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Applications of oxazolidinones as chiral auxiliaries in the asymmetric alkylation reaction applied to total synthesis

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Abstract

Various chiral oxazolidinones (Evans' oxazolidinones) have been employed as effective chiral auxiliaries in the asymmetric alkylation of different enolates. This strategy has been found promising and successful when used as key step (steps) in the total synthesis of several biologically active natural products. In this report, we try to underscore the applications of oxazolidinones as chiral auxiliary in asymmetric alkylation, and particularly in crucial chiral inducing steps in the total synthesis of natural products, showing biological activities. Chiral auxiliaries are generally considered as reliable compounds with well-known configurations, enabling and controlling the synthesis of a large number of enantiomerically pure compounds in a time-efficient manner. Consequently, the use of chiral auxiliaries are frequently was considered as a method of choice in the early phases of drug discovery.

Key words: Asymmetric synthesis, Stereoselective Alkylation, Chiral auxiliary, Evans oxazolidinones, Total synthesis, Natural products,

1. Introduction

One of significant goal in organic synthesis is to achieve a valuable enantiopure compound, starting from commercially and readily available starting materials. Nowadays, it has been realized that asymmetric synthesis is the best approach for enantioselective synthesis of desired targets, especially those showing biological activities.[1] To achieve an asymmetric synthesis various protocols have been developed to induce stereoselectivity into a reaction. Among them, a certain kind of compound so-called chiral auxiliary, chiral reagent, chiral media and above all, a chiral catalyst is commonly used. The chiral auxiliary actually is an enantiopure chiral molecule, which temporarily attaches to the substrate to induce chirality to the resulting compound. The

employment of chiral auxiliaries in the asymmetric reactions is as necessary and important as protection and deprotection in multi-step organic synthesis. In a similar way, the chiral auxiliary is attached to an appropriate substrate to play its role, which is inducing chirality to the product, and it is removed, usually in the final step of the reaction pathway. Nevertheless, dissimilar to protecting groups, which are often passive partners in a reaction, a chiral auxiliary is effectively and powerfully induce chirality with a high stereoselectivity as desired in the target molecule. A good chiral auxiliary should be readily removable under mild conditions. This permits for elusive functionality elsewhere in the molecule to be present without protection. Besides, the selected removal procedure must be all-purpose and wide-ranging, proceed smoothly and cleanly, giving the products in satisfactory yields. The chiral auxiliary also should not destroy the newly generated chiral center as well as other stereogenic centers already fixed in the precursor. The chiral auxiliary especially those synthetic or modified are not usually readily available or if being commercially available, they are expensive. Thus, recyclability and reusability of chiral auxiliary are very important and should be considered when the synthetic strategy for a total synthesis is designed.

In fact, introduction of effective chiral auxiliaries have a great effect in progress and growth of asymmetric synthesis. Most chiral auxiliaries have been derived from natural sources such as amino acids, carbohydrates, terpenes, etc. They can be used as they are isolated or after some structural modifications. However, for induction of high chirality and giving satisfactory yields, they should be used in stoichiometric quantities. Very common chiral auxiliaries employed in several, highly effective asymmetric reactions, are the amino alcohols, which derived from the corresponding naturally occurring α-amino acids. A literature survey shows that many new chiral auxiliaries have actually been developed in the early 1990s, most of them being involved in enolate chemistry. They are mostly new derivatives of oxazolidinone, imidazolidinone, oxazoline, ephedrine, camphor, sugar derivatives, etc.

In general, chiral auxiliaries are regarded as reliable compounds with well-determined configurations, inducing the chirality and controlling the synthesis of a large number of enantiomerically pure compounds in a time-efficient fashion. Consequently, in spite of not being a method of choice nowadays, the use of chiral auxiliaries were frequently considered in the early periods of drug development.

Asymmetric synthesis using chiral auxiliaries has attracted much attention and experienced an outstanding progress over the past decades. It has been found that in spite of requirement of stoichiometric amount, auxiliary-controlled reactions are still powerful tools in the construction of complex molecules especially in their chiral inducing stage.[2, 3] The market availability and ready accessibility of the starting materials along with the facile and versatile cleavage[4] as well as the applicability and consistency in a wide range of stereoselective transformations result in superiority of chiral auxiliaries to withstand nowadays as outstanding and distinct intermediates in the asymmetric synthesis.

Only a few numbers of chiral auxiliaries fulfill these imperative requirements. Probably, the most suitable and common chiral auxiliaries, which meet nearly all these required criteria, are oxazolidin-2-ones so called Evans' 2-oxazolidinone. Initially, it was discovered and presented by Evans' and coworkers in 1981[5] and since then, a large number of structural modifications of these auxiliaries have been accomplished and reported.[6-14] These readily available, powerful and easily removable auxiliaries have been employed in various asymmetric synthesis and shown to be effective in the highly stereoselective formation of a wide range of carbon-carbon and carbon-heteroatom bonds leading to the synthesis of complex molecules. Numerous highly diastereoselective reactions including the asymmetric aldol reactions, alkylations, cycloadditions, Michel additions, aminations, azidations, brominations, hydroxylations, Diels Alder reactions, and 1,4-conjugate additions have been successfully accomplished, using diverse Evans' chiral oxazolidinones as chiral auxiliary.[15-19] They are derived from the corresponding α-amino acids. They are the most popular auxiliaries for conduction of an efficient asymmetric synthesis, being frequently used for stereoselective C-C and C-X (X=O, N, Br, F, etc.) bond formation. Many reviews and reports have attractively collected and summarized the scope of Evans' oxazolidinone systems for the stereoselective formation of carbon-carbon bonds.[20-22] To extend the chemistry of oxazolidinones, originally introduced by Evans and coworkers, several modified derivatives have been presented during the years and employed in various asymmetric synthesis. Useful and invaluable reviews on the applications of oxazolidin-2-ones as the chiral auxiliaries in the asymmetric synthesis have been published during the years.[22-26] Among these reports, the review article published in 1997 by Cowden and Paterson outstandingly presents a collection of fruitfully applied oxazolidinone based chiral auxiliaries.[20] In spite of introduction of a plethora of oxazilidinones derivatives, basic principles that govern induction of chirality and stereocontrol of

the reaction with these derivatives used as chiral auxiliary are basically the same as with the original Evans' auxiliary. However, they have their own merits and drawbacks in inducing and controlling chirality in specific reactions. Most naturally, occurring compounds and pharmaceutical targets exist as one of two possible enantiomers in optically pure form. As a result, total synthesis of natural products and pharmaceutical agents should be designed in a way to obtain the desired target in enantiomerically pure form.[27] Use of chiral auxiliaries are one of many approaches realized and understood to synthetic chemists for the synthesis of the desired enantiopure stereoisomer.[1]

We are interested in asymmetric synthesis [28-34] and total synthesis of natural products.[35-40] Recently, we have published a report concerning the applications of oxazolidinones as chiral auxiliaries in the total synthesis of natural products.[41] However, due to the plentiful work done in several laboratories worldwide, resulting in numerous publications and limitation of space, we have restricted ourselves to cover only the applications of oxazolidinones in the asymmetric aldol reactions.[41] Due to this self-limitation, as a complementary to our previous work,[41] herein, we wish to report the applications of oxazolidinones in the asymmetric alkylation leading to a highly stereoselective alkylation of enolates leading to the total synthesis of various natural products, preferably, those showing remarkable biological activities. In this report, we try to reveal the usefulness of oxazolidinones employed as a chiral auxiliary in an essential asymmetric alkylation, in one or more decisive steps in total synthesis of some natural and complex targets. We feel obliged to mention that a review concerning the applications of oxazolidinones as chiral auxiliaries in the asymmetric 1,4-addition in the total synthesis of natural products will be published separately.

2. Applications of oxazolidinones as chiral auxiliaries in the asymmetric synthesis: An overview

Generally speaking, asymmetric synthesis is a selective synthesis of one enantiomer or diastereomer form of an optically active compound. It is an over growing important strategy in modern synthetic organic chemistry particularly in the total synthesis of biologically active natural products.[42] In general, there are two strategies to the synthesis of enantio- and diastereomeric pure organic compounds. The first approach is to employ a resolution step so-called racemic modification. A second strategy, so-called asymmetric synthesis is simply to start

from an enantiomerically pure substrate, reagent, solvent or catalyst. These starting materials are often chosen from commercially available or readily accessible natural products, or their modified derivatives, obtained from the so-called "chiral pool," for instance amino acids, saccharides, small terpenes. Commercially available chiral amino alcohols reacted with phosgene[43, 44] are also frequently used for this purpose.

Undoubtedly, in general the superior method from different points of view for the preparation of enantiomerically pure compounds is asymmetric catalysis. In this methodology, a catalytic quantity of an enantiomerically pure (or enriched) agent is employed to provide asymmetric environment in the transition state of a reaction, which expectedly resulted in the selective formation of one enantiomer of the product. This catalytic asymmetric high induction, leads into an overall augmentation of asymmetry in the reacting system. Furthermore, a protocol that leads to a successful asymmetric synthesis involves, using an appropriate compound so-called chiral auxiliary. Chiral auxiliaries are generally reliable and versatile, enabling the synthesis of a large number of enantiomerically pure compounds in a time-efficient fashion. Therefore, chiral auxiliaries have been used in the early phases of drug development.[2]

In an asymmetric synthesis, a suitable chiral auxiliary with well-established absolute configuration is initially assembled, provisionally by covalently bonding onto a compound, which can be used as a precursor in chiral inducing step. In this approach, an ideal asymmetric synthesis should proceed with high stereoselectivity and must be highly predictable relative diastereoselectivity. Significantly, using this approach in this step; an undesired diastereomer can be removed by an appropriate conventional method. Ultimately, the temporary directing segment is cleaved to afford the desired enantiomerically pure compound. Ideally, the liberated chiral auxiliary, should be recycled directly. However, some chiral auxiliary should be chemically modified after the recovery for an efficient recyclability.

On contrary to the catalyzed asymmetric synthesis, using chiral auxiliaries is a relatively mature science. Several chiral auxiliaries have been developed and introduced to different substrates that in general are highly predictable in terms of efficiency, level and logic of asymmetric induction, and other practical considerations. A good chiral auxiliary must be a) commercially available or readily accessible in both enantiomeric forms, b) rapid and easy to prepare, c) easy to install, d) give high levels of asymmetric induction, e) easy to remove and f) being recyclable. It should give usually high level of diastereocontrol. The obtained diastereomers can be separated by

conventional methods such as chromatography, crystallization and the logic of asymmetric induction can be determined by X-ray crystallography.

It should be noted that use of chiral auxiliaries may experience some draw backs such as a)both enantiomers of auxiliary neither being commercially available, nor readily accessible, thus should be synthesized *via* difficult reaction approaches b) Similar to protection and deprotection extra steps should be added to the multi-step reactions leading to decrease the yields of the desired products. Assemblage and removal are required c) A stoichiometric quantity of chirality is required.

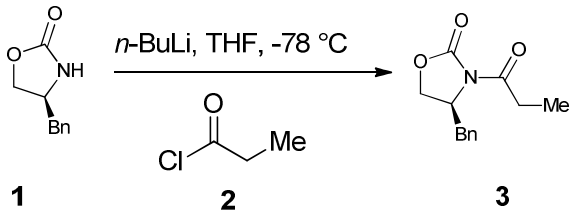
Chiral auxiliaries were first discovered and introduced by E.J. Corey in 1975,[45] using chiral 8-phenylmenthol followed by discovery of chiral mandelic acid by B.M. Trost.[46] As menthol is difficult to synthesize *trans*-2-phenyl-1-cyclohexanol was introduced by J. K. Whitesell in 1985 as an alternative.[47] Undoubtedly, nowadays, the most efficient and frequently used chiral auxiliaries with prevalent applications are chiral oxazolidinones developed and reported by David Evans.[1] Oxazolidinones are a class of compounds containing 2-oxazolidone. In their structures, 2-oxazolidone is a heterocyclic compound containing both nitrogen and oxygen in a 5-membered ring. They are usually prepared from chiral natural amino acids.[43, 44, 48-52] Evans' chiral auxiliaries usually reacts with acid chloride to form an imide. Substituents at the 4 and 5 positions of the oxazolidinones direct any aldol reaction to the alpha position of the carbonyl of the substrate. They have been used in the asymmetric synthesis of a wide variety of enantiomerically pure derivatives.

2.1. In alkylation of enolates

One of the best realized and most popular reaction of acylated Evans' oxazolidinones is diastereoselective alkylation. In spite of the advantages realized for the asymmetric catalysis, organic synthetic chemists, frequently turn to Evans' methodology, especially when optically pure carboxylic acid derivatives are required as final products or as intermediates. Whereas, not graceful as asymmetric catalysis, the applications of chiral auxiliaries remains a very significant and frequently used strategy to asymmetric synthesis. In this line, the total synthesis of cytovaricin by Evans and coworkers is considered as a classic application of oxazolidinones as chiral auxiliaries for one asymmetric alkylation and four asymmetric aldol reactions required to settle the absolute configuration of nine stereogenic centers present in the aforementioned natural

products.[53] Since then, Evans' oxazolidinones are the most well-known and frequently used chiral auxiliaries for stoichiometric asymmetric approach in the total synthesis of natural products.[54] The most conventional applications of Evans' oxazolidinones are α-alkylation and *syn*-aldol reactions, which can provide either enantiomers or diastereomers containing susceptible function groups for further functionalization. In addition, Evans' oxazolidinones owe their popularity to their reliable and readily scalable reaction procedures. Furthermore Evans' oxazolidinones are applicable in asymmetric anti-aldol reactions, Michael addition, addition to C=O and C=N bonds and cycloaddition etc.[15, 16] It is observed that the steric hindrance of substituents at 4 and 5 positions of oxazolidinones are actually, control the stereoselectivities of many alkylations of enolates.

As an extension to the original oxazolidinones, a plethora of modified derivatives has been developed over the years and find applications in asymmetric synthesis. A pool of fruitfully applicable oxazolidinone based on these modified chiral auxiliaries has been collected in an informative review presented by Cowden *et al*.[20] The first step reaction for oxazolidinone acting as a chiral auxiliary in an asymmetric synthesis is the attachment of an appropriate substrate to the selected oxazolidinone derivative, which is commonly accomplished *via* an *N*-acylation reaction using *n*-BuLi as a base and an acid chloride or anhydride (mixed or symmetrical) as the acetylating agents.[55] The utilization of chiral *N*-acyloxazolidinone auxiliaries to control configuration of the generated stereogenic centers has found extensive applications in several reactions (Scheme **1**).[22, 24]



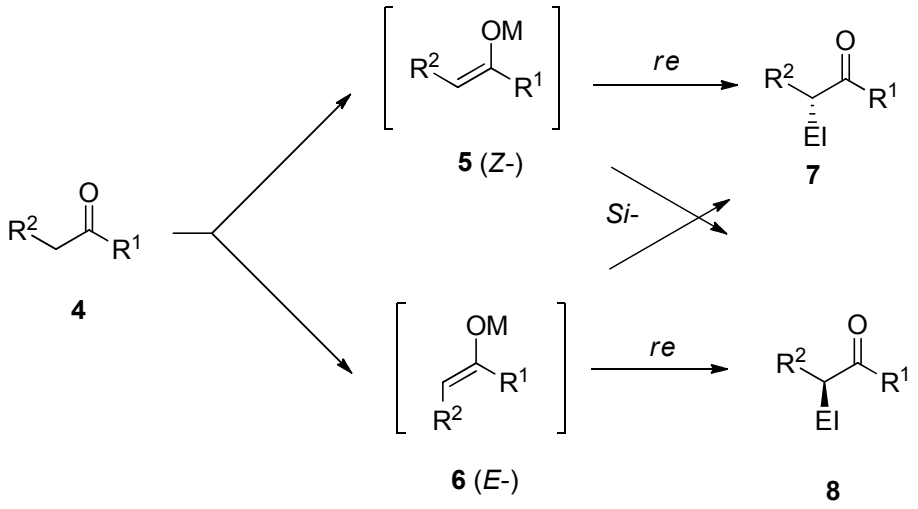
Scheme 1.

An efficient and facile approach for the *N*-acylation without observation of epimerization was achieved and reported by David Ager *et al*.[56] On the other hand, the alkylation of lithium, sodium, and potassium enolates derived from *N*-acyloxazolidinones was successfully achieved

for the preparation of many chiral framework. Noticeably, the reaction is in general limited to very few reactive alkylating agents for instance allyl and benzyl halides.[57]

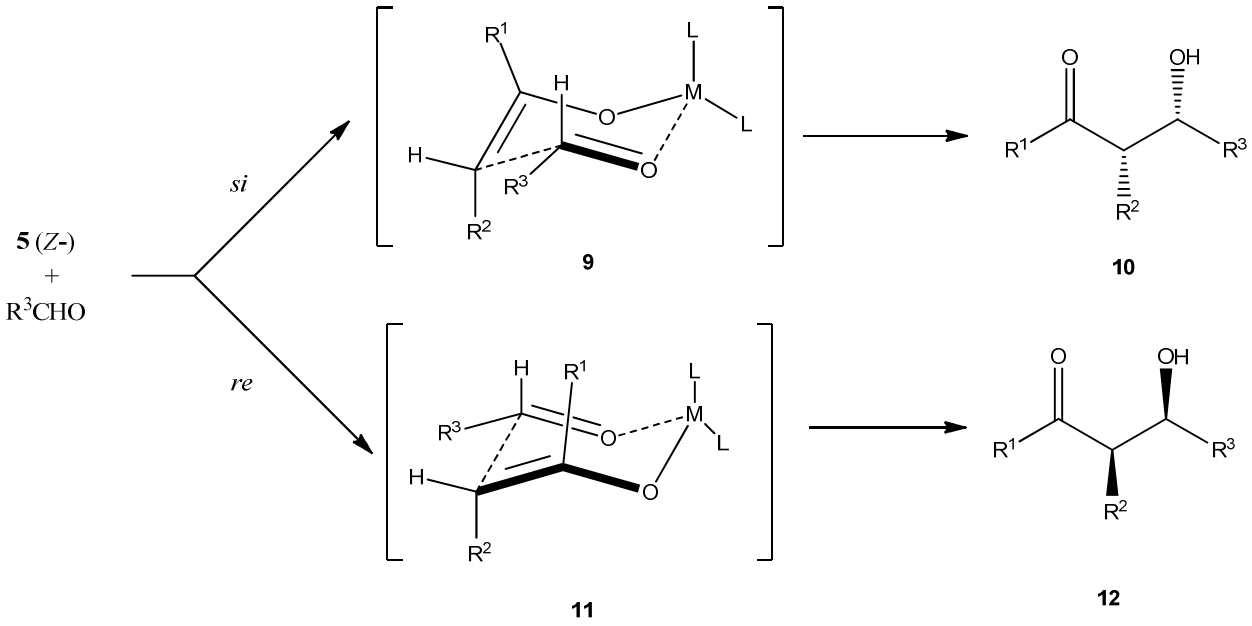
During the years, remarkable progresses in enolate chemistry have been realized and proven as a powerful tool, mostly in asymmetric carbon-carbon and C-X (X= hetero atom) bond formations, One of the most common and famous reaction is the aldol reaction in which the enolate chemistry is playing key role. Two useful reviews revealing different aspects and issues of aldol reaction have been presented by Cowden and Paterson[20] and by Nelson.[58] Cowden and Paterson collected and described auxiliary-, substrate and ligand-mediated stereo- and enantioselective aldol reactions[1]whereas Nelson summarized the catalytic, enantioselective aldol reaction employing chiral Lewis acids and bases.[58]

During the years, chemists have developed various protocols to create regioselective (kinetic vs. thermodynamic) as well as generating enolates stereoselectively. Parameters that govern these controls are presented in reviews.[20,59-61] Under kinetic conditions, two stereoisomers, known as *Z*-(**5**) or *E*-enolates **6** are obtained *via* the enol ether which was generated from keto derivative **4**. Each isomer then can react with the electrophile (*re* -or *si*-face attack) to provide two different products **7** and **8**. There are several parameter and factors, which control the stereoselective formation of the enol ether. Subsequently the stereroselective-generated enol by the π-face attacks the electrophile selectively. Generally, enolate geometry plays the key role in determining the stereochemical result of aldol reaction, which is believed to proceed *via* a cyclic transition state. *Z*-enolate, **5** reacts with an aldehyde to produce 1,2- *syn* products **10** or **12**, while 1,2-*anti* products **14** or **16** are obtained from an *E*-enolate. Now it is well realized that the reaction proceeds *via* a six-membered cyclic transition state, suggested by Zimmerman- (only favored transition states are illustrated, see: **9**, **11**, **13** and **15**) in which the alkyl group of the aldehyde derivative espouses a pseudo equatorial position. In cases of 1,2-*syn* **10** and **12**, or 1,2-*anti* **14** and **16** aldol products, the enantioselectivity can be achieved *via* using a chiral auxiliary or a chiral ligand based enolate (Schemes **2**, **3** and **4**).

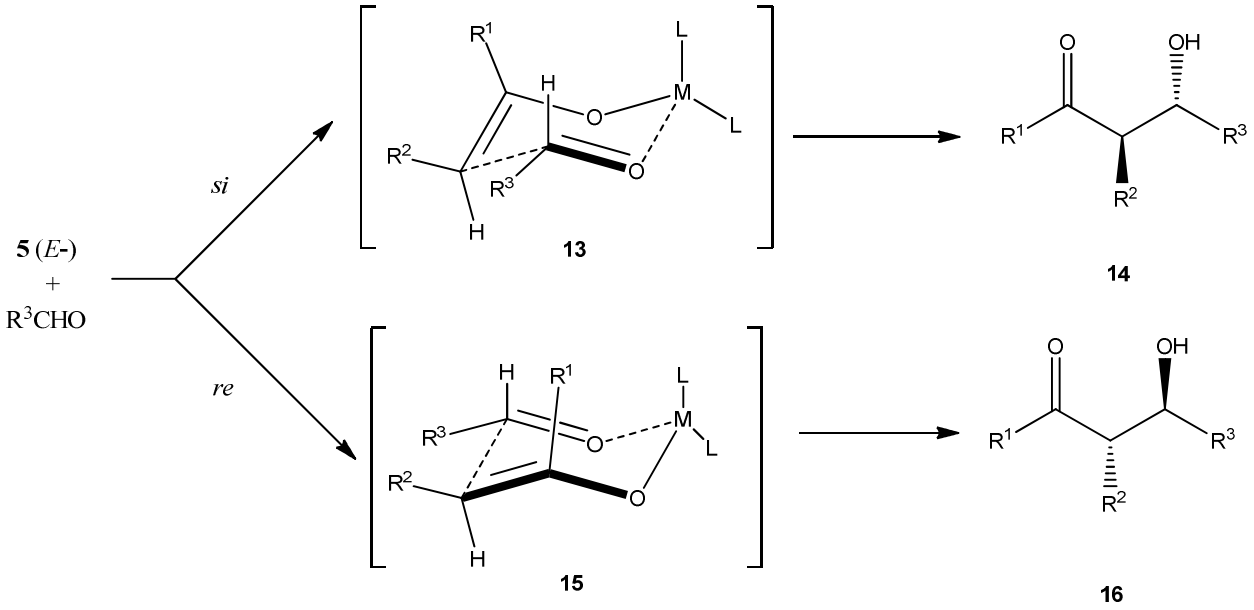


R^1, R^2: alkyl groups; M: metal; EI: electrophile

Scheme 2.

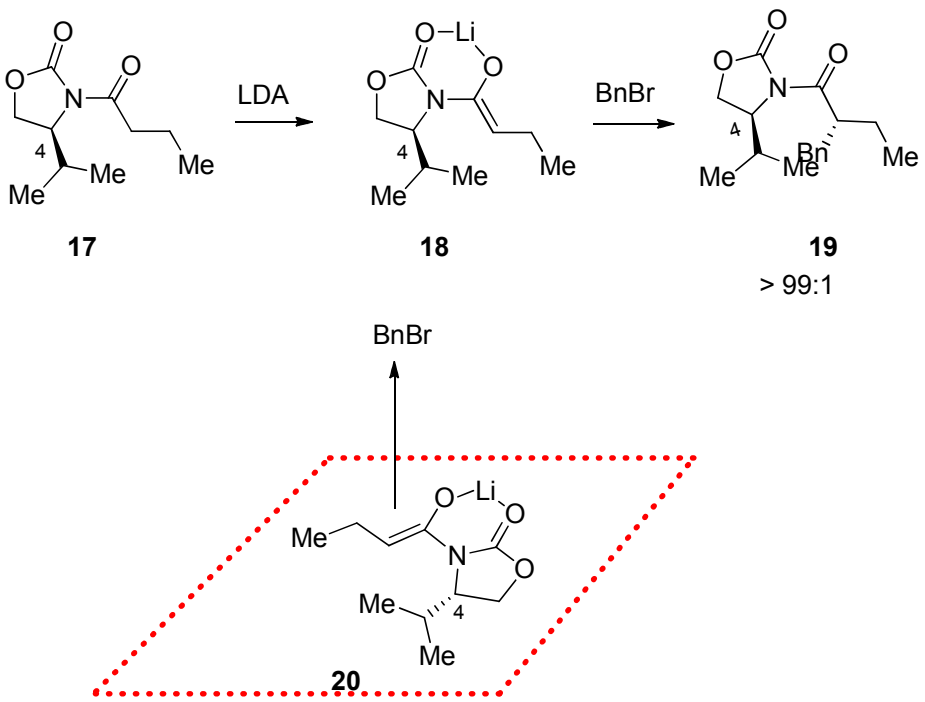


Scheme 3.



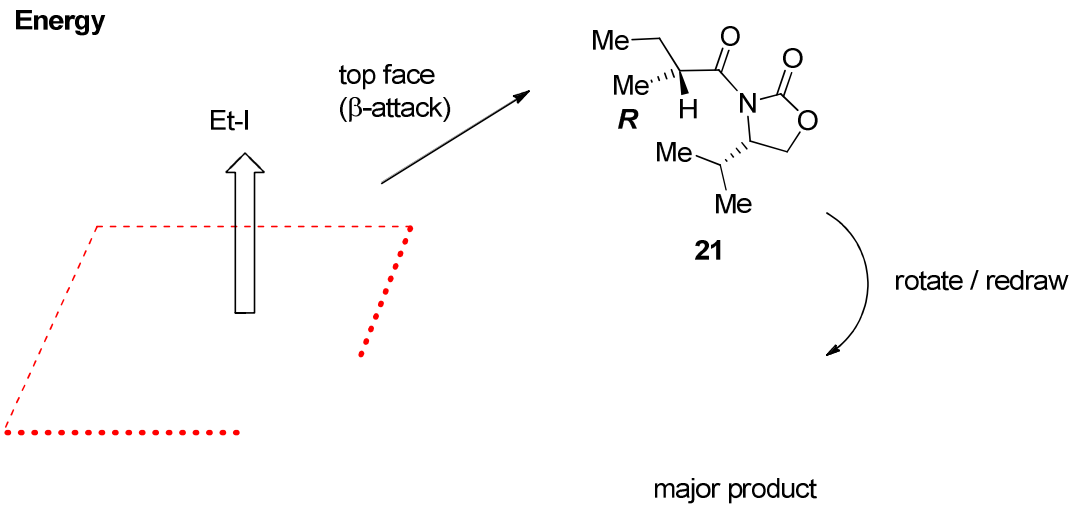
Scheme 4.

Evans, the pioneer, described that *Z*-enolates were often generated with excellent selectivity and then the electrophiles have a tendency to attack from the opposite face to the chiral controlling group at C4 position of oxazolidinone ring.[57] The high to excellent diastereoselectivity of oxazolidinone as chiral auxiliary in alkylation reactions has been realized and well-established. The model shown in Scheme **5** consistently assigns an example and the configuration of the major product.



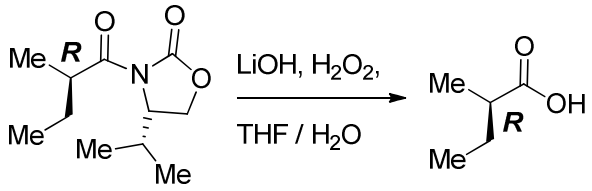
Scheme 5.

In the presence of Evans' oxazolidinones, the transition states for alkylation are not energetically equivalent, thus they are diastereomeric, leading to asymmetric alkylation (Scheme **6**).



Scheme 6.

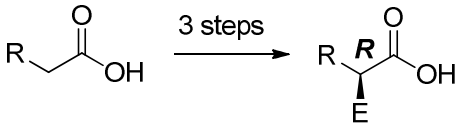
Bulky isopropyl group blocks the attack of the electrophile from the bottom face; therefore, the attack takes place from the top face (Scheme **7**).



21 **22**

Scheme 7.

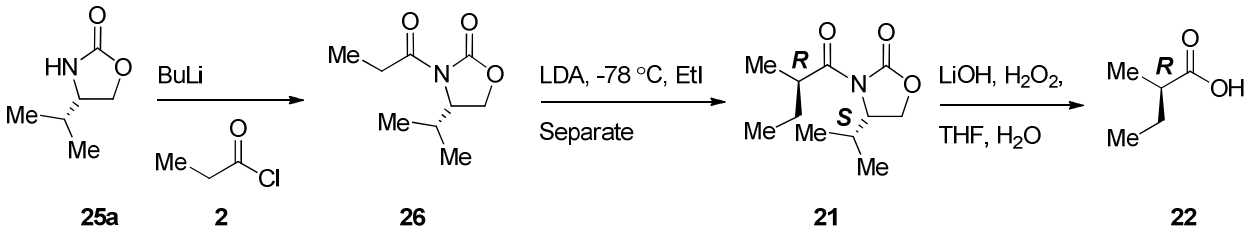
Evans' oxazolidinone approach to α-alkylation of carbonyl compounds was a keystone of modern asymmetric synthesis (Scheme **8**).



23 **24**
> 98% e.e.

Scheme 8.

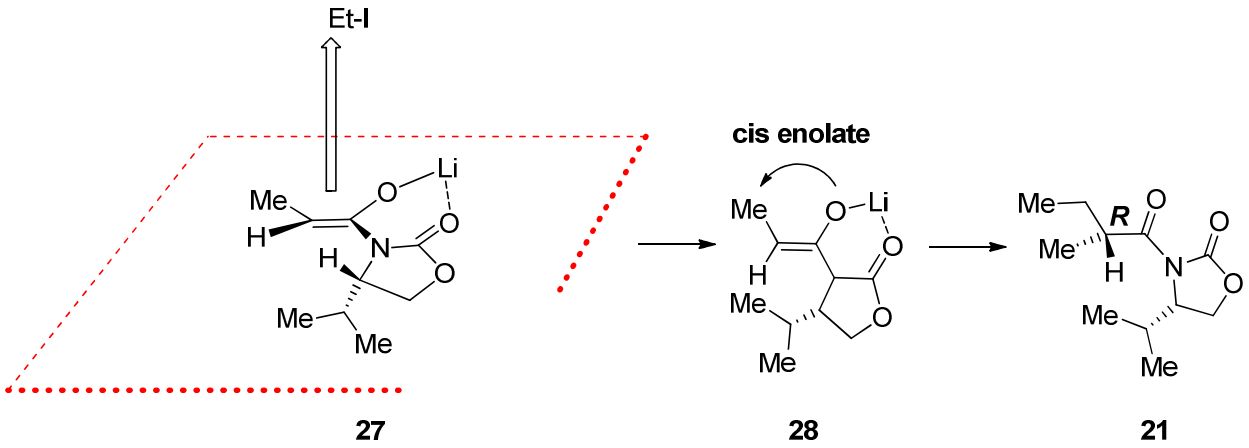
Diastereoisomeric ratios have been measured by i) HPLC, ii) GC or iii) ^{1}H NMR. Diastereomers are separated by common methods (chromatography or crystallization). This reaction affords a single diastereomer, upon the removal of the chiral auxiliary affording a single enantiomer, the acid **22** as the product in 88% *ee* (Scheme **9**).



25a **2** **26** **21** **22**
> 98% d.e. > 98% e.e.

Scheme 9.

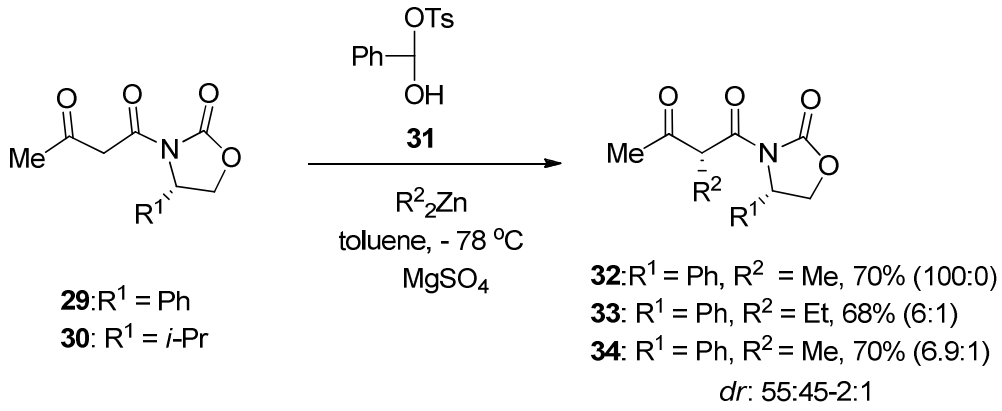
The origin of the high diastereoselectivity, in which only one enolate geometry (*cis*) generated can be attributed to I) chelation of Li to the carbonyl of the auxiliary and II) minimization of steric interaction as H prefers to take position eclipse to *i*-Pr group instead of Me eclipsing *i*-Pr group. In addition, the large *i*-Pr group safeguards only one face of the enolate (Scheme **10**).



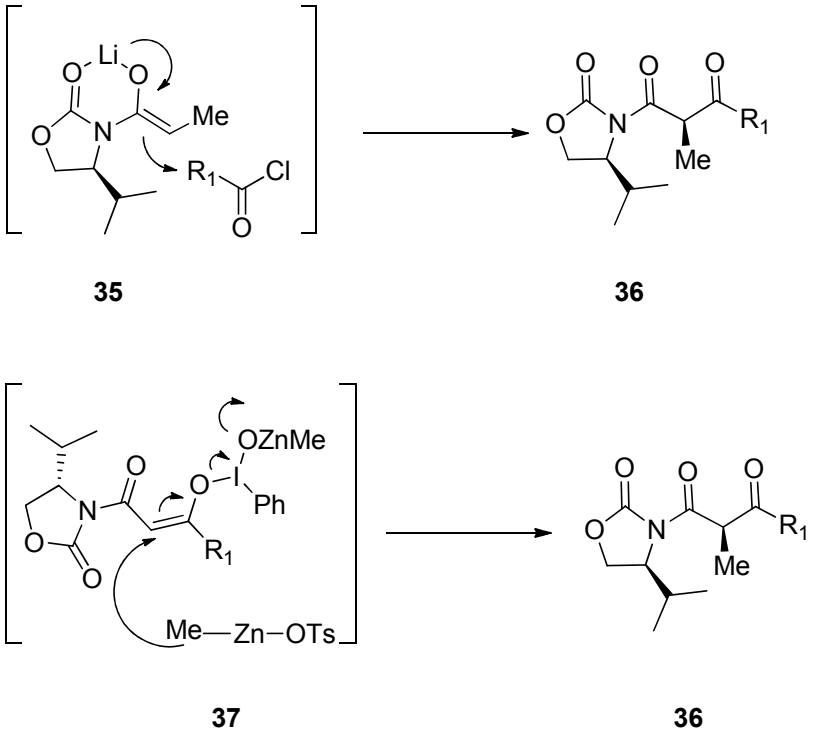
Scheme 10.

Szpilman *et al.* in 2015 reported the first example of highly stereoselective umpolung alkylation of Evans' β-ketoimides. Umpolung alkylation of Evans' auxiliary substituted β-ketoimides provides the diastereomerically pure products in 40-80% yields. The reaction proceeds with diastereoselectivities between 3:1 and 18:1. Umpolung of the β-ketoimide enolate was observed when dialkylzinc used as the nucleophile, along with the action of Koser's reagent. This reaction actually relies on the oxidative umpolung alkylation of β-ketoimides **37** under mild conditions. In fact, this achievement solved a solution of the long-standing challenge of stereoselective alkylation of Evans' β-ketoimides and it is an invaluable alternative to the conventional acylation chemistry intellectually developed by Evans and his coworkers. Remarkably, these β-keto-imides, under neutral mild basic conditions being found configurationally stable.[63] These compounds are very popular as scaffolds in the total synthesis of naturally occurring products,[63] pharmaceutical agents,[64] and also in the synthesis of chiral frameworks. [65] In practice, methylation of β-ketoimide **29** or **30** using dimethyl zinc in the presence of Koser's reagent **31** proceeded smoothly, resulting in corresponding methylated compounds **32** and **34**, respectively, in satisfactory yield and good stereoselectivity (Scheme **11**). Notably, no tosylation products

were isolated from these experiments. The relative stereochemistry of **33**, which was synthesized as above, determined by X-ray analysis of crystals of the chief diastereoisomer. Relied on the known *S*-configuration of the starting material **29** the configuration of the new chiral center was determined to be (*R*) unambiguously. It is worthwhile to note that the sense of stereo-induction accomplished is identical to that obtained from Evans' pioneered work on acylation[66] in which a completely different bond is formed. This reaction takes place *via* acylation of an in situ created Z-lithium enolate **35** (Scheme **12**).[67] On contrary, the present umpolung alkylation gives a product with the same relative configuration. Based on this observation and relied to the earlier mechanistic investigations,[67] it can be suggested that the alkyl group is delivered to the *Si* face of an incipient *Z*-iodine(III)-enolate as illustrated in **37**.[67] Noticeably, in compound **37**, dipole-dipole interactions are minimized, resulted in an anti-periplanar relationship between the two imide carbonyl groups (Scheme **12**), identical to that seen in the X-ray of **33**. It means that the nucleophile alkyl zinc delivers the alkyl group to the less shielded face of the enolate. This assumption is in line with the previously mechanistic investigations.[67]

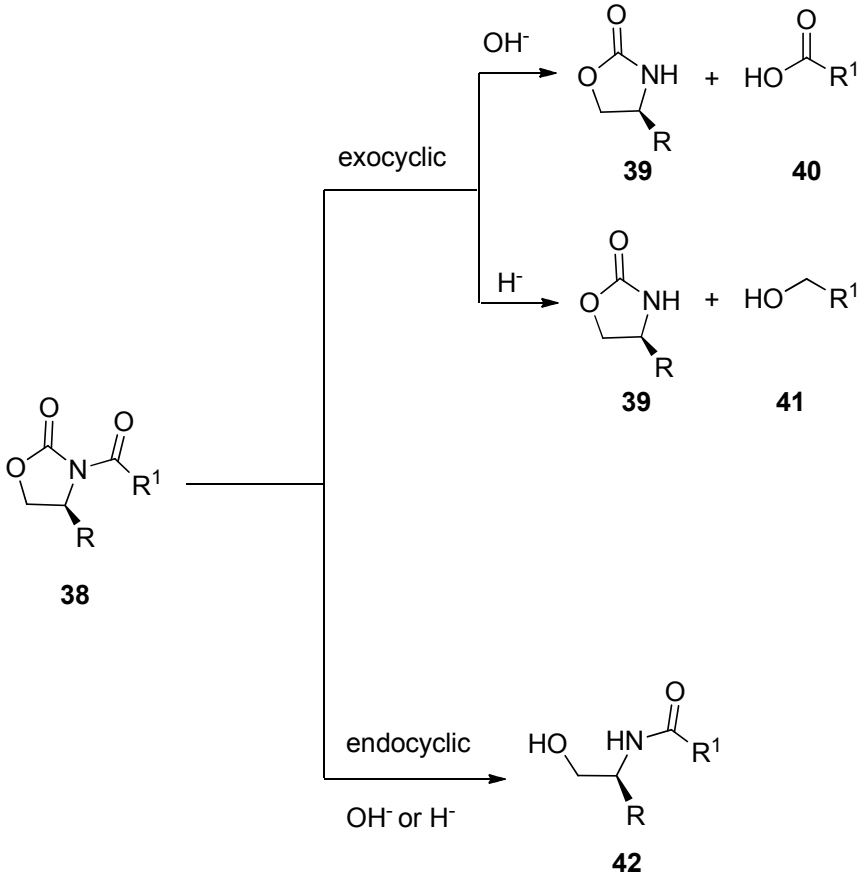


Scheme 11.

