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Applications of Sharpless asymmetric epoxidation in total synthesis

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ABSTRACT

This report presents the applications of enantioselective epoxidation of prochiral allylic alcohols, so called 'Sharpless asymmetric epoxidation', which is frequently referred as 'kinetic resolution'. This reaction results in the corresponding 2,3-epoxy alcohols in high stereoselectivity as excellent starting materials for the synthesis of complex targets, such as naturally occurring biologically active molecules.

Contents

1. Introduction

There is a needed command in industry and academia for the efficient and practical synthesis of pure enantiomers. A number of powerful and efficient catalytic asymmetric reactions have been introduced and developed to meet this over mounting demands. Among these processes, the Sharpless strategy for the asymmetric epoxidation of alkenes stands out and is outstandingly distinct due to its wide and exceptional utility and widespread applications.[1]

The Sharpless asymmetric epoxidation triumph and achievements are probably due to five major reasons. First, epoxides are very versatile intermediates and can be easily converted into diols, aminoalcohols, ethers, etc.[2] Hence the formation of enantiomerically pure epoxides is a very important step in the asymmetric synthesis of organic chiral compounds, especially in the total synthesis of natural products. Second, the Sharpless asymmetric epoxidation works perfectly for many primary and secondary allylic alcohols, which are either commercially available or easily accessible. Third, and perhaps most importantly, the products of the Sharpless asymmetric epoxidation often show enantiomeric excesses above 90%. Fourth, the products of the Sharpless asymmetric epoxidation are predictable since the protocol follows a regular trend and gives stereochemically expected models. Finally, the reactants for the Sharpless asymmetric epoxidation are either commercially available and relatively inexpensive or readily accessible.[3]

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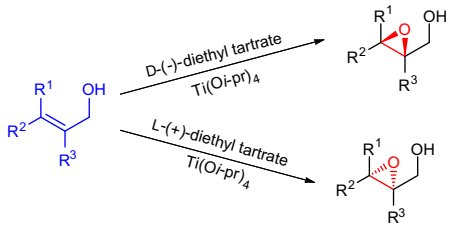
The versatile reactivity of the epoxy alcohol functionality brings about a good opportunity for synthetic organic chemists to take advantage of regio- and stereoselective ring opening; oxidation and reduction, etc. Therefore, the chiral epoxy alcohols are powerful and effective starting materials for the synthesis of complex targets such as biologically active molecules with multiple stereocenters.[4] It should be noted that an overview covering synthetic applications of chiral unsaturated epoxy alcohols prepared via Sharpless asymmetric epoxidation has been published in 2010 by Riera and Moreno.[4]

In 1965, Henbest et al.[5] reported the earliest asymmetric epoxidation of olefins using percamphoric acid but only in low levels of enantioselectivity (8%). However 15 years later, in 1980 the Sharpless asymmetric epoxidation was discovered as a good example of the stereoselective epoxidation of alkenes, using a protocol to achieve full stereochemical control for such an important and key reaction. This protocol stereoselectively converts a prochiral allylic alcohol to an epoxy alcohol using titanium isopropoxide [Ti(O*i*Pr)$_4$], *t*-butyl hydroperoxide (TBHP), and an appropriate chiral diethyl tartrate (DET). Since then Sharpless asymmetric epoxidation has attracted much attention and is used as a tool for the synthesis of optically active epoxides as the known multi-purpose reactive substrate, in laboratories as well as on an industrial scale (Scheme 1).[6]



Scheme 1.

This breakthrough enabled the stereoselective epoxidation of a wide range of alkenes using only 5–10 mol % of the catalyst.[6] Sharpless et al. also discovered that the addition of molecular sieves to the reaction mixture increases the effectiveness of the process.[7] This catalytic system is very resourceful, and can even be used in the epoxidation of highly functionalized molecules. Amides, aldehydes, acetals, silyl ethers, sulfones, and a large number of other groups have been found to be tolerant toward this strategy.[8]

Functional groups that are not compatible are amines, carboxylic acids,[9] phenols,[10] mercaptans, and phosphines (Table 1).[11] Nucleophilic substituents that can lead to an intramolecular ring-opening of the in situ generated epoxide give the undesired cyclized products.[11]

Table 1

Compatible functional groups				Incompatible groups
Acetals, ketals	Azides	Ketones	Silyl ethers	Amines (most)
Acetylenes	Carboxylic esters	Nitriles	Sulfones	Carboxylic acids
Alcohols	Epoxides	Nitro	Sulfoxides	Mercaptanes
Aldehydes	Ethers	Olefins	Tetrazoles	Phenols (most)
Amides	Hydrazines	Pyridines	Ureas	Phosphines

