5 Hz, 2H), 2.16 (m, 2H), 1.81 (s, 3H), 1.54-1.57 (m, 4H), 1.12-1.30 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 142.4, 135.8, 134.2, 129.8, 128.1, 127.8, 63.7, 60.6, 32.4, 29.5, 27.1, 25.1, 19.4, 14.2, 12.6; HRMS (ES+) calcd. For $C_{26}H_{35}SiO_3$ (M-H) 423.2355, found 423.2348.

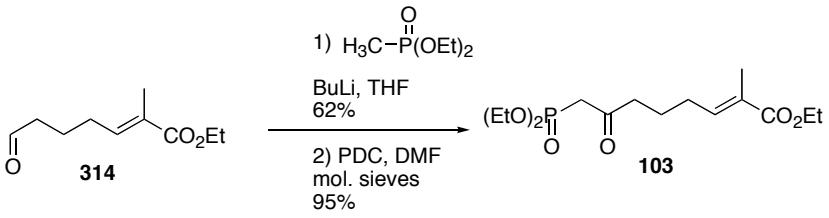


Alcohol **313**: To a stirred solution of ester **312** (208 mg, 0.50 mmol) in THF (5 ml) at 25°C was added TBAF (0.80 mL, 0.80 mmol, 1M in THF). After 2 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). After separation of the organic layer, the aqueous layer was extracted with ether (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by flash chromatography, eluting with 5%-40% EtOAc/hexane, to give **313** (63 mg, 0.33 mmol, 65%) as a clear oil: IR (neat) 3417, 2980, 2938, 2864, 1713, 1649, 1446, 1368, 1270, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67-6.81 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.65 (t, J = 6.0 Hz, 2H), 2.18-2.31 (m, 2H), 1.83 (s, 3H), 1.44-1.76 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 141.9, 128.2, 62.8, 60.6, 32.5, 29.8, 24.9, 14.5, 12.5; HRMS (ES+) calcd. For $C_{10}H_{19}O_3$ (M+H) 187.1134, found 187.1134.



Aldehyde **314**: To a sirred solution of alcohol **313** (448.8 mg, 2.44 mmol) and powdered 4 Å molecular sieves (~1g) in CH_2Cl_2 (10 mL) at r.t, was added sequentially TPAP (42.8 mg, 0.12 mmol) and NMO (428 mg, 3.60

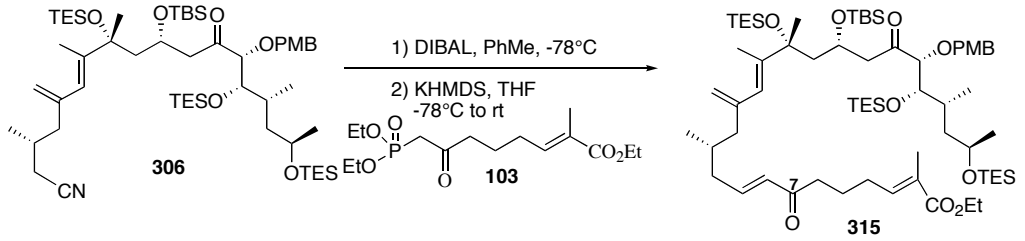
mmol). After 1 h, the reaction was filtered through a small plug of silica gel, eluting with 20% EtOAc/hexane, to give **314** (314.5 mg, 1.7 mmol, 72%) as a coloreless oil: IR (neat) 2980, 2938, 2905, 2869, 1714, 1651, 1456, 1258, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.70 (t, J = 6.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.47 (t, J = 6.2 Hz, 2H), 2.17 (s, 3H), 1.72-1.85 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 168.2, 140.6, 129.1, 60.7, 43.4, 27.9, 21.2, 14.5, 12.6; HRMS (ES+) calcd. For $C_{10}H_{17}O_3$ (M+H) 185.1178, found 185.1171.



Ketophosphonate **103**: To a solution of diethyl methanephosphonate (183 mg, 0.18 mL, 1.2 mmol) in THF (2.0 mL) at -78°C was added *n*-BuLi (0.44 mL, 1.10 mmol, 2.5 M in hexane). After 20 min, the above slurry solution was transferred into a pre-cooled (-78°C) solution of aldehyde **314** (180 g, 1.00 mmol) in THF (1.0 mL) at -78°C dropwise. The resulted solution was warmed up to r.t. within 2 h and quenched with sat. aq. NH_4Cl (20 mL). After separation of organic layer, the aqueous layer was extracted with ether (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified

by flash chromatography, eluting with 10% MeOH / CH_2Cl_2, to give a alcohol intermediate (242 mg, 0.72 mmol, 72%) as a colorless oil.

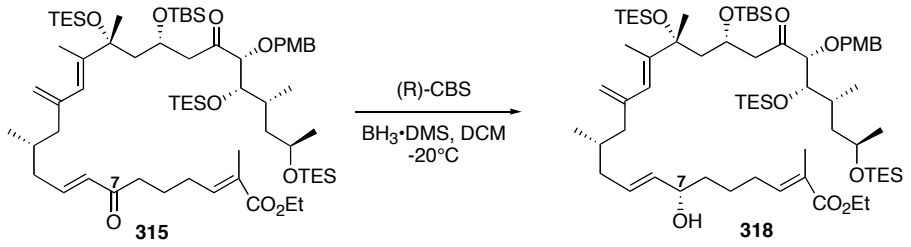
To a solution of the above alcohol intermediate (242 mg, 0.72 mmol) in CH_2Cl_2 (9.0 mL) at r.t. was added PDC (1.1 g, 2.88 mmol) and molecular sieves (~ 1 g). After 2 h, the reaction was quenched with sat. aq. NH_4Cl (20 mL). After separation of organic layer, the aqueous layer was was extracted with EtOAc (3 x 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by flash chromatography, eluting with 10% MeOH / CH_2Cl_2, to give the ketophosphonate **103** (185 mg, 0.55 mmol, 76%) as a colorless oil: IR (neat) 2982, 2930, 1710, 1651, 1445, 1392, 1367, 1258, 1024, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (dt, J = 0.9, 6.3 Hz, 1H), 4.08-4.21 (m, 6H), 3.10 (s, 1H), 3.03 (s, 1H), 2.65 (t, J = 7.2 Hz, 2H), 2.18 (q, J = 7.5 Hz, 2H), 1.81 (s, 3H), 1.68-1.78 (m, 2H), 1.24-1.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 168.5, 141.2, 129.1, 63.0, 62.9, 60.9, 43.7, 43.6, 42.1, 28.1, 22.7, 16.7, 16.6, 14.7, 12.8; HRMS (ES+) calcd. For $C_{15}H_{28}O_6P$ (M+H) 335.1624, found 335.1633.



Enone **315**: To a solution of **306** (15 mg, 15 μmol) in PhMe (0.3 mL) at –78°C was added DIBAL-H (22.5 μL, 23 μmol, 1.0 M in PhMe) dropwise. After 15 min, the reaction was quenched sequentially with MeOH (0.5 mL), sat. aq. tartaric acid (0.1 mL) and H_2O (2 mL). Next, the mixture was warmed to r.t. After 1 h, the mixture was extracted with Et_2O (3 X 10 mL) and the dried ($MgSO_4$) extract was concentrated *in vacuo* to give the unstable aldehyde as a colorless oil. The aldehyde was applied immediately to the next step without further purification.

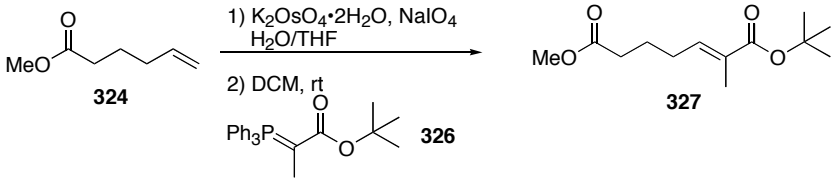
To a solution of **103** (20.0 mg, 0.06 mmol) in THF/H_2O (0.2 mL, 40:1) at r.t. was added $Ba(OH)_2 \bullet 8H_2O$ (21 mg, 0.06 mmol). After 20 min, a solution of the above aldehyde intermediate in THF (0.15 mL) was added dropwise *via* cannula. After 2 h, the reaction was quenched with sat. aq. NH_4Cl (2 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3% EtOAc / hexanes, to give **315** (11.0 mg, 0.009 mmol, 62%) as a colorless oil: $[\alpha]_D^{23}$ (+) 19.6° (c 0.25, $CDCl_3$); IR (neat) 2954, 2924, 2875, 2853, 1713, 1515, 1458, 1379, 1250, 1169, 1124, 1085, 1018, 986, 835, 776, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.90-6.94 (m,

1H), 6.88 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 6.4 Hz, 1H), 6.12 (d, J = 16.0 Hz, 2H), 5.86 (s, 1H), 5.03 (s, 1H), 4.87 (s, 1H), 4.54 (d, J = 10.4 Hz, 1H), 4.19-4.26 (m, 4H), 3.85 (s, 3H), 3.68-3.85 (m, 3H), 3.23 (dd, J = 9.2, 18.0 Hz, 1H), 2.59-2.66 (m, 3H), 2.28-2.38 (m, 1H), 2.21-2.25 (m, 2H), 1.91-2.11 (m, 4H), 1.85 (s, 3H), 1.82 (s, 3H), 1.71-1.82 (m, 4H), 1.64-1.69 (m, 1H), 1.43 (s, 3H), 1.25-1.35 (m, 7H), 1.09 (d, J = 4.0 Hz, 3H), 0.88-1.01 (m, 30H), 0.81 (s, 9H), 0.55-0.68 (m, 18H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 200.2, 168.6, 159.5, 146.9, 144.9, 142.2, 141.6, 132.1, 130.3, 129.9, 128.9, 125.6, 115.6, 113.9, 89.3, 77.3, 72.2, 67.2, 66.1, 60.9, 55.6, 49.8, 46.4, 46.1, 45.5, 40.2, 39.5, 33.6, 32.0, 31.5, 29.1, 28.5, 26.4, 23.5, 23.5, 23.0, 19.6, 18.4, 14.7, 14.5, 12.9, 12.8, 7.8, 7.4, 7.3, 7.2, 5.7, 5.3, -3.8, -4.1; HRMS (FAB+) calcd. for $C_{66}H_{120}O_{10}Si_4Na$ (M+Na) 1207.7959, found 1207.7982.



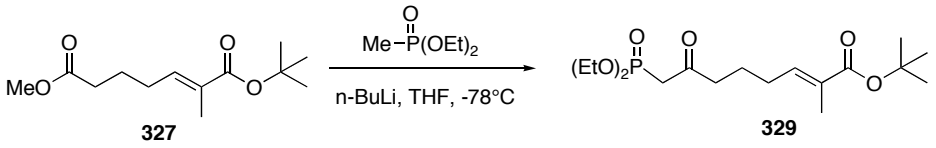
Allylic alcohol **318**: To a solution of (*R*)-2-Methyl-CBS-oxazaborolidine (7.2 μL, 7 μmol, 1.0 M in PhMe) in CH_2Cl_2 (0.1 mL) at r.t. was added a solution of BH_3•DMS (14.0 μL, 7 μmol, 0.5 M in CH_2Cl_2). After 5 min, this solution was cooled to -20°C. A solution of **315** (5.5 mg, 5 μmol) in CH_2Cl_2 (0.15 mL) was transferred into the previous solution *via* cannula at -

20°C. After 2 h, the reaction was quenched with MeOH (0.3 mL) at -20°C. After 10 min at r.t., the mixture was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / hexanes, to give **318** (4.5 mg, 0.0038 mmol) as a colorless oil: $[\alpha]_D^{23}$ (+) 27.3° (c 0.30, $CDCl_3$); IR (neat) 3482, 2954, 2924, 2875, 2853, 1712, 1515, 1458, 1379, 1250, 1169, 1125, 1064, 1017, 835, 776, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 6.4 Hz, 1H), 5.85 (s, 1H), 5.64-5.68 (m, 1H), 5.48-5.53 (m, 1H), 5.01 (s, 1H), 4.84 (s, 1H), 4.54 (d, J = 10.4 Hz, 1H), 4.19-4.26 (m, 4H), 4.09-4.10 (m, 1H), 3.85 (s, 3H), 3.68-3.85 (m, 3H), 3.22 (dd, J = 9.6, 18.0 Hz, 1H), 2.62 (dd, J = 2.8, 18.0 Hz, 1H), 2.21-2.24 (m, 3H), 2.06-2.18 (m, 4H), 1.90-1.94 (m, 2H), 1.86 (s, 3H), 1.82 (s, 3H), 1.53-1.76 (m, 7H), 1.43 (s, 3H), 1.25-1.35 (m, 10H), 1.12 (d, J = 6.0 Hz, 3H), 0.90-1.01 (m, 30H), 0.86 (d, J = 6.4 Hz, 3H), 0.81 (s, 9H), 0.55-0.68 (m, 18H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 168.7, 159.5, 145.4, 142.3, 141.9, 134.9, 130.9, 130.3, 130.0, 128.4, 125.9, 115.1, 113.9, 89.2, 73.3, 72.2, 67.3, 66.1, 60.8, 55.6, 50.0, 46.5, 45.8, 45.5, 39.9, 37.3, 33.6, 32.3, 31.8, 29.8, 28.9, 26.4, 25.0, 23.5, 23.5, 23.1, 19.6, 18.4, 15.4, 14.7, 14.5, 12.9, 12.8, 7.7, 7.5, 7.2, 5.7, 5.3, -3.8, -4.1; HRMS (ES+) calcd. for $C_{66}H_{123}O_{10}Si_4Na$ (M+Na) 1210.8091, found 1210.8195.