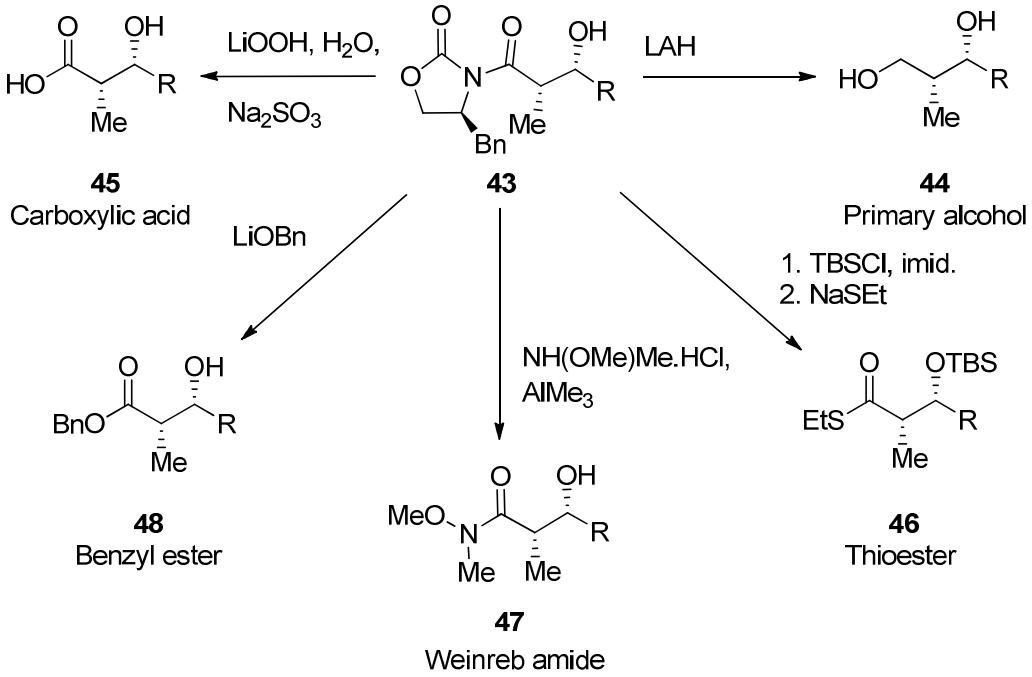


Scheme 12.

Besides, the deprotonation of the α-carbon of an oxazolidinone imide with a strong base i.e, LDA takes place selectively generating the (*Z*)-enolate, which can be subjected to stereoselective alkylation.[68] Upon the stereospecific reaction using an oxazolidinone, the chiral auxiliary was conveniently separated from the product and can be examined for re-using. Notably, two kinds of cleavage of oxazolidinones can be occurred: exocyclic and endocyclic cleavages.[10] The exocyclic cleavage is frequently observed but endocyclic cleavage takes place even when the oxazolidinone derived carboximides **38** is carrying a bulky R_1 group (Scheme **13**). A wide variety of conversions has been introduced to the facile removal of the oxazolidinone auxiliary. A plethora of reagents i.e, KOH, LiOH, $LiBH_4$, LiOR, N_2H_4/*n*-amyl-ONO/NH_4Cl, Cp_2TiCl_2, and Cp_2ZrCl_2 MeONHMe HCl/AlMe have been used for this purpose (Scheme **14**).[4, 10, 19] Very recently, in 2016, a useful concerning the applications of sodium borohydride in the reductive removal of Evans and other chiral auxiliaries has been appeared in the chemical literature.[4] Remarkably, it has been found that the removal of the oxazolidinone auxiliaries occurs with neither racemization nor epimerization and most remarkably the auxiliaries can be readily recovered and reused.



Scheme 13.

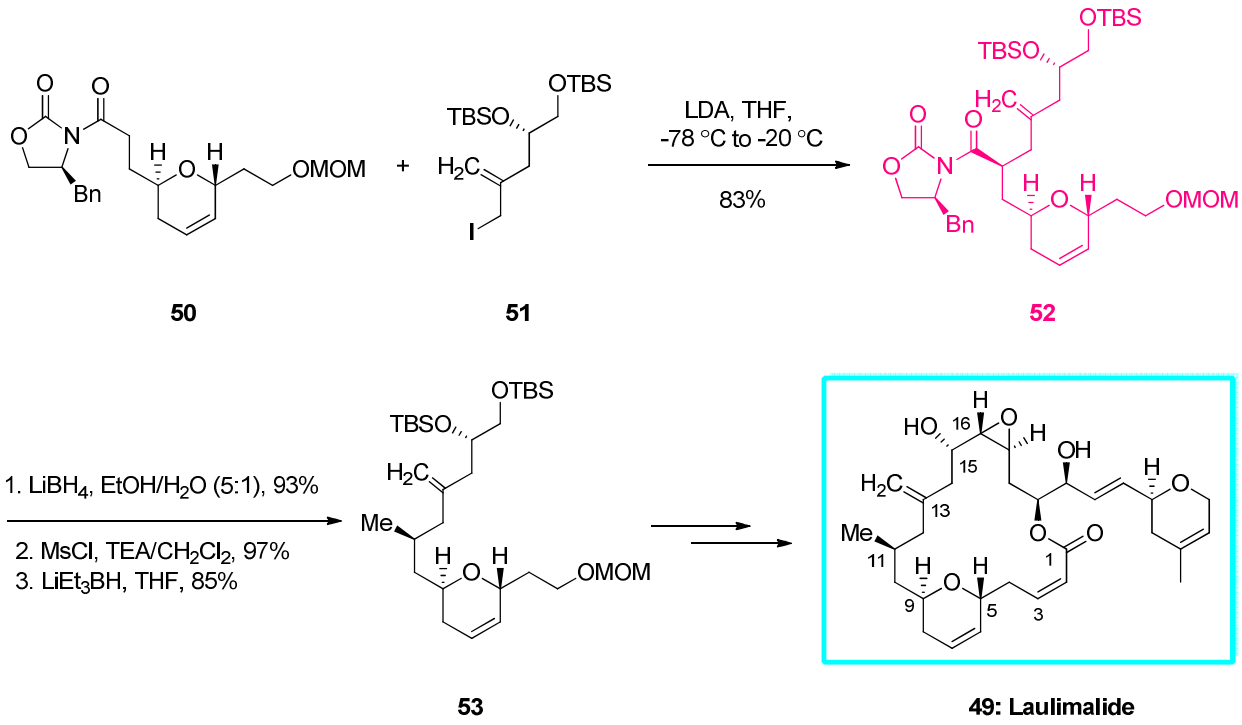


Scheme 14.

2.2 In the total synthesis of natural products

Evans' oxazolidinones are among the most well established and extensively used chiral auxiliaries for stoichiometric asymmetric methods in total synthesis. The most common applications of oxazolidinones are actually, α -alkylation, *syn*-aldol reactions, and 1,4-addition which construct corresponding either enantiomers or diastereomers containing flexible function groups for further elaboration. Most importantly, in spite of the general superiority of the catalyzed asymmetric synthesis, Evans' oxazolidinones are still broadly used as chiral auxiliaries as stoichiometric stereoselective methodology in the total synthesis of some natural products. Significantly, in a crucial and determining step (steps) for the desired induction of chirality to the product and construct a stereogenic center that should be controlled, this kind of chiral auxiliary is required. The chiral auxiliary in this point can completely preserve or totally invert the configuration in a way to have an identical configuration with that of desired natural product as a target.

Laulimalide **49** was initially isolated from a marine sponge.[69] In addition to its observed cytotoxicity against the KB cell line,[70] this macrolide **49** has been an interesting target form the synthetic point of view, for synthetic organic synthetic chemists. The synthesis of the C_1-C_{16} fragment of laulimalide **49** has been accomplished by Nishiyama and coworkers. For providing this fragment in a key step, an asymmetric induction by a chiral oxazolidinone is required. As illustrated in Scheme **15**, the C_1-C_{16} fragment can be obtained by alkylation of the C_3-C_{11} fragment **50** using allyl iodide **51**. The configuration of newly generated stereogenic center at the C_{11} position is induced by the Evans' oxazolidinone strategy. Allyl iodide **51** is coupled with lithium enolate of **50** to afford the alkylated adduct **52** as the sole alkylated product in 60% yield. Conversion of a carboximide to a methyl group, together with removing of the oxazolidinone auxiliary was productively performed in three steps to obtain **53**. The latter, after several steps, gives the desired target **49**.[71]

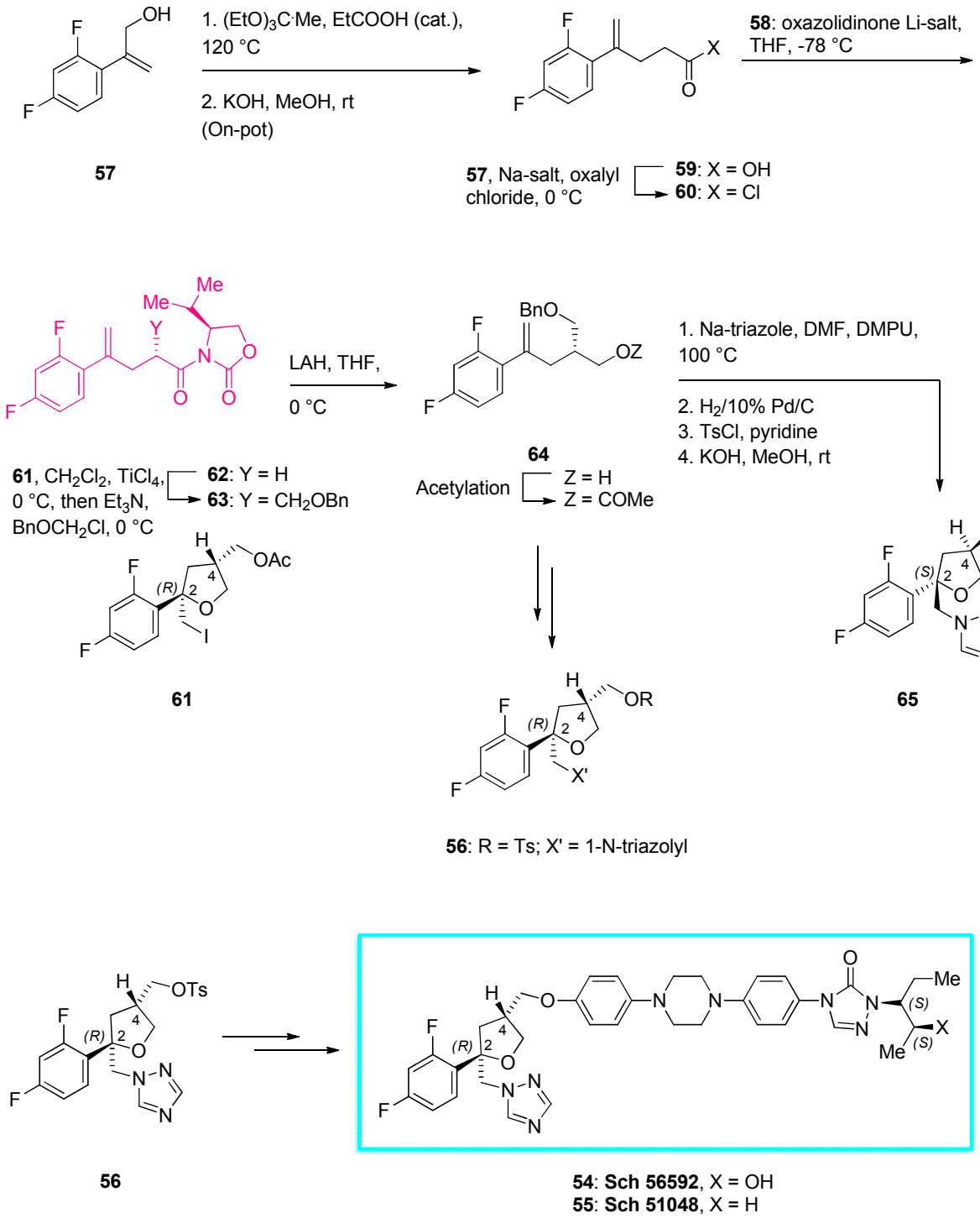


50 **51** **52** **53** **49: Laulimalide**

Scheme 15.

An efficient method for the synthesis of **Sch 56592 54** showing improved therapeutic potency relative to **Sch 51048 55** as an antifungal agent has been reported.[72, 73] There are two strategies for the synthesis of the key (—)-(2*R*)-*cis*-tosylate **56** and its (+)-(2*S*)-enantiomer **65**. Saksena *et al*. reported two approaches for the synthesis of **56** using chiral oxazolidinones provided from (*S*)-valinol and (*R*)-phenylalaninol respectively.[74] In the first route, the acid chloride **60** was provided from allyl alcohol **57** upon treatment with the lithium salt of the (4*S*)- (—)-4-isopropyl-2-oxazolidinone under standard conditions.[57] Compound **60** reacted smoothly with oxazolidinone Li-salt to afford chiral imide **62** in high yield. The benzyloxymethyl functionality was reacted with the lithium enolate of **62** using benzyloxymethyl chloride as the alkylating agent. In spite of the excellent diastereoselectivity, observed (98:2) for the desired benzyl ether **63**, the chemical yields were inappropriately low (30%). Delightfully, when titanium enolates of *N*-acyloxazolidinones were used, appreciable improvements over Li-enolates regarding the practical simplicity and high diastereoselectivity were realized.[75, 76] Therefore, alkylation of **62** with benzyloxymethyl chloride *via* the Evans' titanium enolate strategy [77] afforded the benzyl ether **63** in high chemical yields (> 98% *de*). Reduction of the latter using LAH in THF, afforded the desired (—)-(2*S*)-diol monobenzyl ether **64** in high yield while simultaneous, 80% recovery

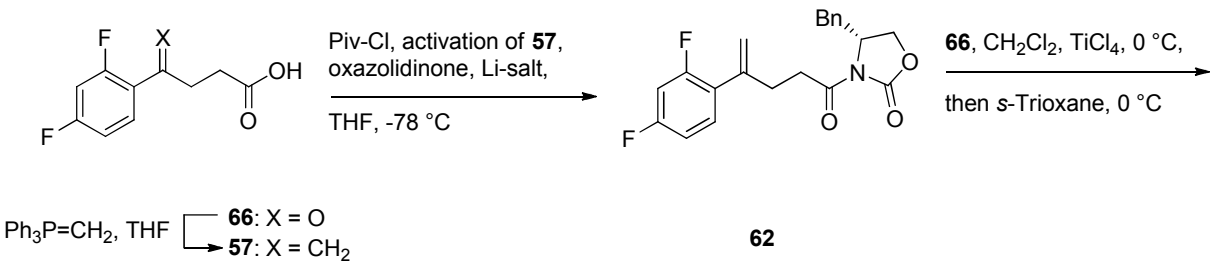
of the chiral auxiliary was possible. After several steps, the desired (−)-(2*R*)-*cis*-tosylate **56** [77] was obtained in overall 90% chemical yield and excellent optical purity (> 99% *ee*). The enantiomeric (+)-(2*S*)-*cis*-tosylate **65** could be principally prepared easily *via* conducting the above sequence using an appropriate chiral auxiliary i.e, (4*R*)-(+)-4-isopropyl-2- oxazolidinone. Compound **64** was converted into **56** [78] in two steps. Compound **56** can be transformed to the desired natural product **54** *via* a multi-step synthesis (Scheme **16**).[74]



Scheme 16.

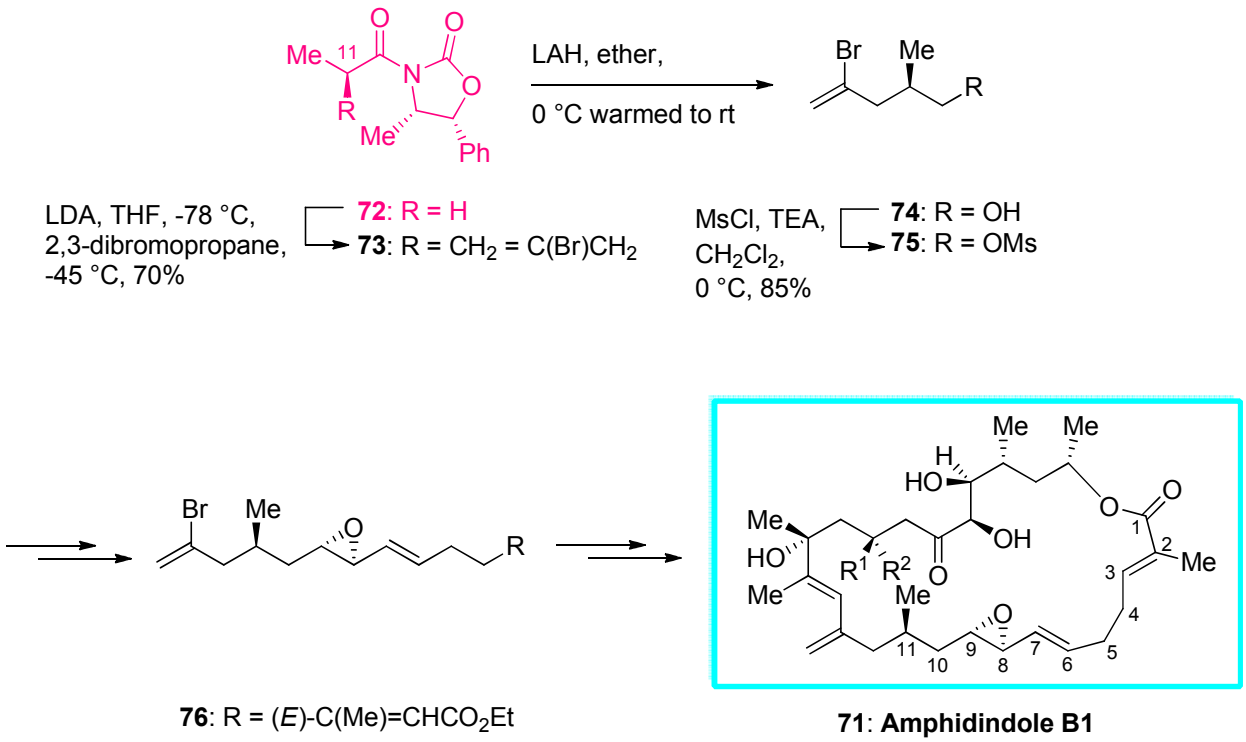
An alternative route for the synthesis of **56** to avoid protection-deprotection processes for obtaining higher yield was also considered. The allyl alcohol **57** was provided in four-steps

starting from 1,3-difluorobenzene.[77] On the other hand, through the other route, the olefinic acid **59** can be synthesized in two facile steps, involving Fridel-Crafts reaction of *m*-difluorobenzene with succinic anhydride to afford the crystalline keto acid **66** in high yield. The latter undergoes a Wittig reaction using two equivalents of methylene triphenyl phosphorane in THF to obtain olefinic acid **59** in satisfactory (60%) yield over two steps. The (*R*)-phenylalaninol derived chiral imide **62** was provided *via* activation of **59** by pivaloyl chloride with subsequent in situ treatment of the resulting anhydride with the Li-salt of (4*R*)-(+)-4-benzyl-oxazolidinone.[57] High diastereoselectivity of hydroxymethylation of **62** was achieved with *s*-trioxane using titanium enolate chemistry,[76] obtaining the aldol product **67** in satisfactory yield. The direct iodocyclization of **67** at ambient temperature gave the desired *cis*-iodo compound **68** in high diastereoselectivity (*cis*:*trans* > 90:10, 90% chemical yield). Lithium borohydride reduction of **68** under controlled condition followed by column chromatography of the obtained, provided the *cis*-iodoalcohol **69** and recovered (4*R*)-benzyl-2-oxazolidinone in about 90% and 71% yields respectively. Then direct substitution of iodine in **69** with sodium-triazole afforded the alcohol **70** in 75% yields. The latter, it can be converted to the (−)-(2*R*)-*cis*-tosylate **56** which in turn can be transformed to the desired natural product **54**. Consequently, two steps in total synthesis were skipped in this manner (Scheme **17**).[74]



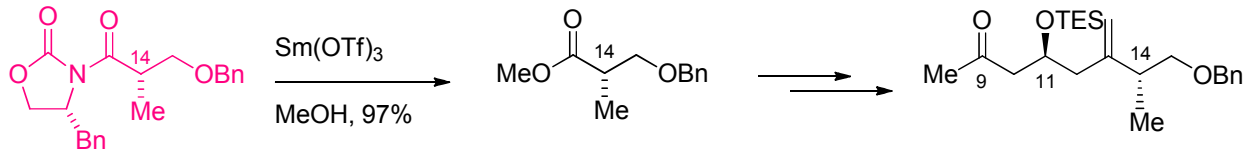
Scheme 17.

Amphidinolides A-Q were isolated from dinoflagellate, genus *amphidinium*. They exhibited high toxicities against cancer tumor cell lines.[78] The enantioselective synthesis of the C_1-C_{28} fragment of this cytotoxic natural product, amphidinolide B1 **71**, has been accomplished in 13 steps giving the desired target in 3.6% overall yield. The reaction starts with propionyl oxazolidinone **72**. The important features of this total synthesis are to make use of oxazolidinone to induce chirality at C11, Sharpless asymmetric epoxidation[79] for the construction of C8, C9-epoxide moiety, the ortho ester along with Claisen rearrangement for the formation of C6, C7-*trans* double bond and an ester functionality at C3 which is used in the final functional group conversions. Initially, oxazolidinone **72** was treated with 2, 3-dibromopropane using the Evans' strategy to provide the alkylated compound **73** in good chemical yield as a 96:4 mixture of diastereomers. Oxazolidinone **73** was then reduced to give the primary alcohol **74**. The latter, it was converted into the mesylate **75** in two steps in 85% yield. Upon filtration, the chiral oxazolidinone can be recovered. After several steps, the natural product **71** was obtained *via* intermediate, conjugate ester **76** (Scheme **18**).[80]

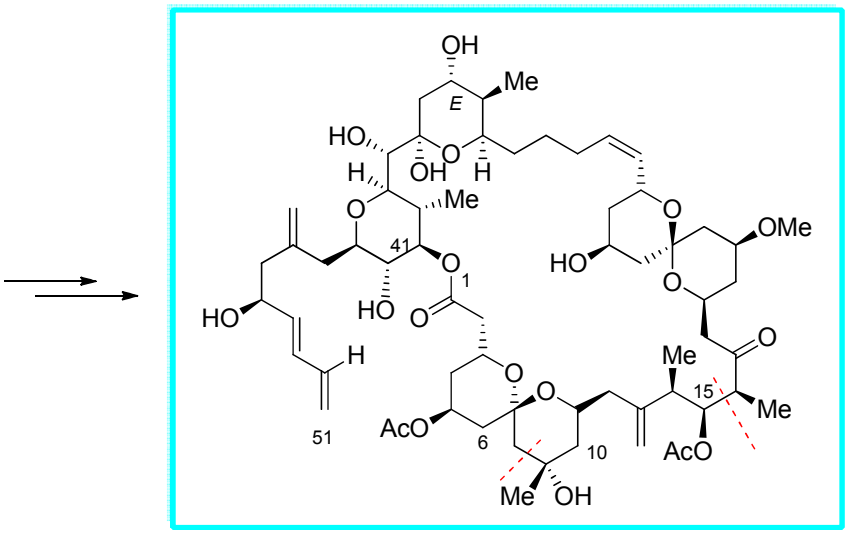


Scheme 18.

The total synthesis of altohyrtin C has been accomplished and reported.[81] Altohyrtin C (spongistatin 2) **77**, was initially isolated from marine sponges. This category of compounds often exhibits biological activities.[82] The reported total synthesis of **77** also confirmed the ambiguous structure assigned to altohyrtin C, which isolated from spongistatin 2.[82] The synthesis of the C_8-C_{15} segment starts with the chiral synthon **79**, easily provided from the titanium enolate alkylation of **78** carrying oxazolidinone as a chiral auxiliary.[76] Subsequent ketal hydrolysis followed by silyl protection gave the C_8-C_{15} methyl ketone segment **80** in a seven-step reaction in 53% overall yield (Scheme **19**).[83]



78 **79** **83**

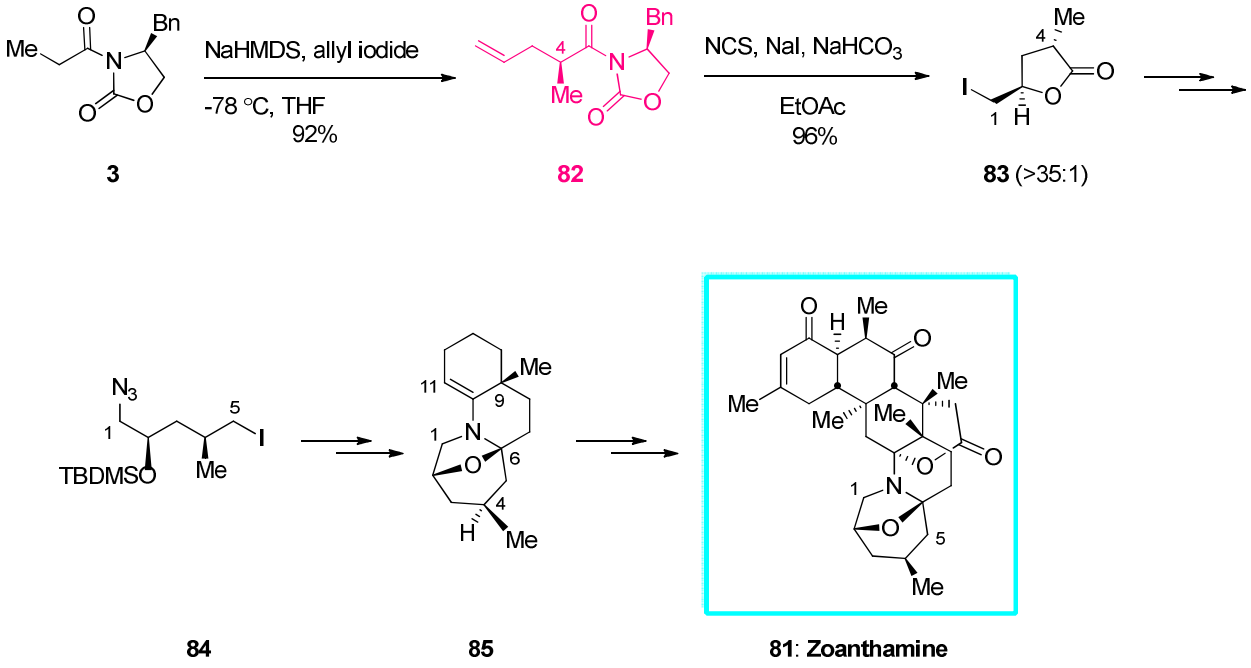


77: **Altohyrtin C**

Scheme 19.

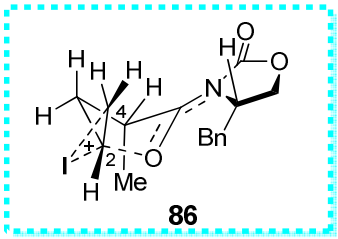
The zoanthamine alkaloids are placed in a family of marine metabolites with interesting arrangement of structural and stereochemical features.[84] Zoanthamine **81** has exhibited a potent inhibitory activity against phorbol myristate-induced inflammations. A brief enantioselective synthesis of the enamine-aminal heterocyclic core existing in the zoanthamine alkaloids was reported by Williams *et al.* in 1998.[85] The attempted total synthesis began with an

enantioselective synthesis of the essential C_1-C_5 amino alcohol segment. As depicted in scheme **20**, Evans' protocol was employed for asymmetric alkylation of **3** affording the known oxazolidinone **82** (98% *de*).[86] Upon iodolactonization, **82**, was converted to the *trans*-disubstituted butyrolactone **83** with excellent diastereoselectivity (ratio > 35: 1). Under buffered conditions, *N*-iodosuccinimide (NIS) was generated in situ in accordance with the protocol reported by the Merck Company researchers.[87] Apparently, the remarkable enhancement in the practical 1,3-asymmertic induction for this kinetic cyclization is caused by iodine to obtain **84**.[88] Then, the latter, which was a required intermediate for the total synthesis has been transformed into the desired natural product **81** in several steps manipulating functional group transformations (Scheme **20**).[85]



Scheme 20.

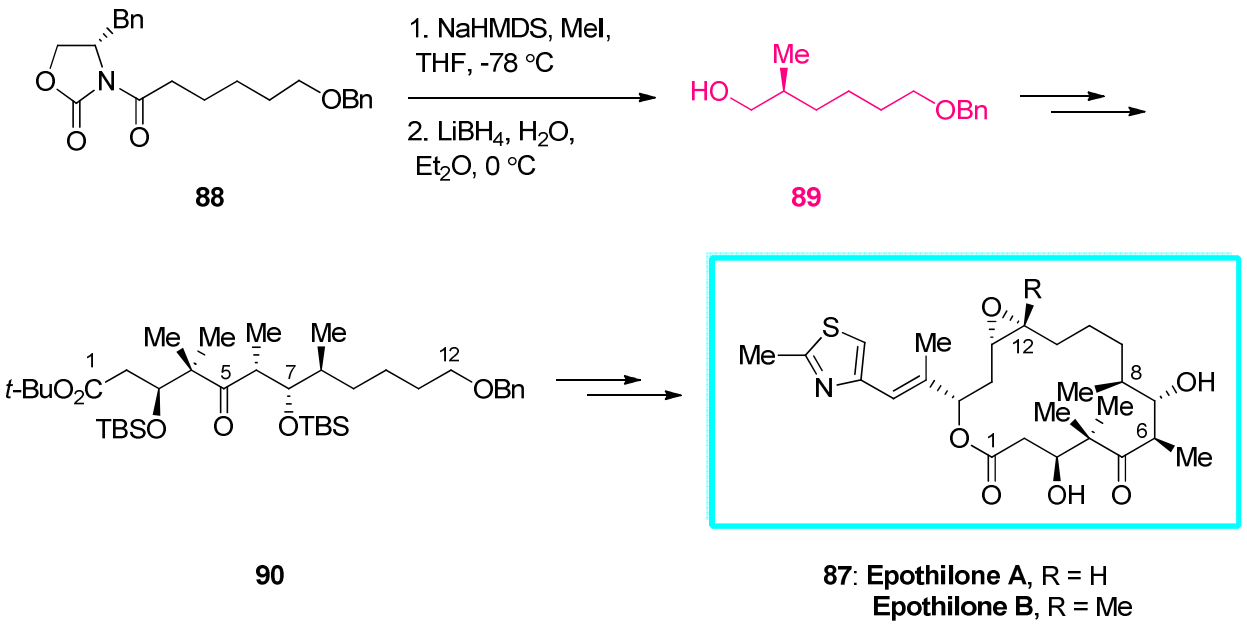
Upon iodolactonization, 2-methyl-4-pentenoic acid gives the respective *cis*-butyrolactone isomer with moderate selectivity. Nevertheless, the chiral auxiliary of **82** provides the potential for a (1,3) strain in the transition state **86** (Fig. **1**). In this way, nonbonded interactions are comforted in the iminium ion, which positioned the C4 methyl group in the pseudo-axial temper. A decrease, down to minimization of 1,3-diaxial interactions led to a pseudo-equatorial orientation for the iodomethyl moiety.[89]



86

Figure 1.

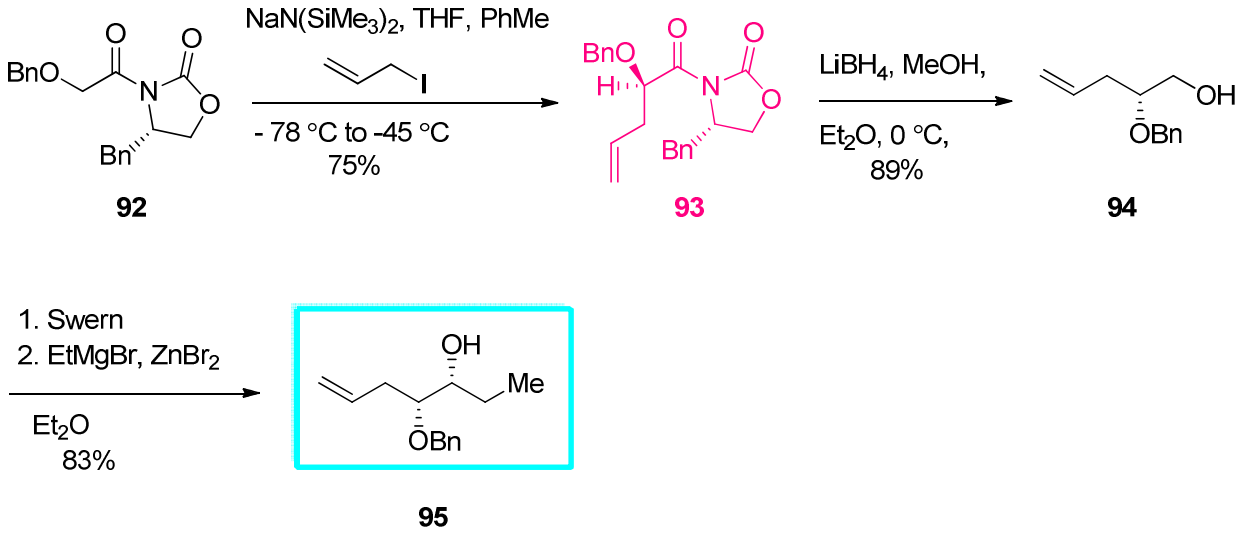
The interesting biological properties of epothilones **87** [90, 91] as powerful antifungal and antitumor agents, showing even better microtubule-stabilizing properties than taxol-like counterpart does. Thus, they universally attracted tremendous attentions of the organic chemists. Its total synthesis has been achieved and reported have been reported.[92] Chakraborty *et al*. used samarium(II) iodide for the diastereo- and regioselective ring opening of a trisubstituted epoxy ketone, which being opened from the more substituted carbon. In this way, they reported an alternative strategy to provide the C_5-C_7 aldol moiety with *β*-hydroxyketo scaffold in the stereoselective synthesis of C_1-C_{12} fragment **90** of epothilones A and B.[93] The total synthesis commenced with oxazolidinone **88** to provide the desired target, the mono-benzyl-protected hexane-1, 6-diol in three steps. Diastereoselective alkylation of the sodium enolate of **88** carrying oxazolidinone as a chiral auxiliary was achieved using MeI as a methylating agent.[57] Conventional reductive removing of the chiral auxiliary[93] (80% in two steps) gave the desired alcohol **89**. Ultimately, after several steps, involving functional group transformations, the desired target compound **90** was obtained. The conversion of an intermediate quite similar to **90** has already been reported for the synthesis of epothilone A (Scheme **21**).[92]



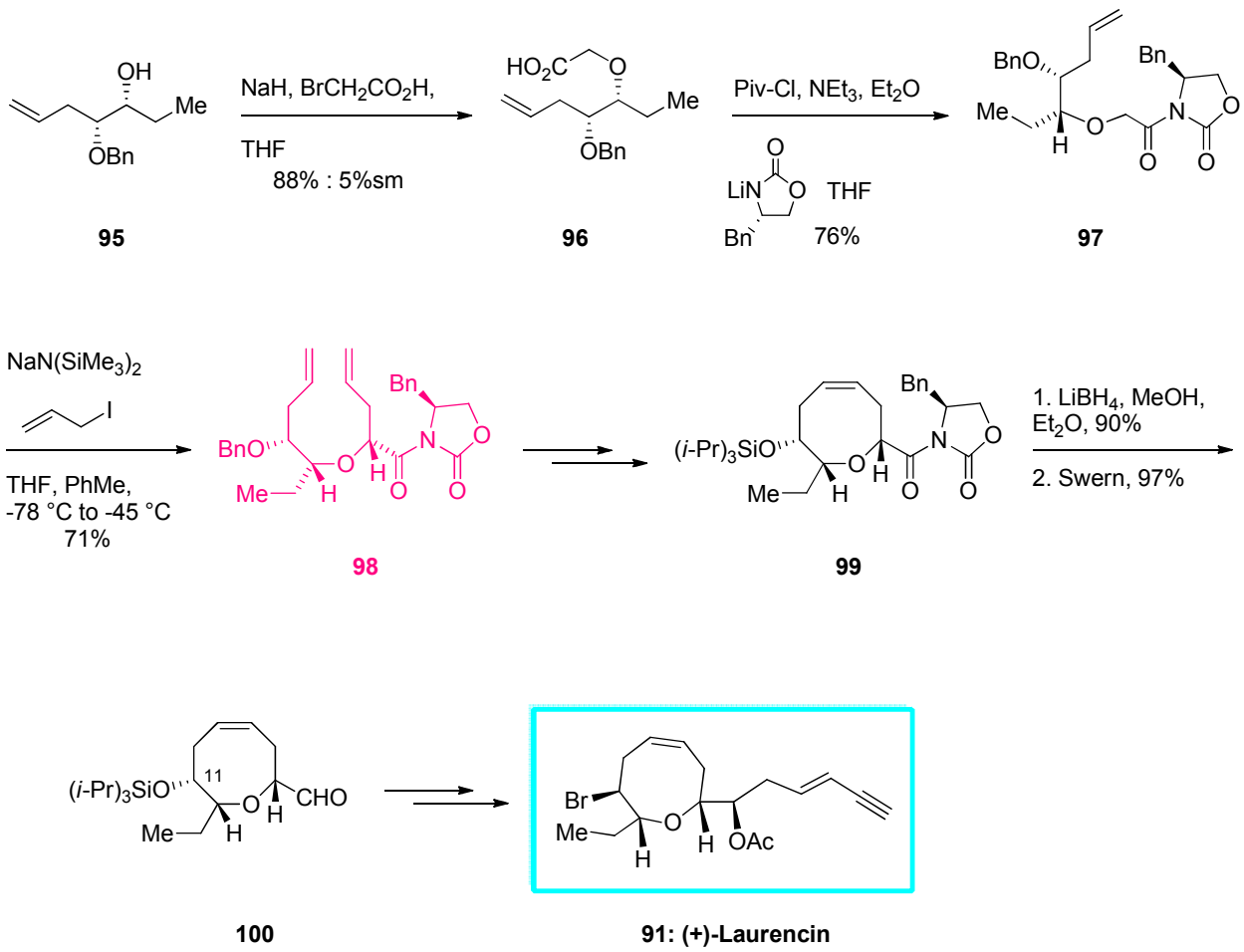
Scheme 21.