The advantages of the catalytic method over the stoichiometric reactions, include easier isolation of the products, requirement of conditions, possible in situ derivatization of the product, and enhanced yields of the sensitive epoxy alcohols. In the latter case, some epoxy alcohols are unstable under the stoichiometric reaction conditions, probably due to the mild Lewis acidity of titanium alkoxides, which could stimulate unwanted ring-opening of the oxirane.[12]

In continuation of our interest in the recent applications of named reactions[13] and particularly with those leading to asymmetric and total synthesis,[14] herein we highlight the applications of Sharpless asymmetric epoxidation as a powerful tool, in the key step (steps) for the total synthesis of various classes of natural products with biological activities.

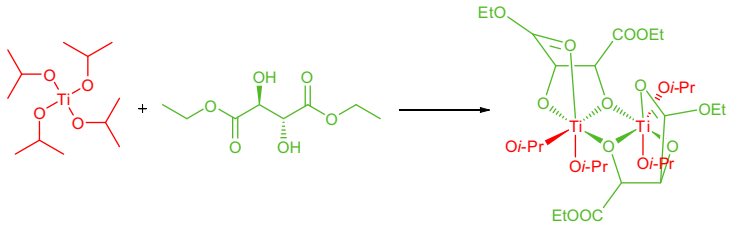
1.1. Mechanism of the Sharpless asymmetric epoxidation

An important and significant feature of this catalytic asymmetric process is based on the fact that the allylic alcohol is coordinated to the metal during epoxidation and in this way the molecule is attached to the chiral complex during the reaction. In fact in the absence of an allylic hydroxyl moiety, no reaction takes place. The allylic hydroxyl group activates the oxidant and controls the delivery of oxygen to the substrate, preferentially to one of the two possible enantiotopic faces of the alkene. In this way, the hydroxyl moiety provides selective epoxidation of the allylic alkenes even in the presence of other C–C double bonds in a same molecule.[15]

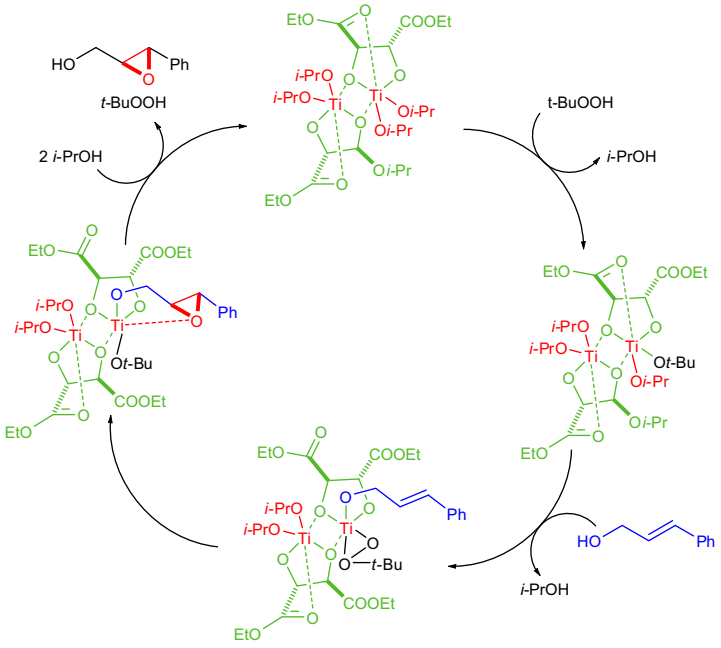
The creation of several Ti–tartrate complexes is possible in the reaction system. Sharpless himself suggested that epoxidation is catalyzed by a single Ti center in a diametric complex with a C2 symmetric axis. IR, ^{1}H, ^{13}C, ^{17}O NMR spectroscopy, and mass spectrometry all suggest that such a dinuclear structure is dominant and abundant in the solution phase. It elevates the reaction much faster than Ti(IV) tetraalkoxide alone and shows selective ligand-accelerated reaction (Scheme 2).[16]

The allylic hydroxyl moiety is coordinated and pre-orientated through its O-atom to the catalyst. The catalyst creates a Sharpless-type transition state via the h2-coordinated TBHP molecule. Three coordination sites are available via exchange of two isopropoxides and dissociation of the coordinated ester carbonyl group. The hydroperoxide should engage the equatorial position and one of the two available axial coordination sites. The allylic alcohol hydroxyl group should occupy the other axial site. To reach the necessary proximity for the delivery of oxygen to the olefin, the diacetal oxygen occupies the equatorial position, and the proximal oxygen is placed in the axial site. The axial site on the lower face of the system is selected for the peroxide due to the larger steric demands, which the alkyl group needs. The allylic alcohol hydroxyl group binds to the remaining axial coordination site, where stereochemical and stereoelectronic effects force the most stable conformation of the system (Scheme 3).[7b]