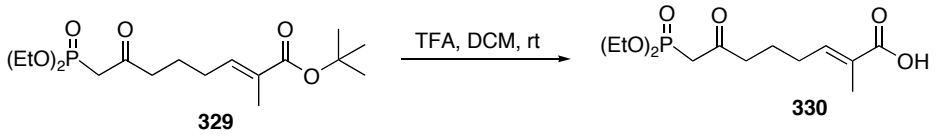
Ester **327**: To a solution of **324** (320 mg, 0.35 mL, 2.50 mmol) in THF/H_2O (35 mL, 1:1) at r.t. was added K_2OsO_4•H_2O (14 mg, 15 μmol) and $NaIO_4$ (2.4 g, 11.25 mmol). After 3 h, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL). After 20 min, the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give an aldehyde intermediate (247 mg, 1.90 mmol, 76%) as a colorless oil. The aldehyde intermediate was used directly in the next step without further purification.

To a solution of the above aldehyde intermediate (247 mg, 1.90 mmol) in CH_2Cl_2 (5.4 mL) at r.t. was added Wittig reagent **326** (725 mg, 2.0 mmol). After 30 min, the reaction was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / hexanes, to give **327** (377 mg, 1.56 mmol, 82%) as a colorless oil: IR (neat) 2977, 1739, 1704, 1652, 1456, 1436, 1367, 1289, 1252, 1159, 1121, 1083, 852, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (dt, J = 1.2, 7.5 Hz, 1H), 3.65 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 2.17 (q, J = 7.5 Hz, 2H), 1.71-1.83 (m, 5H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 167.8, 139.9, 130.5, 80.5, 51.9, 33.9, 28.5, 28.3, 24.2, 12.8; HRMS (FAB+) calcd. for $C_{12}H_{23}O_4$ (M+1) 243.1596, found 243.1598.

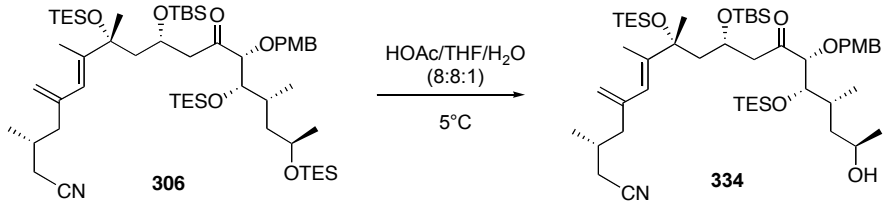


327 **329**

Ketophosphonate **329**: To a solution of methyl diethylphosphonate (318 mg, 0.3 mL, 2.09 mmol) in THF (10 mL) at –78°C was added *n*-BuLi (0.83 mL, 2.09 mmol, 2.5 M in hexane). After 20 min, this resulted solution was transferred dropwise into a solution of **327** (202 mg, 0.83 mmol) in THF (4 mL) at –78°C *via* cannula. After 30 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 80% EtOAc / Hexanes, to give **329** (254 mg, 0.65 mmol, 78%) as a colorless oil: IR (neat) 2978, 2932, 1701, 1652, 1392, 1366, 1254, 1162, 1024, 965, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (dt, J = 1.2, 7.5 Hz, 1H), 4.07-4.17 (m, 4H), 3.09 (s, 1H), 3.01 (s, 1H), 2.63 (t, J = 7.2 Hz, 2H), 2.13 (q, J = 7.5 Hz, 2H), 1.75 (s, 3H), 1.67-1.75 (m, 2H), 1.46 (s, 9H), 1.31 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 167.8, 140.2, 130.4, 80.5, 63.0, 43.7, 42.0, 28.5, 28.1, 22.7, 16.7, 12.8; HRMS (FAB+) calcd. for $C_{17}H_{32}O_6P$ (M+1) 363.1937, found 363.1942.

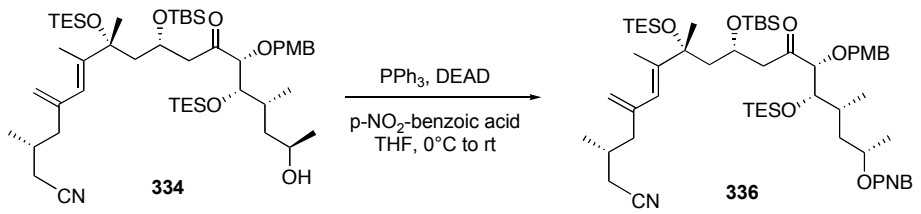


Carboxylic acid **330**: To a solution of **329** (102 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL) at 0°C was added TFA (1.15 g, 0.75 mL, 9.7 mmol). After 5 min, the reaction was warmed to r.t. After 2 h, the reaction was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 4% MeOH / CH_2Cl_2, to give **330** (84.8 mg, 0.28 mmol, 99%) as a colorless oil: IR (neat) 3418, 2986, 2934, 1772, 1715, 1395, 1209, 1163, 1023, 973, 799, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (t, J = 7.5 Hz, 1H), 6.07 (br, 1H), 4.12-4.23 (m, 4H), 3.18 (s, 1H), 3.10 (s, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.22 (q, J = 7.5 Hz, 2H), 1.82 (s, 3H), 1.71-1.80 (m, 2H), 1.30 (t, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.5, 143.5, 128.5, 63.2, 43.6, 41.9, 28.2, 22.5, 16.7, 12.5; HRMS (FAB+) calcd. for $C_{13}H_{24}O_6P$ (M+1) 307.1311, found 307.1322.



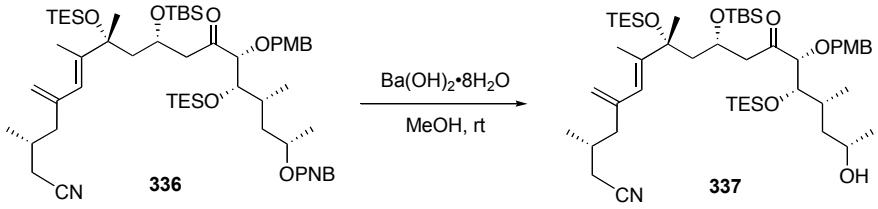
Alcohol **334**: To a flask with **306** (33 mg, 33 μmol) at 5°C was added a premixed solution of HOAc/THF/H_2O (0.8 mL, 8:8:1). After 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes,

to give **334** (27 mg, 32 μmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ (+) 20.4° (c 0.69, $CHCl_3$); IR (neat) 3514, 2955, 2930, 2876, 1712, 1613, 1515, 1459, 1381, 1250, 1166, 1129, 1065, 1024, 985, 940, 835, 776, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.86 (s, 1H), 5.11 (s, 1H), 4.91 (s, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.32 (d, J = 10.8 Hz, 1H), 4.18-4.22 (m, 1H), 3.85-3.91 (m, 2H), 3.84 (s, 3H), 3.71 (d, J = 7.6 Hz, 1H), 3.16 (dd, J = 9.2, 17.6 Hz, 1H), 2.69 (dd, J = 3.2, 17.6 Hz, 1H), 2.39 (dd, J = 4.8, 16.8 Hz, 1H), 2.28 (dd, J = 6.0, 16.8 Hz, 1H), 2.18 (dd, J = 7.2, 13.6 Hz, 1H), 2.10 (dd, J = 7.6 Hz, 13.6 Hz, 1H), 1.89-1.98 (m, 2H), 1.82 (s, 3H), 1.72-1.78 (m, 1H), 1.53-1.55 (m, 1H), 1.44-1.50 (m, 2H), 1.44 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.10 (d, J = 6.4 Hz, 3H), 0.93-1.03 (m, 18H), 0.81 (s, 9H), 0.52-0.69 (m, 12H), 0.09 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 159.6, 143.8, 142.8, 130.1, 125.0, 119.2, 116.4, 113.9, 88.3, 77.9, 74.7, 72.6, 66.2, 65.9, 55.6, 49.5, 47.1, 44.7, 43.9, 33.2, 29.3, 29.1, 26.3, 24.4, 24.2, 19.6, 18.3, 15.5, 14.8, 7.6, 7.4, 7.3, 7.0, 5.7, -3.6, -3.8; HRMS (ES+) calcd. for $C_{49}H_{89}NO_9Si_3Na$ (M+Na) 910.5845, found 910.5826.

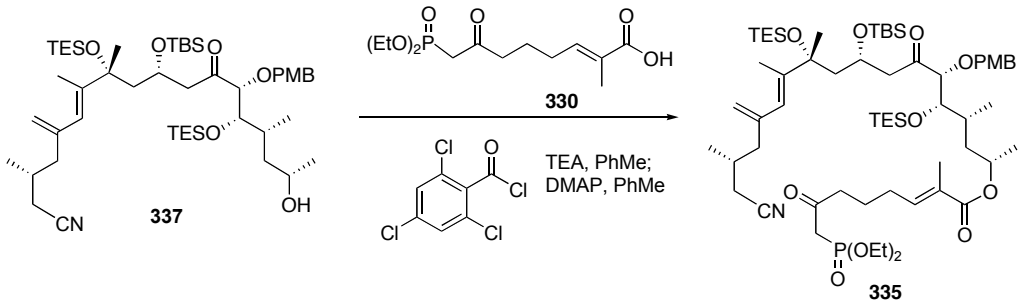


Ester **336**: To a solution of **334** (22 mg, 0.24 mmol), *p*-NO_2-benzoic acid (40 mg, 0.24 mmol) and PPh_3 (63 mg, 0.24 mmol) in THF (0.24 mL) at

0°C was added DEAD (105 mg, 0.11 mL, 0.24 mmol, 40% w/w in PhMe). After 10 min, the reaction was warmed to r.t. After 2 h, the reaction was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give **336** (14 mg, 14 μmol, 58%) as a colorless oil: $[\alpha]_D^{23}$ (+) 42.1° (c 0.56, $CHCl_3$); IR (neat) 2955, 2927, 2876, 2854, 1722, 1611, 1529, 1515, 1457, 1349, 1275, 1250, 1119, 1107, 1014, 835, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 12.0 Hz, 2H), 8.16 (d, J = 11.6 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.78 (s, 1H), 5.20-5.31 (m, 1H), 5.03 (s, 1H), 4.87 (s, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.26 (d, J = 10.8 Hz, 1H), 4.16-4.24 (m, 1H), 3.81-3.84 (m, 4H), 3.70 (d, J = 6.0 Hz, 1H), 3.14 (dd, J = 8.7, 17.4 Hz, 1H), 2.69 (dd, J = 3.0, 17.4 Hz, 1H), 2.34 (dd, J = 4.8, 15.9 Hz, 1H), 2.20 (dd, J = 6.6, 15.9 Hz, 1H), 1.84-2.03 (m, 4H), 1.77 (s, 3H), 1.59-1.75 (m, 4H), 1.39 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H), 0.86-0.97 (m, 18H), 0.77 (s, 9H), 0.50-0.64 (m, 12H), 0.02 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 164.7, 159.6, 150.8, 143.6, 143.3, 136.6, 131.0, 130.1, 129.9, 124.9, 123.9, 119.0, 116.5, 114.0, 87.6, 77.6, 76.4, 72.6, 71.4, 66.5, 55.6, 49.8, 47.4, 44.8, 40.1, 33.2, 29.4, 28.9, 26.3, 24.4, 21.4, 19.6, 18.3, 15.5, 14.5, 7.6, 7.4, 7.3, 5.6, -3.9, -4.2; HRMS (ES+) calcd. for $C_{56}H_{92}N_2O_{10}Si_3Na$ (M+Na) 1059.5958, found 1059.5999.

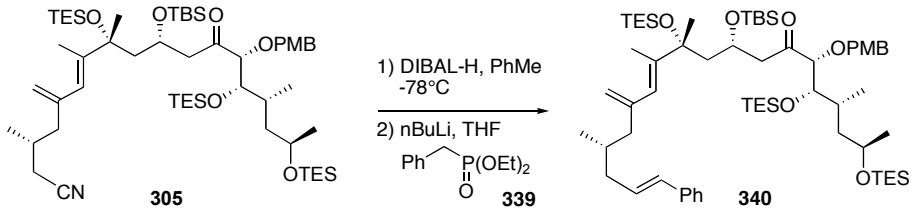


Alcohol **337**: To a flask with **336** (14 mg, 14 μmol) at r.t. was added a stock solution of $Ba(OH)_2 \bullet 8H_2O$ (0.6 mL, 0.1 M in MeOH). After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2% EtOAc / Hexanes, to give **337** (8.3 mg, 10 μmol, 71%) as a colorless oil: $[\alpha]_D^{23}$ (+) 35.4° (c 0.56, $CHCl_3$); IR (neat) 3519, 2955, 2929, 2876, 1715, 1700, 1615, 1515, 1457, 1381, 1250, 1168, 1100, 1065, 1025, 985, 835, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.83 (s, 1H), 5.06 (s, 1H), 4.85 (s, 1H), 4.57 (d, J = 10.5 Hz, 1H), 4.17-4.22 (m, 2H), 3.81 (s, 3H), 3.69-3.81 (m, 3H), 3.19 (dd, J = 9.6, 18.0 Hz, 1H), 2.65 (dd, J = 2.7, 18.0 Hz, 1H), 2.26-2.34 (m, 2H), 2.02-2.20 (m, 2H), 1.85-1.94 (m, 2H), 1.78 (s, 3H), 1.44-1.72 (m, 4H), 1.40 (s, 3H), 1.16 (d, J = 6.0 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 0.81-0.99 (m, 18H), 0.77 (s, 9H), 0.49-0.67 (m, 12H), 0.04 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 159.5, 144.1, 142.5, 130.3, 130.1, 125.2, 119.4, 116.2, 113.9, 89.2, 77.6, 72.2, 66.2, 65.7, 55.6, 49.3, 46.1, 44.6, 33.1, 29.2, 29.1, 26.3, 25.2, 24.5, 19.5, 18.3, 15.6, 13.2, 7.6, 7.4, 7.3, 5.6, -3.7, -4.3; HRMS (ES+) calcd. for $C_{49}H_{89}NO_9Si_3Na$ (M+Na) 910.5845, found 910.5828.