Red algae and marine organisms, which use *Laurencia* species for nutriation, can produce a natural product carrying medium ring ethers.[95] A member of these compounds in marine metabolites including (+)-laurencin **91** as a representative was first isolated from the extracts of *Laurencia glandulifera* by Irie in 1965.[96] The stereoselective total synthesis of (+)-laurencin **91** starting from (*S*)-(+)-4-benzyl-3-benzyloxyacetyl-2-oxazolidinone **92** was accomplished in 18 steps.[97] The key step in this approach is an asymmetric glycolate alkylation leading to acyl oxazolidinone **98**. Another important step is subsequent ring-closure of olefin metathesis to provide the oxocene core of **91**. The synthesis of chiral alcohol **95** started with (*S*)-(+)-benzyl-3-benzyloxyacetyl-2-oxazolidinone **92**.[98] Alkylation of the sodium enolate of **92** using allyl iodide as alkylating agent afforded acyl oxazolidinone **93** (>98:2 *ds*) (Scheme **22**). Conventional reductive removing of the chiral auxiliary was performed using lithium borohydride as reductive agent to afford chiral alcohol **94** in high chemical yield. Upon Swern oxidation[99] the latter, gave the desired secondary alcohol **95** in 83% yields over two steps (> 95:5 *ds*). Having **95**, available everything was ready to examine the key glycolate alkylation-metathesis sequence to obtain the oxocene core of (+)-laurencin. The sodium alkoxide of **95** was alkylated using sodium salt of bromoacetic acid to afford acid **96** in 88% yields along with recovery of 5% of starting alcohol. The latter upon treatment with lithiated (*S*)-(+)-4-benzyl-2-oxazolidinone gave acyl oxazolidinone **97** in good yield. Reaction of the sodium enolate of **97** with allyl iodide led to

asymmetric alkylation to give diene **98** in a short reaction time and good yield (> 95:5 *dr*). Upon usual reductive removal of the chiral auxiliary from triisopropylsilyl ether **99** using lithium borohydride, provided 90% of the primary alcohol, which was subsequently oxidized under Swern oxidation conditions to furnish aldehyde **100** in 97% yield. Having aldehyde **100** in hand, for accomplishment of the total synthesis of (+)-laurencin only introduction of the (*E*)-pentenyl side chain followed by the conversion of the protected alcohol at C11 into the alkyl bromide, is required, which should be attempted (Scheme **23**).[97]



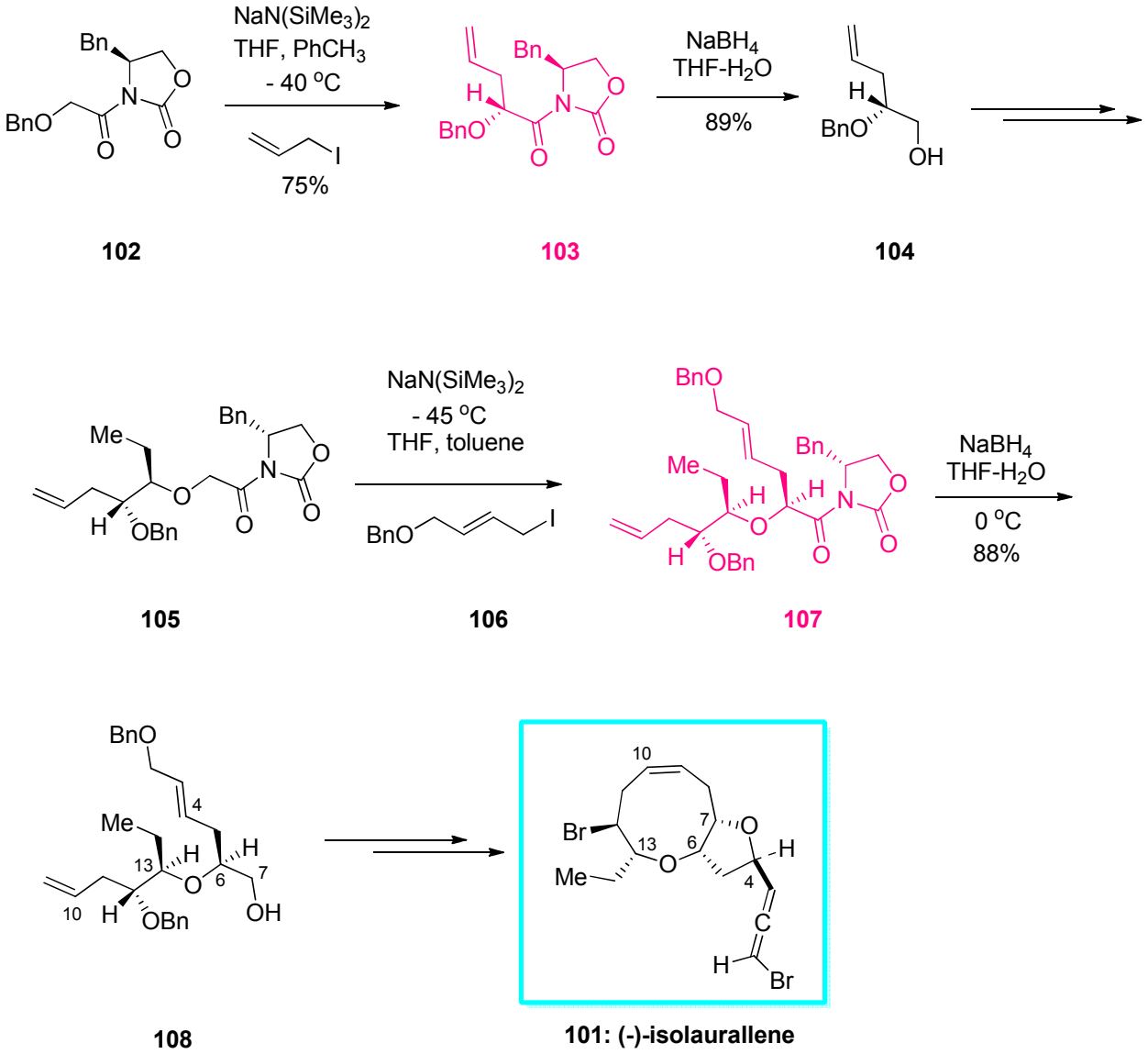
Scheme 22.



Scheme 23.

Isolaurallene initially was isolated from *laurencia nipponica* yamada collected in Izumihama near Hiroo on the Pacific Coast of Hokkaido by Kurata and his research group. The structures were initially assigned based on spectral data and later approved by single crystal X-ray crystallography.[100] A total synthesis of (–)-isolaurallene used alcohol **108** as an intermediate (Scheme **24**).[101, 102] Synthesis of **108** started from diastereoselective alkylation of glycolate oxazolidinones **102** with allyl iodide mediated by $NaN(SiMe_3)_2$ in THF and at - 40 ºC to furnish alkylated product **103** in satisfactory yield and excellent diastereoselectivity. The chiral auxiliary was conventionally removed by reduction using $NaBH_4$, THF-H_2O to give alcohol **104** in 89% yields. Alcohol **104** was then transformed to highly functionalized glycolate oxazolidinones **105** in several steps manipulating functional group transformations. The second diastereoselective alkylation involving glycolate oxazolidinones **105** and allylic iodide **106** was conducted, mediated by $NaN(SiMe_3)_2$ in THF and toluene at – 45 ºC to furnish the alkylated product **107** in

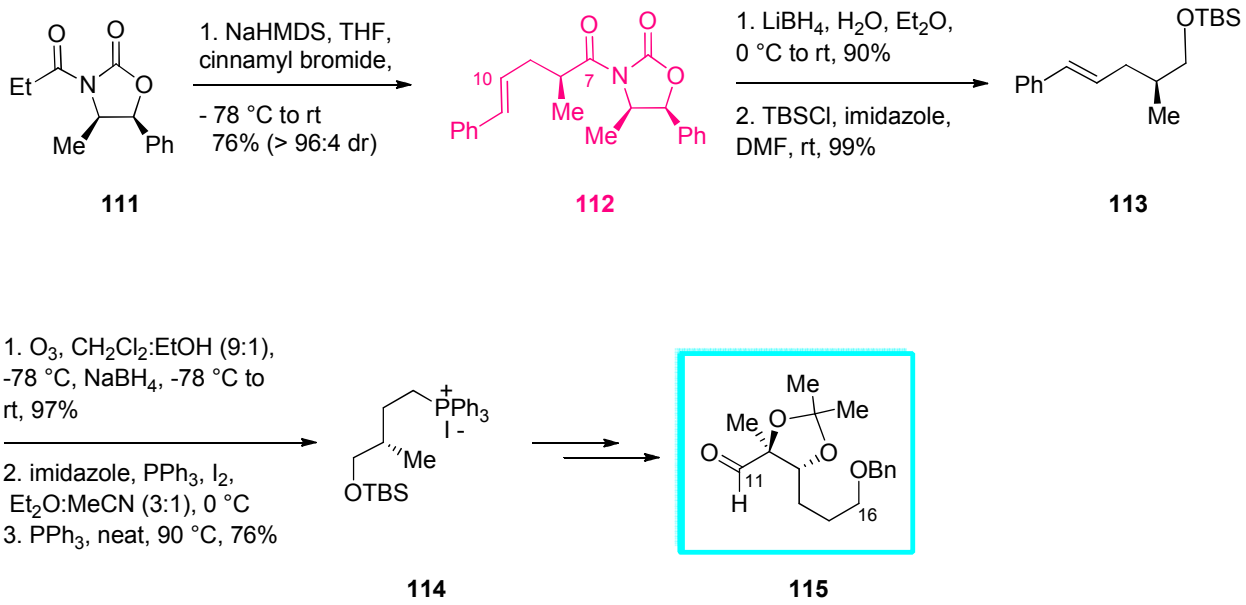
good yield with excellent diastereoselectivity (> 98:2). Once again, the chiral oxazolidinone in **107** was conventionally removed using $NaBH_4$ as reductive agent in THF-H_2O at 0 ºC to furnish alcohol **108** in high yield.



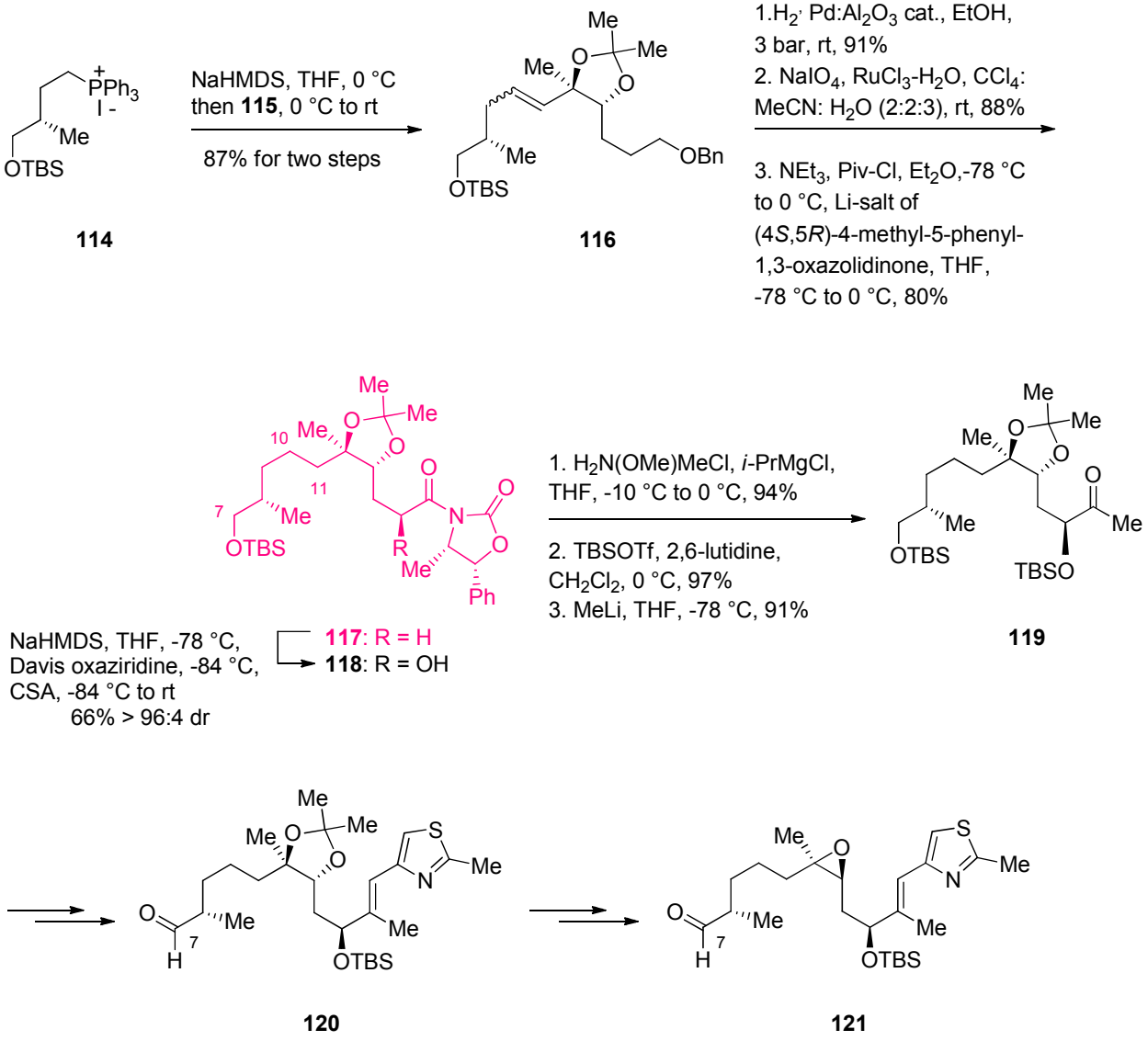
Scheme 24.

Epothilone B **109**[103] exhibits unique microtubule binding affinities and cytotoxity towards tumor cells and multiple drug resistant tumor cell lines.[104] Epothilone B **109**, as an active paclitaxel descendant, and the new *trans*-12,13-acetonide analogue **110** are interesting targets for

organic synthetic chemists. An approach towards the total synthesis of this target makes use of two key steps involving the generation of intermediate **120** *via* the Sharpless asymmetric dihydroxylation reaction and stereoselective Davis'-Evans'-hydroxylation. Mulzer and coworkers accomplished and reported an asymmetric synthesis of the novel *trans*-12, 13-acetonide analogue **110** of epothilone B as well as a highly stereoselective synthesis of epothilone B **109**. In a total synthesis of both aforementioned compounds, an appropriate aldehyde **120** is employed as the starting material.[105] The key segments for the synthesis of **120** are the phosphonium salt **114** (containing C_7-C_{10}) and the aldehyde **115** (containing C_{11}-C_{16}). The already known and provided oxazolidinone **112** (obtained from **111**)[106] was first protected as TBS-ether **113**, which was transformed into phosphonium salt **114**. After a multi-step synthesis, aldehyde **115** was provided (Scheme **25**). The synthesis of the key aldehydes **120** and **121** commenced with a Wittig reaction between **114** and **115**, which expectedly gave olefin **116**. The latter was transformed into the oxazolidinone **117**. It was then subjected to hydroxylation using the sodium enolate of **117**, Davis' oxaziridine, [107] to furnish **118** with the induction of 92% *de* at C15. The oxazolidinone moiety in **118** was substituted by the Weinreb's amide, followed by protection of the 15-hydroxy group as a TBS ether and then the addition of MeLi afforded methyl ketone **119**. A sequential reactions, involving an *E* selective Wittig reaction (*E*:*Z* 30:1)/ selective monodesilylation of the 7-TBS ether/Dess–Martin-oxidation, provided the key intermediate **120**. Then, aldehyde **121** was obtained *via* multi-step reactions (Scheme **26**).[105]

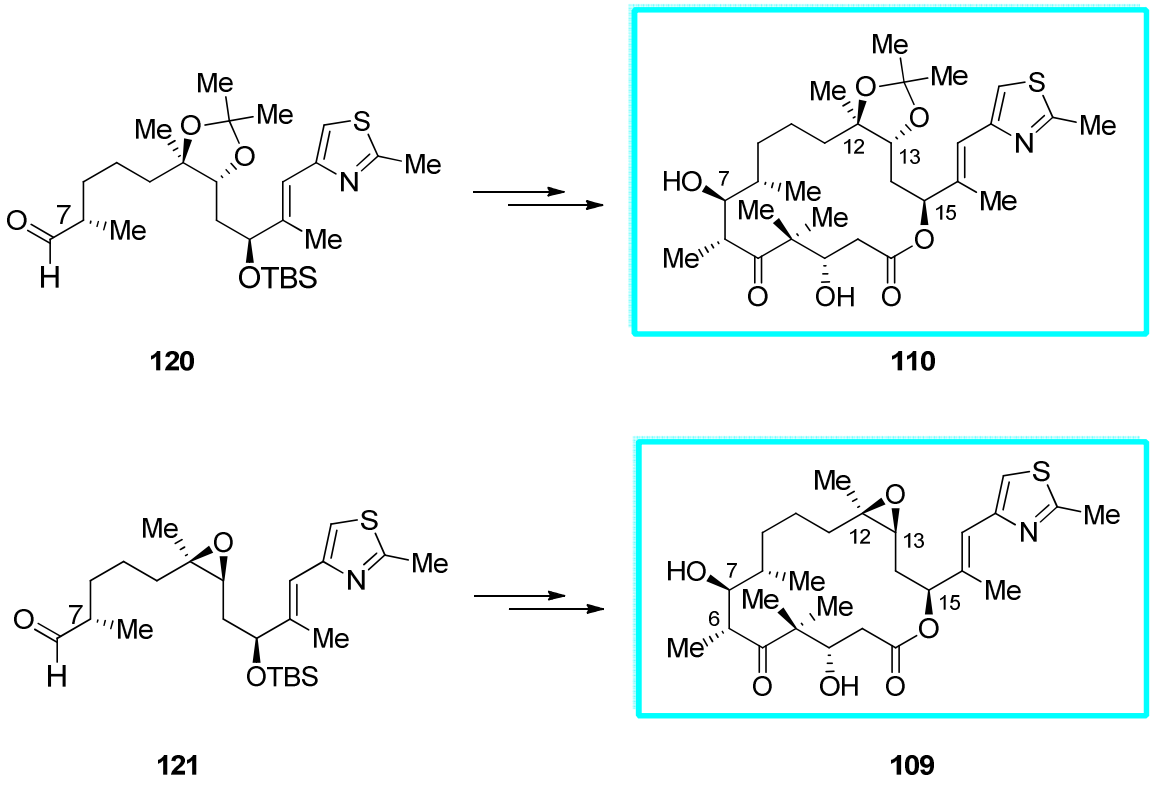


Scheme 25.



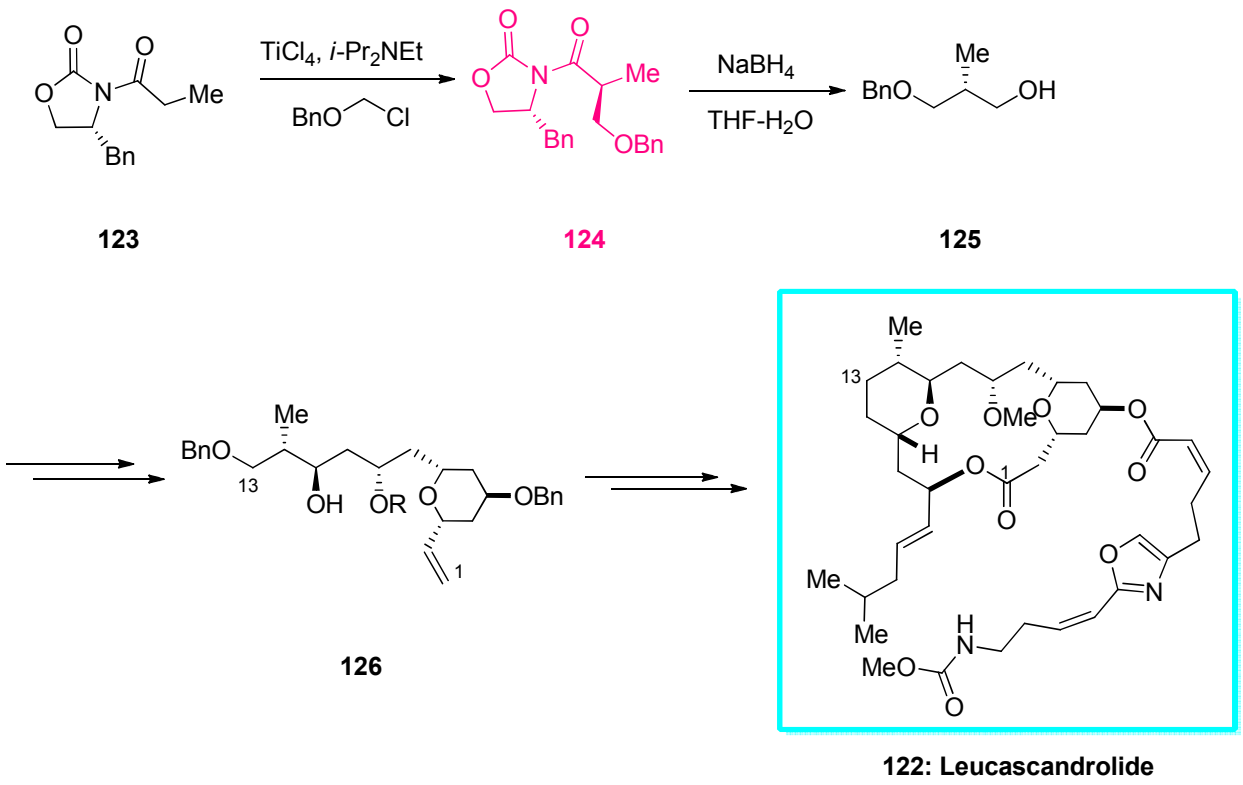
Scheme 26.

Notably, aldehyde **120** was converted into **110** after several steps using functional group transformations. In a similar way, aldehyde **121** afforded compound **109** following the procedure reported previously.[108] At last, compounds **109** [109] and **110** were obtained. Significantly, a highly stereoselective synthesis of **109** and **110**, created chiral centers at C3, C6, C12, C13, and C15 independently by utilizing external sources of chirality. Noticeably, centers C6 and C7 were determined during the aldol addition *via* an internal stereo induction. In the asymmetric synthesis of **110**, the ratio of induction is 6:1, and in the case of **118**, is > 95:5 (Scheme **27**).[105]



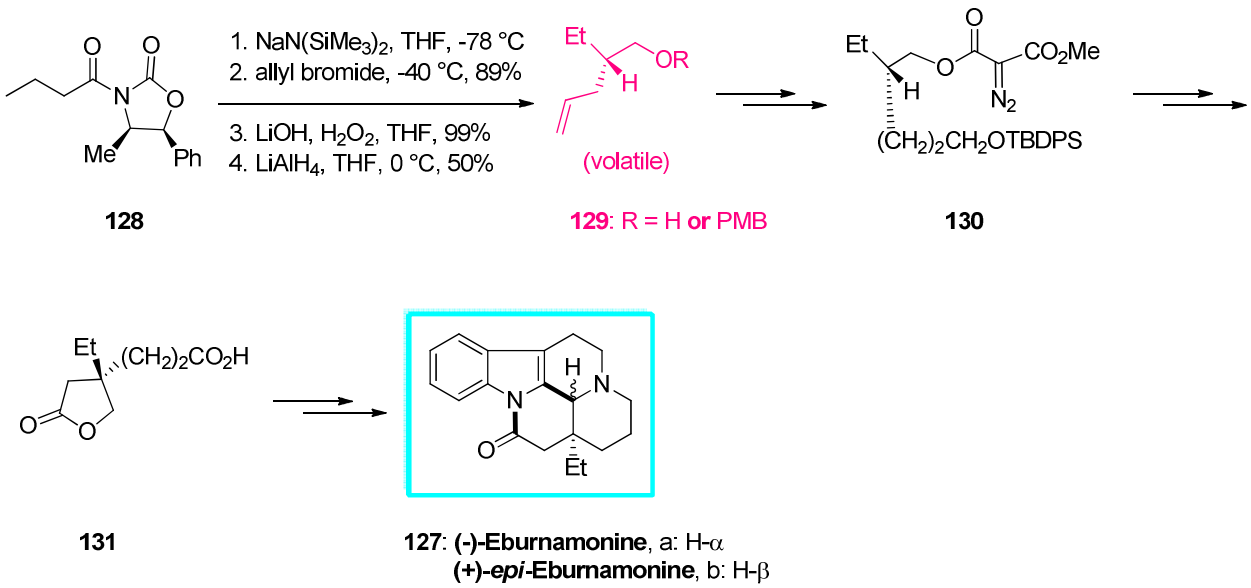
Scheme 27.

Leucascandrolide A **122** was initially isolated from the sponge *Leucascandra caVeolata* in 1996 by Pietra and his group.[110] This natural occurring compound shows strong in vitro cytotoxicity against KB and P388 cancer cell lines and is also found being a potent antifungal, inhibiting the growth of *Candida albicans*. The total synthesis of C_1-C_{13} segment of *Leucascandrolide* A uses alcohol **125** as a key intermediate.[111] The latter was synthesized by alkylation of the titanium enolate of propionyl oxazolidinone **123** with chloromethyl benzyl ether with subsequent conventional reductive removal of the auxiliary in **124** using $NaBH_4$ as reductive agent and THF-H_2O as solvent at room temperature in 95% overall yield (Scheme **28**).



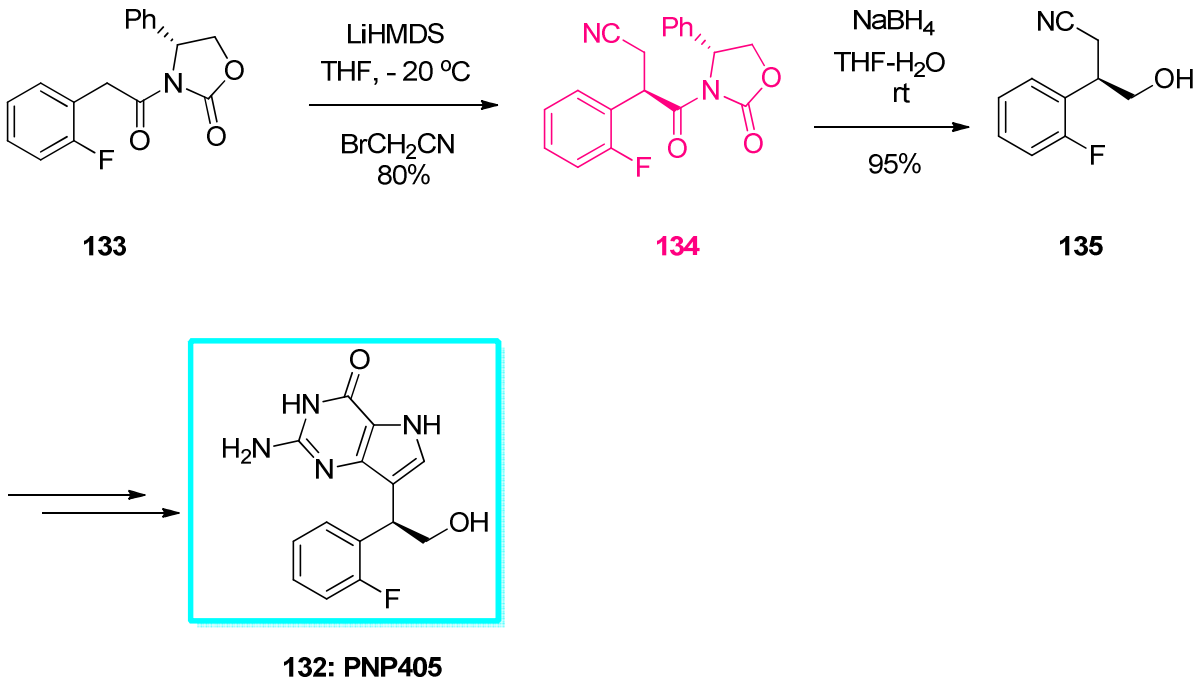
Scheme 28.

Several natural products, such as alkaloids and terpenes, have quaternary carbon centers in their scaffolds. Thus, the synthesis of these kinds of natural products requires the enantioselective generation of the quaternary carbon centers. In this light, the total synthesis of (—)-eburnamonine and (+)-*epi*-eburnamonine was fruitfully accomplished.[112] For the total synthesis, a key chiral compound, i.e. the optically pure 4, 4-disubstituted-lactone **131** was used for the stereoselective synthesis of the pentacyclic indole alkaloids[113] (—)-eburnamonine **127** and (+)-*epi*-eburnamonine **128**. To achieve this total synthesis, initially, the diazomalonate **130** was easily synthesized starting from the already known *N*-butanoyloxazolidinone **128**.[114] Alkylation of **128** using allyl bromide with subsequent hydrolysis[115] followed by reduction afforded the low boiling point, primary alcohol (*S*)-**129**. The absolute configuration of **129** was determined *via* its transformation to the *p*-methoxybenzyl ether **129**. The optical rotation of **129** had the same magnitude but of opposite sign for to the optical rotation of the already structurally elucidated enantiomer.[116] Then (*R*)-**129** was converted to **130** as an intermediate for the synthesis of γ-lactone carboxylic acid **131** in two steps. Finally, the latter as an intermediate was used for achieving the total synthesis of (—)-eburnamonine and (+)-*epi*-eburnamonine (Scheme **29**).[112]



Scheme 29.

PNP405 **132**, is a known purine nucleoside phosphorylase inhibitor. Due to its pharmaceutical importance, it is produced in large scale. It can be synthesized *via* asymmetric alkylation of **133** with bromoaceto nitrile in the presence of LiHMDS in THF at 20 ºC to obtain the desired product **134** in high yield and excellent diastereosectivity (> 99% *de*).[117] Reductive removal of the Evans' chiral auxiliary from **134** by $NaBH_4$ in THF-H_2O at ambient temperature furnished the desired alcohol **135** in excellent yield and > 99% *ee* without racemization observed or the effect of cyano group. On contrary, removal of the Evans' auxiliary *via* reduction using $LiBH_4$ or $LiAlH_4$ resulted in racemization or generation of a complex mixture due to the presence of the cyano group. Alcohol **135** was then transformed to PNP405 **132** in a couple of steps (Scheme **30**).

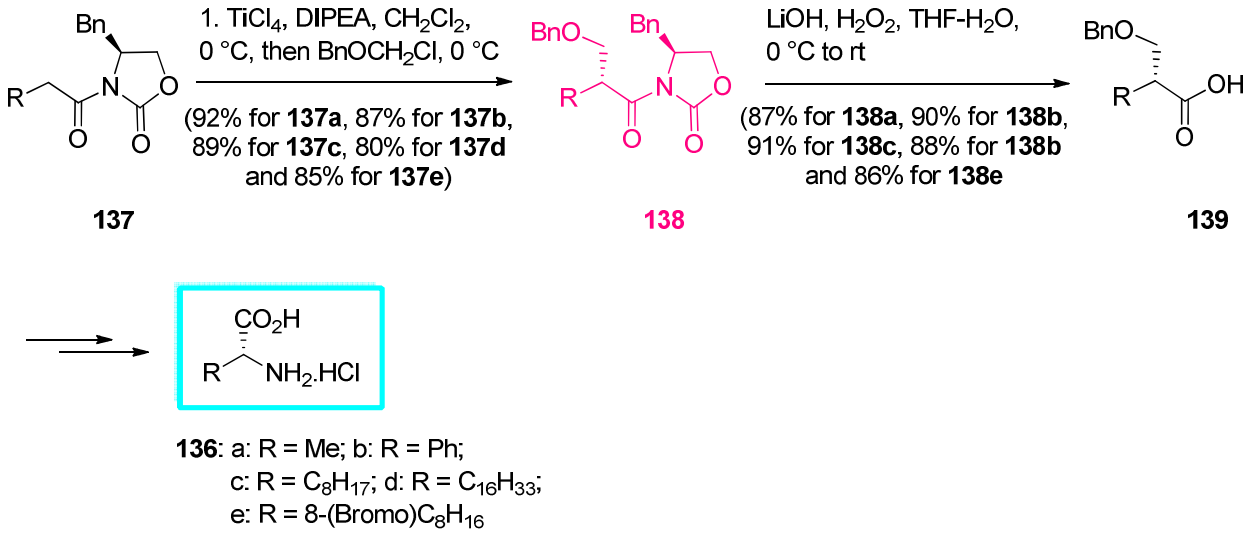


133 **134** **135**

132: PNP405

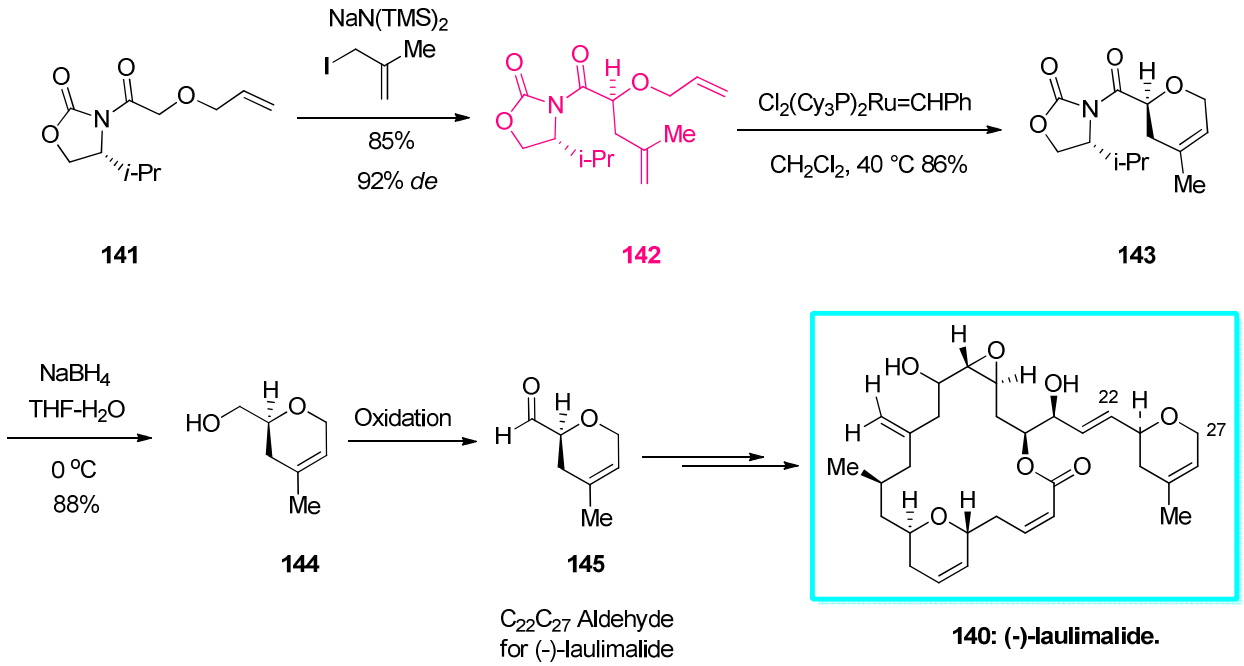
Scheme 30.

Among the wide variety of amino acids, all of the amino acids found, and extracted from any kind of living organisms are α-amino acids. In addition to the 20 essential ones, there are many other α-amino acids, which can be obtained from nature.[118] A novel approach for the highly stereoselective synthesis of chiral α-amino acids has been achieved and reported by Chakraborty and coworkers.[119] In this approach, the acid functionality was created *via* oxidation of a hydroxymethyl group introduced by Evans' protocol in the α-position of the substrate. Then, amino group can be installed by the amide of the original carboxyl group with subsequent occurrence of a modified Hofmann rearrangement. The total synthesis began with the chiral oxazolidinone **137**. Treatment of the latter with $TiCl_4$, mediated by diisopropylethylamine (DIPEA) afforded the enolate which reacted with benzyloxymethyl chloride under Evans' conditions[76] to give the Bn-protected-hydroxymethyl-substituted intermediate **138** with excellent diastereoselectivity (>98%). The chiral auxiliary[115] was then removed using $LiOH\text{-}H_2O_2$ resulting in the generation of an acid **139**.[120] Finally , the desired $_D$-amino acid **136** was obtained as its HCl salt. Remarkably, while $_L$-phenylalanine-based oxazolidinone **137** affords $_D$-amino acids, as claimed, its $_D$-isomer could be similarly employed to obtain the corresponding $_L$-amino acids (Scheme **31**).[119]



Scheme 31.

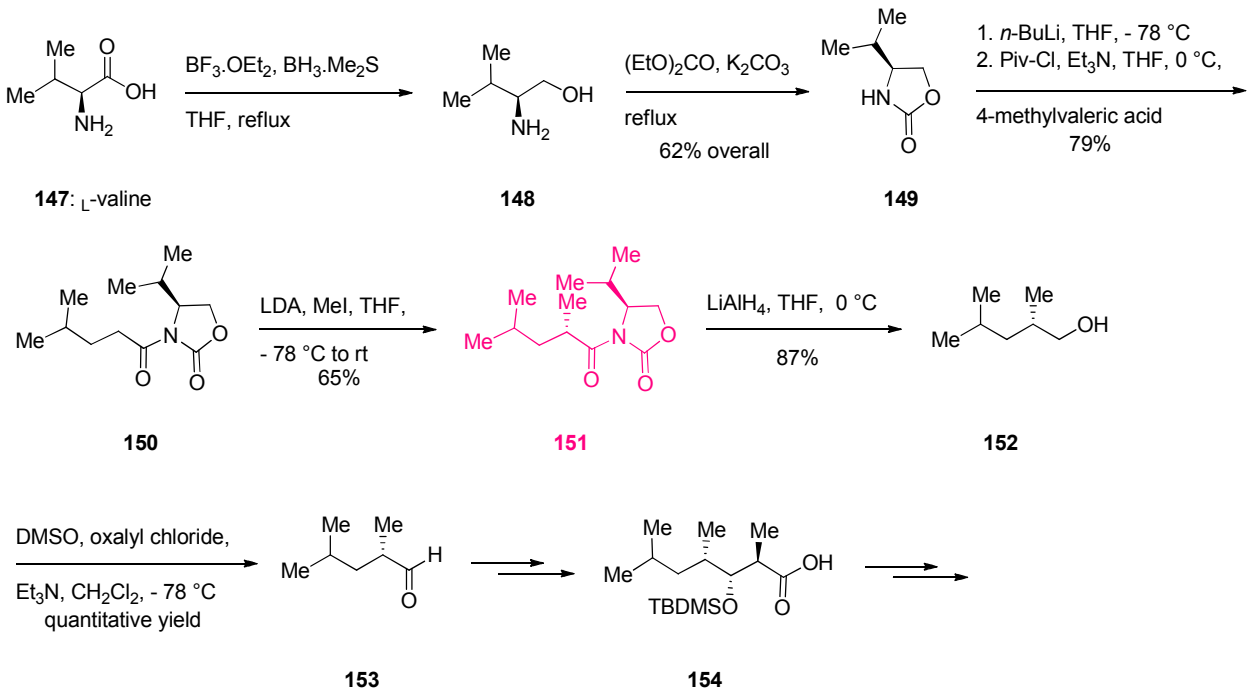
Laulimalide **140** is known as a novel structurally cancer therapeutic lead. It has been recently isolated in trace quantities from Pacific marine sponges.[70] Interestingly laulimalide also promotes abnormal tubulin polymerization and apoptosis in vitro, with a mode of action very similar to the famous Taxol® but with potentially less susceptibility to multidrug resistance.[121] Due to these impressive biological potencies, it has attracted much attention of the community of synthetic organic chemists. Recently an outstanding strategy for the synthesis of C_{22} from the groups of Ghosh, Paterson, and Mulzer has been achieved and reported.[122-124] C_{22} -C_{27} subunit aldehyde **145** is an important intermediate in a total synthesis of (–)-laulimalide **140**. It was synthesized *via* the Swern oxidation of alcohol **144**.[125, 126] The latter in turn was provided by the reductive removal of the oxazolidinone auxiliary in **143** using $NaBH_4$, THF-H_2O, 0 ºC in 88% yield. **143** was provided by alkylation of *O*-allylglycolyl oxazolidinone **141** using methylallyl iodide in mediated by $NaN(TMS)_2$ in THF to furnish **142** in 85% yield and in 92% *de* with subsequent ring-closing metathesis of the diene **142** using the Grubbs catalyst in CH_2Cl_2 at 40 ºC in satisfactory yield (Scheme **32**).[125]

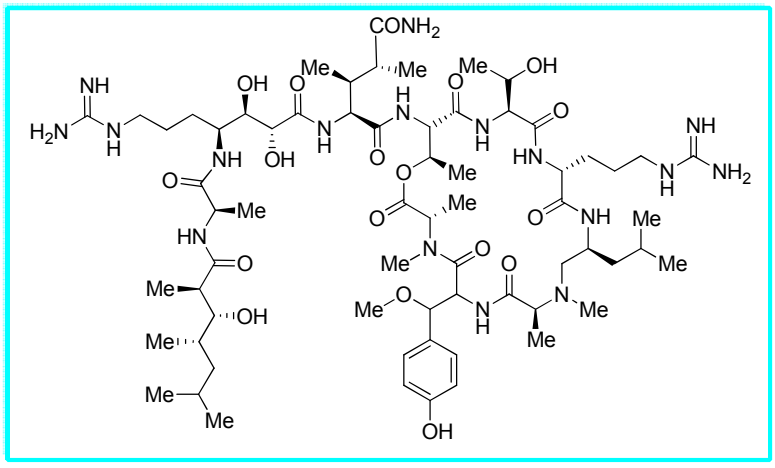


Scheme 32.