The optimal ratio for Ti/tartrate was found to be 2:2. Less than 1 equiv of tartrate decreases the ee because of the non-asymmetric epoxidation. Excess tartrate inhibits the reactivity by forming the inert complex (Ti-tartrate)$_2$. Dimethyl, diethyl, and di-iso-propyl tartrate (DMT, DET, DIPT) all induce high asymmetry. (*E*)-Allylic alcohol-DET affords greater ee than DIPT. The efficiency of the kinetic resolution is increased with steric bulk of the tartrate alkyl ester, hydroperoxide, alkyl moiety, and using the *trans*-olefin substituent. Free and excess alcohol inhibits catalyst reactivity. The use of molecular sieves is required to remove any moisture.[16] Added alcohols had no effect on the relative rates of kinetic resolutions; free ROH is not associated with the active complex for oxygen transfer.[16]



Scheme 2.



Scheme 3.

2. Total synthetic utility

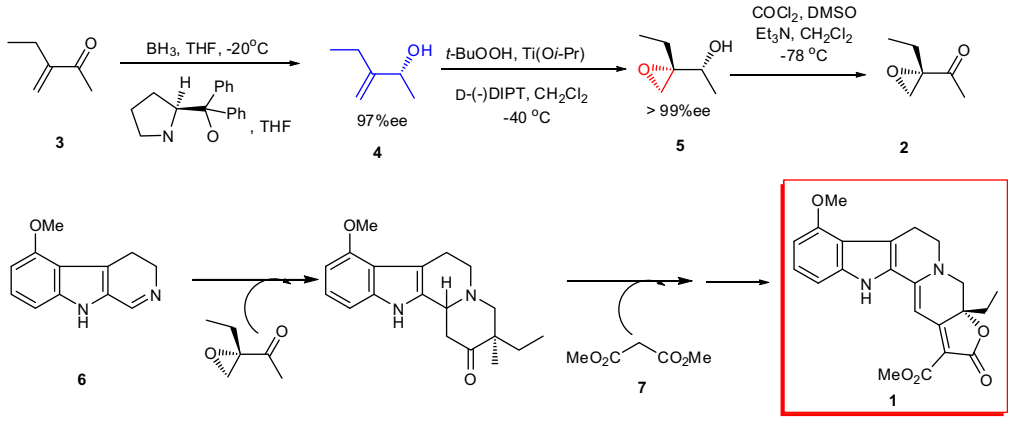
2.1. Alkaloids

A new *Corynanthe*-type indole alkaloid, (−)-9-methoxymitralactonine **1**, with a highly conjugated system was isolated from the young leaves of *Mitragyna speciosa* in Malaysia, which is an original plant for traditional folk drugs in Malay Peninsula, used as a stimulant such as coca or abused as a substitute for opium.[17] For the synthesis of **1**, the synthesis of chiral epoxy ketone as an essential synthon is required. The synthesis of enantiomerically pure **2** was achieved by a combination of Corey asymmetric reduction and Sharpless asymmetric epoxidation. The reduction of enone **3** using chiral oxazaborolidine as a catalyst, gave optically active alcohol (+)-**4** with 97% ee. Next, the allylic alcohol **4** was subjected to Sharpless asymmetric epoxidation under kinetic resolution conditions to give (−)-epoxide **5** with 99% ee. The secondary carbinol **5** was then converted into a ketone by Swern oxidations to give (−)-epoxy-ketone **2**. The basic approach to a new *Corynanthe*-type indole alkaloid, 9-methoxymitralactonine, which features the assembly of three fragments, i. e. 5-methoxy-3,4-dihydro-β-carboline **6**, a chiral epoxy-ketone **2**, and dimethyl malonate **7**, is outlined in Scheme 4.[18]

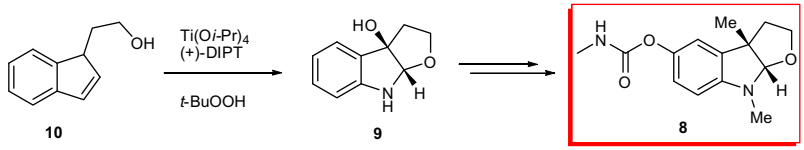
Sunazuka et al. in 2005 reported the total synthesis of calabar bean alkaloid (−)-physovenine **8** in a concise manner starting from optically active (−)-3a-hydroxyfuroindoline **9**, synthesized via modified Sharpless asymmetric epoxidation of tryptophol **10**. A synthetic strategy for madindoline A was developed involving an asymmetric oxidative ring-closure reaction of tryptophol **10** to give **9** via modified Sharpless asymmetric epoxidation using (+)-DIPT (Scheme 5). The latter then underwent a 10 step reaction to produce (−)-physovenine **8** in 19.4% overall yield (>99% ee) (Scheme 5).[7b,19]