Ketophosphonate **335**: To a solution of **330** (16.30 mg, 53 μmol) in PhMe (0.15 mL) at r.t. was added triethylamine (5.36 mg, 7.5 μL, 53 μmol) and 2,4,6-trichlorobenzoyl chloride (12.50 mg, 8.0 μL, 53 μmol). After 6 h, a solution of **337** (8.0 mg, 10 μmol) in PhMe (0.15 mL) was transferred into the above flask *via* cannula and DMAP (6 mg, 53 μmol) was sequentially added. After 16 h, the reaction was purified by chromatography over silica gel, eluting with 70% EtOAc / hexanes, to give **335** (9.0 mg, 7.0 μmol, 75%) as a colorless oil: $[\alpha]_D^{23}$ (+) 25.0° (c 0.42, $CHCl_3$); IR (neat) 2954, 2928, 2875, 2855, 1715, 1701, 1652, 1515, 1457, 1382, 1251, 1164, 1124, 1024, 969, 835, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.66 (t, J = 6.0 Hz, 1H), 5.81 (s, 1H), 5.08 (s, 1H), 5.01-5.04 (m, 1H), 4.90 (s, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.15-4.27 (m, 6H), 3.81 (s, 3H), 3.78-3.81 (m, 1H), 3.66-3.68 (m, 1H), 3.16 (dd, J = 9.0, 17.7 Hz, 1H), 3.10 (s, 1H), 3.03 (s, 1H), 2.55-2.71 (m, 3H), 2.04-2.41 (m, 5H), 1.78 (s, 3H), 1.73 (s, 3H), 1.44-1.72 (m, 9H), 1.40 (s, 3H), 1.33 (t, J = 6.3 Hz, 6H), 1.17 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 0.83-0.97 (m, 12H), 0.79 (s, 9H), 0.50-0.64 (m, 6H),

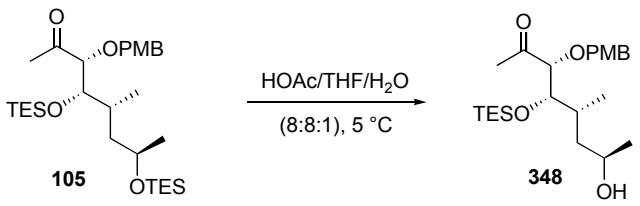
0.04 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 201.9, 168.0, 159.6, 143.6, 143.3, 141.0, 130.2, 130.0, 129.3, 124.9, 119.1, 116.5, 113.9, 87.8, 77.6, 72.5, 69.3, 66.5, 63.0, 63.0, 55.6, 49.9, 47.2, 44.8, 43.8, 42.0, 39.8, 33.4, 32.0, 29.4, 28.8, 28.1, 26.3, 24.4, 23.1, 22.7, 21.2, 19.7, 18.3, 16.8, 16.7, 15.4, 14.5, 12.9, 7.6, 7.4, 7.3, 5.6, -3.8, -4.1; HRMS (ES+) calcd. for $C_{62}H_{110}NO_{12}PSi_3Na$ (M+Na) 1198.6971, found 1198.6989.



Styrene **340**: To a solution of **305** (18.3 mg, 18 μmol) in PhMe (0.37 mL) at -78°C was added DIBAL-H (25.0 μL, 25 μmol, 1.0 M in PhMe). After 10 min, the reaction was quenched sequentially with MeOH (0.2 mL), sat. aq. tartaric acid (0.2 mL) and H_2O (2 mL) at -78°C. After 30 min at r.t., the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give the corresponding unstable aldehyde (18 μmol), which was used immediately to the next step without further purification.

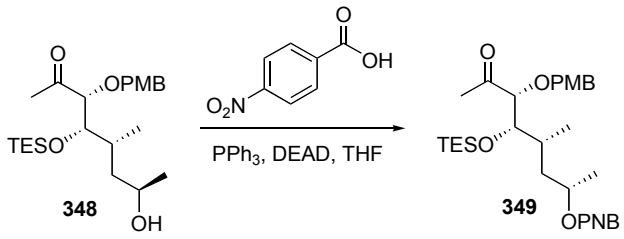
To a solution of phosphonate **339** (41.2 μL, 45 mg, 20 μmol) in THF (0.2 mL) at -78°C was added *n*-BuLi (72.0 μL, 0.18 mmol, 2.5 M in hexane). After 30 min, a pre-cooled (-78°C) solution of the above aldehyde (18 μmol) in THF (0.2 mL) was transferred into the reaction *via* cannula. The reaction was warmed to r.t. over a period of 3 h. After 20 h, the reaction was quenched with

sat. aq. NH_4Cl solution (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1% EtOAc / hexanes, to give **340** (5.6 mg, 5.4 μmol, 30% 2 steps) as a colorless oil: $[\alpha]_D^{23}$ (+) 28.8° (c 0.40, $CHCl_3$); IR (neat) 2954, 2927, 2875, 1714, 1615, 1515, 1458, 1413, 1380, 1302, 1250, 1169, 1124, 1065, 1017, 986, 835, 810, 776, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.38 (m, 7H), 6.85 (d, J = 8.4 Hz, 2H), 6.22-6.39 (m, 2H), 5.84 (s, 1H), 5.00 (s, 1H), 4.82 (s, 1H), 4.51 (d, J = 10.2 Hz, 1H), 4.20-4.26 (m, 2H), 3.83 (s, 3H), 3.67-3.83 (m, 3H), 3.19 (dd, J = 9.3, 17.7 Hz, 1H), 2.54 (dd, J = 3.3, 17.7 Hz, 1H), 1.88-2.29 (m, 4H), 1.87 (s, 3H), 1.55-1.77 (m, 4H), 1.40 (s, 3H), 1.24-1.29 (m, 2H), 1.06 (d, J = 5.7 Hz, 3H), 0.85-1.00 (m, 33H), 0.78 (s, 9H), 0.47-0.65 (m, 18H), 0.06 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 159.4, 145.5, 141.9, 138.4, 131.5, 130.3, 129.9, 128.8, 127.1, 126.4, 125.9, 115.1, 113.9, 89.3, 77.6, 72.2, 67.3, 66.0, 55.6, 50.0, 46.5, 45.9, 45.6, 40.8, 33.6, 32.2, 29.9, 26.4, 23.6, 19.7, 18.4, 15.4, 12.9, 7.7, 7.4, 7.3, 5.7, 5.2; HRMS (ES+) calcd. for $C_{62}H_{110}O_7Si_4Na$ (M+Na) 1101.7226, found 1101.7145.



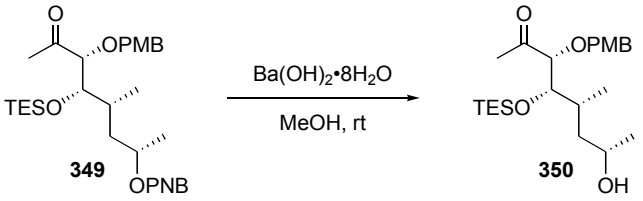
Alcohol **348**: To a flask containing **105** (120 mg, 0.22 mmol) at 0°C was added a premixed solution of HOAc/THF/H_2O (4.0 mL, 8:8:1) dropwise. After

10 min, the solution was allowed to warm to 5°C. After 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) dropwise. Next, the mixture was extracted with Et_2O (3 X 10 mL) and the dried ($MgSO_4$) extract was concentrated *in vacuo* to give product **348** (90 mg, 0.21 mmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ (+) 17.7° (c 0.34, $CHCl_3$); IR (thin film) 3413, 2958, 2910, 2875, 1712, 1613, 1514, 1457, 1354, 1302, 1249, 1172, 1076, 1055, 1009, 820, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.43 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.81-3.91 (m, 2H), 3.80 (s, 3H), 3.74 (d, J = 6.3 Hz, 1H), 2.40 (br, 1H), 2.14 (s, 3H), 1.49-1.65 (m, 2H), 1.32-1.40 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 0.85-0.99 (m, 12H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.8, 159.8, 130.2, 129.7, 114.2, 88.4, 75.3, 72.9, 66.2, 55.7, 43.5, 33.5, 27.5, 24.2, 15.1, 7.4, 5.6; HRMS (FAB+) calcd. for $C_{23}H_{41}O_5Si$ (M+1) 425.2723, found 425.2730.



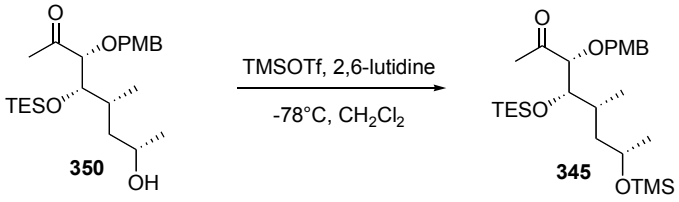
Ester **349**: To a solution of **348** (237 mg, 0.56 mmol), *p*-NO_2-benzonic acid (374 mg, 2.24 mmmol) and PPh_3 (587 mg, 2.24 mmol) in THF (3.7 mL) at 0 °C was added DEAD (1.0 mL, 1.04 g, 2.24 mmol, 40% w/w in PhMe) dropwise. After 10 min, the reaction was warmed to r.t. After 2 h, the reaction

was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-15% EtOAc / Hexanes, to give **349** (46 mg, 0.084mmol, 80%) as a colorless oil: $[\alpha]_D^{23}$ (+) 38.1° (c 0.48, $CHCl_3$); IR (thin film) 2954, 2875, 1719, 1610, 1528, 1514, 1457, 1349, 1275, 1102, 1036, 1013, 823, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.24-5.29 (m, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 3.80-3.83 (m, 3H), 2.16 (s, 3H), 2.01-2.08 (m, 1H), 1.67-1.69 (m, 1H), 1.55-1.61 (m, 1H), 1.39 (d, J = 6.0 Hz, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.3, 164.8, 159.9, 150.8, 136.5, 131.0, 130.3, 129.6, 123.9, 114.2, 87.6, 77.4, 73.1, 71.3, 55.7, 39.9, 33.7, 28.0, 21.4, 14.7, 7.4, 5.5.



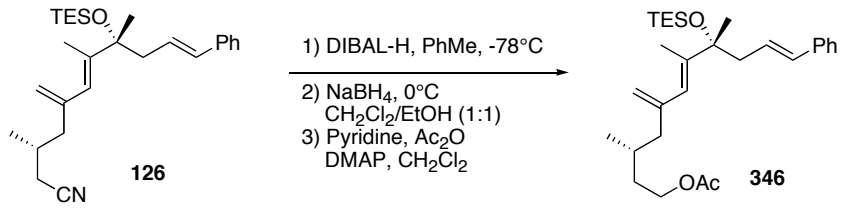
Alcohol **350**: To a solution of **349** (125 mg, 0.23 mmol) in MeOH (4.7 mL) was added $Ba(OH)_2.8H_2O$ (36.1 mg, 0.12 mmol). After 1 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-15% EtOAc / Hexanes, to give **350** (63 mg, 0.15 mmol, 65%) as a colorless oil: $[\alpha]_D^{23}$ (+)

38.4° (c 1.87, $CHCl_3$); IR (thin film) 3439, 2958, 2933, 2875, 1713, 1613, 1514, 1458, 1376, 1302, 1249, 1079, 1035, 820, 786, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.44 (d, J = 11.4 Hz, 1H), 4.38 (d, J= 11.4 Hz, 1H), 3.75-3.80 (m, 6H), 2.14 (s, 3H), 1.70 (br, 1H), 1.50-1.59 (m, 1H), 1.27-1.35 (m, 2H), 1.16 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 7.8 Hz, 9H), 0.85 (d, J = 6.9 Hz, 3H), 0.58 (q, J = 6.9 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.5, 159.8, 130.2, 129.7, 114.2, 88.3, 73.0, 66.4, 55.7, 43.9, 33.8, 27.7, 24.9, 14.7, 7.4, 5.6; HRMS (FAB+) calcd. for $C_{23}H_{40}O_5SiNa$ (M+Na) 447.2543, found 447.2561.



Methyl ketone **345**: To a solution of **350** (77 mg, 0.18 mmol) in CH_2Cl_2 (0.9 mL) at –78°C was added 2,6-lutidine (78 mg, 84.8 μL, 0.73 mmol) and TMSOTf (80 mg, 65.2 μL, 0.36 mmol). After 20 min, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give product **345** (80 mg, 0.16 mmol, 90%) as a colorless oil: $[\alpha]_D^{23}$ (+) 31.8° (c 2.80, $CHCl_3$); IR (thin film) 2955, 2911, 2876, 1715, 1613, 1514, 1458, 1414, 1372, 1352, 1249, 1124, 1088, 1038, 1006, 820, 787, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.42 (d, J = 11.4 Hz, 1H),

4.36 (d, J = 11.4 Hz, 1H), 3.74-3.85 (m, 5H), 3.68 (d, J = 6.9 Hz, 1H), 2.09 (s, 3H), 1.55-1.61 (m, 1H), 1.41-1.50 (m, 1H), 1.25-1.35 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 7.8 Hz, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.58 (q, J = 7.8 Hz, 6H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 159.7, 130.2, 129.7, 114.1, 89.3, 73.1, 66.2, 55.6, 45.2, 32.4, 26.9, 25.3, 12.9, 7.4, 5.7, 0.7; HRMS (ES+) calcd. for $C_{26}H_{48}O_5NaSi_2$ (M+Na) 519.2938, found 519.2914.

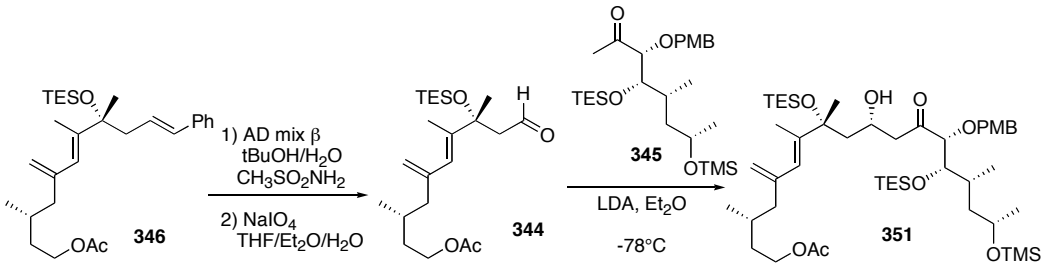


Acetate **346**: To a solution of **126** (45 mg, 0.11 mmol) in PhMe (0.53 mL) at -78°C was added DIBAL-H (0.15 mL, 0.15 mmol, 1.0 M in PhMe). After 10 min, the reaction was quenched sequentially with MeOH (0.2 mL), sat. aq. tartaric acid (0.2 mL) and H_2O (2.0 mL). After stirring 12 h at r.t., the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give the corresponding crude aldehyde (0.11 mmol).