Cyclic depsipeptides have manifested themselves as a very important and remarkable class of biologically active compounds. They are generally isolated from marine natural products.[127] The isolation of callipeltin A as a cyclic depsipeptide showing antiviral and antifungal properties isolated from a shallow water sponge of the genus *Callipelta* was reported by Zampella *et al*. in 1996.[128] Callipeltin A has been screened and approved to be a selective and powerful inhibitor of the cardiac sodium/calcium exchanger.[129] An asymmetric synthesis of the silyl ether of (2*R*, 3*R*, 4*S*)-3-hydroxy-2, 4, 6-trimethylheptanoic acid **146** has been achieved and reported.[130] This synthesis involves the use of oxazolidinone as a chiral auxiliary for both stereoselective alkylation and aldol condensation reactions, which are required in this particular total synthesis.[131] A silyl derivative of (2*R*, 3*R*, 4*S*)-3-hydroxy-2, 4, 6-trimethylheptanoic acid **146**, a group existed in the cyclic depsipeptide callipeltin A was synthesized starting from L-valine **147** in nine steps. The chiral auxiliary required for the synthesis of (4*S*)-4-isopropyl-3-[(2'*S*)-2',4'-dimethylvaleryl)]-2-oxazolidinone **151** was actually the corresponding oxazolidinone **149**. It was Evans and coworkers who reported asymmetric alkylation reactions of chiral imide enolates as an operational strategy to the enantioselective synthesis of α-substituted carboxylic acids. Oxazolidinone **149** was synthesized from L-valine **147** in two steps in good

overall yield.[132, 133] *N*-Acylation using *n*-BuLi and 4-methylvaleric acid activated with pivaloyl chloride gave carboximide **150** in high yield. The 2′-position was methylated upon treatment with LDA followed by reaction with iodomethane to give **151** in satisfactory yield. The absolute configuration of the latter was determined by an X-ray crystallographic analysis. Transformation of the carboximide moiety to the desired aldehyde was accomplished *via* reduction using $LiAlH_4$ with a subsequent Swern oxidation.[134, 135] The unstable aldehyde without further purification underwent the aldol reaction. (2*S*,3*R*, 4*S*)-Trimethyl-3-*tert*-butyldimethylsiloxyheptanoic acid **146** can be transformed in to callipeltin A after several steps (Scheme **33**).[130]



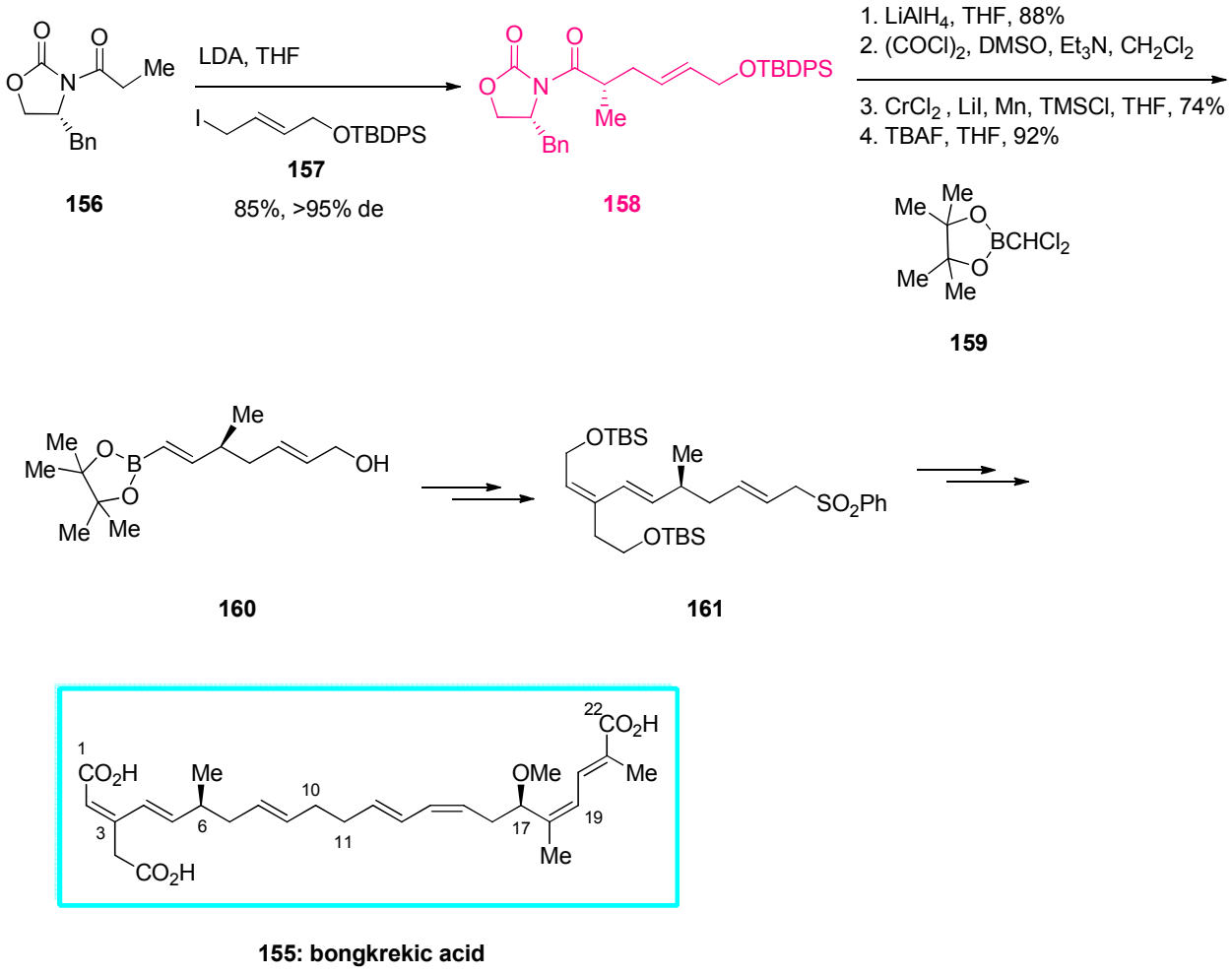


146: Callipeltin A

Scheme 33.

Bongkrekic acid **155**[136] is produced by the microorganism *Pseudomonas cocovenenans*. It is a natural toxic antibiotic. Bongkrekic acid **155**, a polyene-tricarboxylic fatty acid, has in its structure three pairs of conjugated dienes and two allylic chiral centers. In its total synthesis, the stereocontrolled assembly of this characteristic polyene skeleton, in particular the C_2-C_3 and C_{18}-C_{19} trisubstituted (*Z*)-alkenes, is crucial. The oxidation to obtain terminal carboxylic acids is also delicate since the polyene unit might be unstable under harsh conditions.[137] In this route, the

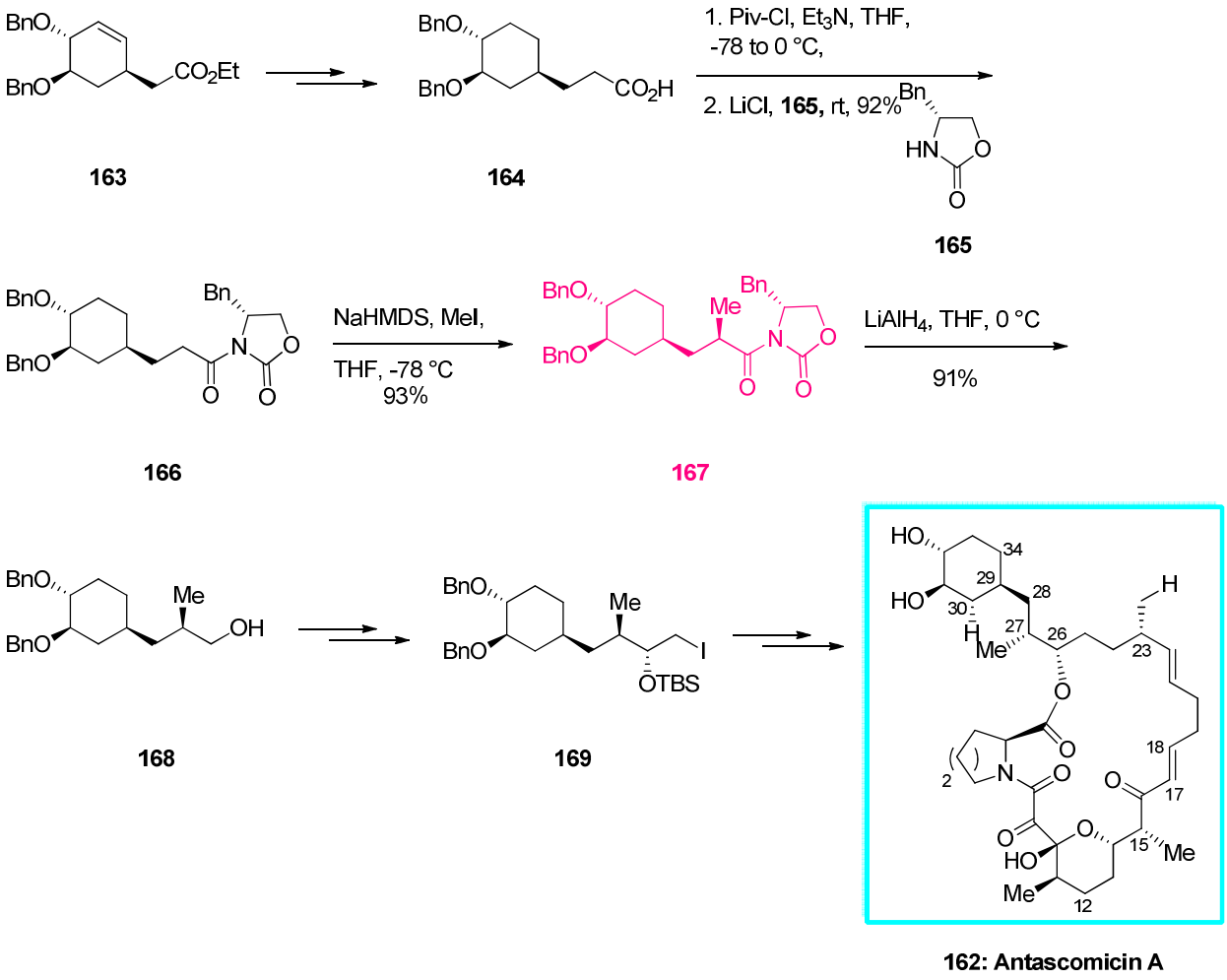
synthesis of the (*E*)-vinyl borane starts with stereoselective an alkylation of Evans' oxazolidinone **156**[57] using (*E*)-1-*tert*-butyldiphenylsiloxy-4-iodo-2-butene **157**[138] as an alkylating agent to afford **158** with excellent diastereoselectivity and in good chemical yield. Upon reductive removing of the chiral auxiliary, the desired alcohol **160** was provided. Ultimately, the alcohol **160** gave the unstable **161** as an intermediate, which directly underwent the next coupling reaction (Scheme **34**).[137]



Scheme 34.

Macrolide antibiotics antascomicins are the products of fermentation broth of a strain of *Micromonospora* isolated from a soil sample collected in China.[139] Antascomicin A shows potent binding affinity to FKBP12 and antagonizes the immunosuppressive effect of FK506. An asymmetric synthesis of the C_{18}-C_{34} segment of antascomicin A, which is an important key

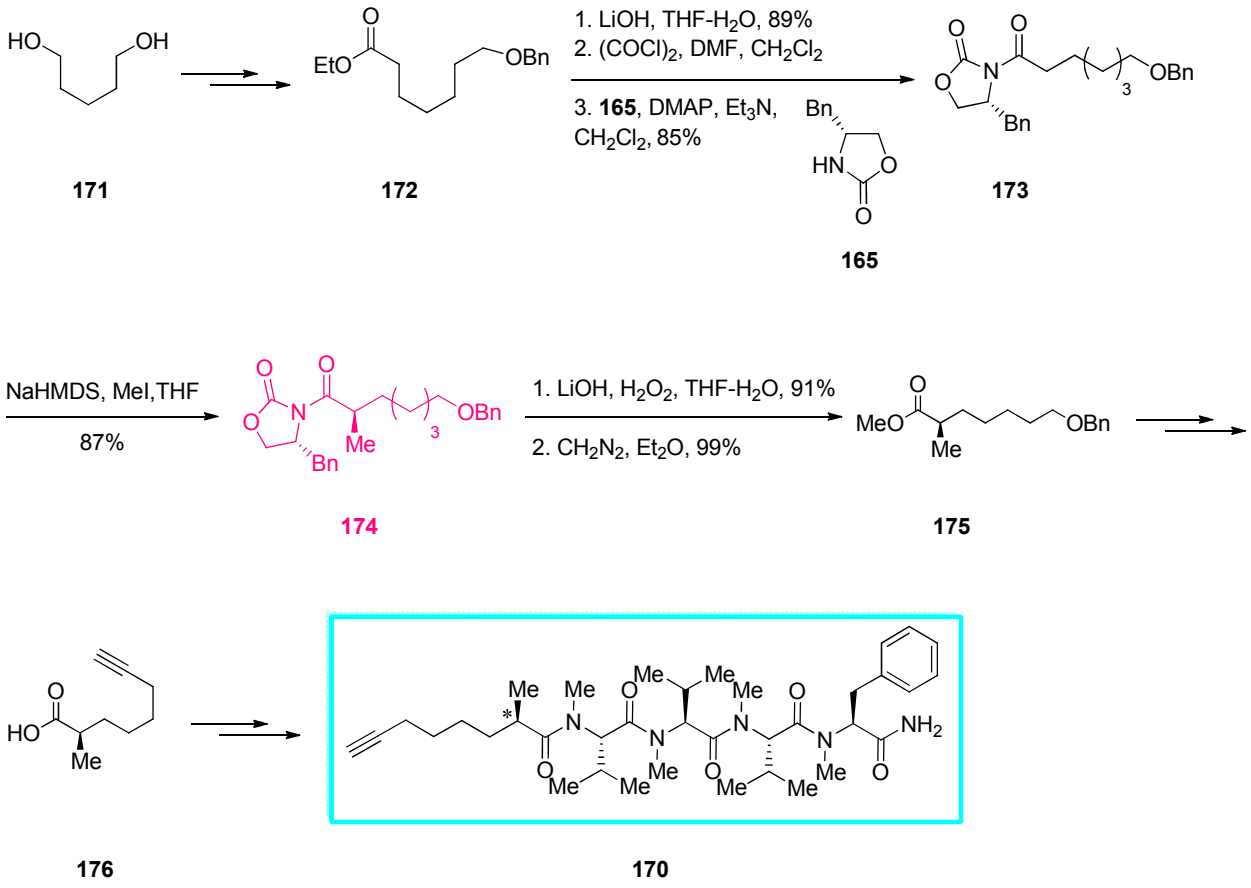
intermediate toward the total synthesis, has been accomplished and reported by Natsugari and coworkers.[140] Installation of the C_{27}-C_{34} carbocycle moiety was accomplished by catalytic Ferrier carbocyclization and Johnson-Claisen rearrangement, which was transformed to iodide **169** through the Evans' asymmetric alkylation and Sharpless epoxidation as key transformations. For the elaboration of the C_{26} and C_{27} stereogenic centers asymmetric Evans' alkylation and Sharpless epoxidation were employed. This approach commences with ester **163** and after several steps carboxylic acid **164** is provided. Coupling[141] of **164** with (*R*)-(+)-4-benzyl-2-oxazolidinone **165** gave oxazolidinone **166** in high chemical yield. The C_{27} methyl group was fruitfully attached *via* the Evans' stereoselective alkylation[57] of **166** under the conventional conditions (NaHMDS, MeI, THF) giving **167** in high chemical yield as a single isomer, proved by the ^{1}H NMR spectra analysis. Reductive removal of a chiral auxiliary using $LiAlH_4$ as the reductive agent afforded alcohol **168**. The latter was converted to iodide **169** after several steps (Scheme **35**).[140]



Scheme 35.

The marine cyanobacteria contain a wide range of natural products with different arrays of structures and functional groups.[142, 143] They have been an abundant source for new biologically active molecules. The total synthesis of dragonamide has been accomplished and reported.[144] The synthesis of moya **176**, which is an intermediate for the total synthesis of dragonamide **170** was commenced from the monoprotection of 1, 5-pentanediol **171**. The latter, it was then transformed to ester **172**, after several step. The latter then was hydrolyzed using LiOH in THF/H_2O and transformed into the acyl chloride using oxalyl chloride and DMF in CH_2Cl_2, followed by treatment with (*R*)-4-benzyl-2-oxazolidinone, DMAP and triethylamine, affording imide **173**.[145] The α-methylation cleanly and smoothly proceeded following the Evans' protocol[146] to generate the *R*-configuration at the newly-formed chiral center in **174**. The chiral auxiliary was removed upon treatment of **174** with hydrogen peroxide in aqueous THF, with

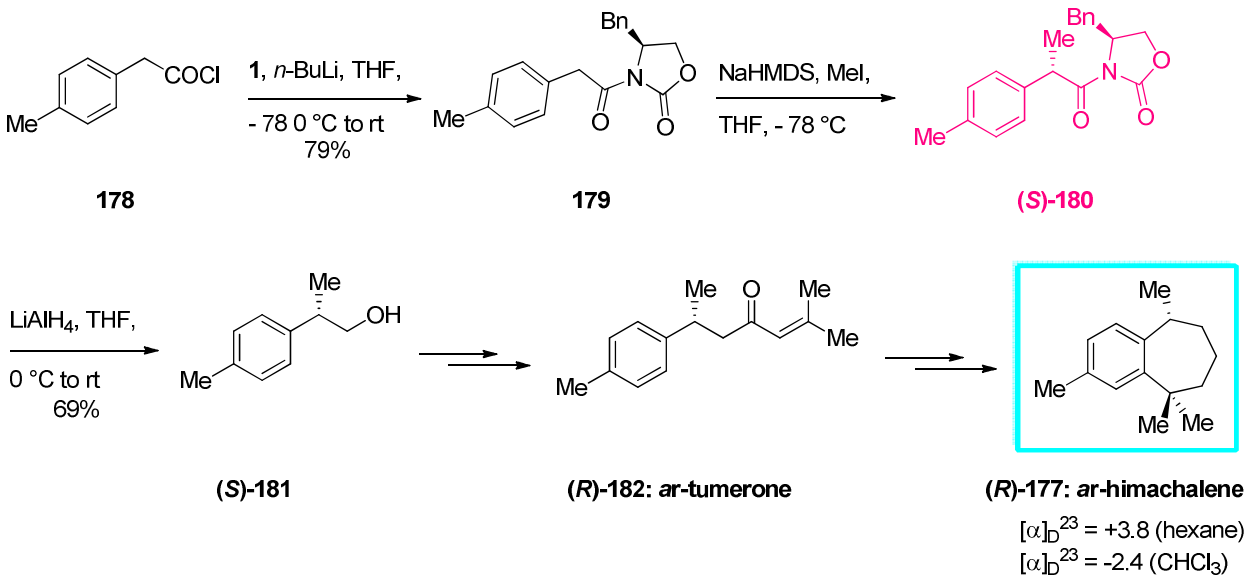
subsequent acidification to afford the corresponding acid, in excellent yield, which in turn gave ester **175** upon esterification with freshly prepared diazomethane. The latter, it was transformed to the free acid **176** after several steps. Acid **176** was then converted to the desired natural product **170** *via* a sequential multi-step synthesis (Scheme **36**).[144]



Scheme 36.

Male-produced pheromone components of the flea beetle *Aphthona flava* were initially isolated in 2001.[147] It was identified as (*R*)-*ar*-Himachalene **177**. The latter, it was synthesized (97.7% *ee*) from (4-methylphenyl) acetic acid by using the Evans' stereoselective alkylation as the key step. Mori *et al*. reported the synthesis of (*R*)-ar-turmerone.[148, 149] (*S*)-(+)-*a*r-Turmerone **182** is recognized as a spice flavor of turmeric.[150] Although, several synthetic approaches have been reported for (±)-**182**,[148] only a few enantioselective synthesis of (*S*)-(+)-**182** can be found in literature,[148, 151-154] including the approach.[155] Since component **177** has the (*R*)-configuration, the synthesis of the unnatural (—)-*a*r-turmerone (*R*)-**182** is required. As shown in Scheme **37**,

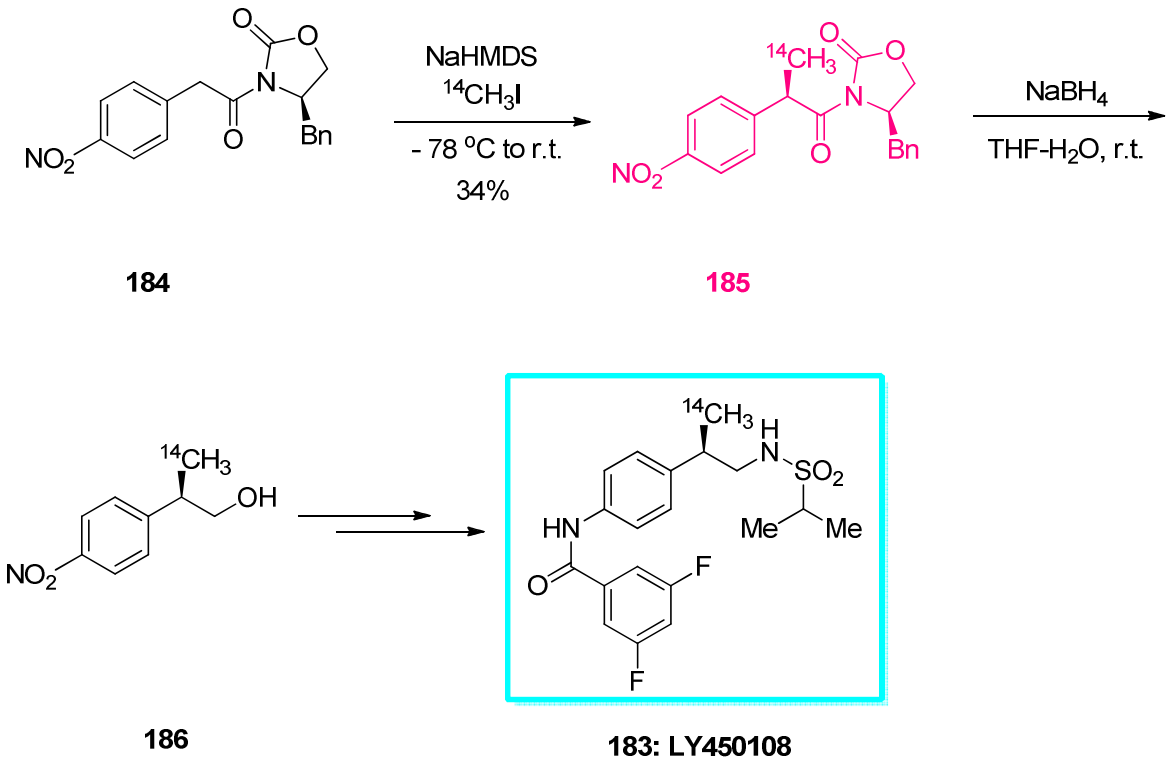
asymmetric synthesis of (*R*)-**182** is achieved *via* the Evans' asymmetric alkylation of (*S*)-4-benzyl-3-(4-methylphenylacetyl)-2-oxazolidinone **179** as an important step to introduce the stereogenic center of (*R*)-**182**. Acyl chloride **178**, (*S*)-4-benzyl-2-oxazolidinone is converted to **179**, which upon methylation with methyl iodide and treatment with sodium hexamethyldisilazanide (NaHMDS) in THF gives gummy (*S*)-**180**.[156] The analysis of the ^{1}H NMR signals determines the diastereomeric ratio of the products as about 95:5. The major isomer was assigned as (*S*)-**180** *via* the well-known stereochemical outcome of the Evans' alkylation. Upon reduction with lithium aluminum hydride, (*S*)-**180** afforded oily alcohol (*S*)-**181** in 53% yield over four steps. The enantiomeric purity of (*S*)-**181** showed *ee* 88%. After several steps, (*R*)-**182** was obtained. Then (*R*)-*ar*-turmerone **182** was transformed to (*R*)-*ar*-himachalene **177** which was interestingly, dextrorotary in hexane whereas levorotary in chloroform. Impure (75% *ee*) (*R*)-3-(4-methylphenyl)butanoic acid crystallized easier than the enantiomerically pure stereoisomer (Scheme **37**).[156]



Scheme 37.

Asymmetric synthesis of ^{14}C-labeled LY450108 **183**, a 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl) propanoic acid (AMPA) potentiator was accomplished by stereoselective alkylation of **184** with methyl-^{14}C iodide in the presence of NaHMDS to give the alkylated product **185** in modest yield.[157] The auxiliary in **185** was removed conventionally using $NaBH_4$ in THF-H_2O at room

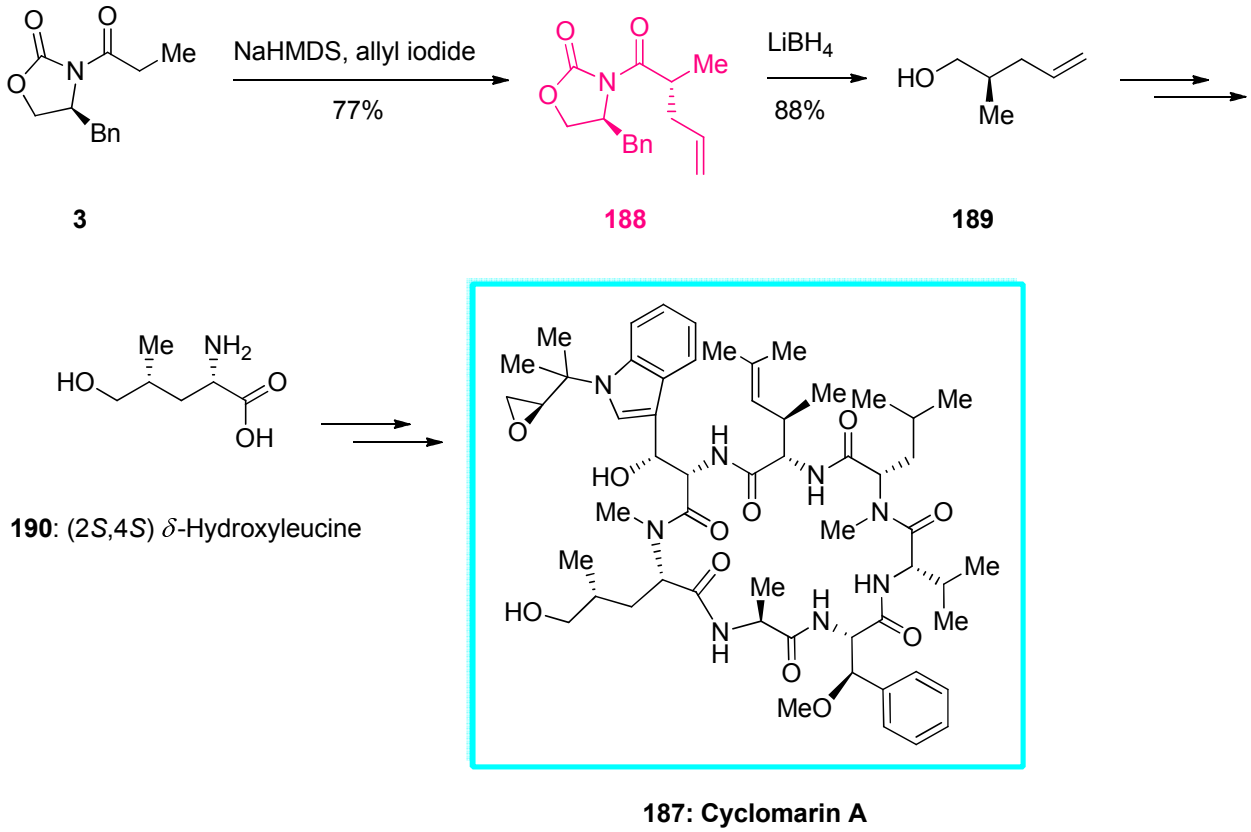
temperature to provide the desired alcohol **186** in 87% yield. Noticeably, the reduction was found being chemoselective as the nitro group was untouched under the above conditions. The alcohol **186** was then converted to the target LY450108-[^{14}**C**] **183** after several steps (Scheme **38**).



Scheme 38.

Cyclomarin A **187** is a novel cyclic peptide, which was initially isolated from *estuarine actinomycete*.[158] The total synthesis of (2*S*, 4*R*)-δ-hydroxyleucine methyl ester, which is the *N*-dimethyl analogue of an amino acid contained within the macrocycle of cyclomarin A has been successfully accomplished and reported in 2005.[159] In this total synthesis a combination of Evans' asymmetric alkylation and Davis' asymmetric Strecker reaction has been employed. Among a number of asymmetric alkylation conditions examined, Evans' oxazolidinone strategy was chosen and performed. This method was a complementary of the pathway chosen by Wen *et al*. who used two Evans' alkylations to fix the stereochemistry of both stereogenic centers.[160] The appropriate propionyl oxazolidinone **3** was provided from (*S*)-phenylalanine.[55, 161] Enolization with the subsequent addition of allyl iodide afforded oxazolidinone **188** as the main diastereomer

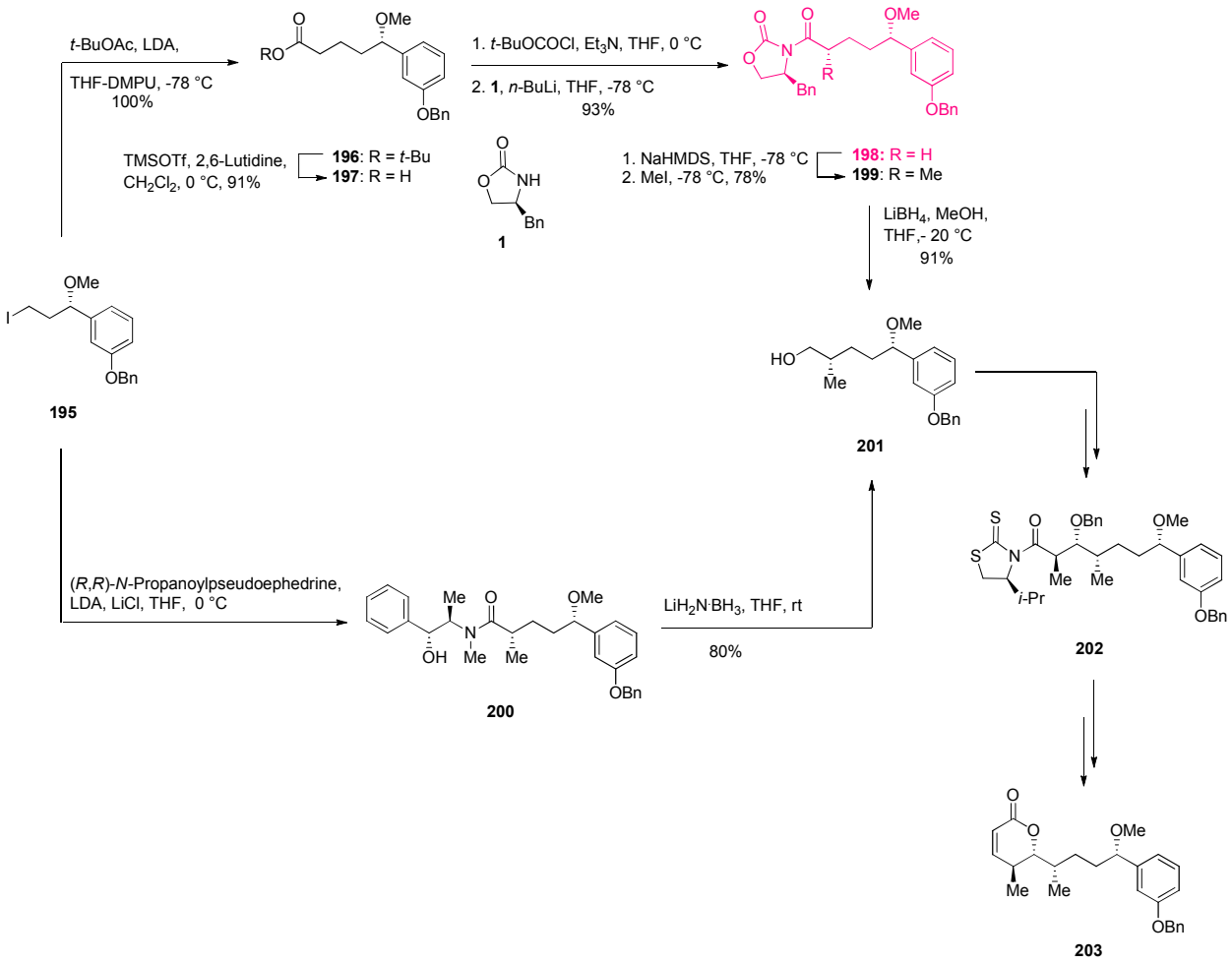
in 96% de. Under reduction conditions, the chiral auxiliary was removed to afford alcohol **189**. The latter was converted to the methyl ester of (2*S*, 4*R*)-δ-hydroxyleucine after several steps (Scheme **39**).[159]



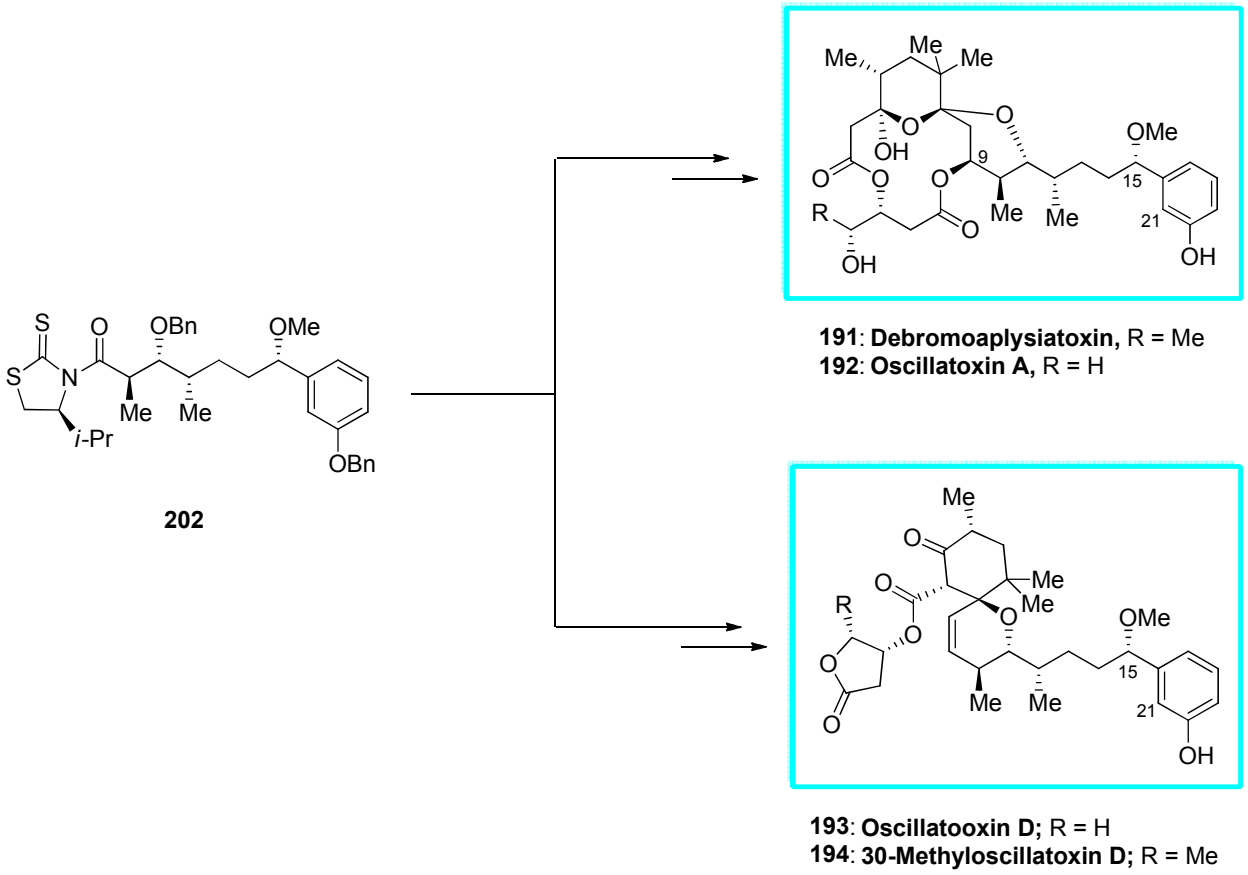
Scheme 39.

Debromoaplysiatoxin **191** is a bicyclic diolide isolated from the sea hare *Stylocheilus longicauda.* [162] During the isolation of **191,** several other structurally related bioactive metabolites such as oscillatoxin A **192**, oscillatoxin D **193** and 30-methyloscillatoxin D **194**.[163, 164] Debromoaplysiatoxin and oscillatoxin A mainly recognized as tumor promoters that operate on protein kinase C, have been studied for better understanding of the carcinogenic processes.[165] On the contrary, oscillatoxin D and 30-methyloscillatoxin D are nontoxic metabolites showing an antileukemic activity.[164] An asymmetric synthesis of the C_9-C_{21} segment of debromoaplysiatoxin and oscillatoxins A and D was designed in 2006. This new strategy involves the cross coupling of titanium enolates from *N*-acyl-1,3-thiazolidine-2-thiones and dialkyl acetals followed by the selective hydrogenolysis of *O*-benzyl protective groups. The

attention has been mainly paid to the installation of the C12 stereogenic-center. To obtain crystalline products, a stereoselective alkylation of a well-established intermediate employing Evans' methodology was envisaged and conducted. Hence, reaction of lithium enolate derived from *tert*-butyl acetate with iodide **195** afforded ester **196** virtually quantitatively, which was readily converted into the respective carboxylic acid **197**. The acylation of (*S*)-4-benzyl-1,3-oxazolidinone with **197** followed by a stereoselective alkylation using methyl iodide were performed in accordance with routine procedures. The ^{1}H NMR spectra analysis of the reaction mixture disclosed the presence of a single diastereomer **199** (*dr* > 97:3), which was isolated in 78% chemical yield upon purification by flash column chromatography. At last, removal of the chiral auxiliary gave alcohol **201** in excellent yield. Thus, the enantiomerically pure alcohol **201** was provided in good yield after five steps. Then, after several steps, the adduct **202** as a benzyl protected derivative of the corresponding anti aldol intermediate was obtained. The latter **202** was used as an intermediate for the synthesis **203**, C_9-C_{21} segment. ^{1}H NMR spectrum analysis of lactone **203** confirmed the configuration of the C_9-C_{21} segment (Scheme **40**).[166]



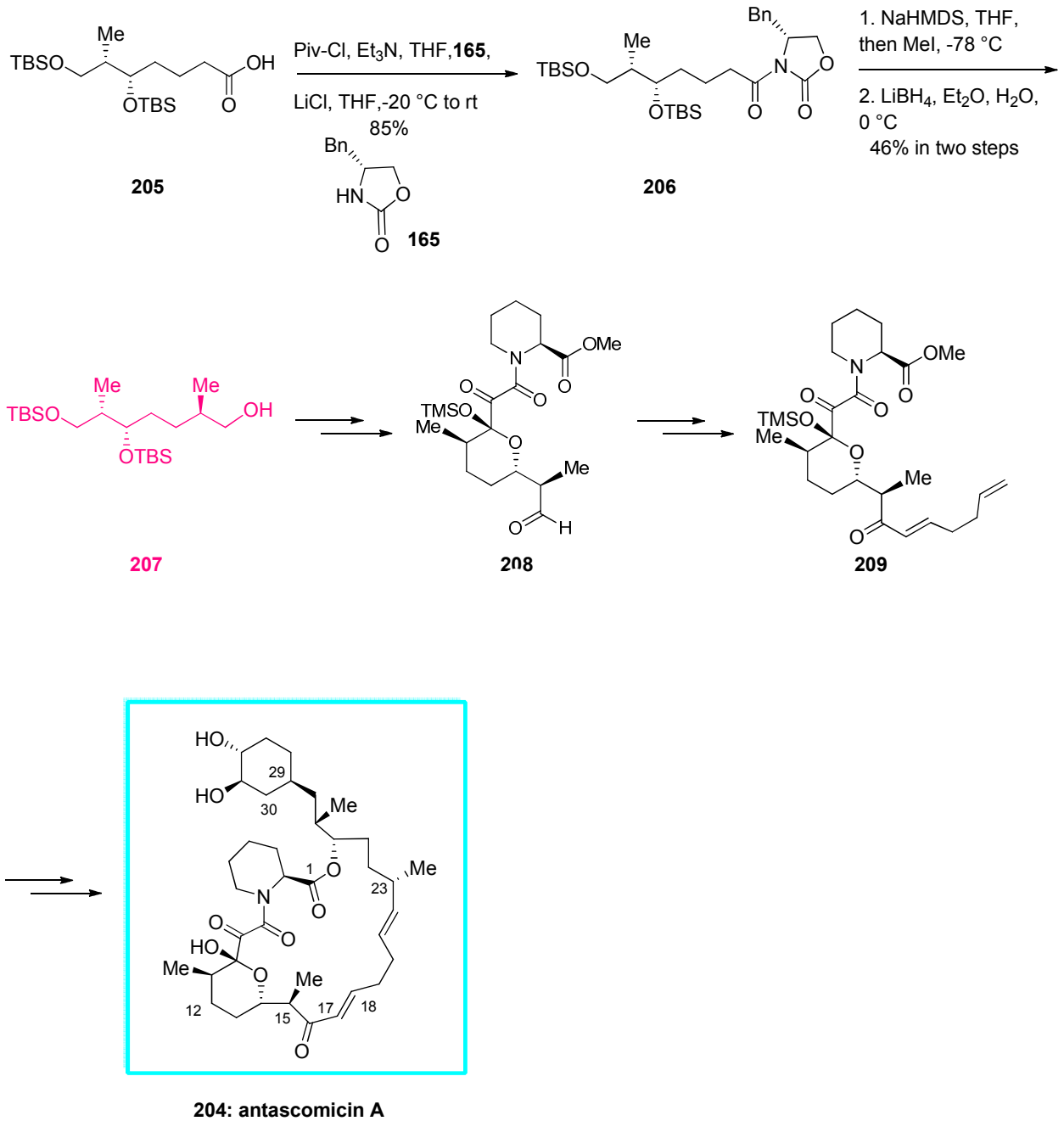
Scheme 40.