Interleukin 6 (IL-6) is a multi-functional cytokine responsible for the regulation of the differentiation and production of antibodies. In 1996, the isolation of the novel indole alkaloids from the culture broth of *Streptomyces nitrosporeus* K93-0711, madindolines A **11** and B **12** as selective inhibitors of IL-6 was reported.[1a,20]

The strategy for the synthesis of madindolines A **11** and B **12** involved suitable reaction sequences, which gave access to the target in 19 linear steps in 7–8% overall yield. It is noteworthy that in the final stage of this multistep reaction, the oxidative ring-closure reaction of (+)-**13** under a modified Sharpless asymmetric epoxidation protocol using (+)-diethyl tartrate (DET). This crucial step yielded (+)-madindoline A (+)-**12** and (−)-madindoline B (−)-**12** in 45% yield in a 2.2:1 ratio (Scheme 6). The (−)-DET ligand was also examined which produced (+)-**11** and (−)-**12** in 49% yield in 1:2.3 ratio, respectively, (Scheme 6). It is also worthwhile mentioning that when this substrate was used, high diastereoselectivity was not observed. Apparently this is due to the steric hindrance caused by the bulky substituent on the nitrogen that inhibits the approach of the Sharpless catalyst to the reaction site.[21]



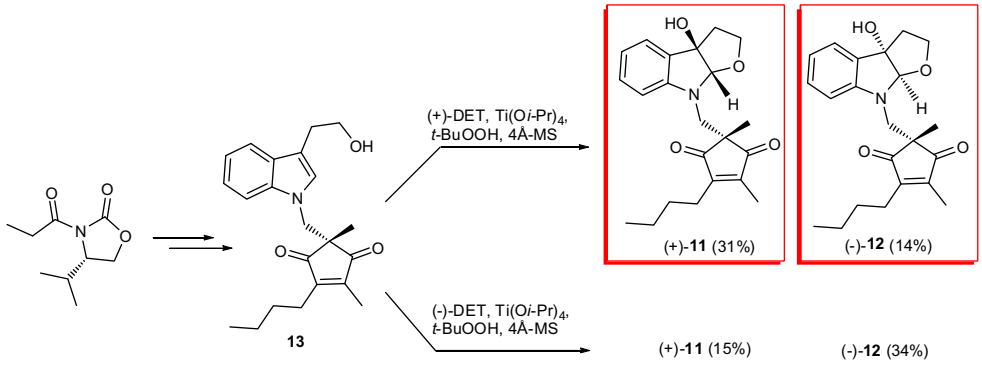
Scheme 4.



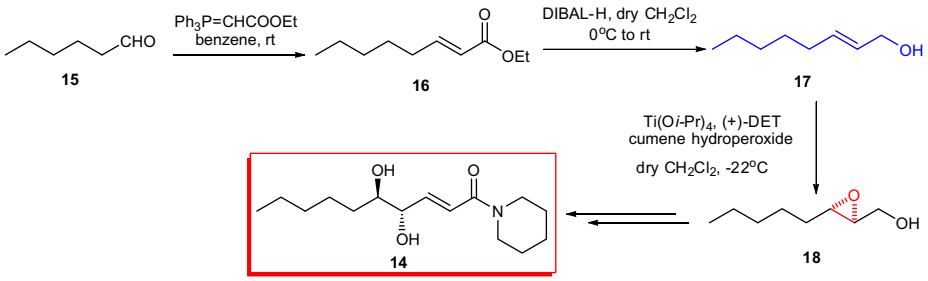
Scheme 5.