To a mixed solution of the above aldehyde (0.11 mmol) in CH_2Cl_2 (0.5 mL) and EtOH (0.5 mL) at 0°C was added $NaBH_4$ (8.4 mg, 0.22 mmol). After 15 min, the reaction was quenched with a brine solution (5 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 6% EtOAc /

Hexanes, to give corresponding alcohol intermediate (38 mg, 0.09 mmol, 85%) as a colorless oil.

To a solution of the above alcohol intermediate (29 mg, 0.07 mmol) in CH_2Cl_2 at 0°C was added sequentially with pyridine (21.4 mg, 22.1 μL, 0.27 mmol), DMAP (8.3 mg, 0.07 mmol) and Ac_2O (13.9 mg, 12.8 μL, 0.14 mmol). After 15 min, the reaction was quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give product **346** (31 mg, 64 μmol, 94%) as a colorless oil: $[\alpha]_D^{23}$ (-) 39.3° (c 0.40, $CHCl_3$); IR (thin film) 3026, 2955, 2913, 2875, 1741, 1496, 1457, 1367, 1236, 1158, 1121, 1053, 1016, 966, 898, 793, 741, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15–7.28 (m, 5H), 6.32 (d, J = 15.9 Hz, 1H), 6.07-6.17 (m, 1H), 5.85 (s, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 3.98-4.07 (m, 2H), 2.41-2.52 (m, 2H), 2.10 (dd, J = 5.7, 13.5 Hz, 1H), 2.00 (s, 3H), 1.85 (dd, J = 7.8, 13.2 Hz, 1H), 1.79 (s, 3H), 1.58-1.67 (m, 2H), 1.43 (s, 3H), 1.28-1.36 (m, 1H), 0.97 (t, J = 7.5 Hz, 9H), 0.75(d, J = 6.6 Hz, 3H), 0.61 (q, J = 7.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 145.3, 143.0, 138.3, 132.0, 128.9, 127.4, 127.3, 126.3, 125.3, 114.9, 78.7, 63.3, 46.4, 46.2, 35.6, 29.0, 27.4, 21.4, 19.6, 15.0, 7.6, 7.2; HRMS (FAB+) calcd. for $C_{29}H_{46}O_3SiNa$ (M+Na) 493.3114, found 493.3130.

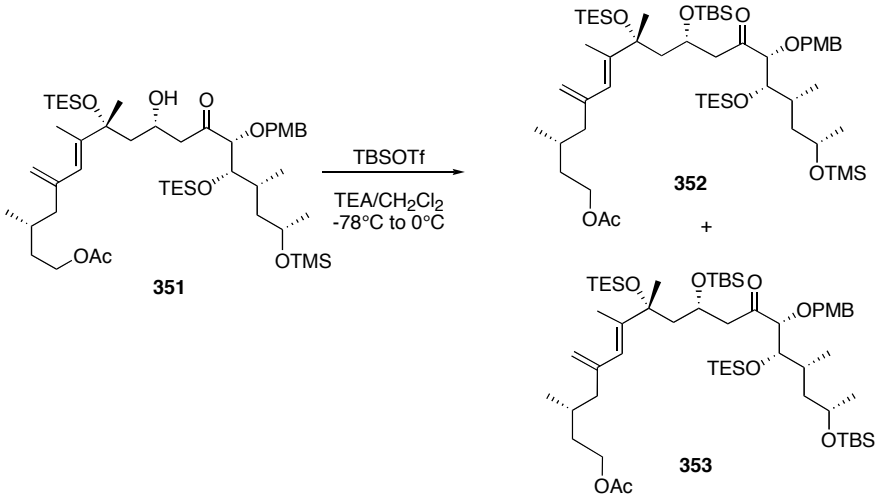


Alcohol **351**: To a solution of **346** (31 mg, 66 μmol) in *t*-BuOH (0.55 mL) and H_2O (0.55 mL) at r.t. was added AD mix β*[48] (92 mg) and $CH_3SO_2NH_2$ (9.5 mg, 0.10 mmol). After 16 h, the reaction was quenched with 10% aq. $Na_2S_2O_3$ (2 mL). After 30 min, the mixture was extracted with EtOAc (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% EtOAc / Hexanes, to give the corresponding diol (29 mg, 58 μmol, 88%, 6:1 d.r.).

To a solution of the above diol (26 mg, 52 μmol) in THF/ Et_2O/ H_2O (1.7 mL, 1:1:1) at r.t. was added $NaIO_4$ (110 mg, 0.52 mmol). After 2 h, the reaction was quenched with a brine solution (2 mL) and extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give the aldehyde **344** (20.4 mg, 52 μmol, 99%) as a colorless oil. The aldehyde **344** was applied to the next step without further purification.

To a solution of **345** (38 mg, 76 μmol) in Et_2O (0.4 mL) at –78°C was added LDA (85.0 μL, 1.0 M in THF). After 20 min, a pre-cooled (-78°C) solution of **344** (20 mg, 50 μmol) in Et_2O (0.25 mL) was transferred in one portion *via* cannula at –78°C. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and extracted with Et_2O (3 X 10 mL). The dried

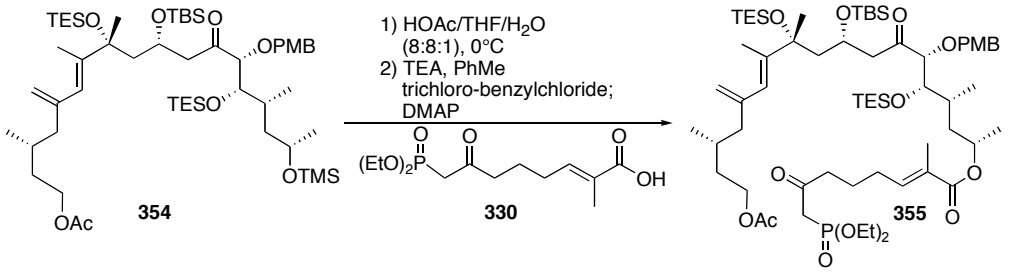
($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give **351** (28 mg, 31 μmol, 62%) as a colorless oil: $[\alpha]_D^{23}$ (+) 15.7° (c 1.55, $CHCl_3$); IR (neat) 3515, 2955, 2912, 2876, 1741, 1717, 1615, 1515, 1417, 1368, 1247, 1117, 1037, 1008, 899, 806, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.87 (s, 1H), 5.01 (s, 1H), 4.83 (s, 1H), 4.50 (d, J = 11.1 Hz, 1H), 4.34-4.51 (m, 1H), 4.33 (d, J = 11.1 Hz, 1H), 4.04-4.14 (m, 2H), 3.80 (s, 3H), 3.71-3.78 (m, 3H), 3.03 (dd, J = 7.5, 17.4 Hz, 1H), 2.29 (dd, J = 4.5, 17.4 Hz, 1H), 2.12 (dd, J = 5.7, 8.7 Hz, 1H), 2.03 (s, 3H), 1.83-1.96 (m, 2H), 1.82 (s, 3H), 1.59-1.73 (m, 3H), 1.52 (s, 3H), 1.42-1.49 (m, 4H), 1.11 (d, J = 6.0 Hz, 3H), 0.86-0.98 (m, 21H), 0.82 (d, J = 6.6 Hz, 3H), 0.51-0.67 (m, 12H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 171.6, 159.6, 144.6, 143.8, 130.3, 130.1, 125.2, 115.6, 114.0, 88.4, 79.8, 77.6, 72.8, 66.2, 65.1, 63.3, 55.6, 48.5, 46.7, 46.2, 44.8, 35.7, 32.5, 29.1, 26.5, 25.2, 21.4, 19.7, 15.1, 13.3, 7.5, 7.4, 7.0, 5.7, 0.7; HRMS (ES+) calcd. for $C_{48}H_{88}O_9Si_3Na$ (M+Na) 915.5634, found 915.5564.



Acetate **352** and **353**: To a solution of **351** (21 mg, 24 μmol) in CH_2Cl_2 (0.10 mL) and Et_3N (0.10 mL,) at –78°C was added TBSOTf (32.0 mg, 28.4 μL, 0.12 mmol). After 5 min, the reaction was warmed to 0°C. After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3% EtOAc / Hexanes, to give **352** (15 mg, 15 μmol, 61%) and **353** (9.1 mg, 9.0 μmol, 38%). For **352**: $[\alpha]_D^{23}$ (+) 30.3° (c 1.08, $CHCl_3$); IR (neat) 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.82 (s, 1H), 5.02 (s, 1H), 4.85 (s, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.24-4.30 (m, 2H), 4.04-4.16 (m, 2H), 3.83 (s, 3H), 3.81-3.83 (m, 1H), 3.67-3.78 (m, 2H), 3.19 (dd, J = 9.0, 17.7 Hz, 1H), 2.54 (dd, J = 3.3, 17.7 Hz, 1H), 2.08-2.10 (m, 1H), 2.05 (s, 3H), 1.86-1.97 (m, 2H), 1.82 (s, 3H), 1.62-1.75 (m, 4H), 1.50-1.54 (m, 1H), 1.43 (s, 3H), 1.30-1.38 (m, 2H), 1.12 (d, J =

5.7 Hz, 3H), 0.83-0.98 (m, 24H), 0.80 (s, 9H), 0.52-0.64 (m, 12H), 0.09 (s, 12H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 171.6, 159.5, 144.9, 142.9, 130.4, 130.0, 125.6, 115.4, 113.9, 88.5, 77.6, 72.4, 66.3, 66.2, 63.4, 55.6, 50.4, 46.9, 46.3, 44.2, 35.7, 32.8, 29.1, 28.5, 26.4, 26.3, 25.1, 21.4, 19.7, 18.4, 15.3, 13.9, 7.7, 7.4, 7.2, 5.7, 0.8, -3.8, -4.2; HRMS (ES+) calcd. for $C_{54}H_{102}O_9Si_4Na$ (M+Na) 1029.6499, found 1029.6522.

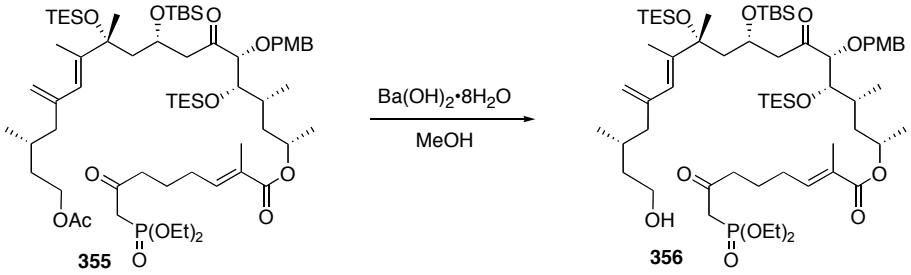
353: $[\alpha]_D^{23}$ (+) 29.3° (c 0.85, $CHCl_3$); IR (neat) 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.83 (s, 1H), 5.04 (s, 1H), 4.88 (s, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.25-4.30 (m, 2H), 4.01-4.17 (m, 2H), 3.83-3.85 (m, 1H), 3.84 (s, 3H), 3.77 (d, J = 4.0 Hz, 1H), 3.70 (d, J = 6.8 Hz, 1H), 3.22 (dd, J = 8.8, 17.6 Hz, 1H), 2.55 (dd, J = 3.2, 17.6 Hz, 1H), 2.12 (dd, J = 6.0, 13.6 Hz, 1H), 2.06 (s, 3H), 1.87-1.98 (m, 2H), 1.84 (s, 3H), 1.64-1.76 (m, 4H), 1.51-1.55 (m, 1H), 1.45 (s, 3H), 1.31-1.39 (m, 2H), 1.12 (d, J = 6.0 Hz, 3H), 0.83-0.98 (m, 33H), 0.80 (s, 9H), 0.52-0.64 (m, 12H), 0.11 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 171.2, 159.1, 144.5, 142.5, 130.0, 129.6, 125.2, 115.0, 113.5, 88.1, 77.4, 76.5, 72.0, 66.1, 65.9, 63.0, 55.3, 50.0, 46.3, 45.9, 43.7, 35.3, 32.3, 29.7, 28.7, 28.1, 26.0, 25.9, 25.7, 24.5, 21.0, 19.3, 18.0, 14.9, 13.5, 7.3, 7.1, 6.8, 5.3, -4.2, -4.6, -4.7; HRMS (ES+) calcd. for $C_{57}H_{108}O_9Si_4Na$ (M+Na) 1071.6968, found 1071.6954.



Ketophosphonate **355**: To a flask with **354** (32 mg, 32 μmol) at 0°C was added a premixed solution of HOAc/THF/H_2O (0.8 mL, 8:8:1). After 2 h, the reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give selectively desilylated alcohol (16 mg, 18 μmol, 55%) as a coloreless oil.