Scheme 41.

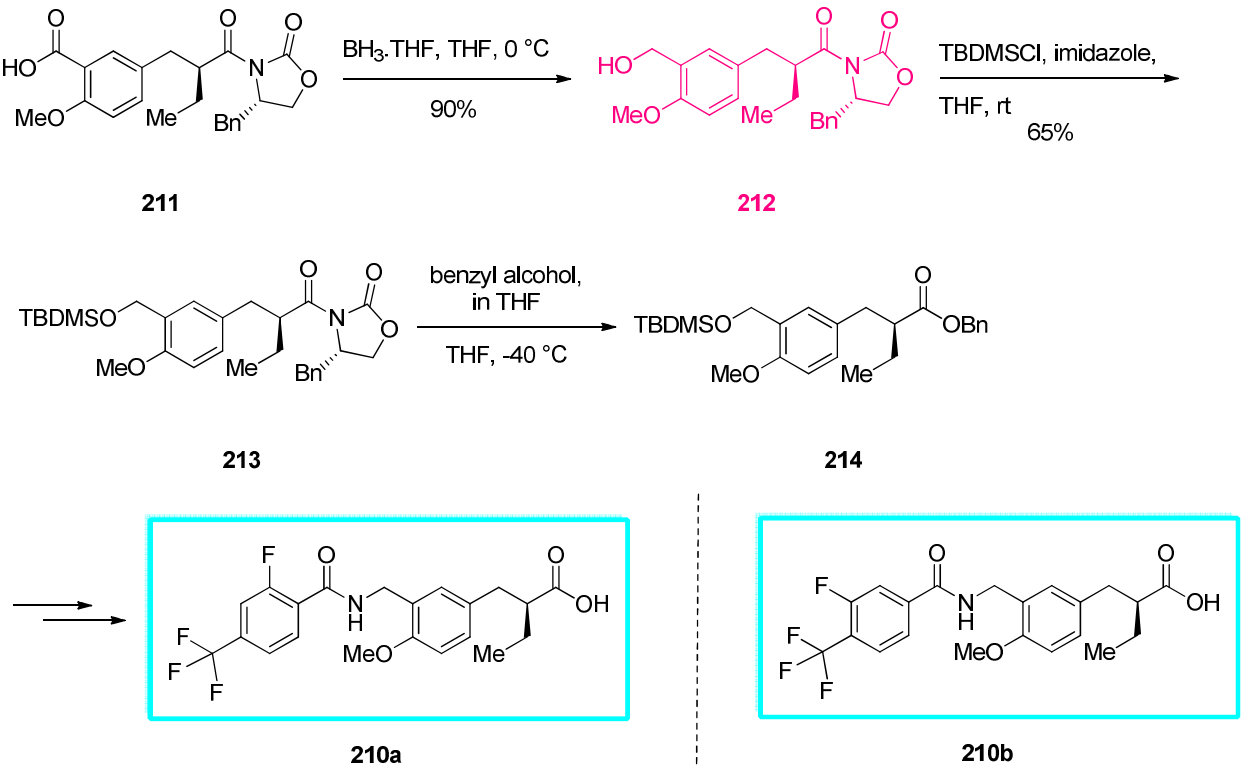
Antascomicins are produced *via* fermentation strain of the genus *Micromonospora* which was initially isolated from a soil sample collected in China.[139] Initial screening and evaluations of **204** showed that it could be promising for the treatment of different neuro-degenerative disorders like Alzheimer's and Parkinson's diseases.[167] An asymmetric synthesis of the C_1-C_{21} segment of this natural product, **204** was accomplished, employing a highly stereoselective aldol reaction that constructs the C_1-C_{17} segment along with a Nozaki-Hiyama-Kishi reaction to couple the obtained segment with the residual C_{18}-C_{21} fragment. Significantly, the asymmetric synthesis of the C_1-C_{16} segment **208** can be accomplished using Evans' oxazolidinone as one of the key steps.[168] In this approach, acid **205** was used for *N*-acylation of the chiral oxazolidinone **165**, followed by the mixed anhydride method [141] to give **206** in high yield. Diastereoselective alkylation of the Na-enolate of **206** using MeI as methylating agent with subsequent reductive removal of the chiral auxiliary under the standard conditions afforded the alcohol **207** as the sole isomer in moderate overall yield. Aldehyde **208**, as an intermediate for the synthesis of dienone

209 was provided from **207** in several steps. The target, antascomicin A **204** was obtained *via* a multi-step synthesis using various functional group transformations in satisfactory overall yield (Scheme **42**).[168]



Scheme 42.

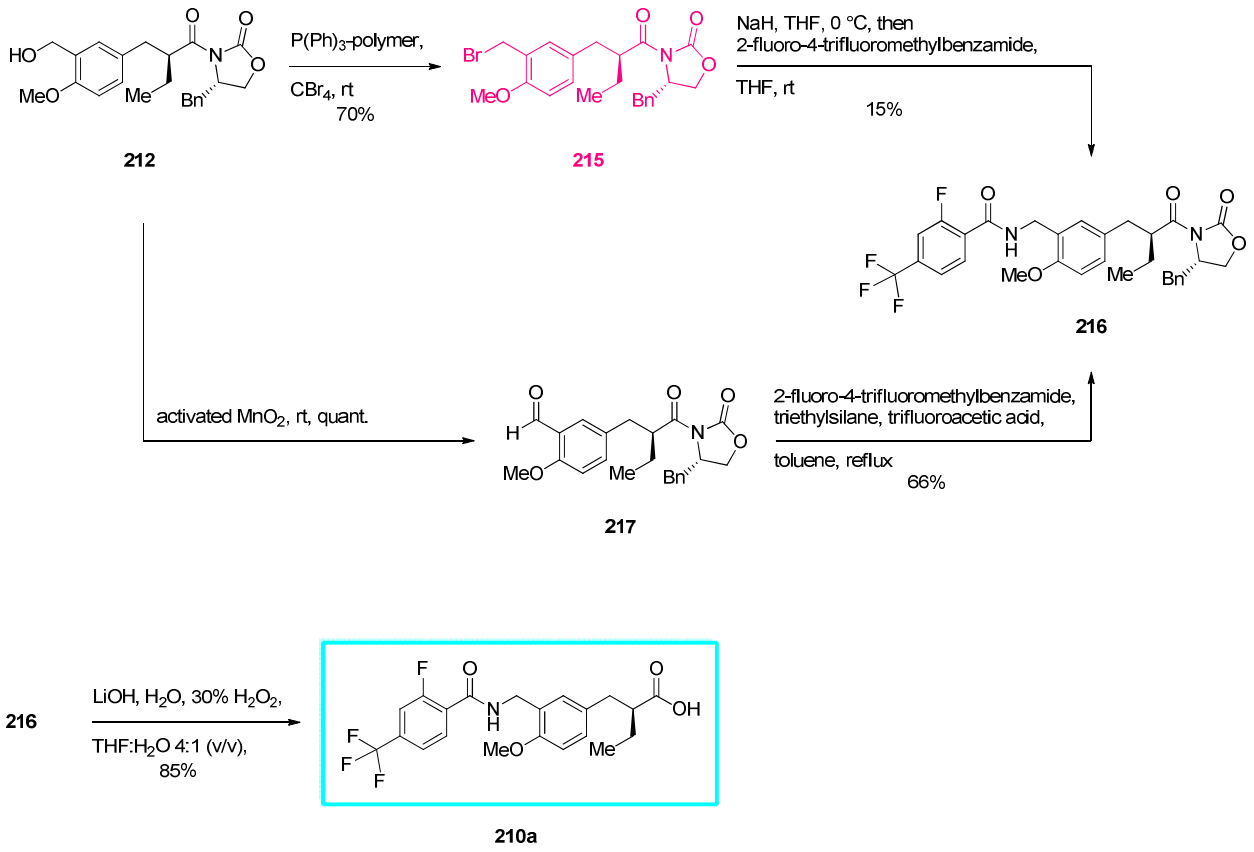
Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor groups, including steroid, thyroid, retinoid, vitamin D and other receptors.[169] PPARα regulates the appearance of genes encoding for proteins mixed up in lipid and lipoprotein homeostasis.[170] Enantiometrically, pure (*S*)-2-ethylphenylpropanoic acid derivatives are dual agonists for human (PPAR) α and δ. Miyachi *et al*. reported an effective and operational synthetic approach to the enantioriched 2-ethylphenylpropanoic acid derivatives **210a** and **210b**. They employed the Evan's stereoselective alkylation and reductive *N*-alkylation as vital steps.[171] In this route, **210** and **210b** were synthesized by the route outlined in Scheme **43**.[172] This approach, suffers from too many reaction steps (seven steps), requiring chromatographic purification of intermediates, and giving low total yield (3% overall yield), as well as being inappropriate for scale-up and pilot plants.[171]



Scheme 43.

Thus, the same authors envisaged an alternative route for the synthesis of **210a**, **210b**. The *N*-alkylation of 2-fluoro-4-trifluoromethylbenzamide (or 3-fluoro-4-trifluoromethylbenzamide) using the bromomethyl derivative **215** was performed. Compound

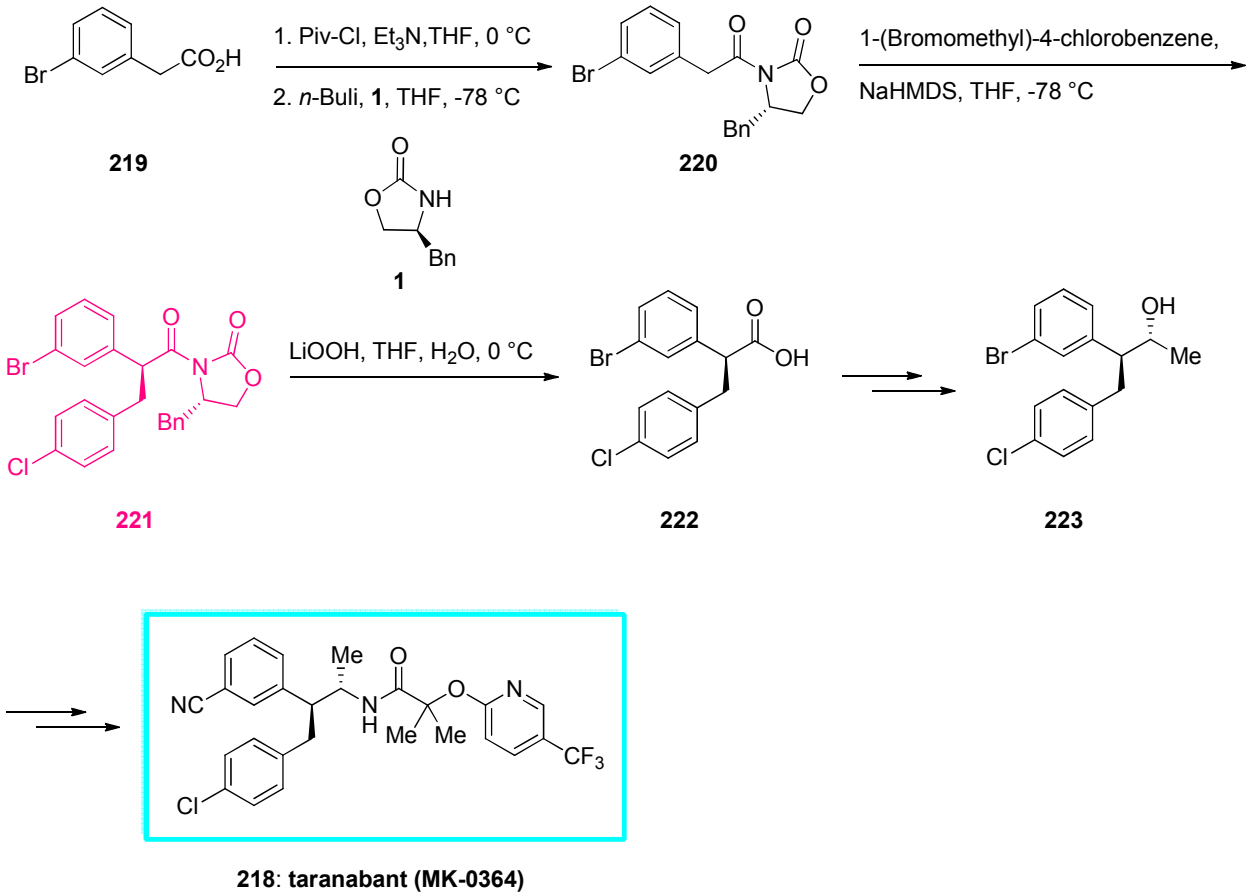
215 was provided by the facile reduction of **211** using the BH_3-THF complex followed by bromination with PPh_3-CBr_4 in 67% yield over two steps. 3-Fluoro-4-trifluoromethylbenzamide was treated with NaH (or LiHMDS, or *t*-BuOK) and then reacted with **215** to give a mixture containing several compounds, including **216**. After direct subjection of the crude to silica gel column chromatography, pure **216** was isolated, albeit in only 15% yield, and an appreciable amount of the starting 3-fluoro-4-trifluoromethylbenzamide was also recovered. Thus, the route starting with a direct *N*-alkylation was considered insignificant. Recently, an efficient reductive *N*-alkylation of amides using TFA/Et_3SiH with an aldehyde was reported by Dube *et al*.[173] This methodology was examined in the synthesis of **210a**, **210b** (Scheme **44**). Accordingly, a mixture of 2-fluoro-4-trifluoromethylbenzamide, aldehyde **217**, triethylsilane and trifluoroacetic acid was refluxed in toluene. Upon completion of this reaction, the desired *N*-alkylation product **216** was successfully prepared and isolated in 66% yield. The oxazolidinone moiety was removed using LiOH/ 30% H_2O_2 system [57] giving desired **210a** in high yield. Notably, **210a** was provided from **211** in a total yield of about 50% over only three steps. In a similar way, **210b** was obtained from **211** in overall yield of around 50% (Scheme **44**).[171]



Scheme 44.

Taranabant (MK-0364), **218**, is recognized as a cannabinoid-1 receptor inverse agonist an also as an anti-obesity agent. In 2007, Lee *et al*. reported a relatively convenient total synthesis of **218.**[174] An alternative stereoselective synthesis of **218** employing the Evans' chiral auxiliary protocol has been reported. As depicted in Scheme **45**, the total synthesis of taranabant (MK-0364) was achieved using a classical Evans' asymmetric reaction route.[175] The total synthesis starts from commercially available, 3-bromophenyl acetic acid **219,** which is coupled with lithiated (*S*)-4-benzyloxazolidin-2-one *via* pivaloyl mixed anhydride provided from pivaloyl chloride in the presence of a base i.e. Et_3N to afford *N*-acyloxazolidinone **220** in relatively high yield. Then, **220** was alkylated in the presence of NaHMDS using 1-(bromomethyl)-4-chlorobenzene to provide the alkylated product **221** in good yield. The ^{1}H NMR spectrum of **221** confirms the formation of the product having very high *de* value. As usual, the chiral auxiliary of acyloxazolidinone **221** was removed by standard conditions (LiOOH) to give the corresponding

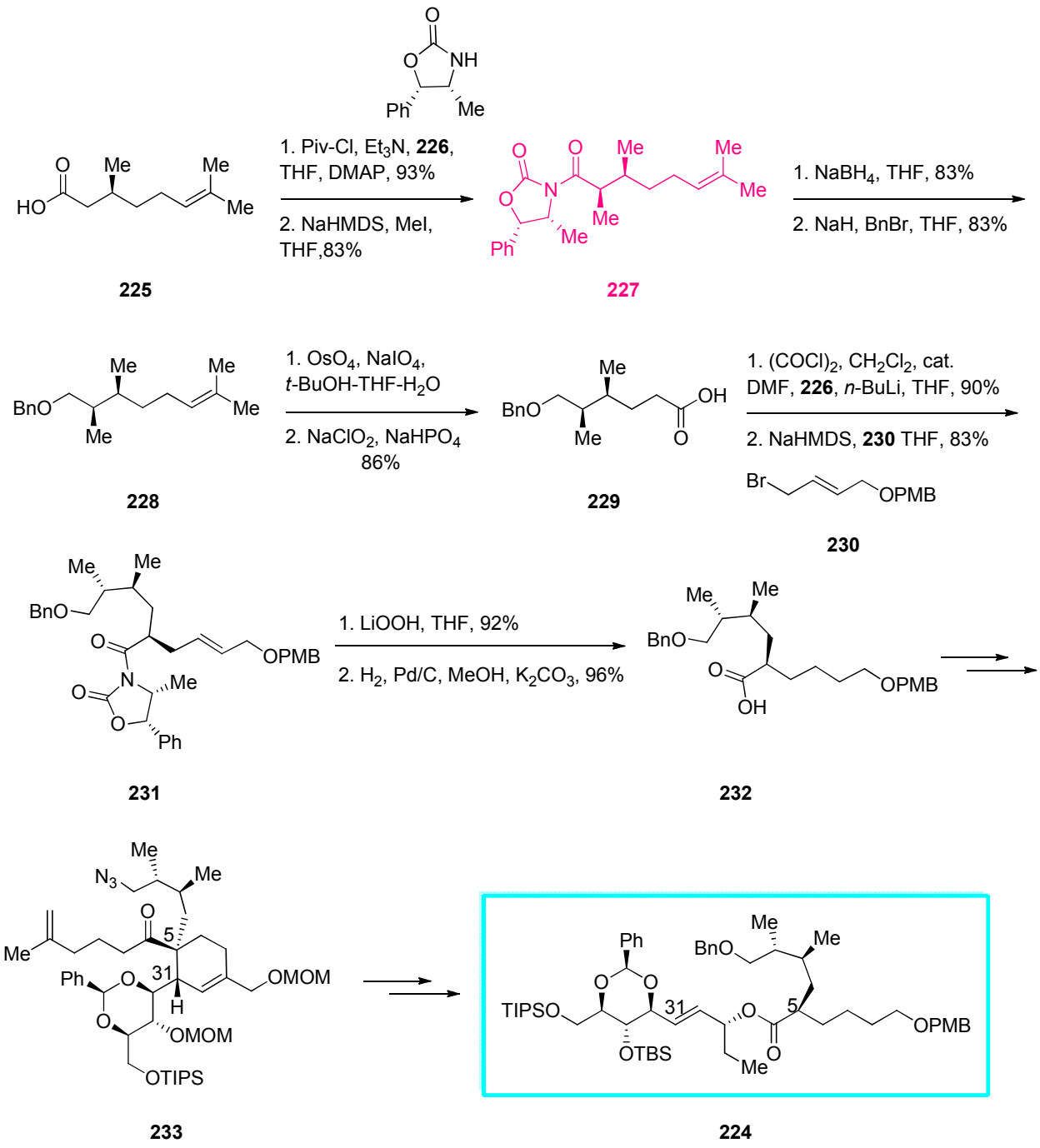
acid **222** uneventfully. Ultimately, bromo alcohol **223** was obtained as an intermediate for the total synthesis of taranabant **218** (Scheme **45**).[174]



Scheme 45.

Pinnatoxins are 'fast-acting' marine toxins generally found in the bivalve *Pinna pectinata (muricata)*.[176] Pinnatoxin A was initially isolated in 1995 by Uemura and coworkers. Interestingly, they characterized its structure in the same year.[177] The outstanding chemical structure of pinnatoxins having an unusual spiroimine gave a persuasive challenge to the organic chemists working in the field of total synthesis.[178] The first strategy for installation of the spiroimine segment relied on a tandem Claisen-Mislow-Evans rearrangement. That induced the quaternary stereogenic center at the core of the ring system.[179] An enantioselective strategy to the spiroimine segment of pinnatoxins was designed, performed and reported by Zakarian and coworkers in 2007.[180] The synthesis of carboxylic acid **232** was commenced with the condensation of (*S*)-citronellic acid[181] with 4*R*-methyl-5*S*-phenyl-2-oxazolidinone **226** to provide

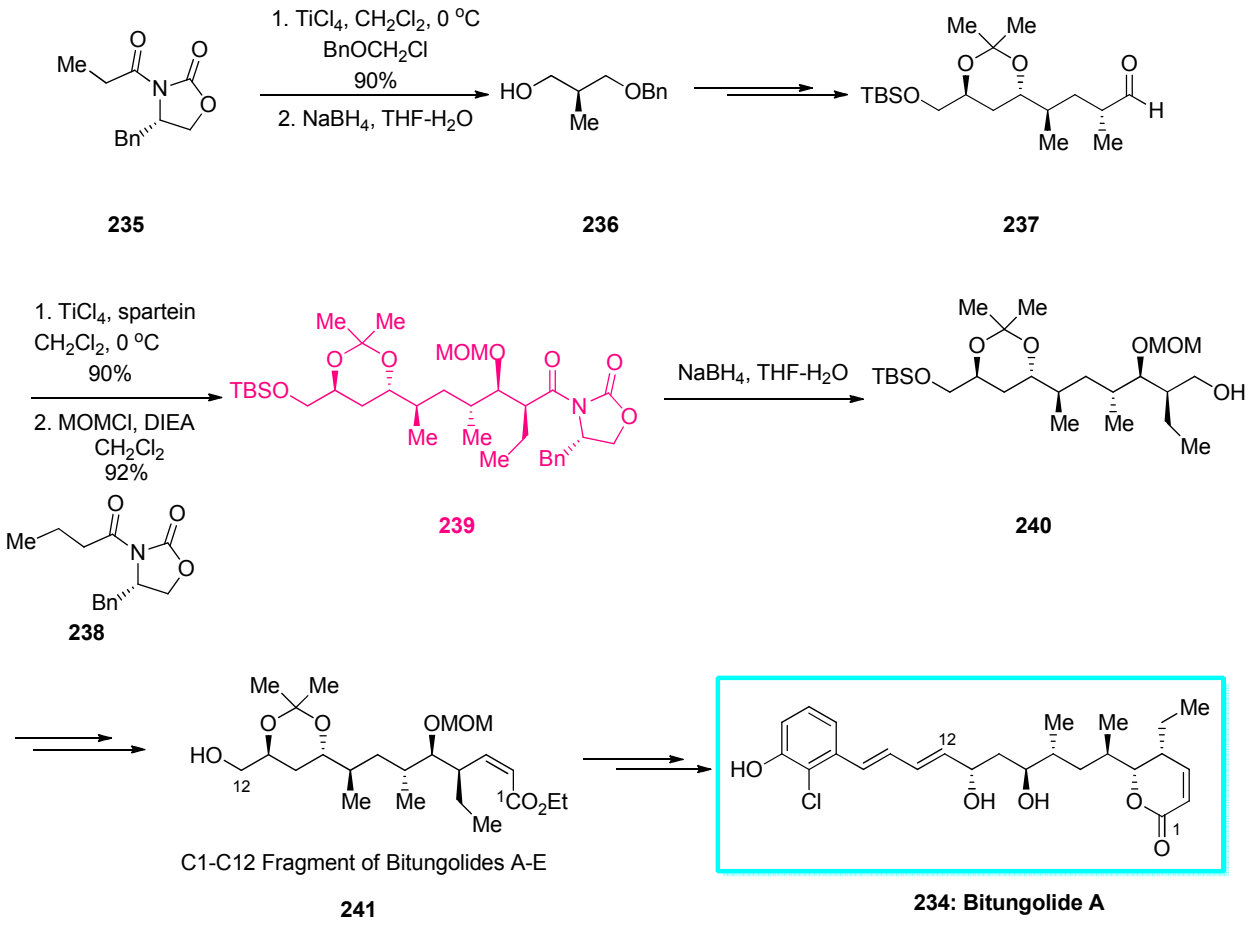
the appropriate Evans' imide. Upon methylation of sodium enolate created from the imide using methyl iodide, **227** was obtained in 83% yield. Sequential standard reduction /benzylation/ oxidative cleavage of the double bond gave acid **229**. Interestingly, at this juncture, the chiral oxazolidinone **226** recovered in the sodium borohydride reduction stage was reunited, followed by allylation with bromide **230** providing imide **231** in good yield. Next, peroxide-assisted hydrolytic removal of the chiral auxiliary was practically conducted. The chemoselective hydrogenation of the double bond afforded acid **232** in ten steps starting from (*S*)-citronellic acid. Finally, after several steps, acid **232** gave ester **233** which is an intermediate for the for the total synthesis of the spiroimine of pinnatoxins **224** in several steps (Scheme **46**).[180]



Scheme 46.

C_1-C_{12} Fragment **241** is a key intermediate in the synthesis of bitungolides A-E.[182] The formation of **241** commences with the asymmetric alkylation of oxazolidinone **235** with chloromethylbenzyl ether mediated by $TiCl_4$ in CH_2Cl_2 at 0 ºC to give the target alkylated product in 90% yield, which upon treatment with $NaBH_4$ in THF-H_2O after removal of the chiral

auxiliary to provide alcohol **236** in 90% yield. This alcohol **236** was further reacted to give aldehyde **237**. Evans' aldol reaction between the enolate of oxazolidinone **238** and aldehyde **237** in the mediated by $TiCl_4$ and sparteine in CH_2Cl_2 at 0 ºC gave the *syn* adduct in 90% yield as a single diastereomer which its secondary hydroxyl group was selectively protected with MOMCl in the mediated by *i*-Pr_2NEt in CH_2Cl_2 to give **239** in high yield. The chiral auxiliary in **239** was clasically removed reductively by $NaBH_4$ in THF-H_2O to provide alcohol **240** in 90% yield (Scheme **47**).

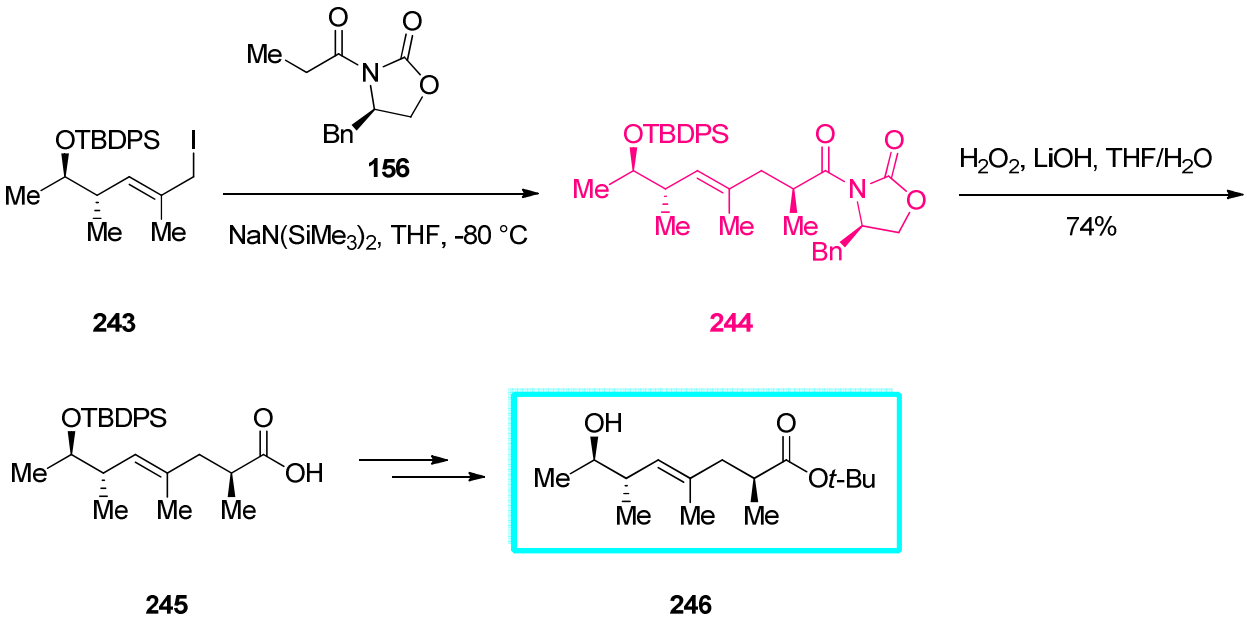


235 **236** **237** **238** **239** **240** **241** **234: Bitungolide A**

Scheme 47.

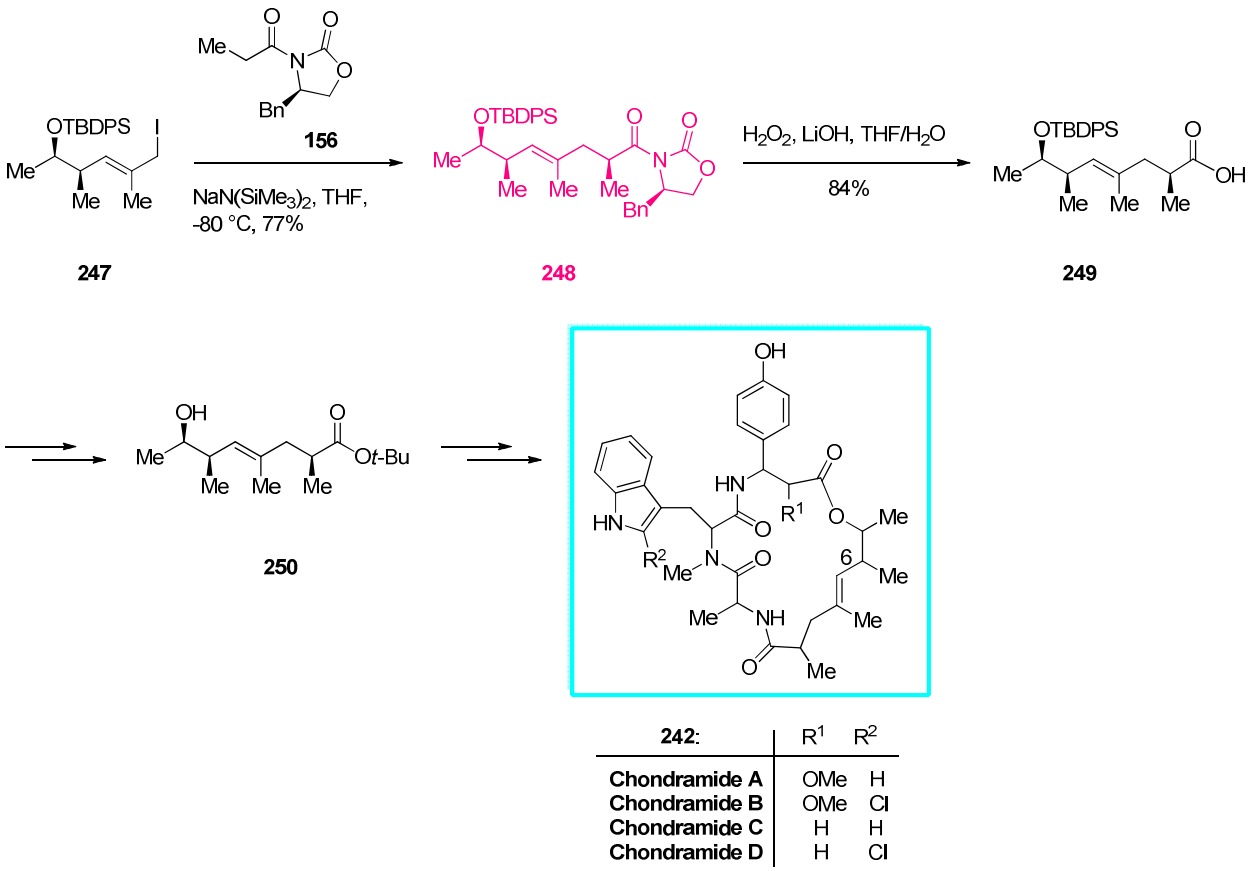
Monitoring of the fermentation broth of the mycobacteria *Chondromyces crocatus* resulted in the isolation of four compounds, i.e. the chondramides A-D **242** showing antifungal and cytostatic depsipeptides activities.[182, 183] A brief protocol to stereoisomers of the 7-hydroxy acid of the chondramides were presented.[185] Following this pathway, allyliodide **243** is acting as an

alkylating agent in the Evans' alkylation protocol as one of the key steps, leading ultimately to hydroxy acid **246**. The latter should help to elucidate the correct stereogenic center of the chondramide depsipeptides. The double bond of **243** is susceptible to isomerization during flash chromatography. Thus, iodide **243** was used crude for the subsequent alkylation of propionyl oxazolidinone **156**. [186] Deprotonation of **156** with $NaN(SiMe_3)_2$ in THF followed by the addition of iodide **243** afforded compound **244** in 71% yield. Upon hydrolysis of the carboxylic acid derivative **244** the OH-protected acid **245** was obtained. At last, hydroxy ester **246** was obtained which was appropriate for esterification with the tripeptide segment of the chondramides (Scheme **48**).[185]



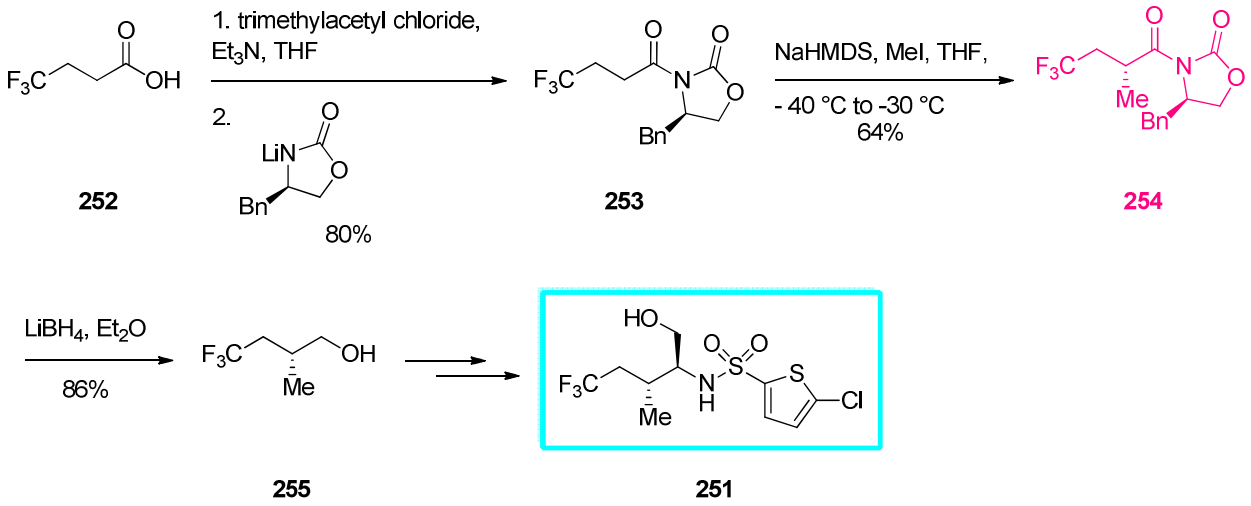
Scheme 48.

Similar to the synthesis of 6, 7-*syn*-hydroxy ester **250**, asymmetric alkylation of **156** afforded **248** (77%, over two steps), then saponification (84%) provided the acid **249** (90%) (Scheme **49**).



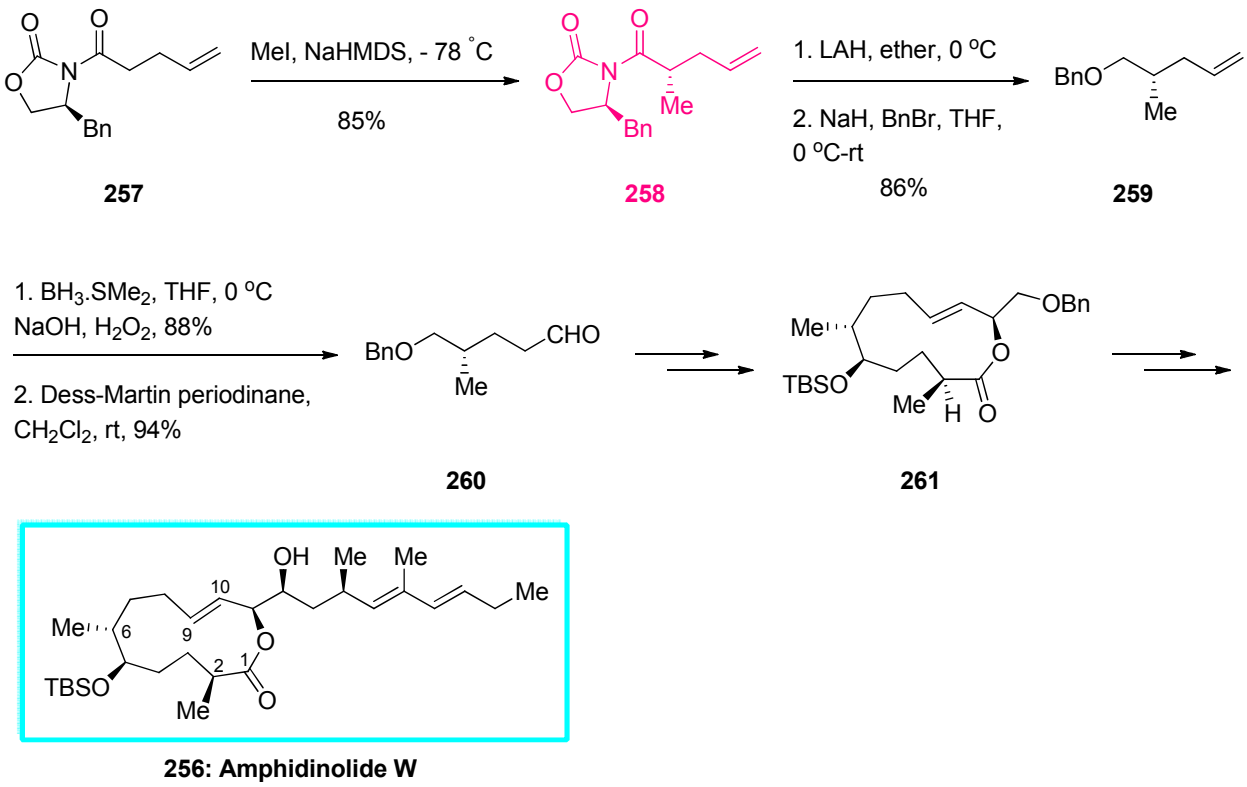
Scheme 49.