Piperidine and pyrrolidine amide alkaloids[22] are known to occur in *Piper nigrum* (Piperaceae, black pepper) and possess a variety of pharmacological activities such as being CNS stimulant,[23] analgesic, and antipyretic.[24] The synthetic approach for natural amide alkaloids **14** starts from commercially available hexanal **15**. Initially, the latter underwent Wittig olefination to afford *E*-α,β-unsaturated esters **16**, which was then converted into allylic alcohol **17**, which in turn was subjected to Sharpless asymmetric epoxidation, creating, two stereocentres to afford epoxy alcohol **18**. Then *trans*-regioselective ring opening of the epoxide alcohol and several other steps lead to the desired natural product **14** (Scheme 7).[25]

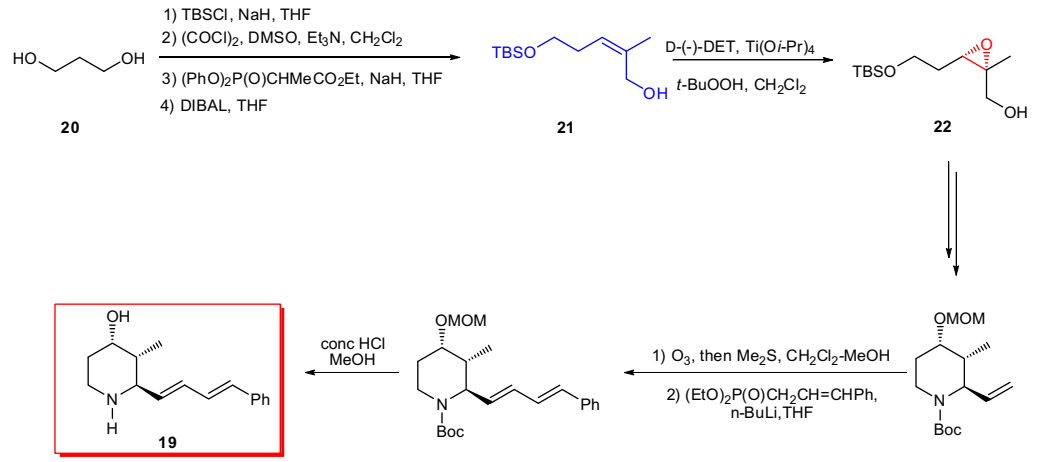
Dienomycin C **19** was isolated from the culture filtrate of the Streptomyces strain MC67-C1 by Umezawa et al. in 1970.[26]



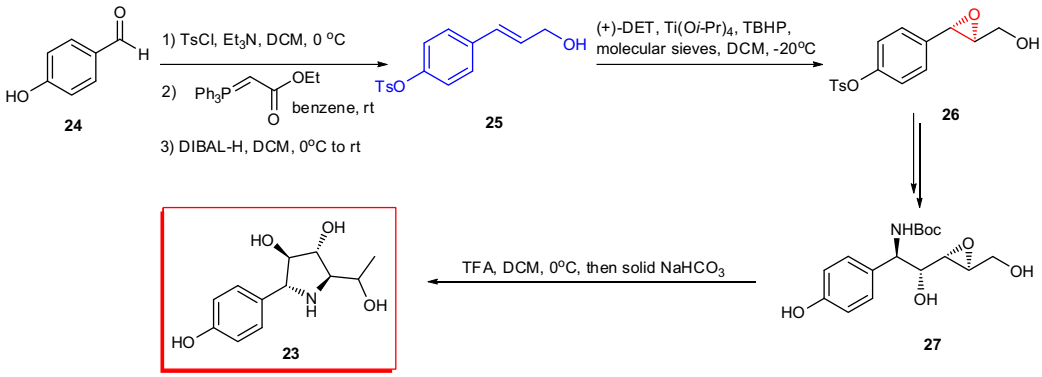
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

The total synthesis of (+)-dienomycin C **19** was achieved via Sharpless asymmetric epoxidation, Pd-catalyzed hydrogenolysis as the formic salt, and Pd(II)-catalyzed cyclization of urethane, which was reported by Yokoyama et al. in 2010.[27] Starting from 1,3-propanediol **20** TBS protected allyl alcohol **21** was obtained by using Swern oxidation followed by *Z*-selective Wittig–Horner reaction along with subsequent diisobutylaluminum hydride (DIBAL-H) reduction, in 51% yield. Sharpless asymmetric epoxidation of allyl alcohol **21** with D-(−)-DET as the key step provided epoxide **22** in 90% yield and with 78% ee. Epoxide **22** was converted into the desired natural product **19** via a multi-step reaction (Scheme 8).[27]