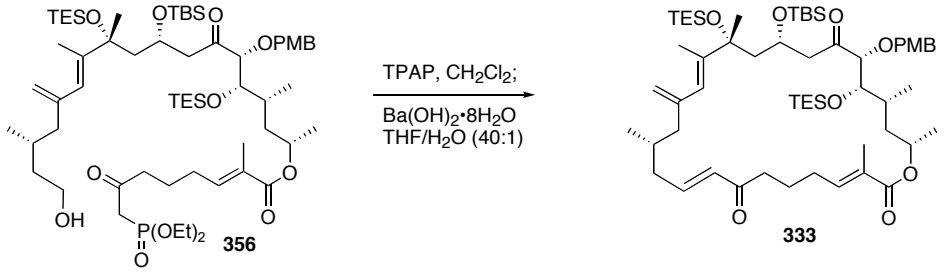
To a solution of **330** (16.3 mg, 53 μmol) in PhMe (0.15 mL) at r.t. was added triethylamine (5.4 mg, 7.3 μL, 53 μmol) and 2,4,6-trichlorobenzoyl chloride (12.5 mg, 8.0 μL, 53 μmol). After 6 h, solvent of the reaction was removed *in vacuo*. A solution of the above alcohol (16 mg, 18 μmol) in PhMe (0.15 mL) was transferred into the above flask *via* cannula and DMAP (6 mg, 53 μmol) was sequentially added. After 16 h, the reaction was purified by chromatography over silica gel, eluting with 70% EtOAc / Hexanes, to give **355** (17 mg, 14 μmol, 77%) as a colorless oil: $[\alpha]_D^{23}$ (+) 26.6° (c 0.87, $CHCl_3$); IR (neat) 2954, 2933, 2876, 1739, 1712, 1613, 1515, 1461, 1366, 1251, 1165, 1124, 1026, 968, 901, 835, 770, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 5.84 (s,

1H), 5.03 (br, 2H), 4.87 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.25-4.30 (m, 2H), 4.05-4.21 (m, 6H), 3.84 (s, 3H), 3.81-3.83 (m, 1H), 3.71 (d, J = 6.0 Hz, 1H), 3.19 (dd, J = 8.8, 17.6 Hz, 1H), 3.13 (s, 1H), 3.07 (s, 1H), 2.68 (t, J = 7.2 Hz, 2H), 2.60 (d, J = 2.8 Hz, 1H), 2.18 (q, J = 7.2 Hz, 2H), 2.08-2.12 (m, 1H), 2.06 (s, 3H), 1.83-1.94 (m, 4H), 1.83 (s, 3H), 1.81 (s, 3H), 1.61-1.77 (m, 5H), 1.52-1.55 (m, 1H), 1.43 (s, 3H), 1.40-1.43 (m, 1H), 1.36 (t, J = 6.8 Hz, 6H), 1.22 (d, J = 6.0 Hz, 3H), 0.85-1.00 (m, 24H), 0.83 (s, 9H), 0.52-0.66 (m, 12H), 0.12 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 201.9, 171.6, 168.0, 159.6, 144.9, 142.5, 141.0, 130.3, 130.1, 130.0, 129.4, 125.7, 115.4, 114.0, 87.9, 76.4, 72.4, 69.3, 66.3, 63.5, 63.0, 63.0, 55.7, 50.3, 47.3, 46.3, 43.8, 43.5, 42.2, 39.6, 35.7, 33.4, 29.1, 28.7, 28.1, 26.5, 26.4, 22.7, 21.4, 21.2, 19.7, 16.8, 16.7, 15.3, 14.6, 12.9, 7.7, 7.4, 7.3, 7.2, 5.6, -3.9, -4.1 ; HRMS (ES+) calcd. for $C_{64}H_{115}O_{14}PSi_3Na$ (M+Na) 1245.7230, found 1245.7180.



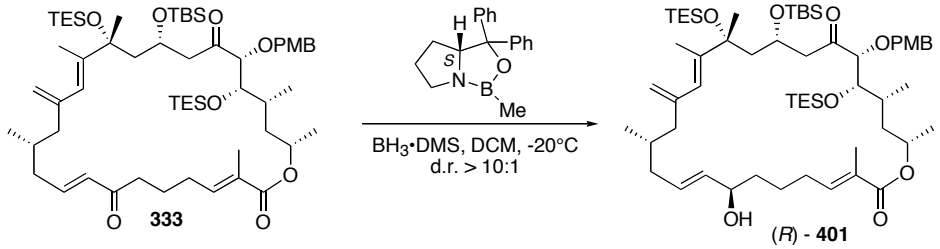
Alcohol **356**: To a flask containing **355** (17 mg, 14 μmol) at r.t. was added a premixed solution of $Ba(OH)_2$•$8H_2O$ (0.4 mL, 0.1 M in MeOH). After 10 min, the mixture was loaded directly on silica gel, eluting with 50% EtOAc / Hexanes, to give **356** (13 mg, 11 μmol, 79%) as a colorless oil: $[\alpha]_D^{23}$ (+) 18.87° (c 0.71, $CHCl_3$); IR (neat) 3444, 2954, 2929, 2876, 1713, 1614, 1515,

1458, 1379, 1251, 1165, 1125, 1059, 1024, 970, 900, 835, 809, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.66 (t, J = 7.5 Hz, 1H), 5.81 (s, 1H), 4.99-5.04 (m, 1H), 4.99 (s, 1H), 4.81 (s, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.09-4.25 (m, 7H), 3.81 (s, 3H), 3.66-3.80 (m, 3H), 3.19 (dd, J = 9.3, 17.4 Hz, 1H), 3.10 (s, 1H), 3.03 (s, 1H), 2.59-2.67 (m, 3H), 2.02-2.18 (m, 3H), 1.51-1.89 (m, 16H), 1.40 (s, 3H), 1.28-1.35 (m, 7H), 1.19 (d, J = 6.3 Hz, 3H), 0.84-0.97 (m, 24H), 0.78 (s, 9H), 0.49-0.64 (m, 12H), 0.05 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 201.9, 168.1, 159.5, 145.4, 142.0, 141.1, 130.3, 130.0, 129.3, 126.1, 115.3, 113.9, 88.0, 77.6, 72.5, 69.3, 66.5, 63.0, 62.9, 61.3, 55.6, 49.8, 47.0, 46.6, 43.8, 42.0, 40.5, 39.8, 33.3, 28.9, 28.6, 28.1, 26.3, 23.1, 22.7, 21.2, 19.5, 18.3, 16.8, 16.7, 15.5, 14.3, 12.9, 7.7, 7.4, 7.3, 5.6, -3.9, -4.3 ; HRMS (ES+) calcd. for $C_{62}H_{113}O_{13}PSi_3Na$ (M+Na) 1203.7124, found 1203.7158.



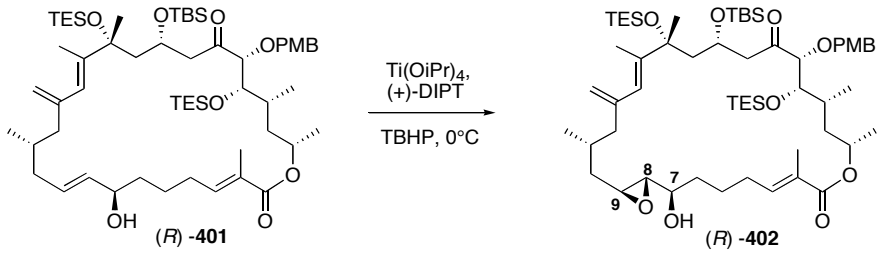
Macrolactone **333**: To a solution of **356** (10 mg, 8.5 μmol) in CH_2Cl_2 at r.t. was added TPAP (3.6 mg, 10 μmol). After 15 min, the reaction was diluted with THF (0.5 mL) and H_2O (13.0 μL), followed by addition of $Ba(OH)_2•8H_2O$ (0.66 mg, 21 μmol). After 3 h, the reaction was directly purified by

chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give **333** (8.0 mg, 8.0 μmol, 93%) as a colorless oil: $[\alpha]_D^{23}$ (+) 1.4° (c 0.21, $CHCl_3$); IR (neat) 2954, 2925, 2875, 2854, 1710, 1673, 1614, 1515, 1461, 1377, 1251, 1171, 1251, 1171, 1120, 1068, 1018, 985, 835, 808, 742 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.28 (m, 2H), 6.90-7.01 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.67 (t, J = 7.5 Hz, 1H), 6.05 (d, J = 15.9 Hz, 1H), 5.74 (s, 1H), 5.01 (s, 1H), 4.86-5.01 (m, 1H), 4.83 (s, 1H), 4.51 (d, J = 10.8 Hz, 1H), 4.18-4.22 (m, 2H), 3.81 (s, 3H), 3.67-3.74 (m, 2H), 3.11 (dd, J = 9.3, 18.3 Hz, 1H), 2.51-2.72 (m, 3H), 2.05-2.26 (m, 3H), 1.80 (s, 3H), 1.75 (s, 3H), 1.47-1.75 (m, 10H), 1.40 (s, 3H), 1.18-1.28 (m, 5H), 0.82-0.97 (m, 24H), 0.78 (s, 9H), 0.52-0.63 (m, 12H), 0.03 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 200.9, 167.6, 159.2, 147.1, 144.5, 142.6, 140.8, 132.3, 130.0, 129.4, 128.4, 125.4, 115.4, 113.6, 87.6, 76.9, 71.7, 68.8, 65.9, 65.3, 55.3, 49.0, 47.5, 46.0, 41.9, 41.7, 37.4, 31.4, 31.3, 28.1, 27.4, 25.9, 22.9, 21.0, 19.4, 17.9, 15.3, 12.7, 12.5, 7.3, 7.0, 6.9, 5.2, -4.2, -4.7; HRMS (ES+) calcd. for $C_{58}H_{100}O_9Si_3Na$ (M+Na) 1047.6573, found 1047.6541.



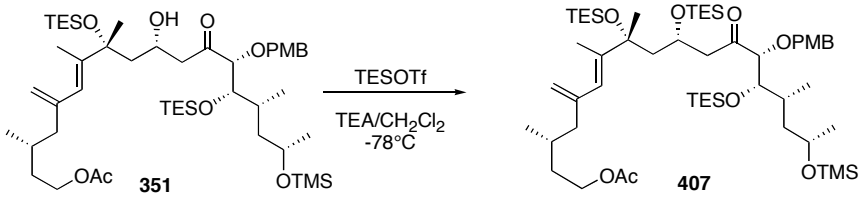
Allylic alcohol (*R*)-**401**: To a solution of (S)-2-methyl-CBS-oxazaborolidine (54.9 μL, 55 μmol, 1.0 M in PhMe) in CH_2Cl_2 (0.2 mL) at r.t. was added a solution of catechol borane (0.11 mL, 0.11 mmol, 1.0 M in CH_2Cl_2). After 10 min, the resultant solution was cooled to -20°C. A solution of macrolactone **333** (14 mg, 14 μmol) in CH_2Cl_2 (0.32 mL) was added dropwise *via* cannula. After 2 h, the reaction was quenched with MeOH (1.0 mL), concentrated *in vacuo* and purified by preparative TLC, eluting with 25% EtOAc/Hexane, to give (*R*)-**401** (8.0 mg, 7.9 μmol, 58%, dr = 10:1) as a colorless oil: $[\alpha]_D^{23}$ (+) 8.4° (c 0.38, $CHCl_3$); IR (neat) 3459, 2954, 2917, 2875, 2849, 1709, 1614, 1515, 1461, 1377, 1251, 1173, 1125, 1070, 1018, 835, 776, 743 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.73 (t, J = 7.6 Hz, 1H), 5.78 (s, 1H), 5.68-5.72 (m, 1H), 5.49 (dd, J = 6.8, 15.2 Hz, 1H), 5.05 (s, 1H), 4.97-5.04 (m, 1H), 4.87 (s, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.22-4.28 (m, 2H), 4.10-4.17 (m, 1H), 3.85 (s, 3H), 3.68-3.74 (m, 2H), 3.16 (dd, J = 9.2, 18.0 Hz, 1H), 2.58 (dd, J = 3.2, 18.0 Hz, 1H), 2.32-2.40 (m, 1H), 2.18-2.25 (m, 3H), 1.98-2.04 (m, 4H), 1.86 (s, 3H), 1.83 (s, 3H), 1.75-1.84 (m, 2H), 1.53-1.70 (m, 7H), 1.44 (s, 3H), 1.30-1.36 (m, 1H), 1.24 (d, J = 5.6 Hz, 3H), 0.89-1.00 (m, 24H), 0.82 (s, 9H), 0.54-0.66 (m, 12H), 0.09 (s, 3H),

0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 167.8, 159.2, 145.1, 142.6, 141.8, 134.5, 130.3, 129.9, 129.7, 128.4, 125.7, 115.1, 113.6, 87.8, 77.4, 76.6, 72.4, 71.8, 68.5, 65.3, 55.3, 49.5, 46.4, 45.0, 41.1, 39.4, 36.6, 32.2, 31.3, 28.6, 27.6, 25.9, 23.7, 21.1, 19.8, 17.9, 15.0, 12.6, 11.9, 7.3, 7.0, 6.8, 5.2, -4.2, -4.6; HRMS (ES+) calcd. for $C_{58}H_{102}O_9Si_3Na$ (M+Na) 1049.6729, found 1049.6682.



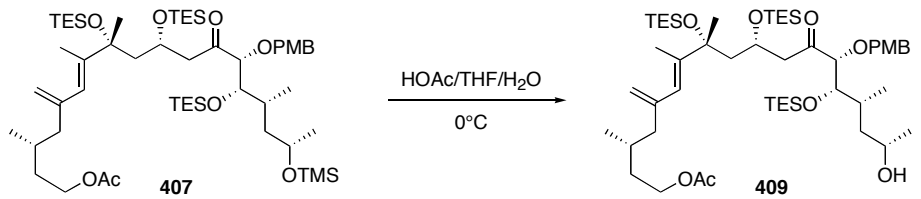
Hydoxyl epoxide (*R*)-**402**: To a solution of (+) DIPT (50.8 μL, 41 μmol, 0.8 M in CH_2Cl_2) at r.t. was added CH_2Cl_2 (0.1 mL) and 4 Å MS (15 mg). The resulted mixture was cooled to -20°C and $Ti(O^iPr)_4$ (10.0 mg, 10 μL, 35 μmol) was added. After 30 min, TBHP (6.0 μL, 35 μmol, 5.5 M in decane) was added. After another 30 min, a solution of alcohol (*R*)-**401** (6.0 mg, 6.0 μmol) in CH_2Cl_2 (0.15 mL) was transferred *via* cannula and the reaction was warmed up to 0°C. After 16 h, the reaction was cooled back to -20°C and a brine solution of NaOH (0.5 mL, 1N) was added. After 5 min, the reaction was diluted with brine (0.5 mL) and CH_2Cl_2 (0.5 mL). The mixture was warmed up to r.t. and extracted with CH_2Cl_2 (3 X 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by preparative TLC, eluting with 25% EtOAc/Hexane, to give vinyl epoxide (*R*)-**402** (3.0 mg, 3 μmol, 50%) as a

colorless oil: $[\alpha]_D^{23}$ (+) 7.5° (c 0.20, $CHCl_3$); IR (neat) 3467, 3017, 2954, 2917, 2875, 2849, 2107, 1709, 1515, 1462, 1378, 1251, 1173, 1125, 1070, 1018, 835, 756, 667 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.78 (t, J = 7.6 Hz, 1H), 5.80 (s, 1H), 5.06 (s, 1H), 4.95-5.00 (m, 1H), 4.87 (s, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.21-4.26 (m, 2H), 3.85 (s, 3H), 3.68-3.74 (m, 3H), 3.21 (dd, J = 9.2, 18.0 Hz, 1H), 3.04-3.10 (m, 1H), 2.78-2.81 (m, 1H), 2.62 (dd, J = 3.2, 18.0 Hz, 1H), 2.50 (br, 1H), 2.25-2.35 (m, 4H), 1.85-1.90 (m, 1H), 1.85 (s, 3H), 1.80 (s, 3H), 1.75-1.84 (m, 3H), 1.53-1.70 (m, 7H), 1.45 (s, 3H), 1.30-1.36 (m, 1H), 1.25 (d, J = 5.6 Hz, 3H), 0.91-1.01 (m, 24H), 0.81 (s, 9H), 0.56-0.67 (m, 12H), 0.10 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 167.8, 159.2, 144.7, 142.3, 141.3, 129.8, 129.6, 128.8, 125.7, 115.3, 113.6, 87.8, 77.4, 71.8, 68.6, 68.5, 65.3, 61.3, 55.3, 54.5, 49.7, 47.0, 45.4, 41.9, 39.6, 33.4, 30.9, 30.7, 28.5, 27.9, 25.9, 24.1, 21.1, 20.0, 17.9, 15.1, 12.5, 12.0, 7.3, 7.0, 6.9, 5.2, -4.2, -4.7; HRMS (ES+) calcd. for $C_{58}H_{102}O_{10}Si_3Na$ (M+Na) 1065.6679, found 1065.6685.