A practical and efficient stereoselective synthesis of biologically active hydroxyl thiophene sulfonamide **251** has been described.[187] The paramount of the total synthesis of this compound is the generation of two stereogenic centers. The biologically potent hydroxyl thiophene sulfonamide **251** is recognized as a novel *γ*-secretase inhibitor, which is used for the treatment of Alzheimer's disease. In this strategy, the total synthesis was started from commercially purchasable 4, 4, 4-trifluorobutyric acid **252** which was transformed into a mixed anhydride, and then treated with lithiated oxazolidinone to provide carboximide **253.** The stereoselective methylation was performed by the formation of an anion with sodium bis(trimethylsilyl) amide in THF at -40 °C. Subsequent addition of methyl iodide under thermal conditions gave **254** as single diastereomer in 64% yield. Treatment of the latter with $LiBH_4$ afforded chiral alcohol **255** in high yield. Compound **255** was transformed to target **251** *via* a multi-step synthesis (Scheme **50**).[187]



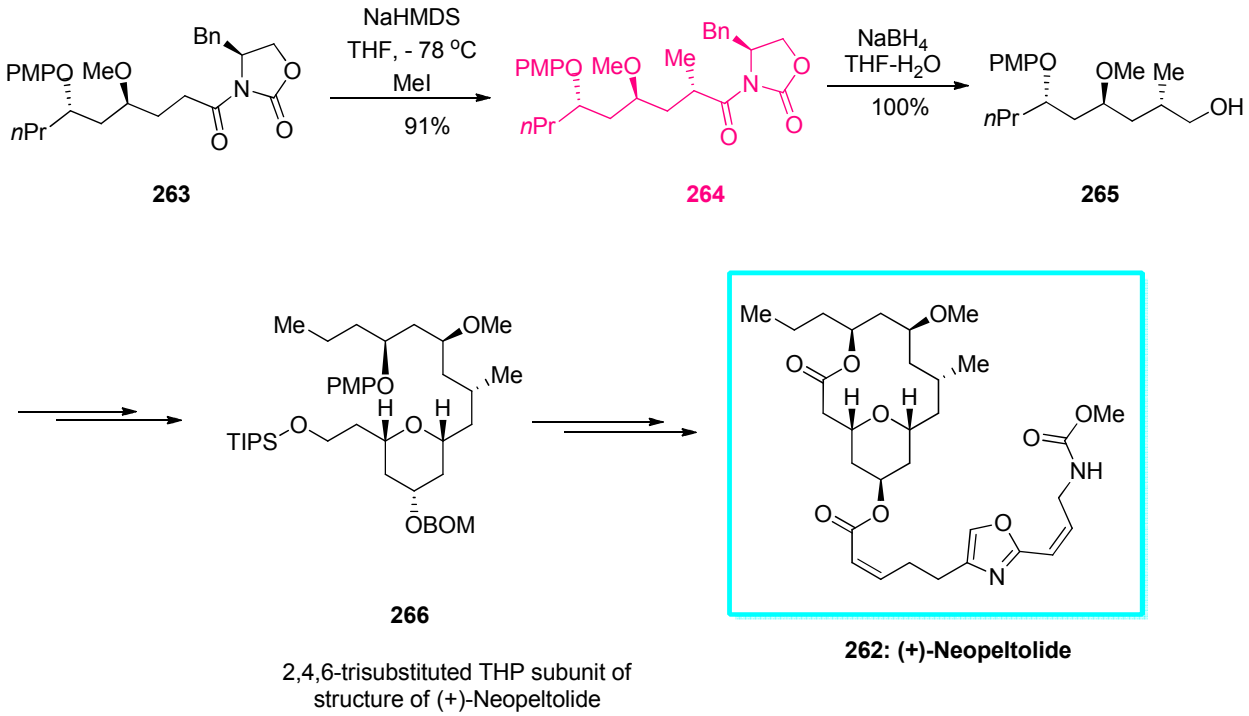
Scheme 50.

Amphidinolides, macrolides isolated from marine *Amphiscolops sp*,[188] show a strong biological potency, chiefly with an antitumor activity and scarce abundance. This group of macrolides has thus attracted the attention of synthetic organic chemists.[189] Amphidinolide W **256** is a 12-membered macrolide initially isolated by Kobayashi[190] in 2002. It exhibited high cytotoxicity against murine lymphoma L1210 cells in vitro. It is structurally different from other members in the family, as it has no an *exo*-methylene unit in its structure.[190] Ghosh and coworkers accomplished the total synthesis of amphidinolide W.[191] This research group developed a highly efficient approach to the macrolactone core of amphidinolide W.[192] The synthesis started with the already provided oxazolidinone **257**,[193] which upon asymmetric methylation using methyl iodide afforded **258** with high diastereoselectivity (17:1). The stereochemical outcome was confirmed by hydrolysis of **258** to the corresponding acid and comparison of resulted data with the previously reported values.[194] Reductive cleavage of auxiliary[195] with the sequence of benzylation/hydroboration/Dess-Martin oxidation[196] gave the aldehyde **260.** The latter was entered into the next Evans' aldol reaction and finally from other several reactions, finally the desired isomer of the macrolactone derivative **261**, the macrolactone core of amphidinolide W was fruitfully obtained in 42% overall yield (Scheme **51**).[193]



Scheme 51.

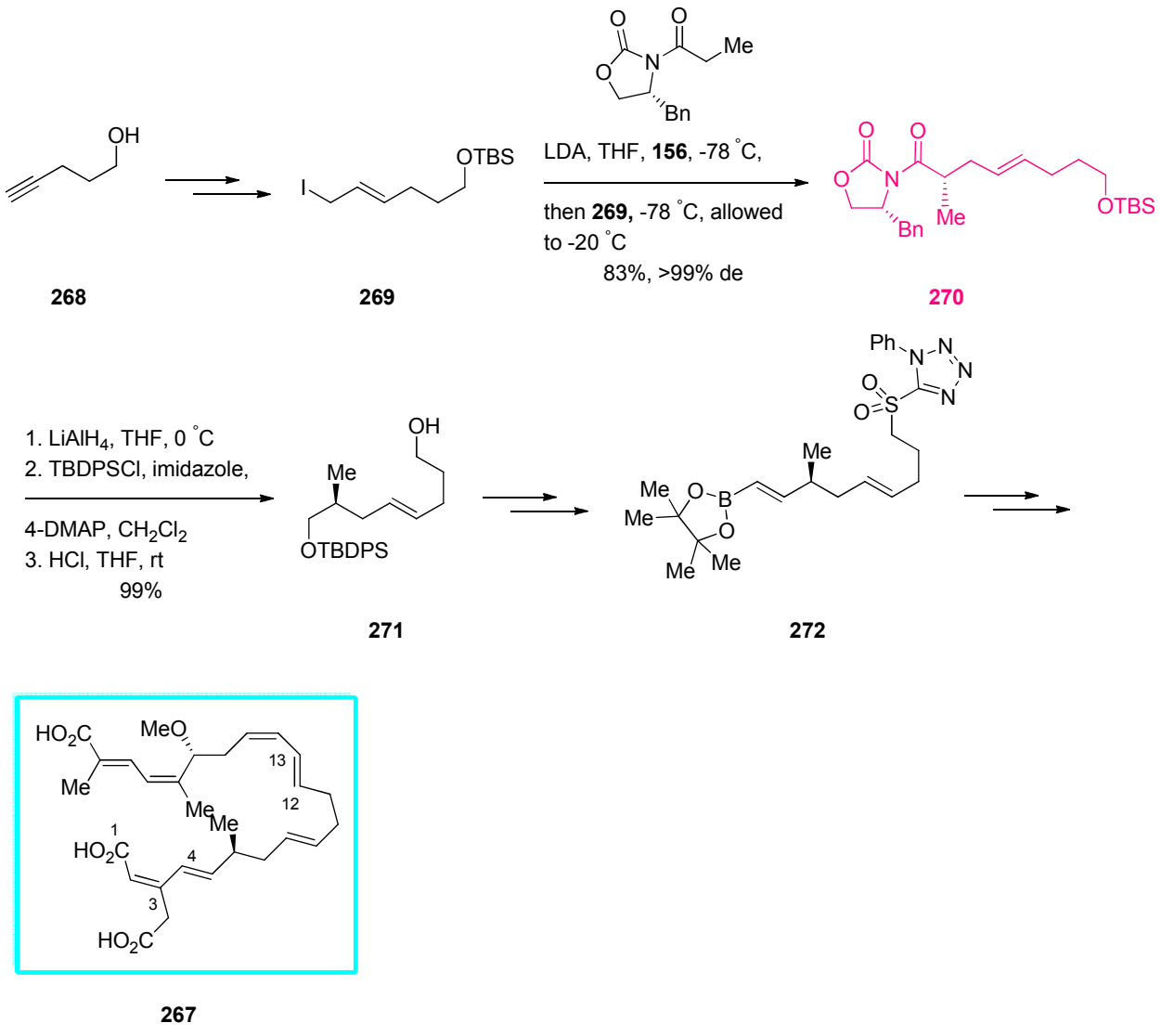
(+)-Neopeltolide **262** was initially isolated in 2007 from the north coast of Jamaica by Wright his research group, from a deep-water sponge.[197] (+)-Neopeltolide was found as a potent in vitro anti-proliferative agent towards the growth of several cancer cell lines. 2, 4, 6-Trisubstituted tetrahydrofuran subunit **266** acts as a key intermediate in the synthesis of the correct structure of (+)-neopeltolide **262**.[198] Its total synthesis makes use of **265** with correct chiral centers as the precursor for **266**. Alcohol **265** was synthesized by diastereoselective alkylation of **263** with methyl iodide mediated by NaHMDS in THF at - 78 ºC to provide methylated product **264** as a single diastereomer in high yield. The chiral auxiliary in **264** was conventionally removed by $NaBH_4$ in THF-H_2O to provide alcohol **265** in virtually quantitative yield (Scheme **52**).



Scheme 52.

Bongkrekic acid (BKA) **267** is a natural toxic antibiotic generated by the bacterium Burkholderia cocovenenans.[136] An efficient total synthesis of (+)-BKA, has been reported by Shindo *et al*. the apoptosis inhibitor bongkrekic acid, using a torquoselective olefination and the Kocienski-Julia olefination followed by the Suzuki-Miyaura coupling as the segment-binding steps. It is noteworthy that after combining the three segments, it took only two steps to complete the synthesis, indicating the high efficiency of this synthesis to provide BKA and its analogues. Furthermore, the torquoselective olefination also contributes to the shortening of the synthesis. The longest linear sequence is only 18 steps and completed in 6.4% overall yield, which is an improvement over previous process (32 steps and 0.6% overall yield). Noticeably, the total synthesis of BKA had already been reported by Corey group[199] in 1984 and by Shindo group in 2004.[137] Corey *et al*. did not claim the isolation BKA in pure form, due to its instability. Likewise, another semi-convergent synthetic approach[137] was too long (32 steps in the longest linear sequence). In an approach for the second-generation synthesis of BKA, in 2009, Shindo and coworkers reported a three-component convergent strategy employing a doubly terminally functionalized fragment B.[200] The synthesis of Segment B began with the stereoselective alkylation of the Evans' oxazolidinone **156** using **269** readily prepared from 4-pentyn-1-ol **271** in

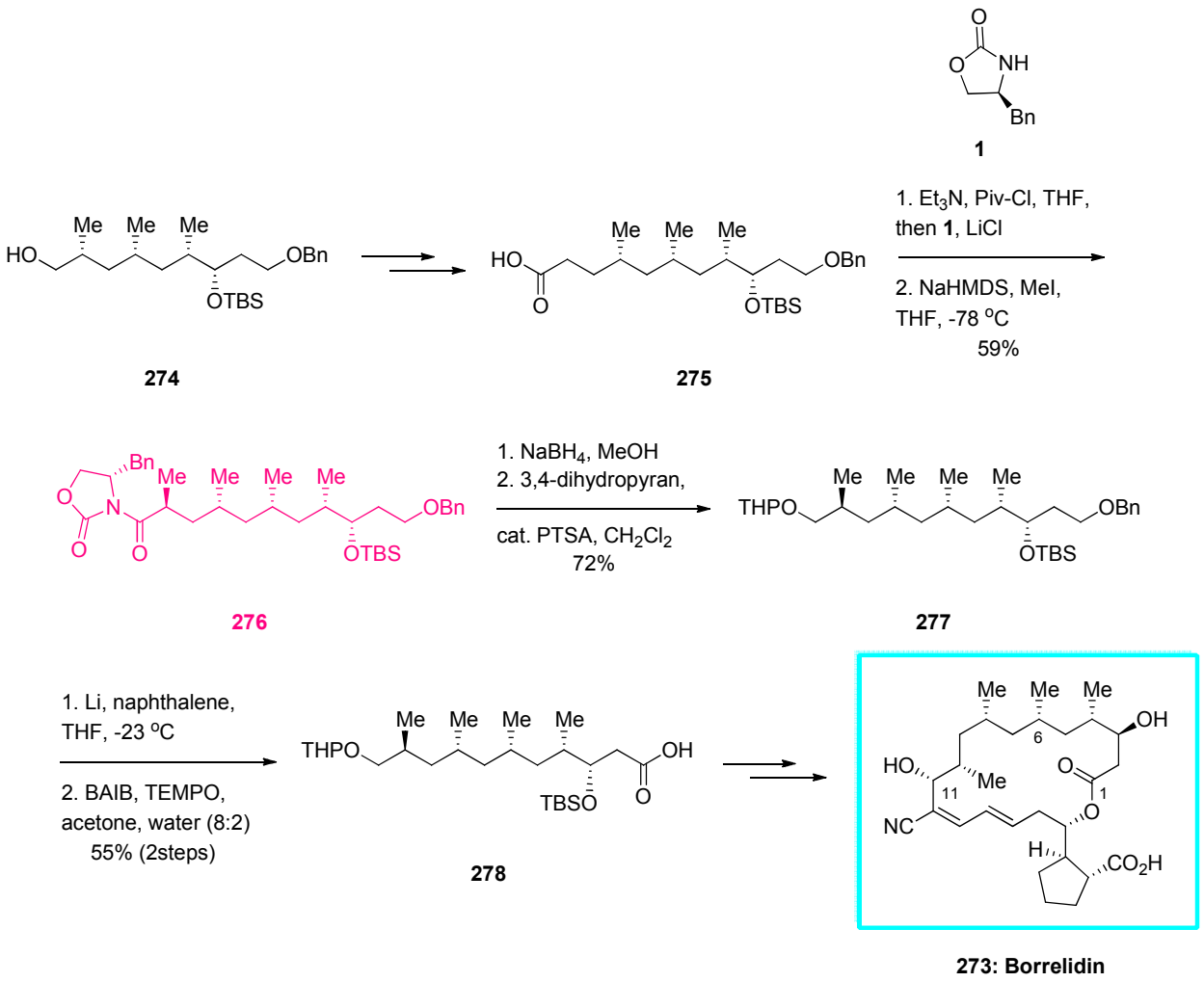
five steps to obtain **270** with excellent diastereoselectivity and in good chemical yield. Removal of the chiral auxiliary was conducted with a conventional reduction, followed by protection of the alcohol with a TBDPS protective group to provide **271**. The doubly terminally functionalized middle fragment **272** was synthesized after several steps (Scheme **53**).[200]



Scheme 53.

Borrelidin **273**, is a 18-membered macrolide antibiotic showing *anti-Borrelia* activity. It was initially isolated from Streptomyces rochei by Berger *et al.* in 1949.[201] Its structure was suggested by Keller-Schierlein in 1967,[202] and its absolute configuration was confirmed *via* X-ray crystallographic analysis and finalized by Anderson *et al*.[203] An asymmetric total synthesis of

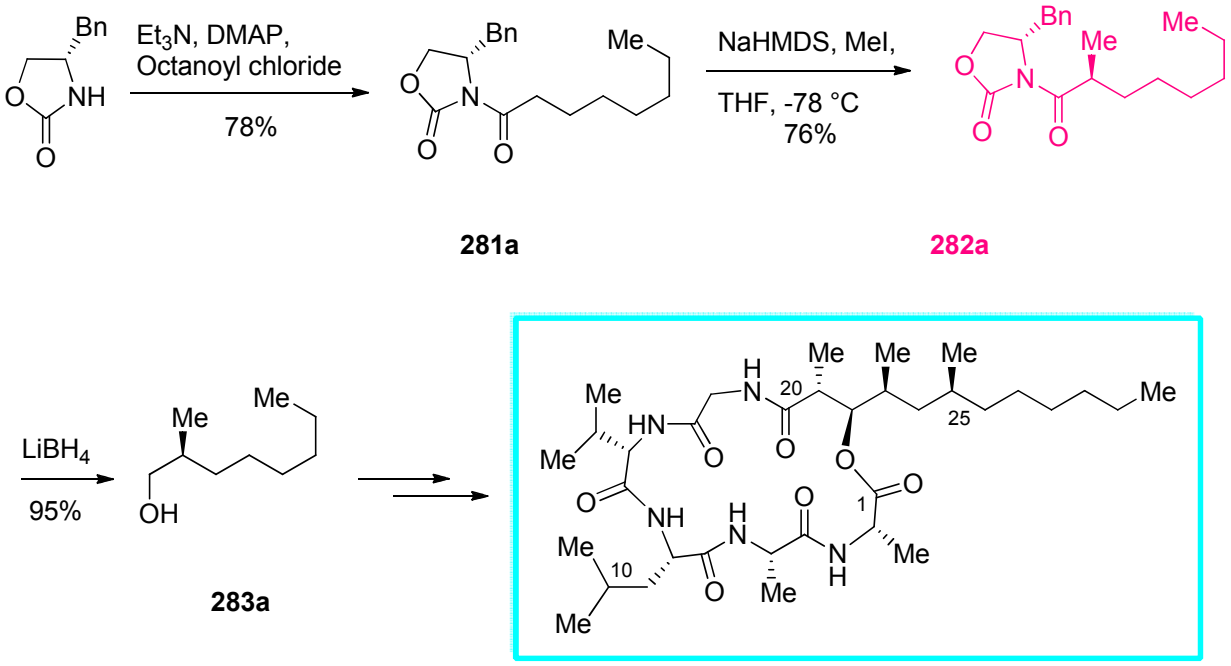
borrelidin was reported in 2009 by Yadav and coworkers. In the preparation of the C_1-C_{11} segment of borrelidin, all the chiral centers were induced *via* desymmetrization protocols, including Sharpless asymmetric epoxidation, regioselective opening of chiral epoxide and our subject, asymmetric alkylation using the Evans' chiral oxazolidinones.[204] As depicted in Scheme **54**, synthesis of the intermediate **278** was commenced from compound **274**. The acid group in compound **275** was activated *via* preparation of the mixed anhydride coupled with the Evan's chiral auxiliary followed by methylation using methyl iodide to provide compound **276**. The latter was then reduced to the corresponding alcohol, which was protected using DHP, as THP ether to obtain **277**. Deprotection of the benzyl group in the presence of Li-Naphthalene gave benzyl the group, free alcohol, which, upon smooth and clean oxidation, using TEMPO, BAIB,[205] afforded the desired compound **278** (Scheme **54**).[204]



Scheme 54.

Emericellamides A and B are components of marines family. They were isolated from marine-derived fungus *Emericella sp*.[206] From structural points of view, they hold two main portions: a pentapeptide and an adjoining di- or trimethyl hydroxy acid. Emericellamides A and B exhibited antibacterial potencies toward methicillin-resistant *Staphylococcus aureus*. A diverse and flexible protocol considering peptide chemistry, employing stereoselective alkylations and decisive macrolactamization was accomplished and reported by Xu, Yea and coworkers.[207] The overall yield of this total synthesis for emericellamide A **279** was reported to be 22% over eight steps, whereas the total synthesis of emericellamide B **280** was achieved in only 14% overall yield. The synthesis started with generation of both enantiomers of *N*-octanoyl-4-benzyloxazolidinone using conventional procedures. (*S*)-4-benzyloxazolidinone **1** gave **281a** in

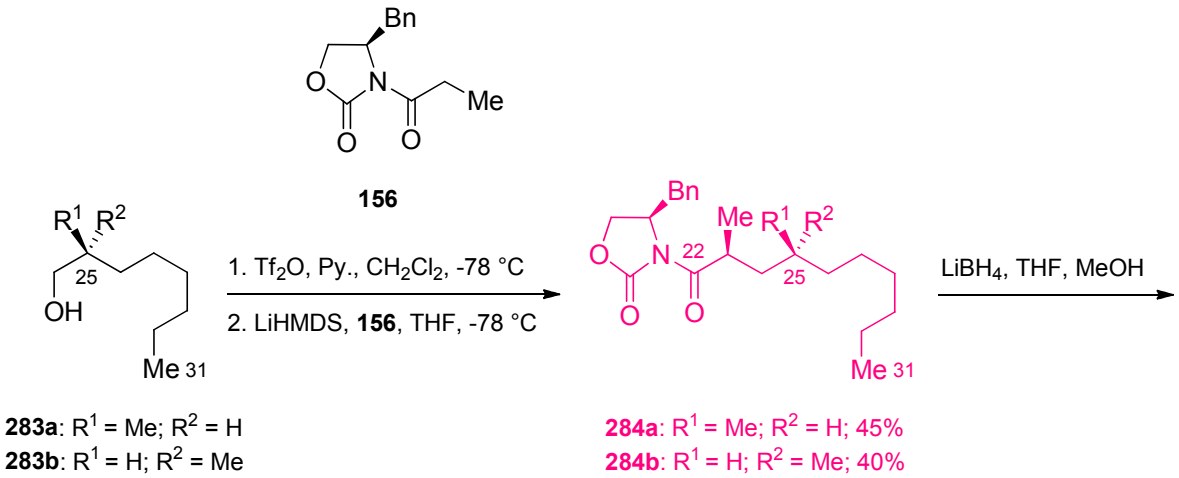
good yield. Upon treatment with NaHMDS and reaction with methyl iodide in THF, the latter provided the alkylated product **282a** in satisfactory yield as a sole diastereoisomer. Reductive removal of the Evans' auxiliary upon treatment with $LiBH_4$ afforded the substituted alcohol **283a** virtually in quantitative yield.[208] The latter was employed as a precursor to synthesize substituted acid portion of both emericellamides A and B. Alcohol **283b** was provided from (*R*)-4-benzyloxazolidinone in a similar sequential reaction for the synthesis of the C25 epimer of emericellamide B (Scheme **55**).[207]

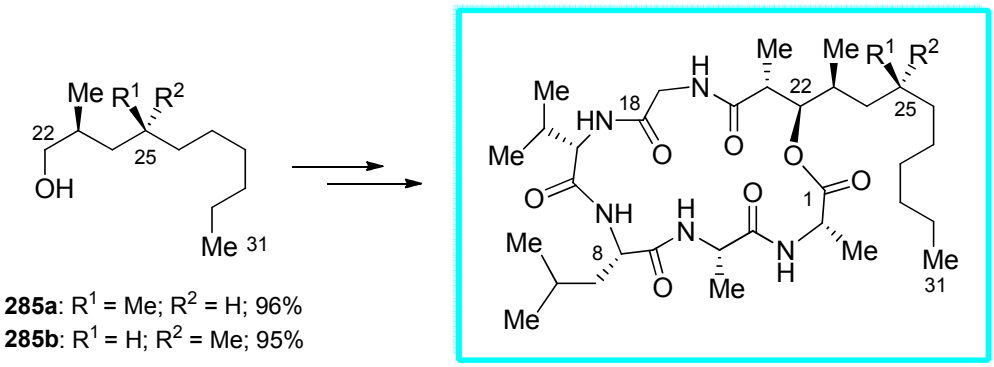


Scheme 55.

For the total synthesis of emericellamide B, alcohols **283a** and **283b** were independently reacted with triflic anhydride and the provided alcohol was used to alkylate (*R*)- (—)-4-benzyl-3-propionyl-2-oxazolidinone **156**, again following the Evans' strategy, thus adding the extra methyl substituent on the side chain. Then, the reductive removal of chiral auxiliary provided **285a** and **285b**. Finally, after several steps including functional group conversions, compound **286** was provided. Un-delightfully, the analysis data for **286** were even more inconsistent and hopeless with those of the natural products **280**. A comparison of the δ values for the C13 spectra shows that there are more differences between **286** and the natural product than those recorded for **280**.

As a result, **280** was implicated to have the correct stereochemistry in accordance with emericellamide B (Scheme **56**).[207]

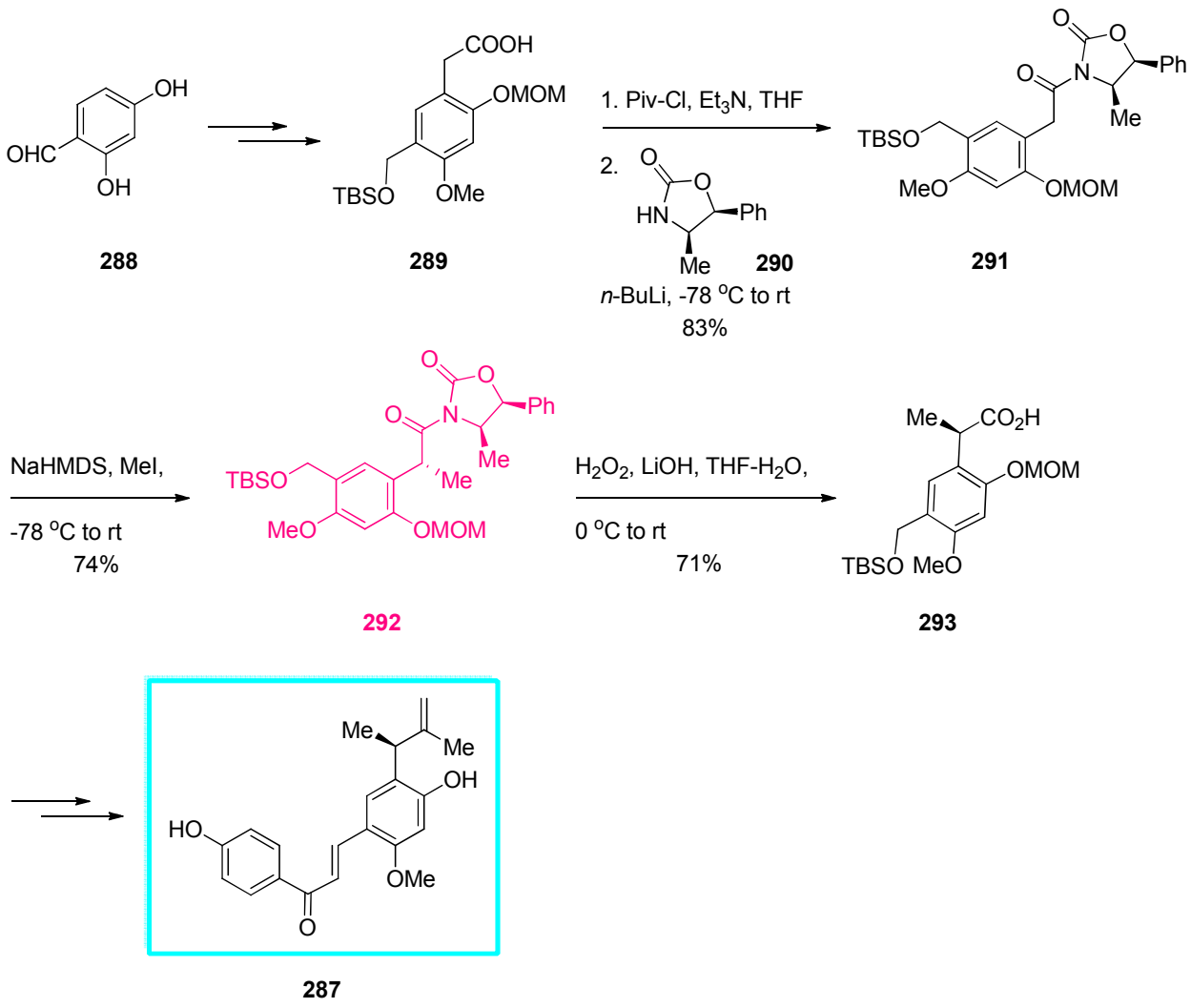




Scheme 56.

Licochalcone E was initially isolated from the roots of *Glycyrrhiza inflate* since cytotoxicity was observed against the HT1080 cell line.[209] Further biological properties were observed from the extract this natural product.[210, 211] The absolute configuration of (—)-licochalcone E **287** was determined and being revealed as (*S*) *via* the first asymmetric total synthesis of this natural product. Interestingly, the chirality in (*S*)- (—)-licochalcone E **287** can be induced *via* stereoselective methylation of an appropriate Evans' oxazolidinone derivative. This

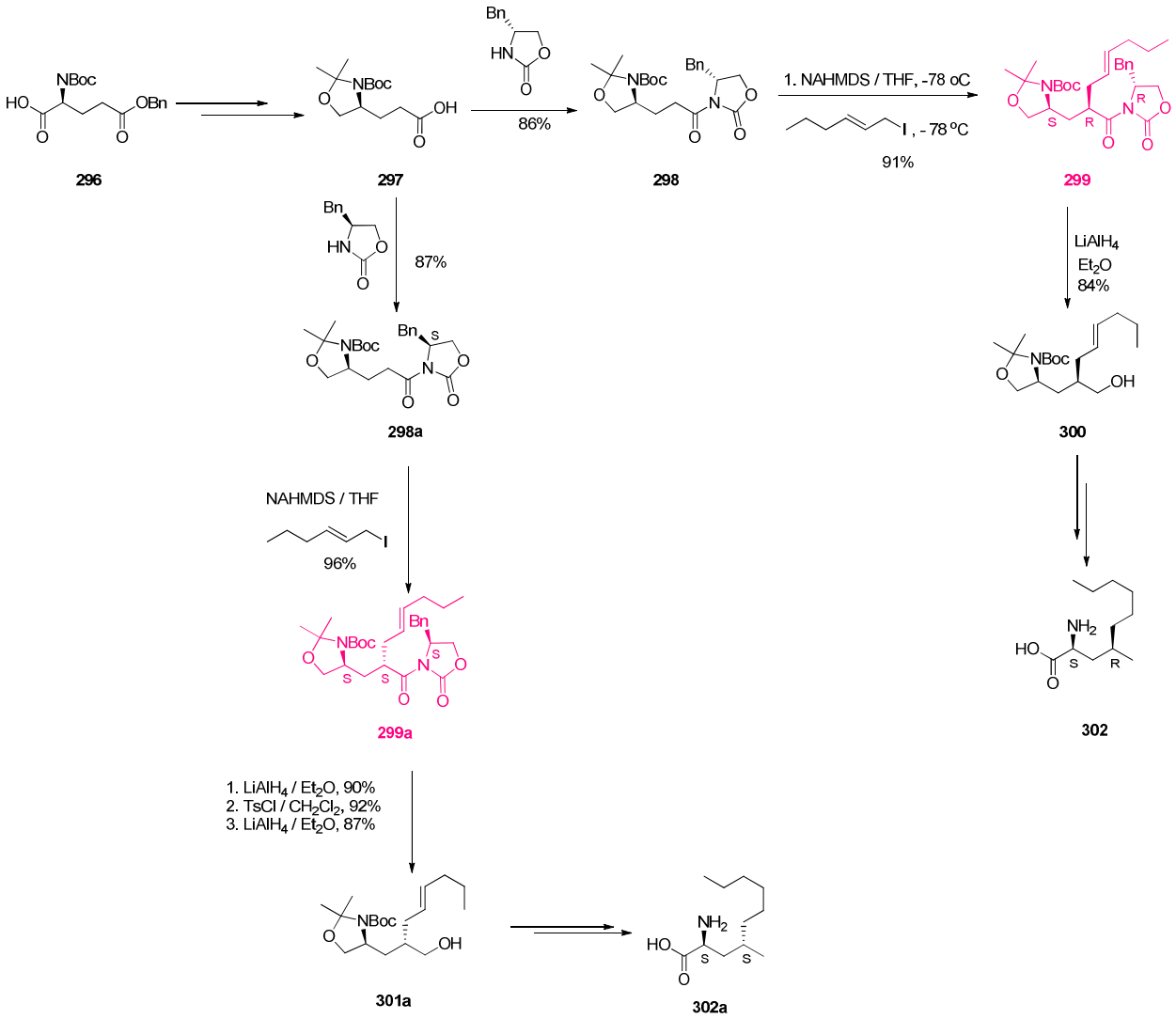
method not only is applicable flexible to synthesize (*S*)- (−)-licochalcone E **287** but also is quite versatile and flexible for the synthesis of its analogs for biological evaluations. The synthesis of the key intermediate **291** from 2, 4-dihydroxybenzaldehyde **288** is depicted in Scheme **57**.[212] 2-Arylacetic acid **289** was provided *via* a multi-step synthesis, upon reaction with pivaloyl chloride mediated with Et_3N to provide mixed anhydride, which upon treatment with the lithium anion of (4*R*, 5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone **290** gave the imide **291** in high yield over two steps. (4*R*, 5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone **290** was selected as Evans' auxiliary since it was found to disclose a well-defined absolute stereochemistry unambiguously with high *ee via* a stereoselective reaction.[213] Delightfully, the imide **291** happened to give the same enantiomer as the natural licochalcone E after several additional other reactions required reactions. Having the key intermediate **291**, the required chirality was induced to the molecule as illustrated in Scheme **57**. Upon treatment with NaHMDS and reaction with methyl iodide, the Evans' oxazolidinone auxiliary **291** gave methylated imide **292** in satisfactory yield. It is also found to be formed as a single isomer proven by ^{1}H NMR spectra analysis. Upon hydrolysis with LiOH and H_2O_2 the Evans' oxazolidinone was converted to acid **293** also in satisfactory yield (Scheme **57**).[214]

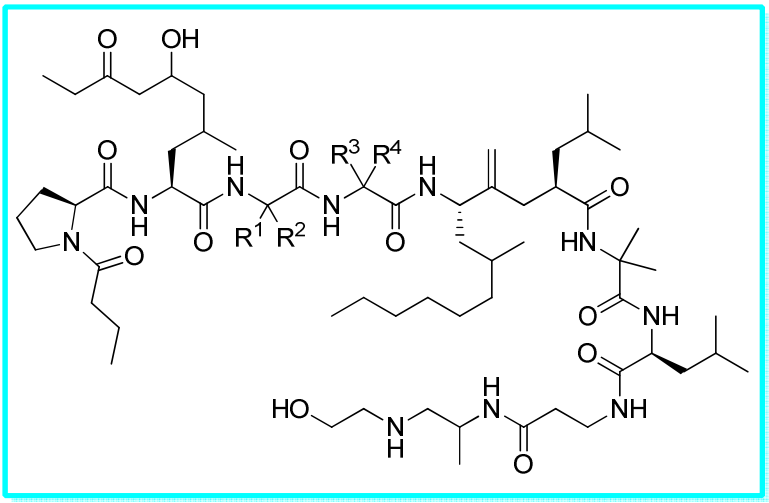


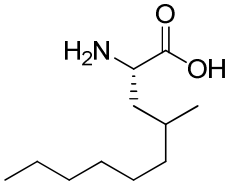
Scheme 57.

Peptaibiotics are well-recognized as an outstanding, persistently growing family of polypeptides with more than 850 known members during the past 50 years. Non-proteinogenic amino acids for instance 4-hydroxyproline (Hyp), 2-amino-6-hydroxy-4-methyl-8-oxo-decanoic acid (AHMOD), β-Alanine (β-Ala) and some others are widespread in their structures. Among them, C^{α}-dialkylamino acids and most importantly α-aminoisobutyric acid (Aib) and, $_{L}$ -or $_{D}$-isovaline (Iva) if present, play a pivotal role in determining in biological activities of peptaibiotics.[215-218] An efficient synthesis of (2*S*, 4*S*)- and (2*S*, 4*R*)-2-amino-4-methyldecanoic acids was achieved using a glutamate derivative as starting material. Notably an appropriate Evans' oxazolidinone is involved in a decisive asymmetric alkylation step. The two synthesized diastereomers NMR data were compared with those of the natural product, already reported. Consequently, the

configuration of this novel amino acid unit in culicinins was unambigeously assigned as (2*S*, 4*R*). As depicted in Scheme **58**, the commercially available reagent *N*-Boc-γ -benzyl $_{L}$-glutamate **296** was initially converted into the N, O-protected carboxylic acid **297** readily in accordance to procedure, already reported.[219] Next the acid was linked to the chiral auxiliary, (*R*)-4-benzyl-2-oxazolidinone under the mild reaction conditions developed and reported by Ho *et al*.[86] The resultant important intermediate **298** was then submitted to Evans' asymmetric alkylation at low temperature. In this step, initially, 1-iodohexane was used as an electrophilic reagent. Nevertheless, the desired product was not obtained, probably due to the poor electrophilic intensity of the iodoalkane, used. Thus, an 'auxiliary line' was required. Therefore, 1-iodohex-2-ene, with more electrophilic intensity was used instead of 1-iodohexane. Compound **298** can be enolized at low temperature. Addition of 1-iodohex-2-ene afforded the alkylated R-adduct **299** as the major diastereomer, which could be readily separated from its diastereomer by column chromatography. The chiral auxiliary was removed under reductive conditions to afford the alcohol **300**. After several steps, the desired amino acid **302** was obtained. The NMR data of **302** was compared with that of obtained from natural product and found being identical. Acid **297** was reacted with the (*S*)-4-benzyl-2-oxazolidinone instead of its enantiomer affording compound **298a**, which was transformed into free amino acid **302a** in eight steps. Then, the NMR data of **302**, **302a** and those of the natural product were cautiously compared. Significantly, no difference was found between the ^{1}H NMR data of the two diastereomers and those of the natural product.[220] Delightfully, their ^{13}C NMR shifts were found being pretty different. It was then concluded that, the configuration of this amino acid residue in the natural products should be (2*S*, 4*R*).