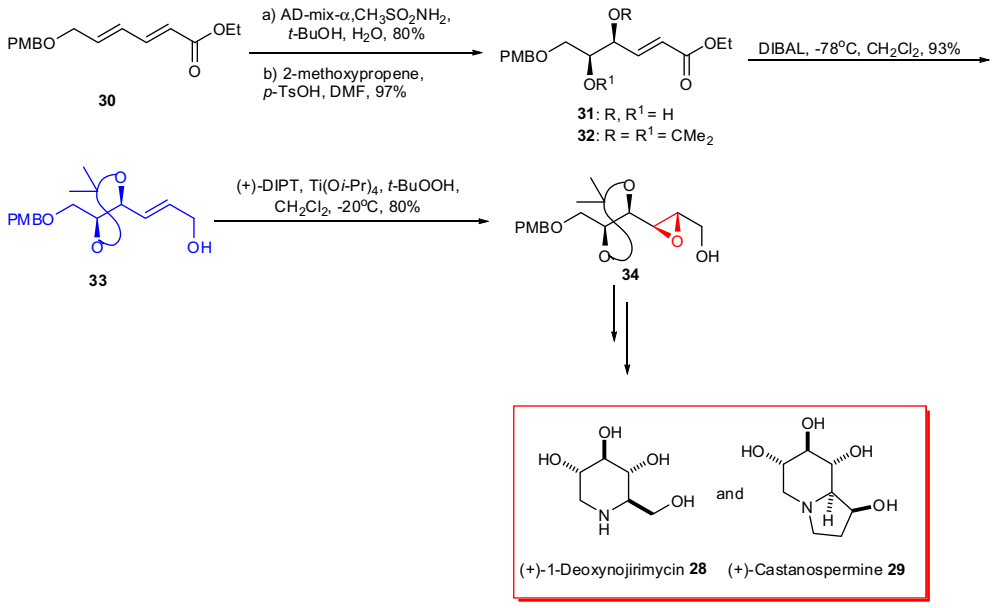
Radicamine A and B are important groups of naturally occurring polyhydroxylated pyrrolidine alkaloids isolated and identified by Kusano et al. from *Lobelia Chinensis* (Campanulaceae). A simple and efficient stereoselective synthesis of naturally occurring pyrrolidine alkaloid, radicamine B **23** was accomplished in 14 steps using the commercially available aldehyde **24** with an overall yield of 75%. The synthesis utilizes Sharpless asymmetric epoxidation as a key step.[28] The synthesis of (+)-radicamine B **23** was initiated from commercially available *p*-hydroxybenzaldehyde **24**, which was converted into its *p*-tosyl cinnamyl alcohol **25** in three steps, following the literature procedure.[29] Sharpless asymmetric epoxidation of **25** using (+)-DET furnished **26** in 98% yield and with excellent enantioselectivity (99.5% ee). After 8 steps epoxy alcohol **27** was achieved which finally, via removal of Boc-group with TFA in DCM at 0 °C followed by treatment with saturated $NaHCO_3$, smoothly yielded alkaloid (+)-radicamine B **23** in good yields (Scheme 9).[28]

(+)-Deoxynojirimycin **28** and (+)-castanospermine **29** are natural polyhydroxylated alkaloids.

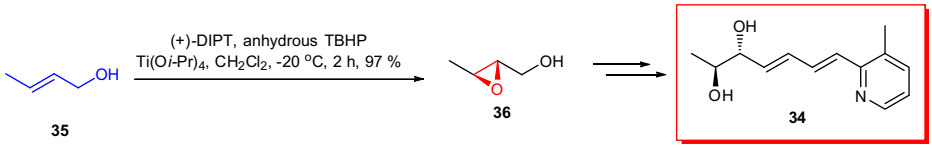
Somfai et al. proposed a strategy for the synthesis of (+)-1-deoxynojirimycin **28** and (+)-castanospermine **29** in which they controlled the stereochemistry via Sharpless asymmetric dihydroxylation and epoxidation reactions. The other stereocenter in **29** was achieved by Sakurai reaction.[30] Starting from diene **30**, the desired absolute configuration was achieved via an asymmetric hydroxylation followed by Sharpless asymmetric epoxidation. (+)-Deoxynojirimycin **28** was obtained in 36% yield from a multi-step synthesis (11 steps) from diene **30**, while (+)-castanospermine **29** was obtained in 13% after 19 steps employing the same starting material.[30] Asymmetric dihydroxylation of *p*-methoxybenzyl ether **30** afforded diol **31**. Protection of the acetonide followed by reduction of the ester resulted in allylic alcohol **32** (93%). Epoxidation of **32** using the Sharpless protocol led to a poor yield of **33** (Scheme 10).[30]

Ishibashi et al. reported the isolation and characterization of Fuzanin D **34**. The total synthesis of fuzanin D **34** was accomplished using 2-buten-1-ol **35** as the starting material which was subjected to Sharpless asymmetric epoxidation conditions to afford epoxy alcohol **36** in 97% yield. Ten further steps employing different functional groups' manipulation led to the formation of fuzanin D **34** (Scheme 11).[31]

Yadav et al. reported the total synthesis of (−)-Brevisamide **37** using (*R*)-2,3-*O*-isopropylidene glyceraldehyde **38** as the starting material which was converted into the corresponding allylic alcohol **39** in a multi-step synthesis. The latter was then subjected to Sharpless asymmetric epoxidation conditions to produce the epoxy



Scheme 10.