Acetate **407**: To a solution of **351** (40 mg, 45 μmol) in CH_2Cl_2 (0.15 mL) and Et_3N (0.15 mL) at –78°C was added TESOTf (32.0 mg, 28.3 μL, 0.12 mmol). After 20 min, the reaction was quenched with sat. aq. NH_4Cl (3 mL).

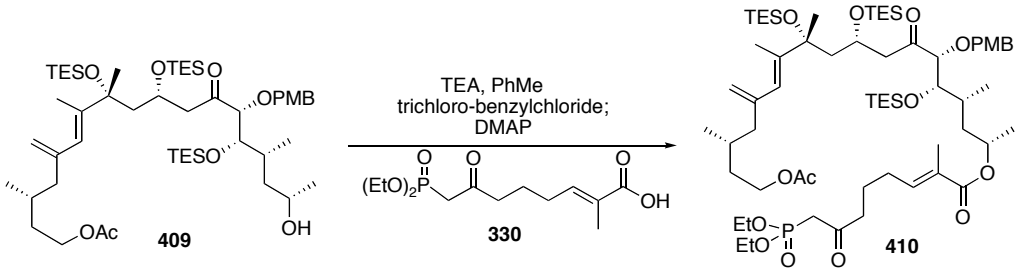
The mixture was extracted with Et_2O (3 X 10 mL) and the dried ($MgSO_4$) extract was concentrated *in vacuo* to give **407** (36 mg, 36 μmol, 82%) as a colorless oil: $[\alpha]_D^{23}$ (+) 18.6° (c 1.58, $CHCl_3$); IR (neat) 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.84 (s, 1H), 5.04 (s, 1H), 4.89 (s, 1H), 4.59 (d, J = 10.8 Hz, 1H), 4.29-4.35 (m, 1H), 4.27 (d, J = 10.8 Hz, 1H), 4.10-4.17 (m, 2H), 3.84 (s, 4H), 3.76-3.78 (m, 1H), 3.71 (d, J = 7.2 Hz, 1H), 3.19 (dd, J = 8.4, 17.6 Hz, 1H), 2.54 (dd, J = 3.3, 17.6 Hz, 1H), 2.11-2.15 (m, 1H), 2.06 (s, 3H), 1.86-1.98 (m, 2H), 1.85 (s, 3H), 1.63-1.77 (m, 4H), 1.52-1.56 (m, 1H), 1.45 (s, 3H), 1.30-1.38 (m, 2H), 1.13 (d, J = 6.4 Hz, 3H), 0.83-0.98 (m, 30H), 0.86 (d, J = 6.4 Hz, 3H), 0.52-0.64 (m, 18H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 171.2, 159.1, 144.4, 142.6, 130.1, 129.7, 125.1, 115.0, 113.5, 88.2, 77.4, 76.4, 72.0, 65.9, 63.0, 55.3, 50.0, 46.5, 46.0, 44.0, 35.3, 32.3, 29.7, 28.7, 28.0, 24.7, 21.0, 19.3, 14.9, 13.3, 7.3, 7.1, 7.0, 6.8, 6.6, 6.4, 5.3, 5.1, 0.4; HRMS (ES+) calcd. for $C_{54}H_{102}O_9Si_4Na$ (M+Na) 1029.6499, found 1029.6470.



407 **409**

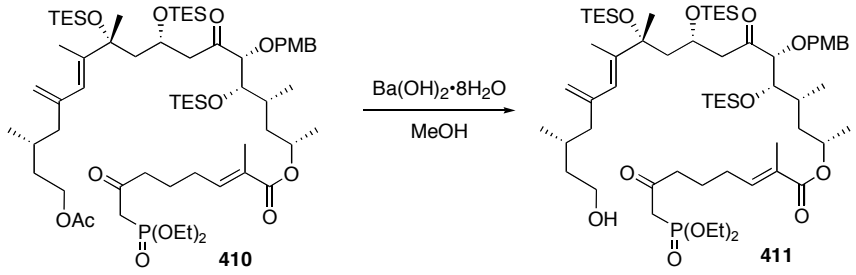
Alcohol **409**: To a flask with **407** (180 mg, 0.18 mmol) at 0°C was added a freshly prepared stock solution of HOAc/THF/H_2O (3.0 mL, 8:8:1)

dropwise. After 40 min, the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) carefully and the mixture was extracted with Et_2O (3 X 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give **409** (102 mg, 0.11 mmol, 61%) as a colorless oil: $[\alpha]_D^{23}$ (+) 23.7° (c 0.60, $CHCl_3$); IR (neat) 3546, 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.87 (s, 1H), 5.02 (s, 1H), 4.86 (s, 1H), 4.55 (d, J = 10.8 Hz, 1H), 4.23-4.29 (m, 1H), 4.23 (d, J = 10.8 Hz, 1H), 4.12-4.17 (m, 2H), 3.85 (s, 4H), 3.75-3.85 (m, 3H), 3.18 (dd, J = 9.2, 17.6 Hz, 1H), 2.54 (dd, J = 2.8, 17.6 Hz, 1H), 2.13 (dd, J = 5.6, 13.6 Hz, 1H), 2.06 (s, 3H), 1.86-1.94 (m, 2H), 1.83 (s, 3H), 1.63-1.80 (m, 4H), 1.52-1.56 (m, 1H), 1.45 (s, 3H), 1.38-1.45 (m, 2H), 1.19 (d, J = 6.0 Hz, 3H), 0.88-1.01 (m, 33H), 0.55-0.68 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 171.2, 159.1, 144.9, 141.7, 130.0, 129.8, 125.5, 114.9, 113.5, 88.5, 77.4, 77.2, 76.4, 71.8, 65.8, 63.2, 55.3, 49.5, 46.2, 45.8, 44.1, 35.4, 33.2, 29.7, 28.7, 28.5, 24.5, 21.0, 19.3, 14.9, 13.6, 7.3, 7.0, 6.95, 6.87, 5.2, 5.1; HRMS (ES+) calcd. for $C_{51}H_{94}O_9Si_3Na$ (M+Na) 957.6103, found 957.6157.



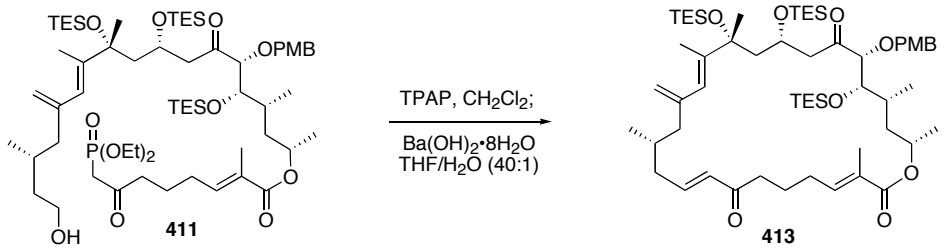
Ketophosphonate **410**: To a solution of phosphonate acid **330** (74 mg, 0.24 mmol) in PhMe (0.5 mL) at r.t. was added triethylamine (26.2 mg, 36.0 μl, 0.24 mmol) and 2,4,6-trichlorobenzoyl chloride (56 mg, 36.0 μL, 0,24 mmol). After 6 h, solvent of the reaction was removed *in vacuo*. A solution of the alcohol **409** (60 mg, 64 μmol) in PhMe (0.5 mL) was transferred into the above flask *via* cannula and DMAP (29.6 mg, 0.24 mmol) was sequentially added. After 16 h, the reaction was purified by chromatography over silica gel, eluting with 70% EtOAc / Hexanes, to give **410** (50 mg, 41 μmol, 64%) as a colorless oil: $[\alpha]_D^{23}$ (+) 25.3° (c 1.50, $CHCl_3$); IR (neat) 2954, 2933, 2876, 1739, 1712, 1613, 1515, 1461, 1366, 1251, 1165, 1124, 1026, 968, 901, 835, 770, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 5.85 (s, 1H), 5.03 (br, 2H), 4.88 (s, 1H), 4.62 (d, J = 10.8 Hz, 1H), 4.25-4.31 (m, 1H), 4.25 (d, J = 10.8 Hz, 1H), 4.05-4.21 (m, 6H), 3.84 (s, 3H), 3.81-3.83 (m, 1H), 3.72 (d, J = 6.0 Hz, 1H), 3.16 (dd, J = 8.8, 17.6 Hz, 1H), 3.12 (s, 1H), 3.07 (s, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.60 (dd, J = 2.8, 17.6 Hz, 1H), 2.16 (dd, J = 7.6, 14.8 Hz, 2H), 2.08-2.12 (m, 1H), 2.06 (s, 3H), 1.83-1.94 (m, 4H), 1.83 (s, 3H), 1.81 (s, 3H), 1.61-1.77 (m, 5H), 1.52-1.55 (m, 1H), 1.43 (s, 3H), 1.40-1.43 (m, 1H), 1.36 (t, J = 6.8 Hz, 6H), 1.22 (d, J =

6.0 Hz, 3H), 0.90-1.00 (m, 30H), 0.86 (d, J = 6.4 Hz, 3H), 0.54-0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 201.5, 201.4, 171.2, 167.7, 159.2, 144.5, 142.3, 140.6, 129.9, 129.7, 129.0, 125.2, 115.0, 113.6, 87.4, 76.0, 72.0, 68.9, 66.0, 63.1, 62.6, 62.5, 55.3, 49.9, 46.8, 45.9, 43.4, 43.1, 41.8, 39.3, 35.3, 33.0, 28.7, 28.2, 27.7, 22.3, 21.0, 20.8, 19.3, 16.4, 16.3, 14.9, 14.1, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd. for $C_{64}H_{115}O_{14}PSi_3Na$ (M+Na) 1245.7230, found 1245.7181.



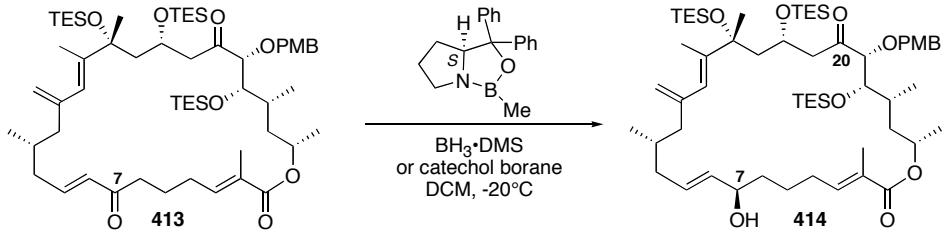
Alcohol **411**: To a flask containing **410** (50.0 mg, 41 μmol) at r.t. was added a premixed solution of $Ba(OH)_2$•$8H_2O$ (1.5 mL, 0.1 M in MeOH). After 10 min, the mixture was purified by chromatography over silica gel, eluting with 50% EtOAc / Hexanes, to give **411** (42 mg, 36 μmol, 88%) as a colorless oil: $[\alpha]_D^{23}$ (+) 19.8° (c 0.78, $CHCl_3$); IR (neat) 3444, 2954, 2929, 2876, 1713, 1614, 1515, 1458, 1379, 1251, 1165, 1125, 1059, 1024, 970, 900, 835, 809, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.69 (t, J = 7.6 Hz, 1H), 5.85 (s, 1H), 5.03-5.06 (m, 2H), 4.85 (s, 1H), 4.62 (d, J = 10.4 Hz, 1H), 4.12-4.27 (m, 7H), 3.84 (s, 3H), 3.81 (dd, J = 3.2, 6.8 Hz, 1H) 3.70-3.76 (m, 3H), 3.19 (dd, J = 9.2, 17.2 Hz, 1H), 3.13 (s, 1H), 3.07

(s, 1H), 2.68 (t, J = 7.2 Hz, 2H), 2.60 (dd, J = 2.8, 17.6 Hz, 1H), 2.18 (q, J = 7.6 Hz, 2H), 2.10 (dd, J = 5.2, 18.4 Hz, 1H), 1.83-1.91 (m, 3H), 1.83 (s, 3H), 1.81 (s, 3H), 1.51-1.81 (m, 7H), 1.43 (s, 3H), 1.38-1.43 (m, 1H), 1.36 (t, J = 7.2 Hz, 6H), 1.23 (d, J = 6.0 Hz, 3H), 0.87-1.00 (m, 33H), 0.54-0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 201.5, 201.4, 167.7, 159.2, 144.9, 141.7, 140.7, 130.0, 129.7, 129.0, 125.6, 114.9, 113.5, 87.6, 77.5, 75.9, 72.0, 68.9, 66.2, 62.6, 62.5, 61.0, 55.3, 49.5, 46.6, 46.2, 43.4, 43.1, 41.8, 40.1, 39.5, 32.9, 29.7, 28.4, 28.3, 27.7, 22.3, 20.8, 19.2, 16.4, 16.3, 15.1, 14.1, 13.9, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd. for $C_{62}H_{113}O_{13}PSi_3Na$ (M+Na) 1203.7124, found 1203.7054.