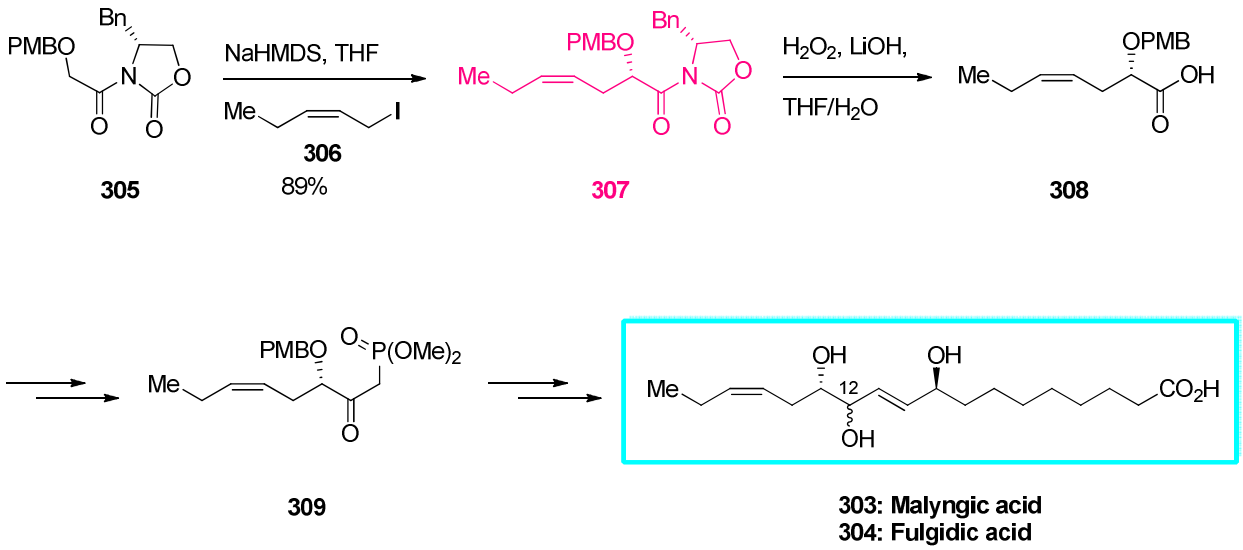


294: culicinin A: $R^1 = R^3 = H$, $R^2 = R^4 = Me$
culicinin B: $R^1 = R^2 = R^3 = Me$, $R^4 = H$
culicinin C: $R^1 = H$, $R^2 = R^3 = R^4 = Me$
culicinin D: $R^1 = R^2 = R^3 = R^4 = Me$

295: (2*S*)-2-Amino-4-methyldecanoic acid

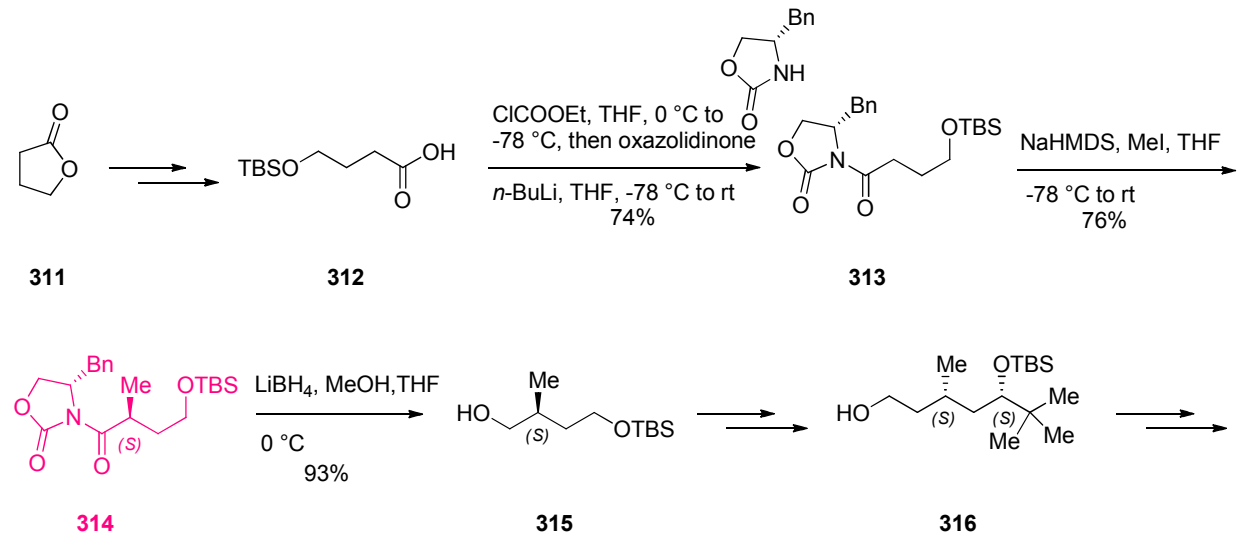
Scheme 58.

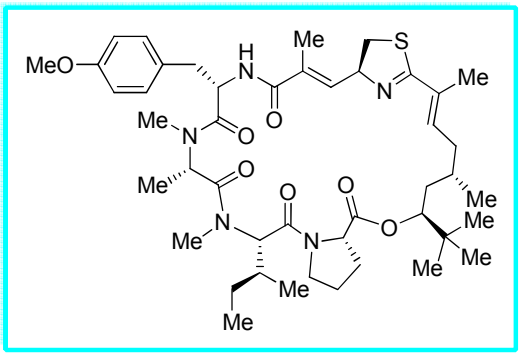
Malyngic acid **303** is placed in the oxylipin family of natural products. It was initially isolated by Cardellina and coworkers from the marine blue-green algae *Lyngbya majuscula*. On the basis of chemical degradation, combined with analysis of spectroscopic data, compound **303** was characterized as a trihydroxy unsaturated fatty acid.[222] Fulgidic acid **304**, was initially isolated from the terrestrial higher plant *Rudbeckia fulgida*, by Herz and coworkers. It was characterized by comparison of its NMR spectra with those of malyngic acid **303** as the C12-epimer of **303**.[223] An asymmetric total synthesis of malyngic acid **303** was accomplished from the known oxazolidinone derivative **305** in 26% yield over eight steps.[224] The total synthesis was started from **305** [225] which undergoes Evans' asymmetric alkylation with (*Z*)-1-iodo-2-pentene **306**[226] to afford **307** in high yield.[227] Removal of the oxazolidinone moiety of **307** using alkaline hydrogen peroxide under standard conditions provided carboxylic acid **308**. After two steps, the latter was transformed into keto phosphonate **309** in excellent yield. Fulgidic acid **304**, the C12-epimer of malyngic acid **303**, was also prepared from **305** in 25% yield over eight steps (Scheme **59**).[224]



Scheme 59.

Apratoxins A **310** is a marine secondary metabolite. It was first isolated from the remarkably prolific *Lyngbya majuscula* collected in Guam and Palau. It exhibits activity in vitro toward LoVo cell lines and the KB.[228, 229] A stereoselective strategy to the key intermediate **316** in which the Evans' alkylation is employed has been reported. In this approach, as depicted in Scheme **60**, commercially purchasable lactone **311**, is converted into free acid part **312** in 81% overall yield after two steps. The latter was then activated with ethyl chlorocarbonate and the resulting mixture in situ was subsequently reacted with the lithium salt of oxazolidinone to provide amide **313** in satisfactory yield. The latter was subjected to methylation with MeI to furnish product **314** with high diastereoselectivity (*dr* > 98:2) and satisfactory chemical yield. The auxiliary was removed under standard conditions ($LiBH_4$, H_2O) affording the primary alcohol **315** in excellent yield. After several steps, the key intermediate **316** was obtained from **315**. Compound **316** in turn could be transformed to the desired natural product, (*E*)-dehydroapratoxin A **310** (Scheme **60**).[230]



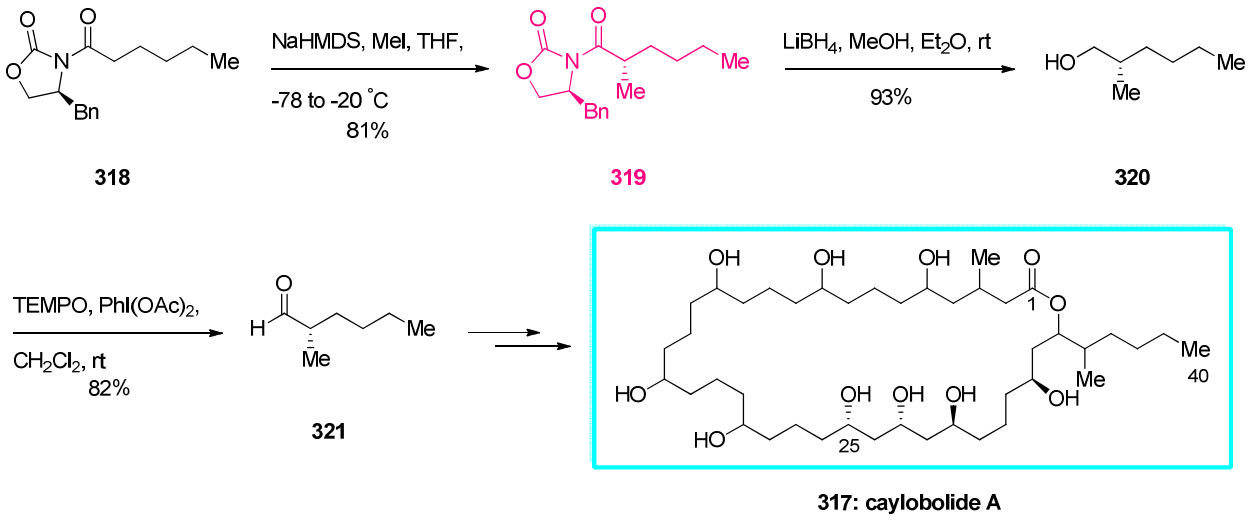


310: (*E*)-Dehydroapratoxin A

Scheme 60.

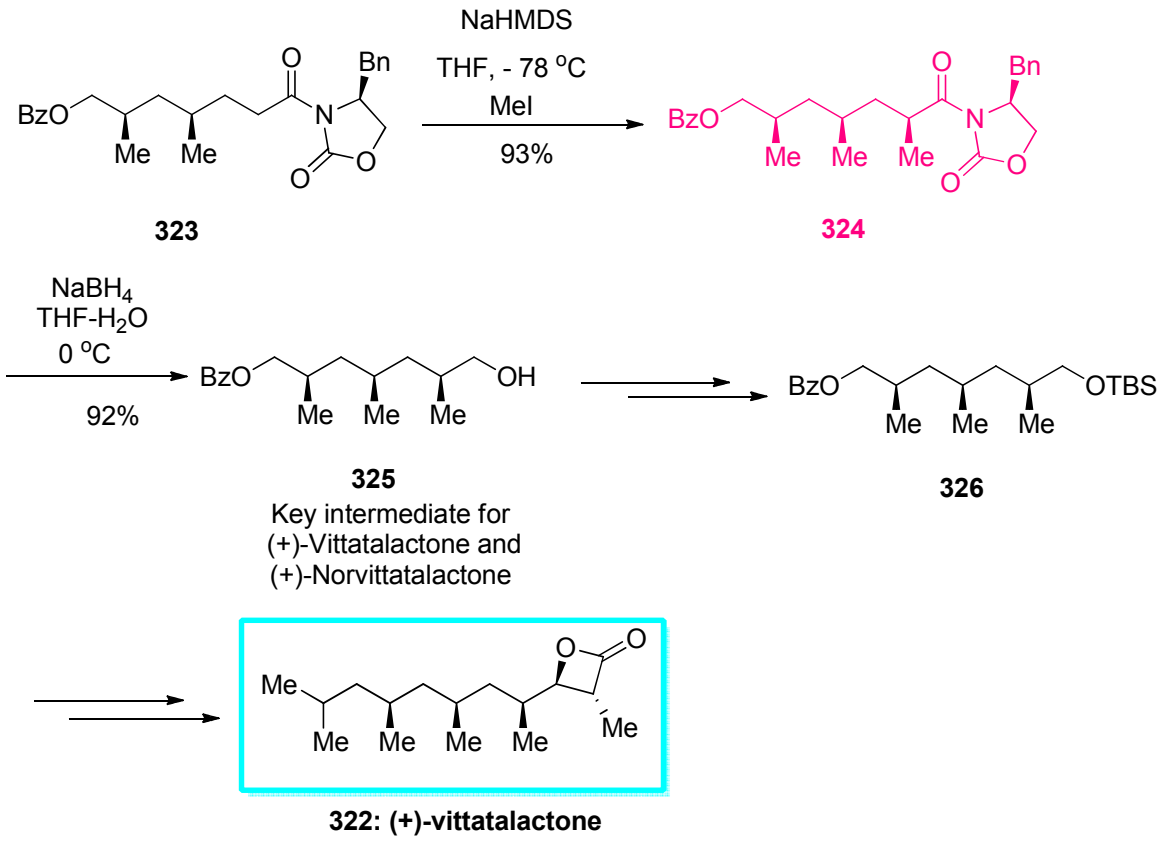
In 2002, Molinski and coworkers isolated caylobolide A **317** *via* bioassay-guided purification from the marine cyanobacteria *Lyngbya majuscule* collected at Cay Lobos, Bahamas.[231] Caylobolide A contained eight undetermined stereogenic centers. Thus, there are 256 diastereomeric structural possibilities. It has another significant feature. It is the repeating 1,5-diol moieties existed along the 36-membered lactone core. Besides, it has a fascinating macrocyclic structure. Caylobolide A has exhibited cytotoxic potencies towards the human colon tumorcell line HCT 116. In 2011, a convergent and flexible synthesis of two possible diastereomers of the C_{25}-C_{40} segment in (−)-caylobolide A, has been achieved and reported by Jennings *et al*.[232] According to this approach, for the synthesis of the C_{25}-C_{40} sub-unit of **317**, the synthesis of chiral aldehyde **321** is required as depicted in Scheme **61**. Thus, a stereoselective alkylation of the known chiral oxazolidinone **318** using NaHMDS and MeI afforded **319** in high

yield with excellent diastereoselectivity (>15:1 *dr*). As usual, the oxazolidinone moiety was removed upon smooth reduction with $LiBH_4$ giving the chiral primary alcohol **320** in excellent yield. Upon oxidation of the hydroxyl group of **320**, using TEMPO and $PhI(OAc)_2$ as oxidants, the desired aldehyde **321** was obtained in high yield. Chiral aldehyde **321** is recognized as the key intermediate for the synthesis of C_{25}-C_{40} fragment in (—)-caylobolide A (Scheme **61**).[233]



Scheme 61.

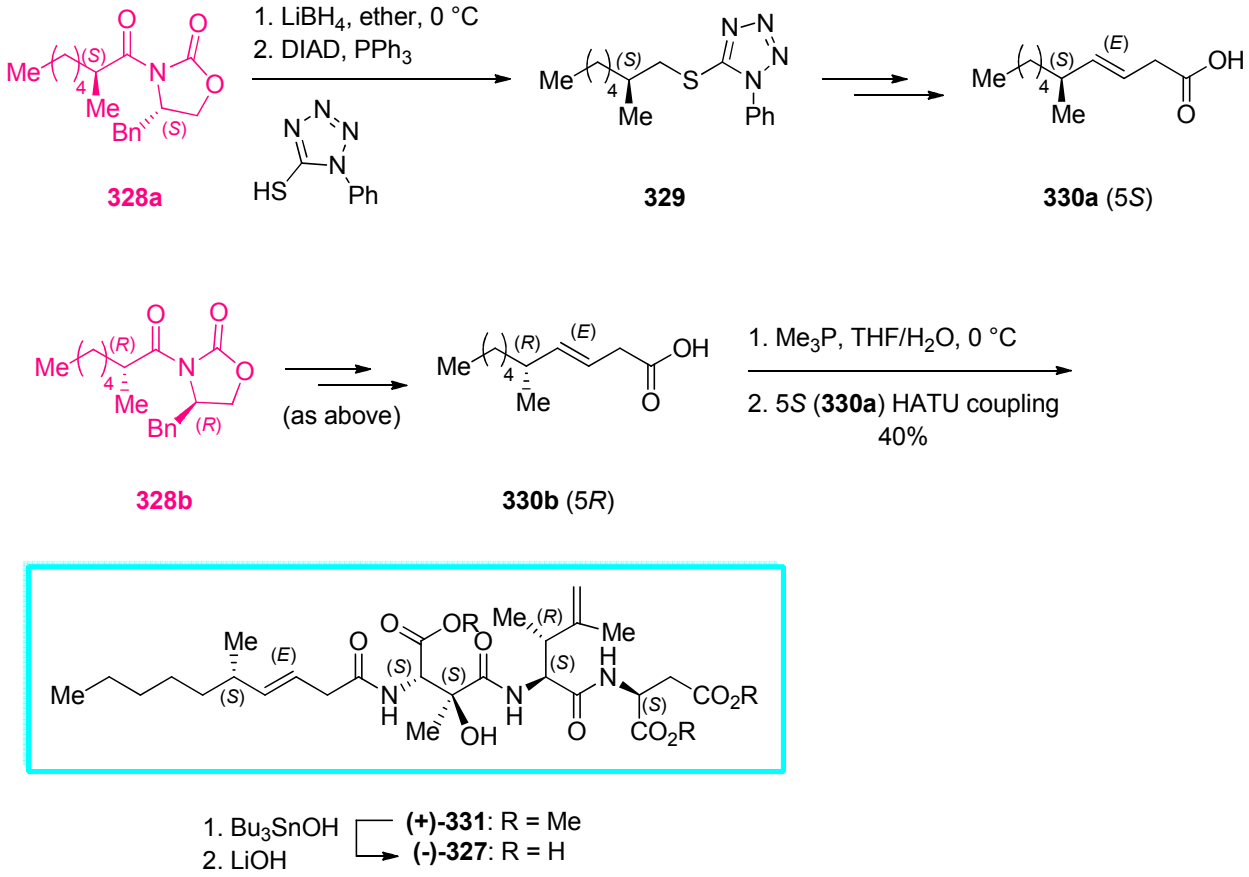
Compound **326** is a key intermediate for the synthesis of (+)-vittatalactone and (+)-norvittatalactone.[234] It has been isolated from the striped cucumber beetle *Acalymma vittatum*. The latter was synthesized *via* stereoselective alkylation of **323** with methyl iodide mediated by NaHMDS in THF at -78 ºC to give **324** in high yield and excellent diastereoselectivity (> 98:2). The chiral auxiliary in **324** was next conventionally removed ($NaBH_4$, THF-H_2O, 0 ºC) to give the alcohol **325** in high yield, chemoselectively, since benzoate group was not reduced and un-affected (Scheme **62**).[234]



Scheme 62.

A *Streptomyces*-derived lipidated peptide metabolite **327** has recently attracted enormous attention of the organic chemists. Among them, Lear and coworkers focused on elucidation of the structure of dipeptide **327**, which was successfully established. In 2004, the application of the latter was patented by the Yamanouchi Pharmaceutical Co. It was found that **327** can inhibit the growth of Plasmodium falciparum.[235] The absolute configuration of **327** was determined *via* degradation and Marfey's derivatization investigations. The total synthesis of a potent antimalarial lipid-peptide **327** was revealed in 2012.[90] In this approach Lear and coworkers used stereocontrolled routes along with a catalytic Mannich reaction, Sharpless epoxidation, Evans' alkylation, and Kocienski-Julia olefination to obtain nonproteinogenic amino acids. In this pathway, the preparation of Evans' oxazolidinones **328a/b** were required [236] for synthesis of chiral trans fatty acids **330a** and **330b**. Then **328** was converted to the thiotetrazoles **329** upon reduction under standard conditions and Mitsunobu reaction. Next, *via* a multi-step reaction, and Jones oxidation, the fatty acids **330a** (5*S*) and **330b** (5*R*) were obtained. At last, after several

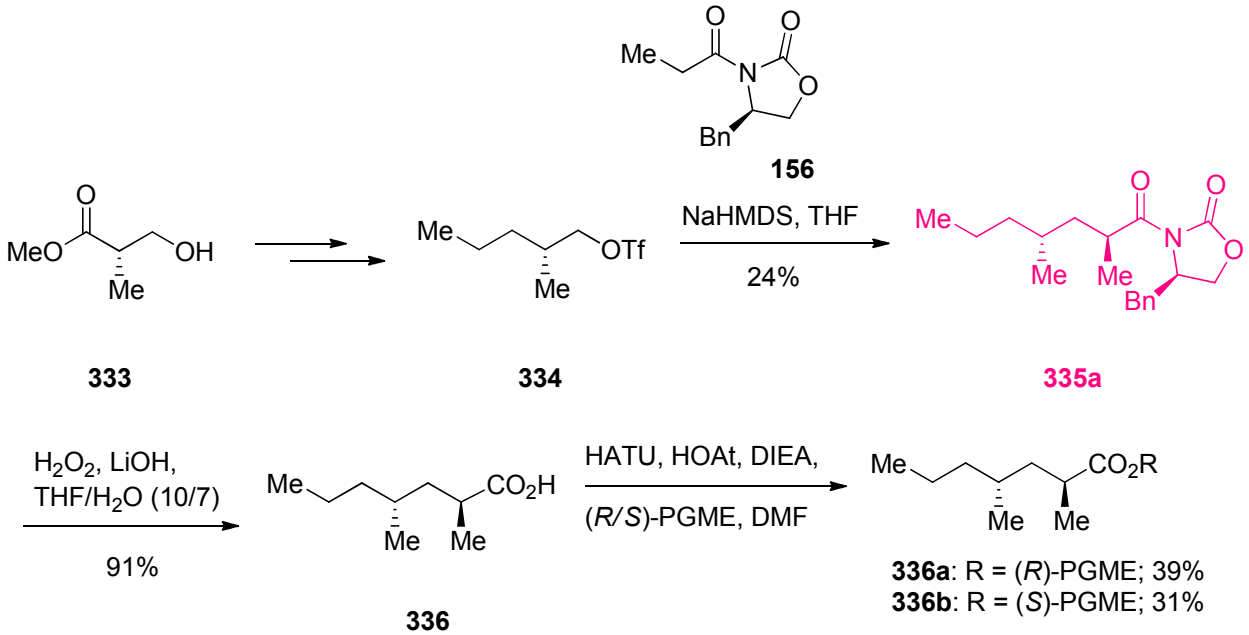
additional steps, involving functional group transformations, the trimethyl ester derivative (+)-**331** obtained from **330a** which could be converted to **327** (Scheme **63**).[90]



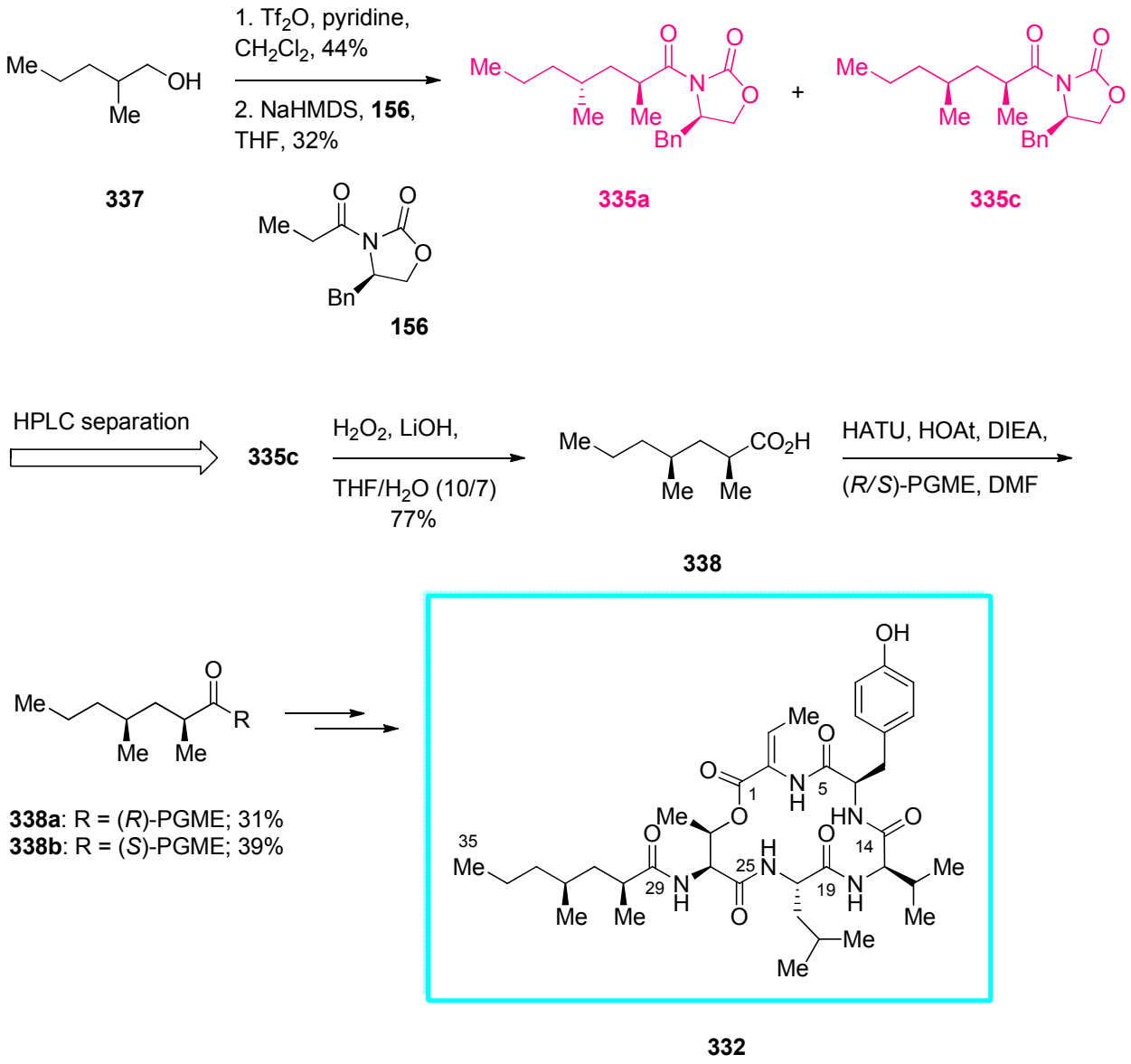
Scheme 63.

A cyclic depsipeptide tumescenamide C **332**, is a novel member related of tumescenamides. It has been isolated from a culture broth of an actinomycete *Streptomyces* sp. Its structure was fully characterized. Tumescenamide C was a relative of tumescenamides A and B, containing a sixteen-membered ring system, which bears two proteinogenic and three non-proteinogenic amino acids. In its structure, it has a methyl-branched fatty acid. The planar structure was established by spectra analysis, whereas its absolute configuration was defined by chemical degradation and most importantly by an asymmetric synthesis. It has been found that tumescenamide C shows an antimicrobial activity with a high level of selectivity towards Streptomyces species.[237, 238] For the definite determination of the absolute configuration of C32, the total synthesis of (2*S*, 4*R*)-**336** and (2*S*, 4*S*)-**337** was envisaged.[239] If the stereoselective

alkylation using Evans' protocol is performed, it was expected to obtain the 2S configuration.[106] Initially, Kakeya and coworkers synthesized (*R*)-2-methypentyl trifluoromethanesulfonate **334** from (*S*)-methyl-3-hydroxy-2-methypropanoate **333** in six steps in 23% overall yield in accordance with a procedure reported, previously.[240] Next, diastereoselective alkylation of (4*R*)-propionyloxazolidinone **156** using the chiral triflate **334** was performed to provide (2*S*, 4*R*)-2, 4-dimethylsubstituted oxazolidinone **335a** and its C2 diastereomer **335b** in 8:1 ratio. The mixture was separable by column chromatography to obtain **335a** in 24% yield. Removal of the chiral auxiliary from **335a** was conducted under standard conditions (treatment with alkaline hydrogen peroxide) to give **336** (Scheme **64**). On the other hand, **338**, a C4 diastereomer of **336**, was synthesized starting from commercially purchasable racemic alcohol **337**. The latter was transformed to triflate through a subsequent reaction with oxazolidinone **156** to give a 2*S* mixture of **335a** and **335c** in 32% yield and a 2*R* mixture of **335b** and **335d** in 4% yield respectively. The major mixture was readily separated from the minor mixture by column chromatography on silica gel. While **335a** and **335c** showed similar elution qualities on a reversed-phase HPLC column, they were sufficiently separated on a small scale pure enough for the next two steps. Purified **335c** was subjected to oxidative hydrolysis with alkaline hydrogen peroxide to afford **338** (Scheme **65**).[239]



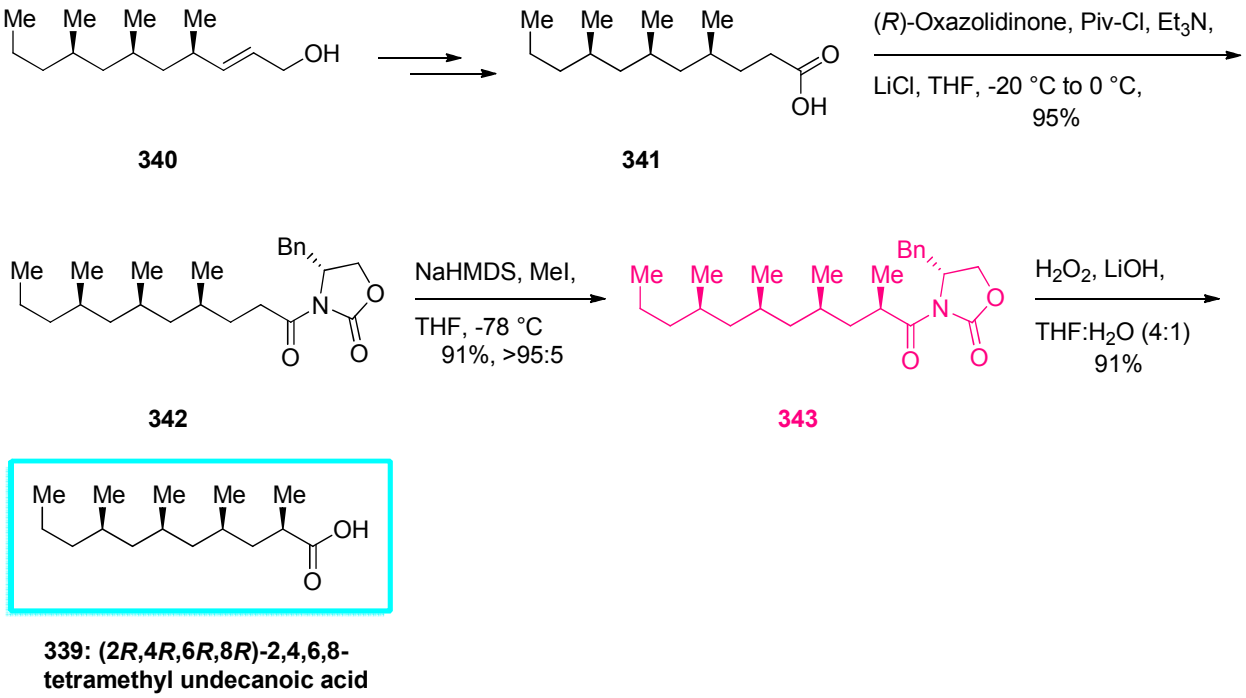
Scheme 64.



Scheme 65.

A *syn*/*syn*-deoxypropionate segment is wide spread in many natural products such as (2*R*, 4*R*, 6*R*, 8*R*)-2, 4, 6, 8-tetramethylundecanoic acid **339**. A brief total synthesis of (2*R*, 4*R*, 6*R*, 8*R*)-2, 4, 6, 8-tetramethylundecanoic **339** acid have been accomplished *via* a lipase catalyzed desymmetrization protocol to generate two methyl stereogenic centers. Asymmetric alkylation reactions were employed in the total synthesis of **339**.[241] In this approach, the total synthesis of (2*R*, 4*R*, 6*R*, 8*R*)-2, 4, 6, 8-tetramethyl undecanoic acid **339** was accomplished starting from the readily available, allylic alcohol intermediate **340**. After two steps, acid **341** was obtained and

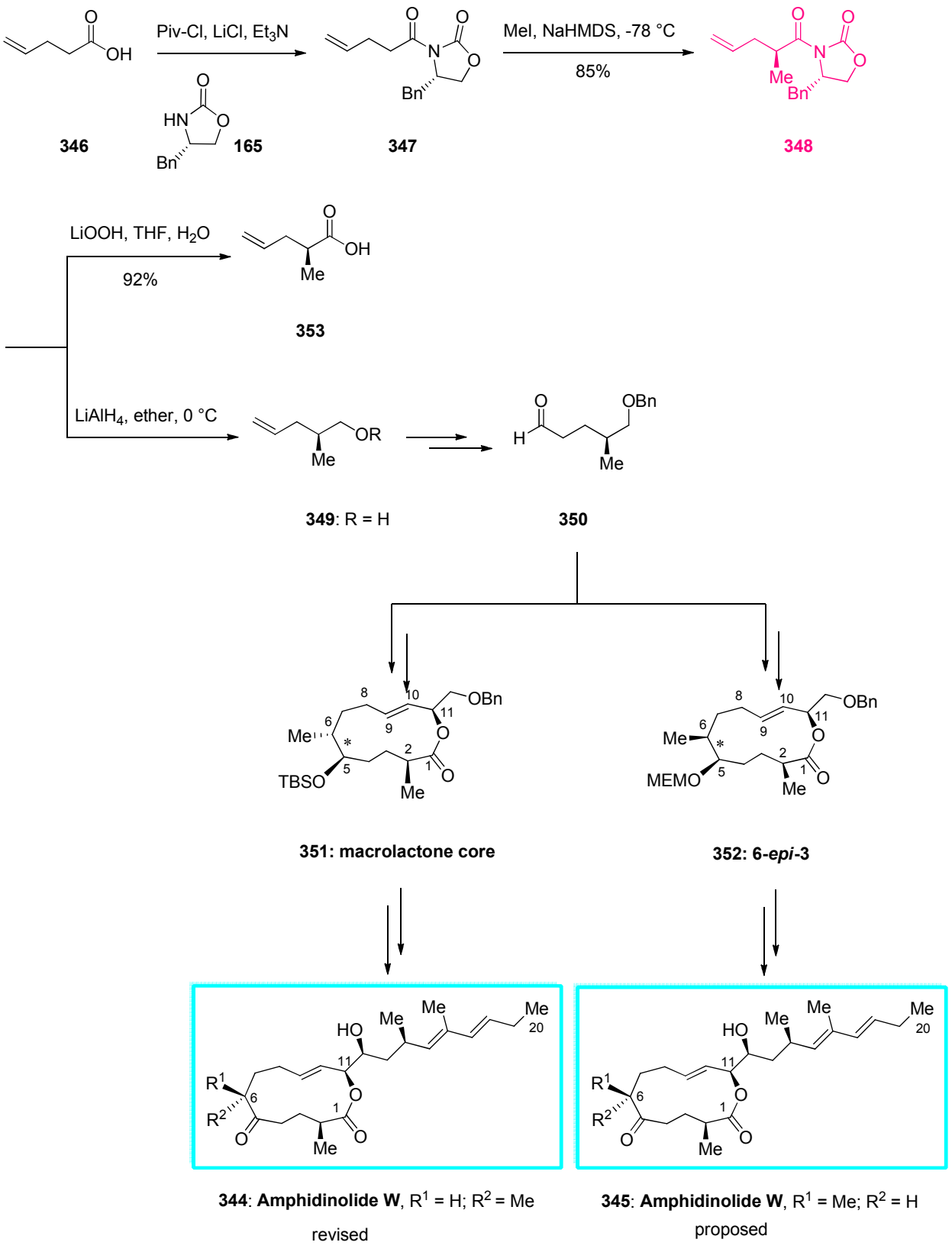
coupled with Evans' (*R*)-oxazolidinone using pivaloyl chloride mediated by Et_3N and LiCl to give the compound **342** in excellent yield. Upon methylation, the Na-enolate of compound **342** using methyl iodide furnished the compound **343** in excellent yield. Finally, compound **343** was treated with $LiOH/H_2O_2$ in THF/H_2O (4:1) to give the desired (2*R*, 4*R*, 6*R*, 8*R*)-2, 4, 6, 8-tetramethylundecanoic acid **339**[242, 243] in excellent chemical yield and >99% *dr* and *ee* (Scheme **66**).[241]



Scheme 66.

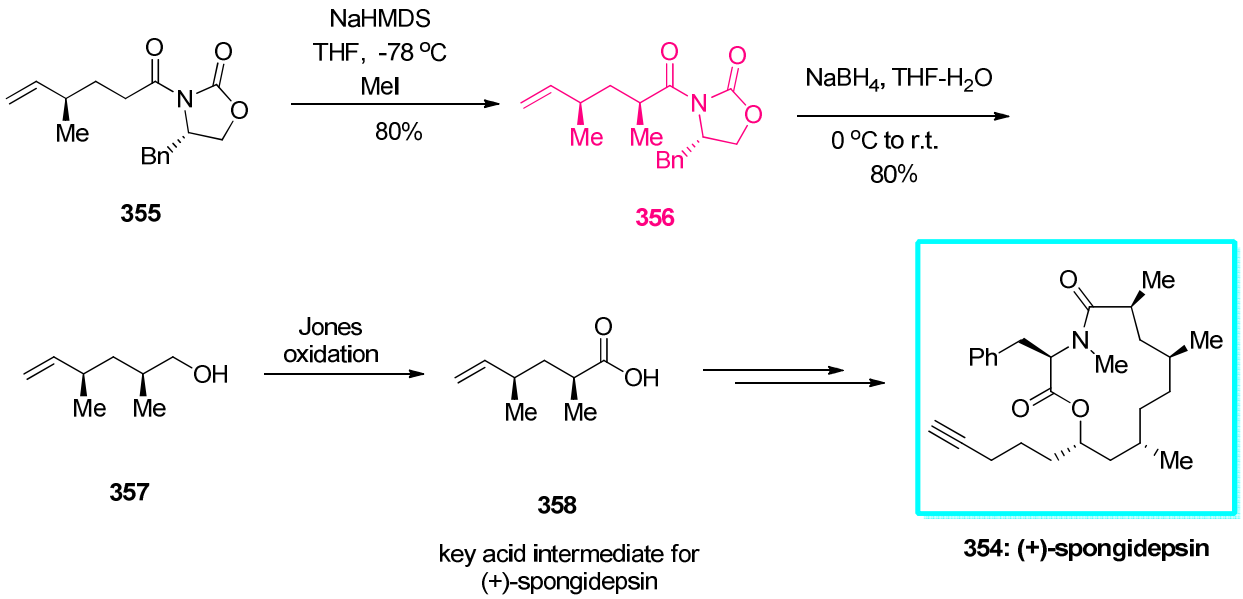
In 2002, amphidinolide W **344**, a 12-membered macrolide, was isolated by Kobayashi and coworkers. It exhibits potent cytotoxicity against murine lymphoma L1210 cells in vitro.[190] A versatile strategy for the total synthesis of a 12-membered macrolactone core and a 6-*epi* analogue of amphidinolide W has been designed, performed and reported.[244] The total synthesis was started from the commercially available 4-pentenoic acid **346**. The strategy was designed based on of a highly stereo and regioselective introduction of the chiral centers employing Evans' asymmetric alkylation followed by aldol reactions. Other important reactions employed in this synthesis are Julia-Kocienski olefination, Kita's macrolactonization, ring closing metathesis (RCM) reaction and Yamaguchi's esterification. These reactions were remarkable for the buildup

of the macrolactone cores. However, the prominent feature of this synthesis is highly stereocontrolled Evans' and *syn*-aldol reaction mediated by dibutyl boron triflate, employing an oxazolidinone-based chiral auxiliary. These reactions are inducing chirality to the C5 and C6 centers. The C2 center was designed in a way to be created from the Evans' chiral auxiliary *via* alkylation. The remaining C11 center could be fixed using $_D$-mannitol.[245, 246] In this approach, the synthesis of fragment **350** was examined as the initial target. Thus the required *N*-pentenoyl oxazolidinone **347** for the implementation of stereoselective alkylation was provided through *N*-acylation of the readily available (4*S*)-4-benzyloxazolidin-2-one using a mixed anhydride. It was provided from the reaction 4-pentenoic acid **346** and pivaloyl chloride mediated by lithium chloride and triethylamine in THF.[192] Then, methylation of oxazolidinone **347** using CH_3I in the presence of NaHMDS resulted in **348** in high yield and high diastereoselectivity (17:1). The diastereomeric purity was determined by the analysis of ^1H and ^{13}C NMR spectra. The stereochemical result could be reconfirmed by hydrolysis of **348** into the corresponding already known acid *via* comparing its analytical data with the previously reported values. The oxazolidinone derivative **348** was removed under standard conditions using lithium aluminium hydride[195] in Et_2O to afford alcohol **349**. The latter was difficult to purify due to its volatile nature. The desired aldehyde **350** as a required precursor for the synthesis of the 12-membered macrolactone core **351** and its 6-*epi* analogue **352** of amphidinolide W were obtained in two steps (Scheme **67**).[244]



Scheme 67.