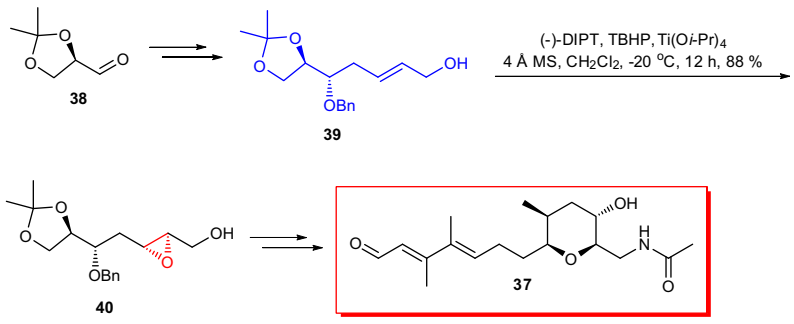
Scheme 11.

alcohol **40** in 88% yield, which was then transformed into the desired compound through seventeen reaction steps (Scheme 12).[32]

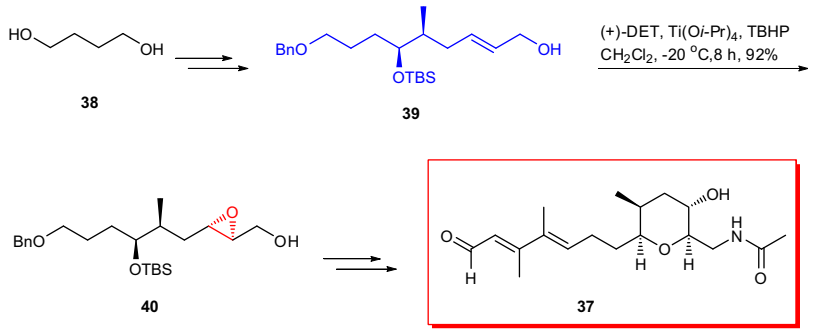
Another approach to the total synthesis of brevisamide **37** was achieved by Yadav et al. in 2013. The synthesis started from commercially available 1,4-butanediol **38**, which was initially transformed into allylic alcohol **39**. The latter was subjected to Sharpless asymmetric epoxidation conditions of compound **39** using (+)-DET for induction of the desired epoxide **40**. The latter uses this induced configuration and in 10 steps gives the desired compound **37** (Scheme 13).[33]

The synthesis of azepanes **41a** and **41b** and piperidine derivatives **42a** and **42b** has been reported, commencing from a common, familiar, and easily available D-glucose as a starting material. Initially, it was transformed into the corresponding allylic alcohol **43**. Submission of the latter to Sharpless asymmetric epoxidation protocol using D-(−)-diethyl tartrate gave the corresponding epoxy alcohols **44a** and **44b** in the ideal ratio of 92:08. Expectedly but not significantly, the use of L-(+)-diethyl tartarate controls the stereoselectivity in favor of the corresponding epoxy alcohol **44b** affording **44a**/**44b** in a poor ratio of 17:83. Epoxy alcohols **44a** and **44b** are both useful for the preparation of azepanes **41a** and **41b** and piperidine derivative **42a** and **42b** iminosugars in five and seven steps, respectively (Scheme 14).[34]