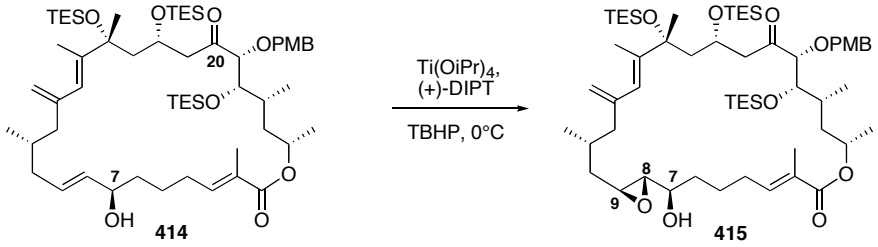
Macrolactone **413**: To a solution of **411** (42 mg, 36 μmol) in CH_2Cl_2 (1.2 mL) at r.t. was added TPAP (15 mg, 43 μmol). After 1 h, the reaction was added sequentially with THF (3.3 mL), H_2O (82.8 μL) and $Ba(OH)_2 \bullet 8H_2O$ (43 mg, 0.13 mmol). After 3 h, the reaction was directly purified by chromatography over silica gel, eluting with 5% EtOAc / Hexanes, to give **413** (30.6 mg, 30 μmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ (+) 1.6° (c 0.45, $CHCl_3$); IR (neat) 2954, 2925, 2875, 2854, 1710, 1673, 1614, 1515, 1461, 1377, 1251,

1171, 1120, 1068, 1018, 985, 835, 808, 742 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H), 6.94-7.01 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.71 (t, J = 7.6 Hz, 1H), 6.09 (d, J = 16.0 Hz, 1H), 5.77 (s, 1H), 5.05 (s, 1H), 4.96-5.04 (m, 1H), 4.87 (s, 1H), 4.53 (d, J = 10.8 Hz, 1H), 4.21-4.27 (m, 1H), 4.21 (d, J = 10.8 Hz, 1H), 3.84 (s, 3H), 3.67-3.74 (m, 2H), 3.15 (dd, J = 9.2, 17.6 Hz, 1H), 2.56-2.67 (m, 3H), 2.08-2.27 (m, 3H), 1.90 (s, 3H), 1.78 (s, 3H), 1.47-1.78 (m, 9H), 1.43 (s, 3H), 1.26-1.42 (m, 2H), 1.25 (d, J = 6.0 Hz, 3H), 0.90-1.00 (m, 30H), 0.83 (d, J = 6.4 Hz, 3H), 0.54-0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 200.8, 167.6, 159.2, 147.0, 144.5, 142.7, 140.8, 132.3, 130.0, 129.5, 129.2, 125.3, 115.5, 113.6, 87.9, 71.7, 68.9, 65.4, 55.3, 49.2, 47.1, 45.8, 41.8, 40.6, 37.4, 32.0, 31.5, 31.4, 27.4, 22.9, 21.0, 19.5, 15.2, 14.2, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd. for $C_{58}H_{100}O_9Si_3Na$ (M+Na) 1047.6573, found 1047.6494.



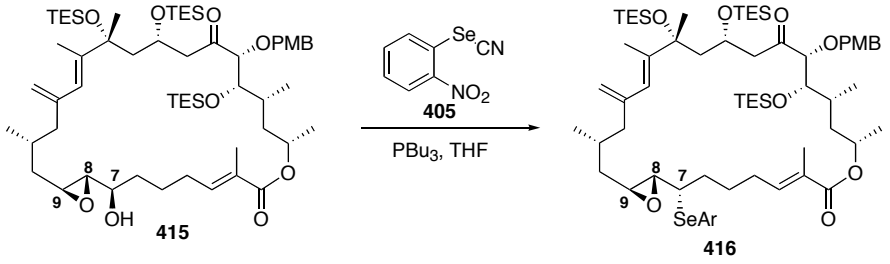
Allylic alcohol **414**: To a solution of (S)-2-methyl-CBS-oxazaborolidine (10.1 μL, 10 μmol, 1.0 M in PhMe) in CH_2Cl_2 (0.3 mL) at r.t. was added catechol borane (0.20 mL, 0.20 mmol, 1.0 M CH_2Cl_2). After 10 min, the resulted solution was cooled to -20°C. A solution of macrolactone **413** (26 mg,

25 μmol) in CH_2Cl_2 (0.65 mL) was added into the above solution dropwise *via* cannula. After 2 h, the reaction was quenched with MeOH (2.0 mL) and concentrated *in vacuo*. The resultant mixture was purified by preparative TLC, eluting with 25% EtOAc/Hexane, to give **414** (14 mg, 14 μmol, 56%) as a colorless oil: $[\alpha]_D^{23}$ (+) 7.6° (c 0.88, $CHCl_3$); IR (neat) 3459, 2954, 2917, 2875, 2849, 1709, 1614, 1515, 1461, 1377, 1251, 1173, 1125, 1070, 1018, 835, 776, 743 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.72 (t, J = 7.6 Hz, 1H), 5.79 (s, 1H), 5.68-5.72 (m, 1H), 5.49 (dd, J = 6.8, 15.2 Hz, 1H), 5.05 (s, 1H), 4.97-5.04 (m, 1H), 4.87 (s, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.28-4.32 (m, 1H), 4.22 (d, J = 10.8 Hz, 1H), 4.13-4.17 (m, 1H), 3.85 (s, 3H), 3.65-3.73 (m, 2H), 3.16 (dd, J = 9.2, 18.0 Hz, 1H), 2.53 (dd, J = 3.2, 18.0 Hz, 1H), 2.21-2.24 (m, 4H), 1.98-2.04 (m, 4H), 1.88 (s, 3H), 1.82 (s, 3H), 1.75-1.84 (m, 2H), 1.53-1.70 (m, 7H), 1.44 (s, 3H), 1.30-1.36 (m, 1H), 1.24 (d, J = 5.6 Hz, 3H), 0.89-1.00 (m, 30H), 0.82 (d, J = 6.0 Hz, 3H), 0.54-0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 167.8, 159.2, 145.1, 142.6, 141.7, 134.5, 130.4, 129.9, 129.8, 128.5, 125.6, 115.1, 113.5, 88.1, 77.2, 76.6, 72.4, 71.7, 68.6, 65.5, 55.3, 53.5, 49.5, 46.4, 44.9, 41.1, 39.4, 36.6, 32.2, 31.4, 28.6, 27.5, 23.7, 21.1, 19.8, 15.0, 12.6, 11.9, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd. for $C_{58}H_{102}O_9Si_3Na$ (M+Na) 1049.6729, found 1049.6678.



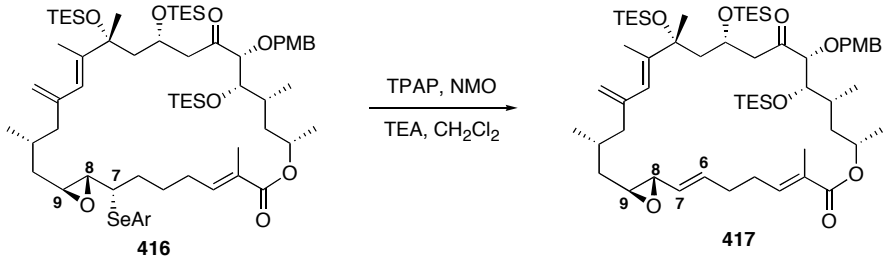
Hydroxyl epoxide **415**: To a solution of (+) DIPT (0.11 mL, 89 μmol, 0.8 M in CH_2Cl_2) was added CH_2Cl_2 (0.30 mL) and 4 Å MS (30 mg). The resulted mixture was cooled to -20°C and $Ti(O^iPr)_4$ (21.6 mg, 20.0 μL, 76 μmol) was added. After 30 min, TBHP (14.2 μL, 76 μmol, 5.5 M in decane) was added dropwise. After another 30 min, a solution of alcohol **414** (13 mg, 13 μmol) in CH_2Cl_2 (0.30 mL) was added dropwise *via* cannula and the reaction was allowed to warm to 0°C. After 16 h, the reaction was cooled back to -20°C and a brine solution of NaOH (0.5 mL, 1.0 M) was added. After 5 min, the reaction was diluted with brine (0.5 mL) and CH_2Cl_2 (0.5 mL) and warmed up to r.t. Next, the mixture was extracted with CH_2Cl_2 (3 X 15 mL) and the dried ($MgSO_4$) extract concentrated *in vacuo*. The crude mixture was purified by preparative TLC, eluting with 25% EtOAc/Hexane, to give vinyl epoxide **415** (7.0 mg, 7.0 μmol, 54%) as a colorless oil: $[\alpha]_D^{23}$ (+) 12.2° (c 0.36, $CHCl_3$); IR (neat) 3467, 3017, 2954, 2917, 2875, 2849, 2107, 1709, 1515, 1462, 1378, 1251, 1173, 1125, 1070, 1018, 835, 756, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.77 (t, J = 7.6 Hz, 1H), 5.80 (s, 1H), 5.06 (s, 1H), 4.95-5.00 (m, 1H), 4.87 (s, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.22-4.30 (m, 1H), 4.21 (d, J = 10.8 Hz, 1H), 3.85 (s, 3H), 3.75-3.84 (m,

1H), 3.67-3.74 (m, 2H), 3.22 (dd, J = 9.2, 18.0 Hz, 1H), 3.05-3.10 (m, 1H), 2.78-2.81 (m, 1H), 2.54 (dd, J = 3.2, 18.0 Hz, 1H), 2.38 (br, 1H), 2.21-2.30 (m, 4H), 1.89-1.92 (m, 1H), 1.89 (s, 3H), 1.84 (s, 3H), 1.75-1.86 (m, 3H), 1.53-1.70 (m, 7H), 1.45 (s, 3H), 1.30-1.36 (m, 1H), 1.26 (d, J = 5.6 Hz, 3H), 0.91-1.01 (m, 30H), 0.56-0.67 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 167.8, 159.2, 144.7, 142.4, 141.2, 129.9, 129.8, 128.9, 125.6, 115.4, 113.6, 88.1, 77.1, 71.8, 68.7, 68.2, 65.4, 61.3, 55.3, 54.2, 49.8, 46.5, 45.4, 41.8, 39.5, 33.3, 31.1, 30.8, 28.5, 27.7, 24.1, 21.1, 20.1, 15.1, 12.5, 11.8, 7.3, 7.0, 6.9, 5.3, 5.1; HRMS (ES+) calcd. for $C_{58}H_{102}O_{10}Si_3Na$ (M+Na) 1065.6679, found 1065.6774.



Selenide **416**: To a solution of vinyl epoxide **415** (5.0 mg, 5 μmol) in THF (0.15 mL) at r.t. was added **405** (33 mg, 0.15 mmol) and PBu_3 (29 mg, 36.2 μL, 0.15 mmol). After 1 h, the reaction mixture was directly purified by preparative TLC, eluting with 25% EtOAc/Hexane, to give selenide **416** (3.0 mg, 2.5 μmol, 50%) as a colorless oil: $[\alpha]_D^{23}$ (-) 9.9° (c 0.22, $CHCl_3$); IR (neat) 2956, 2932, 2874, 1701, 1515, 1457, 1250, 1074, 1007, 806, 730 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d = 6.9 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.48-7.54 (m, 1H), 7.48-7.55 (m, 3H), 6.87 (d, J = 8.4 Hz, 2H), 6.69 (t, J = 7.6

Hz, 1H), 5.84 (s, 1H), 5.05 (s, 1H), 4.96-5.00 (m, 1H), 4.87 (s, 1H), 4.56 (d, J = 10.5 Hz, 1H), 4.25-4.30 (m, 1H), 4.21 (d, J = 10.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 2H), 3.26 (dd, J = 9.6, 17.4 Hz, 1H), 3.20 (d, J = 8.1, 14.4 Hz, 1H), 2.99-3.04 (m, 1H), 2.96 (dd, J = 8.1, 15.0 Hz, 1H), 2.57 (dd, J = 2.8, 17.4 Hz, 1H), 2.21-2.30 (m, 4H), 1.89-1.92 (m, 1H), 1.84 (s, 3H), 1.79 (s, 3H), 1.45-1.78 (m, 10H), 1.42 (s, 3H), 1.30-1.36 (m, 1H), 1.25 (d, J = 5.6 Hz, 3H), 0.91-1.01 (m, 30H), 0.56-0.67 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 167.5, 159.1, 147.7, 144.5, 142.4, 140.3, 133.4, 131.3, 129.9, 129.7, 129.2, 126.1, 126.0, 125.5, 115.4, 113.5, 88.5, 77.2, 71.7, 68.9, 65.6, 62.1, 59.6, 55.3, 49.6, 45.9, 45.7, 44.8, 41.1, 39.6, 31.7, 31.6, 30.9, 28.3, 26.2, 21.0, 19.9, 15.2, 12.6, 12.1, 7.3, 7.0, 6.9, 5.3, 5.1; HRMS (ES+) calcd. for $C_{64}H_{106}NO_{11}Si_3Se$ (M+1) 1228.6239, found 1228.6516.