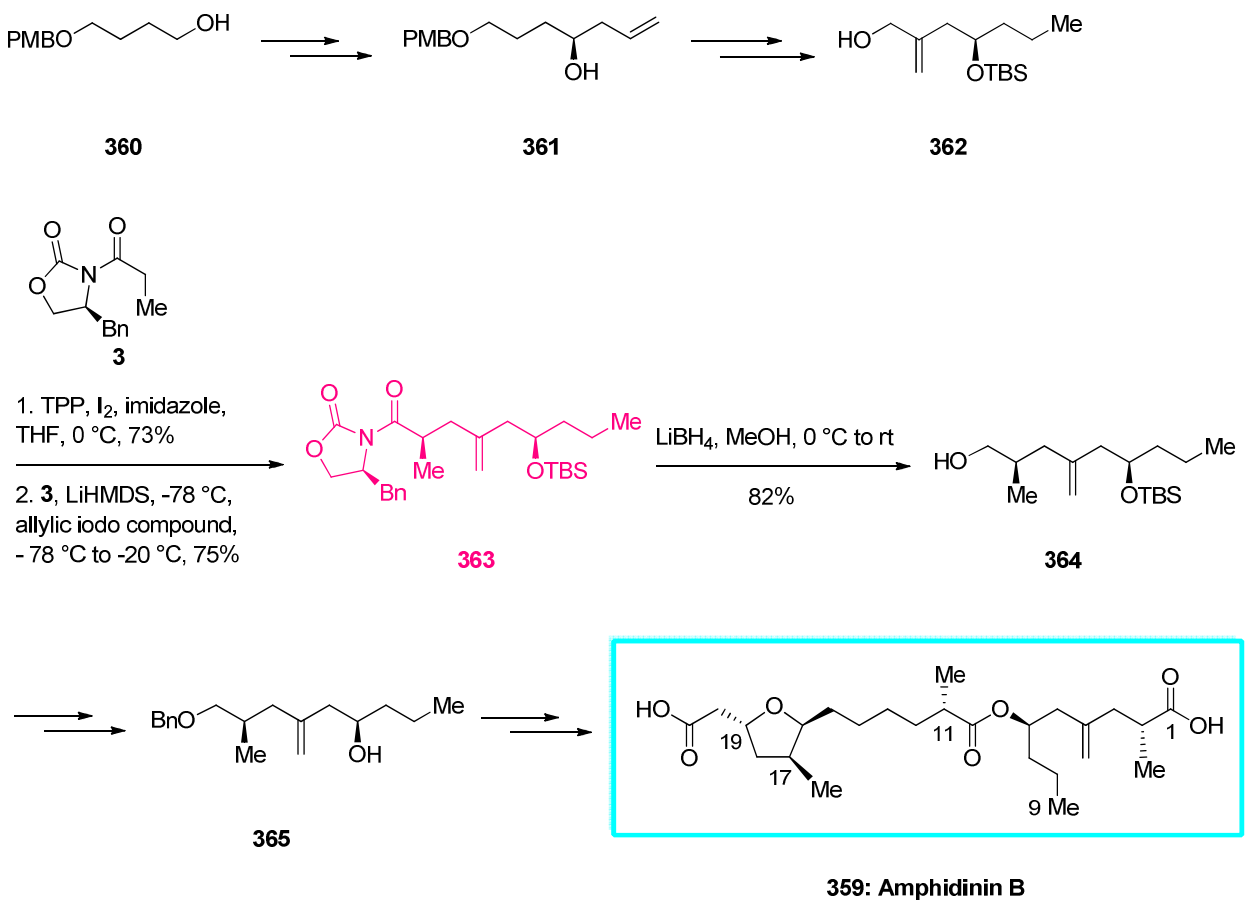
(-)-Spongidepsin **354** is a cyclodepsipeptide isolated initially from the *Vanuatu marine spongeSpongiasp*. This compound shows cytotoxic and antiproliferative potencies towards J774.A1, WEHI-164, and HEK-293 cancer cell lines.[247] Notably, (-)-spongidepsin is a 13-membered macrolactam containing five chiral centers. In its total synthesis acid **358** acts as a key intermediate.[248] Preparation of **358** involved stereoselective alkylation of **355** with methyl iodide mediated by NaHMDS in THF at – 78 ºC to afford the methylated product **356** in 80% yield as an 8:2 diastereomeric mixture. It followed by conventional reductive removal of the chiral auxiliary in **356** by $NaBH_4$ in THF-H_2O to give alcohol **357** in satisfactory yield. Then the latter was oxidized to acid **358** using Jones reagent (Scheme **68**).



Scheme 68.

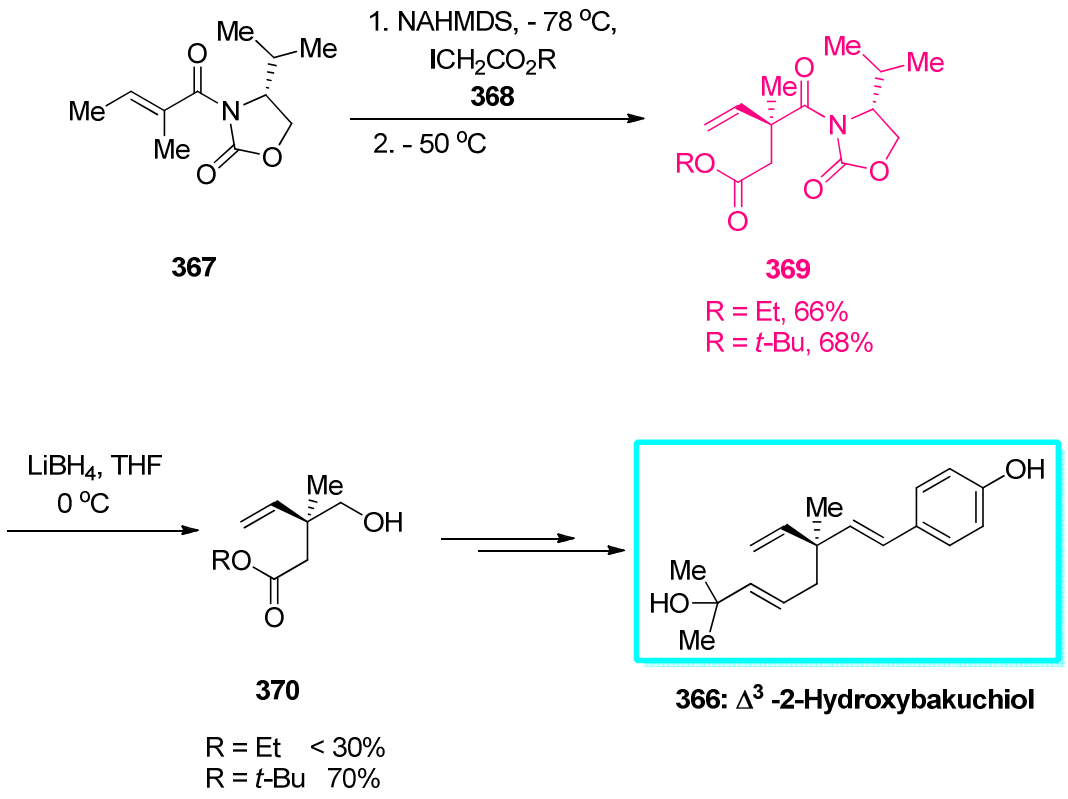
In 2006, Kobayashi and coworkers[249] accomplished to isolate amphidinin B **359** from the dinoflagellate Amphidinium sp. (strain number Y-56). The same authors reported the structural characterization of Amphidinin B **359** as a linear polyketide. It exhibited potency toward MCF-7 (breast cancer cell line).[250] From the structural point of view, *amphidinin* B **359** contains a core tri-substituted tetrahydrofuran scaffold with a chiral side-chain at C16. In the side chain, an *exo* methylene, two branched methyl groups, a propyl and two carboxyl groups are attached whereas another methyl group is attached at C17 on the tetrahydrofuran framework. C19 is also substituted with an ethanoic acid moiety. In 2013, an efficient, flexible, highly stereoselective

synthesis of amphidinin B **359** is accomplished by Krishna and coworkers.[251] Their approach for the total synthesis of Amphidinin B involved some important name reactions such as Sharpless asymmetric epoxidation, Evans' aldol, Julia olefination, oxa-Michael, Keck allylation, Mannich reaction, Evans' asymmetric alkylation, and Yamaguchi esterification. The C_1-C_9 **365** segment in Amphidinin B was provided in nine steps, starting from mono-PMB ether of 1,4-butane diol **360.** On the other hand, the synthesis of segment **365** was started with compound **361**, synthesized as reported previously.[252] Reaction of alcohol **362** (provided in three steps from **361**), with triphenylphosphine in the presence of iodine and imidazole in THF gave the corresponding allyl iodide, which upon Evans' alkylation[253] with *N*-propionyl oxazolidinone gave **363** in good yield as a single isomer as confirmed by analysis ^{1}H or ^{13}C NMR spectra of crude reaction mixture. Reductive removal of the chiral auxiliary under standard conditions ($LiBH_4$ in MeOH) gave the corresponding alcohol **364** in 82% yields. Compound **365**[250] was obtained in 71% yield over two steps. After several steps, the desired natural product **359** was obtained (Scheme **69**).[251]



Scheme 69.

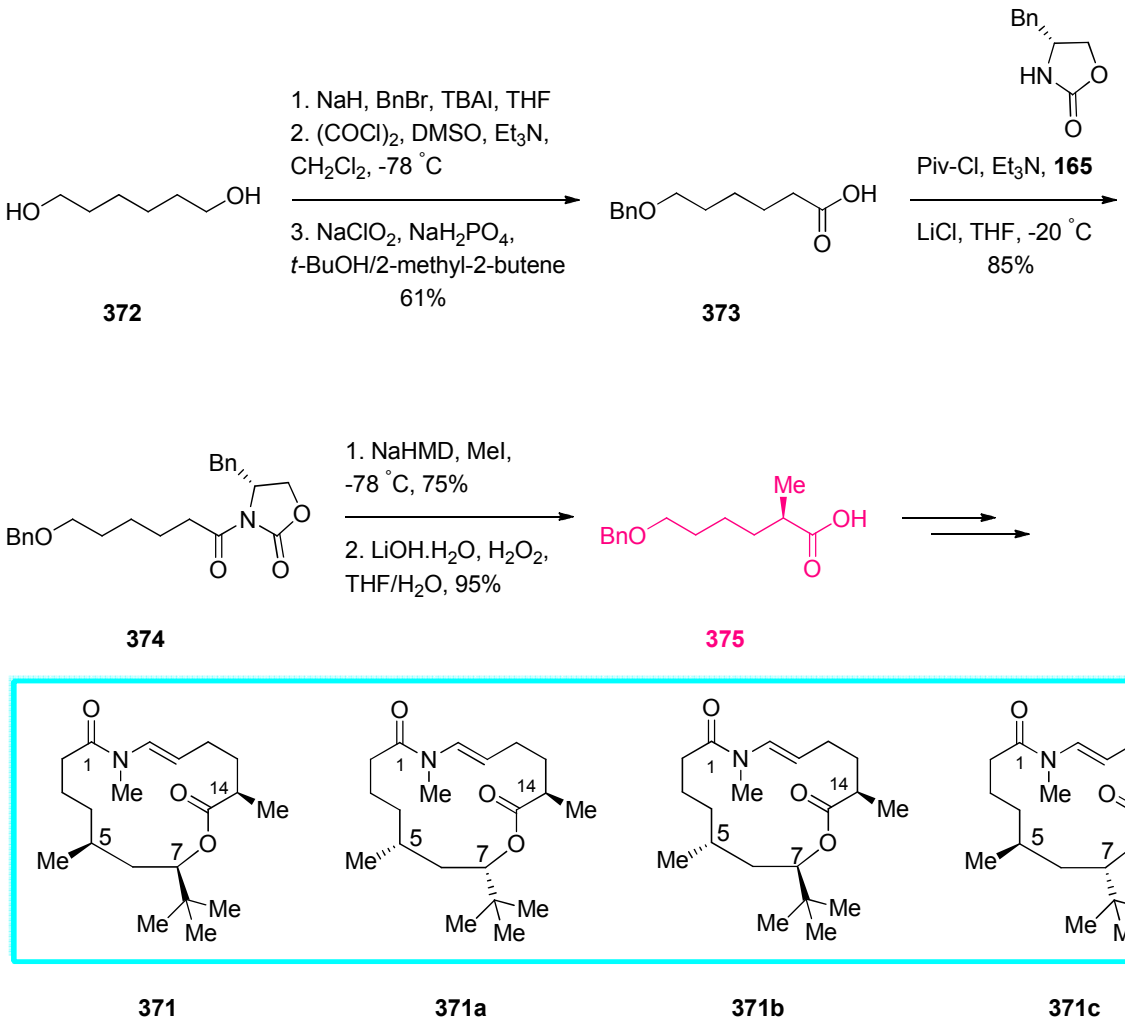
Bakuchiol and Δ^3 -2-Hydroxybakuchiol **366** is a member of one family of monoterpene phenols occurring in medicinal plant *Psoralea corylifoliaL*. Its crude extract has been used over a long time as Chinese traditional medicine.[254] For its total synthesis **370** acts as a key intermediate reported by Xu and *et al*. [255] For the synthesis of **370** they used Evans' asymmetric alkylation of **367** with **369** giving the desired intermediate **369** in 66-68% yield with excellent diastereoselectivity (> 20:1). Conventional reductive removal of Evans' auxiliary in **369** using $NaBH_4$ in THF-H_2O at room temperature did not afford alcohol **370** in satisfactory yields. However, reductive removal with $LiBH_4$ from ethyl and *t*-butyl esters gave the desired alcohol **370** in < 30% and 70% yield respectively (Scheme **70**).[255]



Scheme 70.

Marine cyanobacteria is a rich source of new biopotential secondary metabolites with unique structural frameworks. A class of macrolides with a rare *N*-methyl enamide, 1,3-methyl and tertiary butyl containing a branch linked through lactone such as laingolide, laingolide A or

madangolide were first isolated from *Lyngbya bouillonii*.[256] Structurally related is a neuroactive 15-membered macrolide palmyrolide. They contain a rare *N*-methyl enamide and 1,3-methyl and tertiary butyl containing branch linked through lactone. An asymmetric synthesis of palmyrolide A, the 15-membered neuroactive macrolide and its epimer has been accomplished and reported.[257] The route was planned in a way that configurations of the required stereoisomers were similar to the absolute configuration of palmyrolide A. In this line, for the preparation of all stereoisomers of palmyrolide A, an efficient synthesis was designed for the fragment **375** starting from commercially purchasable 1, 6-hexanediol **372**. Selective benzyl group protection on 1, 6-hexanediol afforded a monobenzyl ether, which upon sequential oxidation gave acid **373.** Reaction of **373** with pivaloyl chloride followed by treatment with lithiated (*R*)-4-benzyl-2-oxazolidinone gave **374**. The latter was methylated using methyl iodide, which was subsequently subjected to basic hydrolysis to give **375** in 60% yields from **373** (*dr* 97.4: 2.6 upon methylating stage) (Scheme **71**).[257]



372 **373** **374** **375**

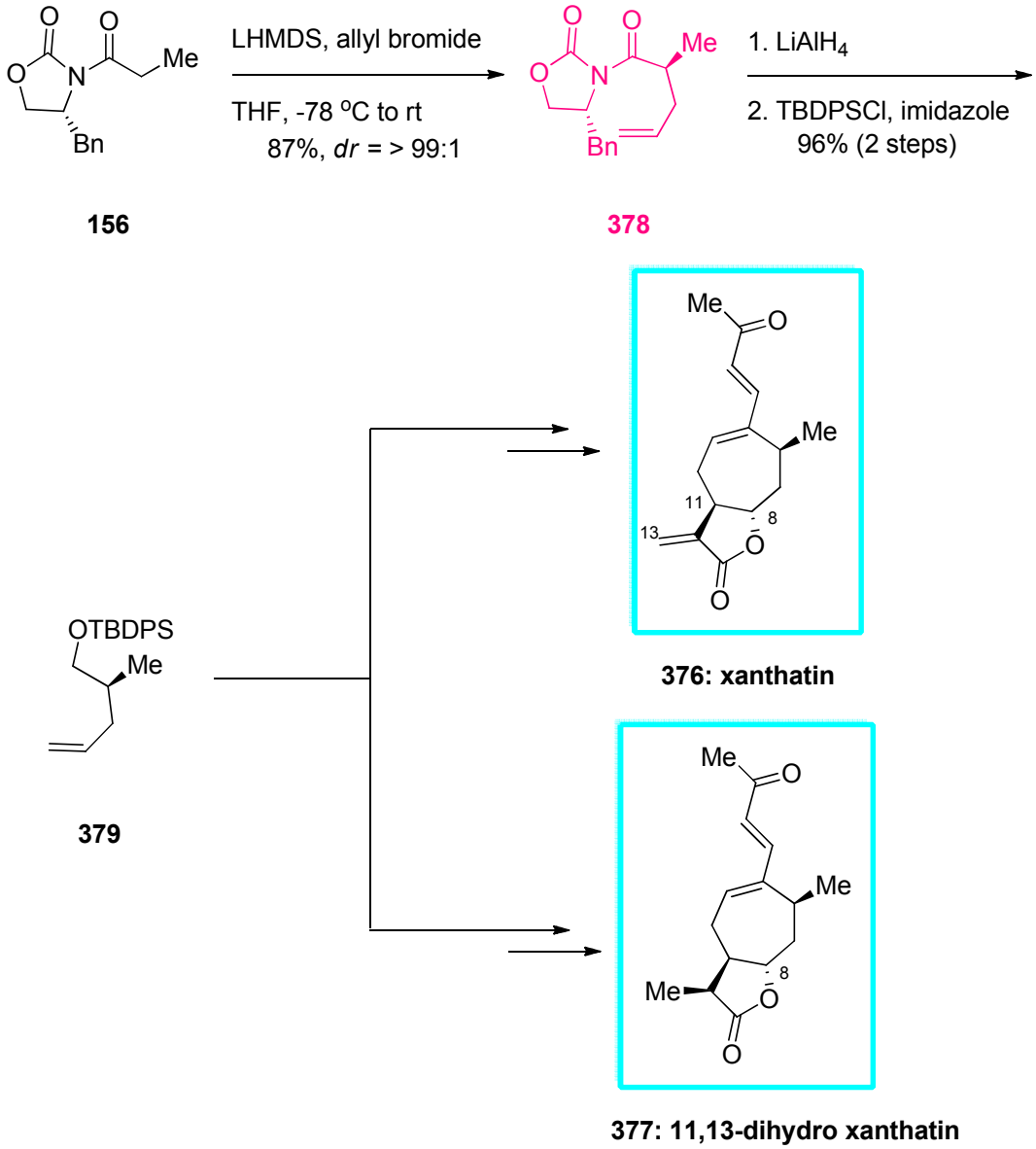
371 **371a** **371b** **371c**

proposed structures **371** and **371a**, and revised structure **371b**, 5,7-*epi* isomer **371c**

Scheme 71.

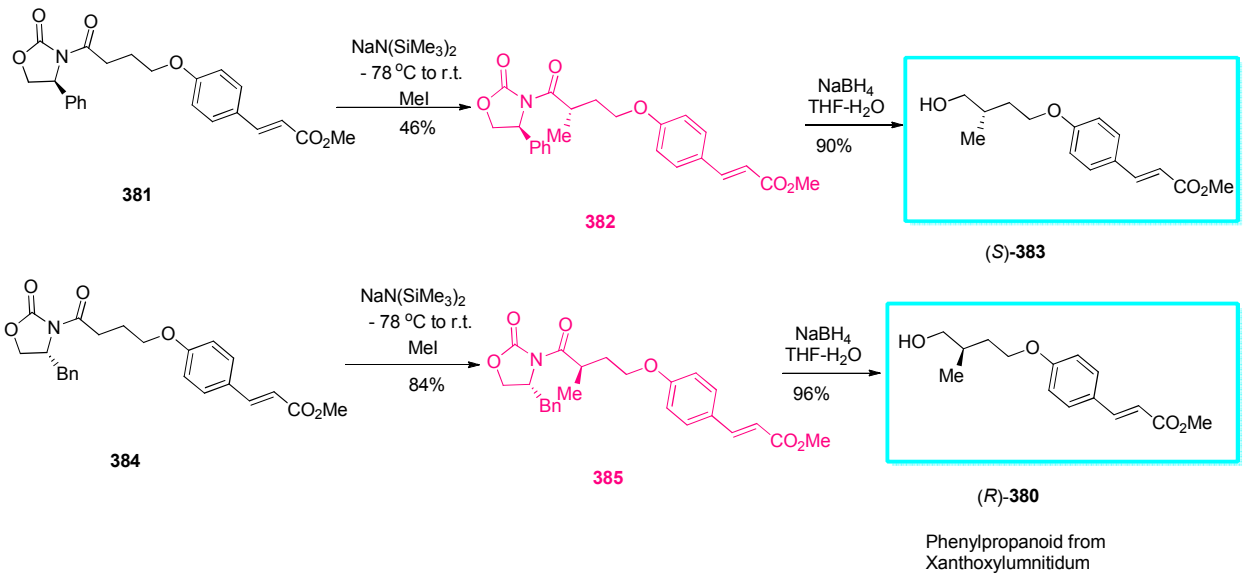
Xanthanolide sesquiterpenoids were initially isolated from the plants of the *genus Xanthium* from family of Compositae, with more than 100 compounds have been isolated so far.[258] These compounds exhibit imperative biological activities, such as allelopathic, antitumor, antimicrobial, anti-MRSA, anti-ulcerogenic, and anti-inflammatory activities. Among them xanthatin **376** has attracted much attention. It has been revealed that they have a seven-membered carbocycle containing a *cis*- or *trans*-fused *γ*-butyrolactone at their C8 position. In 2013, the total synthesis of xanthatin **376** and 11, 13-dihydroxanthatin **377** was fruitfully accomplished *via* the stereocontrolled conjugate allylation to an optically pure *γ*-butenolide. Shindo and coworkers reported a straight and highly effective synthetic approach for

xanthanolides *via* a stereocontrolled conjugate allylation to a γ-butenolide to provide xanthatin **376** and 11, 13- dihydroxanthatin **377** in 14 and 13 steps, respectively.[259] This synthetic approach provides a powerful tool for the synthesis of congener xanthanolides and other natural products bearing the *trans*-fused γ-butyrolactone.[260] This strategy was started with the stereoselective alkylation of the Evans' oxazolidinone **156** using allyl bromide to afford **378** in high yield with a high degree of diastereoselectivity. The latter, it was reduced under standard conditions using lithium aluminum hydride. Upon the protection of the resulting alcohol, using TBDPSCl, **379** was obtained in excellent yield over two steps. Finally, the desired natural products **376** and **377** can be obtained from the intermediate **379** (Scheme **72**).[259]



Scheme 72.

Several natural phenylpropanoids were isolated from plants.[261] Although, their structures are not very complex, their absolute configurations were not determined and reported for unstipulated reasons. Both (*S*)- and (*R*)-enantiomers **383** and **380**, can be have been isolated from *Xanthoxylum nitidum*, but both were totally synthesized [262] in high enantiomeric purity *via* using Evans' chiral auxiliary in their stereoselective alkylation with subsequent reductive removal of the auxiliary employing Prashad method. Asymmetric alkylation of **381** with methyl iodide mediated by $NaN(SiMe_3)_2$ in THF furnished **382** in moderate yield but high 87.7% *de*. Reductive removal of the chiral auxiliary in **382** by $NaBH_4$ in THF-H_2O at room temperature furnished (*S*)-**383** in 90% yield. This reductive removal of the Evans' auxiliary in **382** was found being chemoselective since the methyl ester moiety in the molecule was not reduced and remained unaffected. Since the optical rotation of the synthetic (*S*)-**383** was opposite to that of natural product **380**, the configuration of the latter was designated as (*R*). This confirmed the, alkylation of **384** was successfully achieved to give **385** in 84% yield with 90.2% *de*. Upon conventional reductive removal of the chiral auxiliary in **385** using $NaBH_4$, THF-H_2O, (*R*)-**380** in 96% yield was obtained. The obtained spectral data and the amount of optical rotation of the product synthesized *via* total synthesis were in agreement with those reported already for natural product **380**. This also confirmed the (*R*)-configuration for naturally occurring **380** (Scheme **73**).[262]



Scheme 73.

Aliskiren **386** is well-known non-peptidic renin inhibitor.[263] It has been prescribed and market purchasable as an oral drug for the treatment of hypertension.[264] This molecule involves four chiral centers in an aliphatic carbon chain, which naturally makes its synthesis extremely stimulating as well as challenging. Thus, the structural complexity as well as the interesting biological activity of aliskiren has attracted much attention and stirred up great interest of synthetic and medicinal chemist since its innovation.[265] The synthesis of aliskiren **386**, as marketed drug has been successfully achieved and reported. (2*S*, 7*R*, *E*)-2-Iso-propyl-7-(4-methoxy-3-(3-methoxypropoxy) benzyl)-*N*, *N*, 8-trimethylnon-4-enamide **391a**, is an advanced intermediate toward aliskiren. To approach towards **391a**, three different protocols designed for the construction of the E-olefin functionality in the latter by using the olefin cross-metathesis. These strategies employ Horner-Wadsworth-Emmons (HWE), and Julia-type olefinations. The most recent one for the synthesis of **391a** is a substantially improved protocol in terms of the yield (ca. 33%), and diastereo- and *E*/*Z*-selectivity. In this protocol the Evans' chiral auxiliary-assisted asymmetric allylation for the synthesis of the suitable enantiopure (higher than 97% *ee*) intermediates and a modified Julia-Kocienski olefination for the highly selective synthesis of *E*-**391a** with up to 13.6:1 *E*/*Z* ratio from the chiral intermediates are considered as key steps. Consequently, the results obtained in fact are an appealing option for the total synthesis of aliskiren.[266] As depicted in Scheme **74**, the reaction

of market purchasable **387** with allyl bromide or 3, 3-dimethylallyl bromide proceeded cleanly and smoothly to afford **388a** and **388c**, respectively, in excellent yields. In other hand **388b** was readily prepared *via* a two-step procedure involving the allylation of **387** with *trans*-1,4-dibromo-2-butene. It followed by reductive elimination of the bromo group in the presence of $NaBH_3CN$.[267] Hydrolytic cleavage of Evans' chiral auxiliary in **388a-c** gave the corresponding carboxylic acids **389a-c**. Interestingly, **389a-c** could be synthesized on bench scale (dozens of grams) with continual efficiency and can be used as versatile intermediates for the synthesis of various chiral precursors for other designed protocols.

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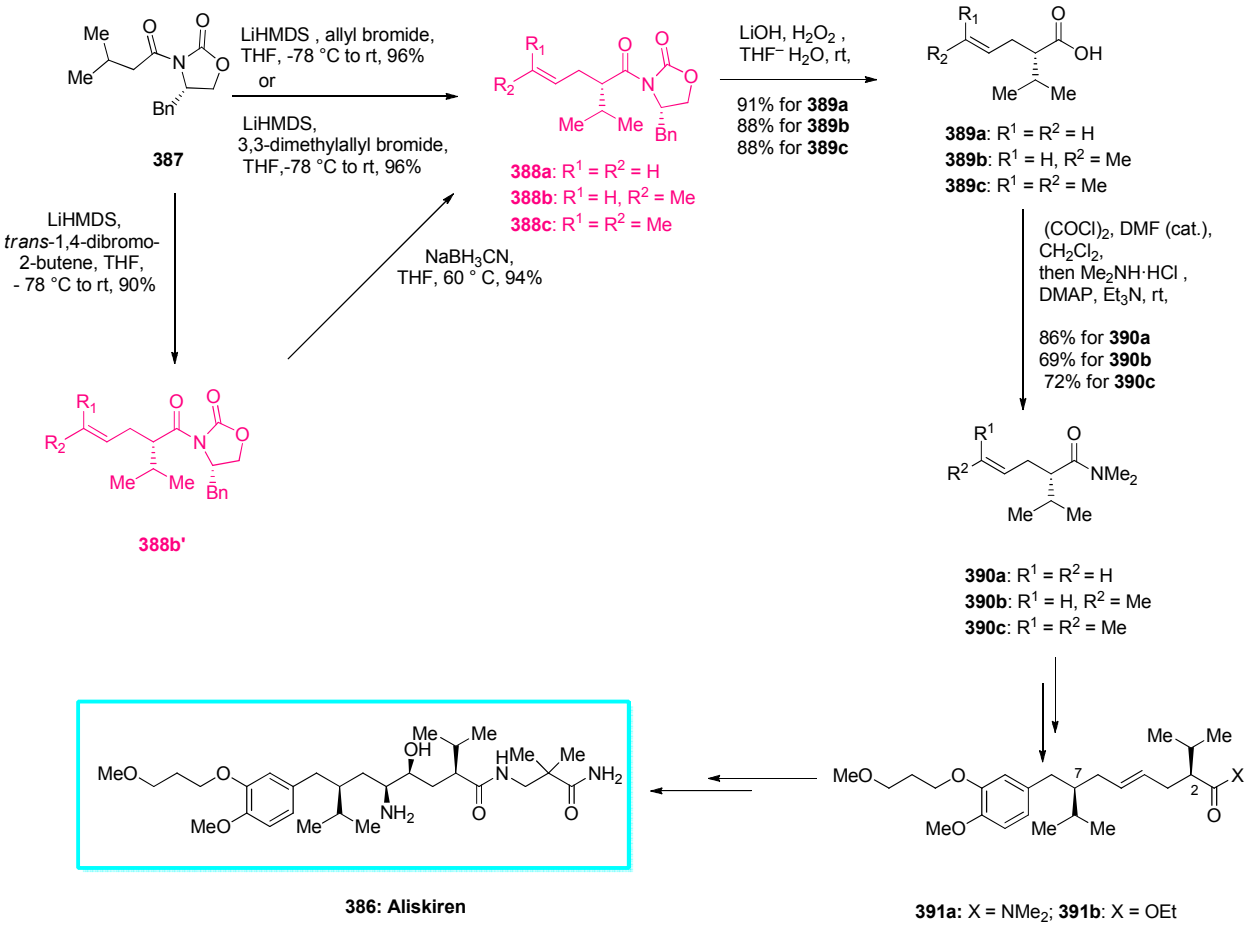
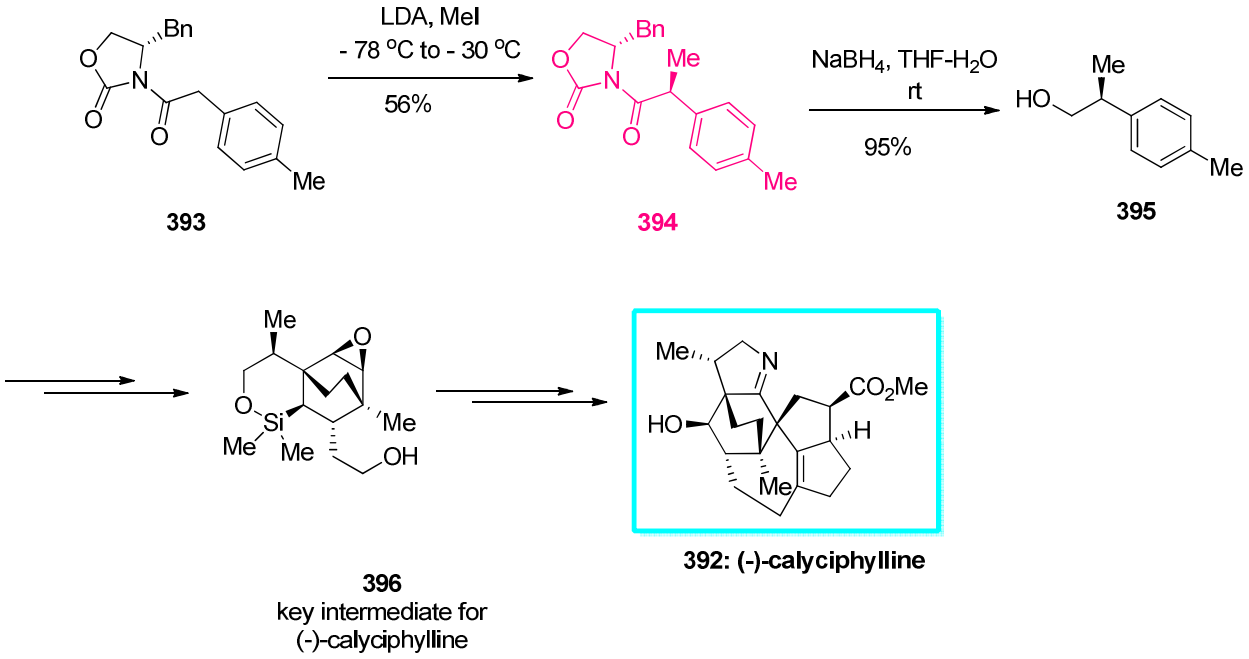


Scheme 74.

Bicyclic ester intermediate **396** is a key intermediate in the synthesis of (–)-calyciphylline.[268, 269] The synthesis started with the of alcohol **395** by asymmetric alkylation of **393** with methyl iodide

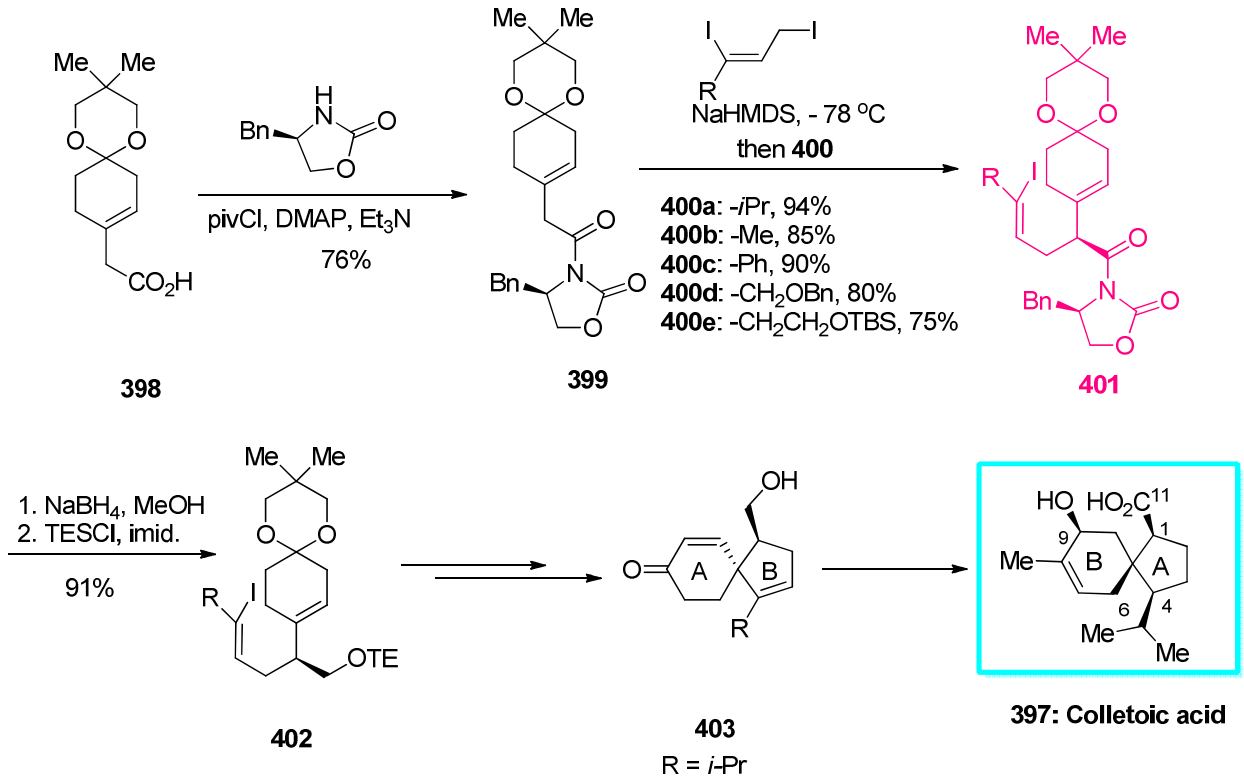
in the presence of LDA to afford alkylated product **394** in 56% yield with > 99% diaster-eoselectivity. Compound **393** has oxazolidinone moiety as chiral auxiliary. Conventional removal of the chiral auxiliary in **394** *via* reductive cleavage using $NaBH_4$ in THF-H_2O at room temperature provided alcohol **395** in 95% yield (Scheme **75**).



Scheme 75.

11β-HSD1. 11β-HSD1 has been found as promising biological target for the treatment of Met S. However, a development of selective compounds is needed to promote its therapeutic value in biological systems. In part of its total synthesis the Evan's chiral auxiliary was employed for the construction of the acyclic precursor **401** to provide the acorane core **403** in excellent yield using a modified Heck reaction. The colletoic acid core derivatives exhibited modest activity against 11β-HSD1 and will used for further biological evaluation. A protocol for the total synthesis of the core of colletoic acid has been improved and reorted in 2016. In this protocol the Evans' chiral auxiliary,[57] is used and removed under mild conditions (Scheme **76**). The synthesis of compound **398** had previously been reported.[270] Reaction of (*R*)-4-benzyl-2-oxazolidinone with pivaloyl chloride gives the mix-anhydride,[57] followed by addition of **398**, provided **399** in

multigram scale. The generation of the enolate of compound **399** was achieved in the presence of NaHMDS and quenched with electrophile **400a-e** to give the required precursor **401** in excellent enantioselectivity (*ee* ≥ 98%) in excellent diastereoselectivity (*dr* > 20: 1) as well as excellent chemical yield. Upon removal of benzyl-2-oxazolidinone using $NaBH_4$ in methanol provided the corresponding hydroxyl group which upon protection with TESCl in the presence of imidazole provided the Heck reaction precursor. The intramolecular Heck reaction catalyzed by palladium (0) in CH_3CN/THF at 60 ºC gave the α, β-unsaturated spirocycle **403** as a single diastereoisomer upon protecting group removal using aqueous HCl.[270] The conducted Heck reaction was observed to proceed in high regio and stereo control in the tested substrates. It is proposed that the exo-transition state is favored to avoid conflicting interactions between the palladium complex and the R group in the transition state. Having intermediate **403** available in hand, different colletoic acid-like compounds as well as colletoic acid in multi-milligram scale for further mechanistic investigation were synthesized.[271]



Scheme 76.

Conclusion

In this report, we tried to reveal the importance of the applications of several chiral oxazolidinones in asymmetric synthesis and in particularly in the total synthesis of several naturally occurring compounds, exhibiting diverse biological activities. In this approach, a chiral center is generated. Noticeably, the configuration of this newly generated chiral center must be controlled in a way, being either completely preserved or totally inverted during all required steps, depends on, ultimately being identical to the configuration of the same stereogenic center which was already defined in the target natural product in a crucial step (steps) in the total synthesis of some biologically active natural products. In spite of practically known superiority of catalyzed asymmetric reactions, over all other established approaches, the use of the chiral auxiliary in certain asymmetric synthesis and its application in total synthesis of some natural products is inevitable. Among them, the asymmetric α-alkylation of an appropriate enolate as the determining chiral inducing step has been found promising with the use of an appropriate chiral auxiliary. When the strategy of using a chiral auxiliary contemplated and justified, in most cases an appropriate Evans' oxazolidinone is the chiral auxiliary of choice particularly in an asymmetric alkylation of an enolate. A part from the requirement of stoichiometric amount, which implies to all known chiral auxiliaries, Evans' oxazolidinones, enjoys several merits, which make them a superior chiral auxiliary. Nowadays some of them are commercially available or can be readily prepared from market purchasable chiral amino alcohols. They are perfect intermediates and owe their importance chiefly, to their power to induce stereogenic center during C-C bond formations *via* asymmetric alkykations, aldol reaction and 1,4-asymmetric addition. For these important reasons, the chemistry of chiral oxazilidinones as commercially available or easily accessible is still a vivacious area of research and study for their applications stands first especially in a strategic asymmetric C-C bond forming key step in the total synthesis of natural products. Sophisticated and necessary C-C bond stereoselective formations in one or more steps of total synthesis of natural products are frequently provided by the application of oxazolidinones as chiral auxiliary. In this report, the applications of oxazolidinone as a chiral auxiliary for alkylations *via* an alpha substitution to generate stereoselective C-C bond in one or more steps of the total synthesis of a natural product were comprehensively showcased. This report discloses the unprecedented role of Evans' oxazolidinones in the efficient and highly stereoselective C–C bond formations. We hope that it stimulates, those organic synthetic chemists who are already engaged to continue using them and

motivate the beginners to consider Evans' oxazolidinons chiral auxiliary in general and particularly for stereoselective alkylations in their designed route for total synthesis in their future attempts and endeavors.

Acknowledgments

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Graphical Abstract

In this review, a number of applications of chiral oxazolidinones in the asymmetric alkylation reaction applied to total synthesis are described.

Applications of oxazolidinones as chiral auxiliaries in the asymmetric alkylation reaction applied to total synthesis

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