Allyl epoxide **417**: To a solution of selenide **416** (5.7 mg, 5.0 μmol) in CH_2Cl_2 (0.25 mL) at r.t. was sequentially added triethylamine (19 mg, 26.0 μL, 0.18 mmol), TPAP (16 mg, 45 μmol) and NMO (35 mg, 0.3 mmol). After 30 min, the reaction mixture was purified directly by preparative TLC, eluting with 25% EtOAc/Hexanes, to give vinyl epoxide **417** (2.5 mg, 2.4 μmol, 48%) as a

colorless oil: $[\alpha]_D^{23}$ (-) 1.3° (c 0.15, $CHCl_3$); IR (neat) 3467, 3017, 2954, 2917, 2875, 2849, 2107, 1709, 1515, 1462, 1378, 1251, 1173, 1125, 1070, 1018, 835, 756, 667 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.73 (t, J = 7.6 Hz, 1H), 5.85-5.92 (m, 1H), 5.78 (s, 1H), 5.27 (dd, J = 8.0, 15.2 Hz, 1H), 5.01-5.04 (m, 2H), 4.85 (s, 1H), 4.57 (d, J = 10.4 Hz, 1H), 4.28-4.32 (m, 1H), 4.21 (d, J = 10.4 Hz, 1H), 3.85 (s, 3H), 3.70-3.74 (m, 2H), 3.25 (dd, J = 9.6, 17.2 Hz, 1H), 3.09 (dd, J = 2.0, 6.4 Hz, 1H), 2.90-2.94 (m, 1H), 2.54 (dd, J = 2.8, 17.2 Hz, 1H), 2.06-2.28 (m, 4H), 1.94 (d, J = 2.4, 10.8 Hz, 1H), 1.86 (s, 3H), 1.80-1.86 (m, 3H), 1.79 (s, 3H), 1.53-1.70 (m, 7H), 1.46 (s, 3H), 1.30-1.36 (m, 1H), 1.25 (d, J = 6.0 Hz, 3H), 0.90-1.01 (m, 27H), 0.86 (d, J = 6.0 Hz, 3H), 0.54-0.68 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 167.6, 159.1, 144.6, 142.4, 140.5, 134.3, 130.1, 129.8, 129.5, 128.7, 125.2, 115.3, 113.5, 88.4, 76.4, 71.7, 68.9, 65.7, 59.6, 58.5, 55.3, 49.4, 46.1, 45.6, 40.6, 40.2, 32.1, 30.9, 30.5, 29.7, 28.0, 27.8, 20.4, 19.8, 15.2, 13.0, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd. for $C_{58}H_{100}O_9Si_3Na$ (M+Na) 1047.6573, found 1047.6664.

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[84] Preparation of LDA Solution: To a solution of diisopropylamine (101.9 mg, 0.14 mL, 1.0 mmol) in THF (0.46 mL) at –78°C was added *n*-BuLi (0.4 mL, 1.0 mmol, 2.5 M in THF). After 5 min, the white slurry was warmed to –10°C and stirred for an additional 15 min.

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APPENDICES

A.1. Experimental Details for Compound 212

The crystalline sample used was that supplied without further work. Determination of the crystallographic parameters, data collection and structure solution and refinement was done as described elsewhere, with the following details:

A well shaped crystal of dimensions 0.1x 0.1 x 0.05 mm^3 was selected and mounted on the tip of a thin glass fiber using a dab of Paratone. Crystal quality evaluation and preliminary indexing were performed from four images of 10 degrees rotation about omega, each separated from the others by 50 degrees. Proving to be a satisfactory crystal, a full set of 80 frames of 10 degrees rotation about omega was collected. The frames were integrated using the determined unit cell, using the program TwinSolve as included in Rigaku/MSC's software package CrystalClear to yield a massively redundant data set of 31794 reflections. Correction for the effects of absorption anisotropy was carried out by means of multiscans[1] as programmed in TwinSolve. Finally, a data set consisting of 5066 unique reflections in the range (-9 – 9, -15 – 15, -36 – 33) was generated with an R(merge) of 0.080. The reported unit cell was refined using all 2733 reflections with intensities greater than 10 times their e.s.d.s in the range $2.92° < q < 35.92°$.

The structure was solved using direct methods as programmed in SHELXS-90,[2] which revealed the positions of most atoms in the molecule excepting the carbon atoms belonging to the TES group. The solution was

refined using the program SHELXL-97,[3] followed by Fourier synthesis, which revealed the positions of the remaining atoms. Though all hydrogen atoms could be clearly identified from the Fourier map, in order to preserve a favorable data-to-parameter ratio the hydrogen atoms were placed in geometrically idealized positions, with the C-H distance allowed to refine. The hydrogen atoms were given a displacement parameter equal to 1.5 times (methyl group) or 1.2 times (all other hydrogens) the equivalent isotropic displacement parameter of the atom it is attached to. During the final cycle of least squares refinement, all non-hydrogen atoms were refined with anisotropic displacement parameters. The refined value of the absolute structure parameter (Flack parameter)[4] of 0.02(2) indicates that the model obtained accurately depicts the absolute structure of the molecule.

An ORTEP[5] of the final model is given in Figure 1, with displacement ellipsoids drawn at the 50% probability level. All unique atoms are labeled, and atoms generated by symmetry are left unlabelled.[6]

Figure A.1. ORTEP with 50% displacement ellipsoids

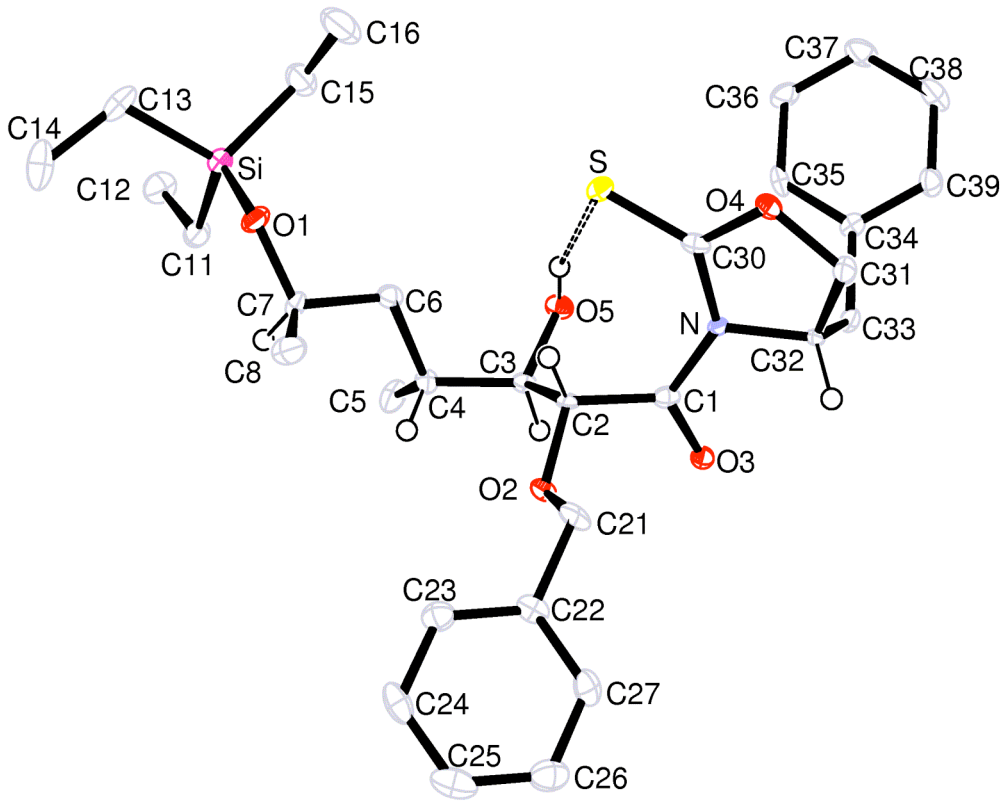

Table A.1. Crystal data and structure refinement for **212**

Identification code	**212**	
Empirical formula	$C_{31}H_{45}NO_5SSi$	
Formula weight	571.83	
Temperature	100(2) K	
Wavelength	1.54060 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.0726(4) Å	a= 90°.
	b = 12.9005(8) Å	b= 90°.
	c = 30.1667(15) Å	g = 90°.
Volume	3141.6(3) $Å^3$	
Z	4	
Density (calculated)	1.209 Mg/m^3	
Absorption coefficient	1.585 mm^{-1}	
F(000)	1232	
Crystal size	0.1 x 0.1 x 0.05 mm^3	
Theta range for data collection	2.92 to 71.36°.	
Index ranges	-9<=h<=9, -15<=k<=15, -36<=l<=33	
Reflections collected	31794	
Independent reflections	5066 [R(int) = 0.080]	
Completeness to theta = 68.74°	94.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.9304	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5066 / 0 / 359	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0512, wR2 = 0.0704	
R indices (all data)	R1 = 0.0739, wR2 = 0.0757	
Absolute structure parameter	0.02(2)	
Largest diff. peak and hole	0.278 and -0.229 $e.Å^{-3}$	

Table A.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **212**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
S	6152(1)	9516(1)	9007(1)	17(1)
Si	306(1)	9396(1)	7665(1)	17(1)
O(1)	1890(3)	10208(2)	7703(1)	18(1)
O(2)	4713(3)	12926(2)	9119(1)	13(1)
O(3)	5223(3)	12216(2)	9964(1)	16(1)
O(4)	8457(3)	9597(2)	9601(1)	16(1)
O(5)	2727(3)	10498(2)	9415(1)	16(1)
N	6608(3)	10825(2)	9718(1)	10(1)
C(1)	5486(4)	11635(2)	9657(1)	13(1)
C(2)	4683(4)	11838(2)	9205(1)	12(1)
C(3)	2862(4)	11522(2)	9233(1)	11(1)
C(4)	1924(4)	11653(2)	8795(1)	13(1)
C(5)	64(4)	11712(3)	8886(1)	22(1)
C(6)	2331(4)	10797(2)	8460(1)	14(1)
C(7)	1966(4)	11101(3)	7981(1)	16(1)
C(8)	3313(4)	11796(3)	7794(1)	23(1)
C(11)	-1664(4)	10052(3)	7835(1)	20(1)
C(12)	-3210(4)	9382(3)	7773(1)	26(1)
C(13)	236(5)	9005(3)	7071(1)	24(1)
C(14)	-261(5)	9876(3)	6750(1)	36(1)
C(15)	681(4)	8227(3)	8016(1)	27(1)
C(16)	2423(5)	7769(3)	7967(1)	41(1)
C(21)	6360(4)	13303(2)	9039(1)	18(1)
C(22)	6264(4)	14409(3)	8879(1)	15(1)
C(23)	5565(4)	14626(3)	8470(1)	21(1)
C(24)	5550(4)	15639(3)	8309(1)	24(1)
C(25)	6232(5)	16429(3)	8560(1)	27(1)
C(26)	6929(4)	16218(3)	8966(1)	27(1)

C(27)	6941(4)	15205(3)	9123(1)	20(1)
C(30)	7066(4)	10008(2)	9447(1)	13(1)
C(31)	9075(4)	10194(2)	9976(1)	16(1)
C(32)	7595(4)	10821(2)	10131(1)	11(1)
C(33)	6647(4)	10374(2)	10527(1)	14(1)
C(34)	6465(4)	9205(2)	10520(1)	11(1)
C(35)	5353(4)	8710(2)	10244(1)	15(1)
C(36)	5275(4)	7636(2)	10233(1)	20(1)
C(37)	6295(4)	7050(3)	10500(1)	26(1)
C(38)	7408(5)	7534(3)	10776(1)	23(1)
C(39)	7491(4)	8611(3)	10790(1)	18(1)

Table A.3. Bond lengths [Å] and angles [°] for **212**

S-C(30)	1.647(3)	C(31)-C(32)	1.516(4)
Si-O(1)	1.657(2)	C(32)-C(33)	1.532(4)
Si-C(13)	1.860(3)	C(33)-C(34)	1.516(4)
Si-C(15)	1.868(4)	C(34)-C(35)	1.380(4)
Si-C(11)	1.873(3)	C(34)-C(39)	1.391(4)
O(1)-C(7)	1.427(4)	C(35)-C(36)	1.388(4)
O(2)-C(2)	1.427(3)	C(36)-C(37)	1.377(4)
O(2)-C(21)	1.437(4)	C(37)-C(38)	1.376(5)
O(3)-C(1)	1.211(3)	C(38)-C(39)	1.392(4)
O(4)-C(30)	1.325(4)		
O(4)-C(31)	1.458(3)	O(1)-Si-C(13)	105.19(14)
O(5)-C(3)	1.436(3)	O(1)-Si-C(15)	110.20(14)
N-C(30)	1.384(4)	C(13)-Si-C(15)	109.38(17)
N-C(1)	1.395(4)	O(1)-Si-C(11)	110.51(13)
N-C(32)	1.480(3)	C(13)-Si-C(11)	111.18(16)
C(1)-C(2)	1.533(4)	C(15)-Si-C(11)	110.27(16)
C(2)-C(3)	1.528(4)	C(7)-O(1)-Si	125.8(2)
C(3)-C(4)	1.530(4)	C(2)-O(2)-C(21)	112.3(2)
C(4)-C(5)	1.528(4)	C(30)-O(4)-C(31)	110.5(2)
C(4)-C(6)	1.532(4)	C(30)-N-C(1)	131.7(3)
C(6)-C(7)	1.527(4)	C(30)-N-C(32)	110.6(2)
C(7)-C(8)	1.518(4)	C(1)-N-C(32)	117.6(2)
C(11)-C(12)	1.530(4)	O(3)-C(1)-N	118.5(3)
C(13)-C(14)	1.539(5)	O(3)-C(1)-C(2)	120.0(3)
C(15)-C(16)	1.532(5)	N-C(1)-C(2)	121.4(3)
C(21)-C(22)	1.508(4)	O(2)-C(2)-C(3)	106.7(2)
C(22)-C(27)	1.377(4)	O(2)-C(2)-C(1)	108.8(2)
C(22)-C(23)	1.387(4)	C(3)-C(2)-C(1)	108.2(3)
C(23)-C(24)	1.394(5)	O(5)-C(3)-C(2)	109.8(3)
C(24)-C(25)	1.383(5)	O(5)-C(3)-C(4)	113.2(2)
C(25)-C(26)	1.375(4)	C(2)-C(3)-C(4)	113.5(2)
C(26)-C(27)	1.390(4)	C(5)-C(4)-C(3)	109.7(3)