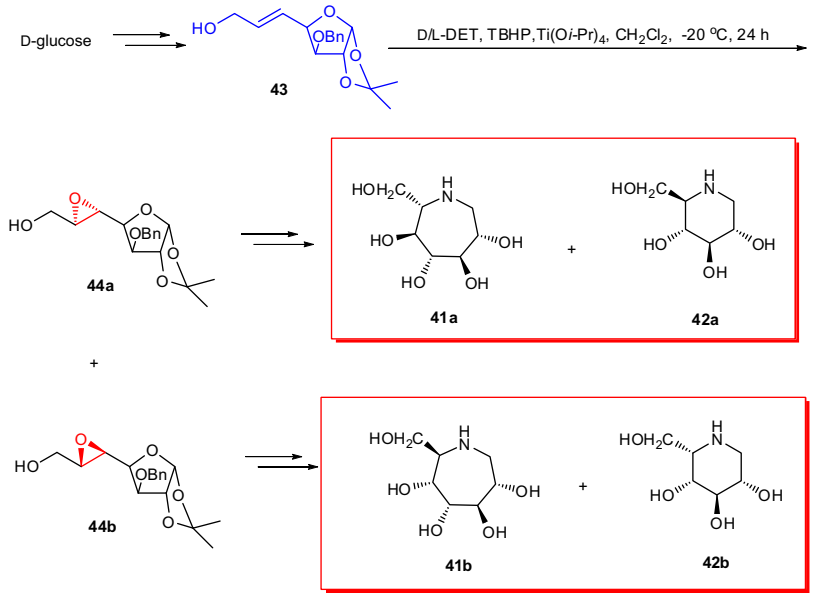
(−)-Andrachcinidine **45** is among the wide range of 2,6-disubstituted piperidine alkaloids which were isolated from *Andrachne aspera* spreng along with other piperidine alkaloids as a complicated mixture.[35] The total synthesis of (−)-andrachcinidine **45** was accomplished, using *n*-butyraldehyde as the starting material, which was transformed into the corresponding allylic alcohol **46**. The latter was transformed into epoxy alcohol **46** when submitted to Sharpless asymmetric epoxidation protocols using



Scheme 12.



Scheme 13.

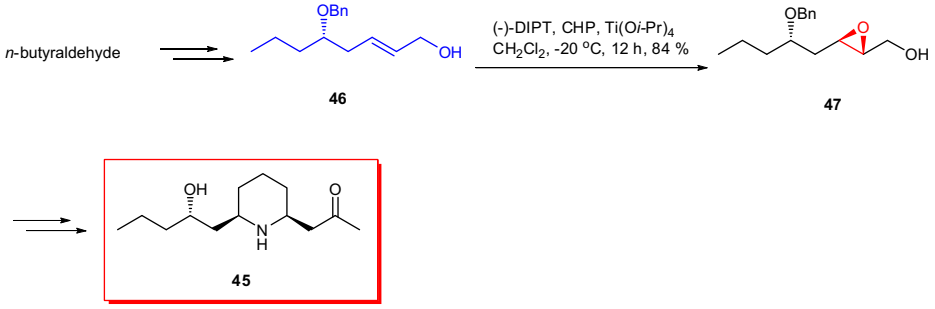


Scheme 14.

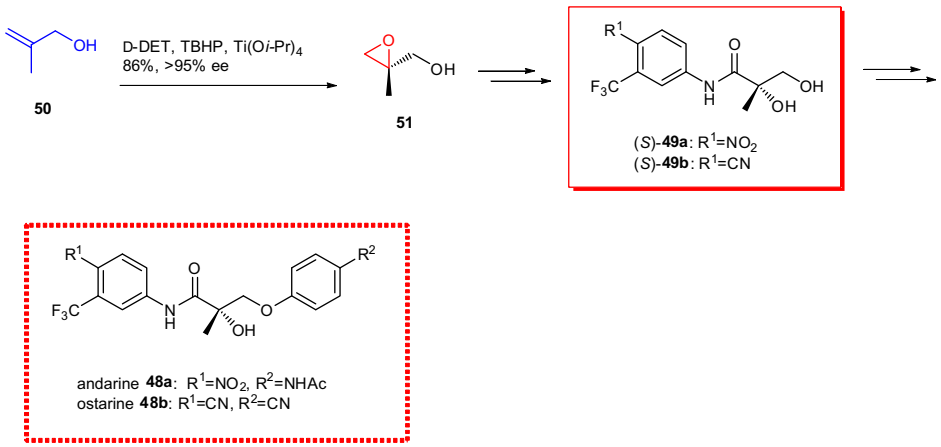
(−)-DIPT to afford **47** in 84% yield. Fifteen more steps were required for the formation of (−)-andrachcinidine **45** (Scheme 15).[36]

Andarine **48a** and structurally related ostarine **48b** are in the family of arylpropionamide. In addition to other phase-I ultrations, both drug candidates can be hydrolyzed leading to the dephenylated molecules **49a** and **49b**.[37] The total synthesis of *O*-dephenylandarine **49a** and *O*-dephenylostarine **49b** involved, using the corresponding allylic alcohol **50** as a starting material which was transformed into 2-methylglycidol (*R*)-**51** via submission into Sharpless asymmetric epoxidation protocol in 86% chemical yield and ee >95%. Five more steps were required for the conversion of 2-methylglycidol (*R*)-**51** into *O*-dephenylandarine **49a** and *O*-dephenylostarine **49b** (Scheme 16).[38]

Penaresidin A **52** was extracted from Okinawan marine sponge *Penares* sp. in 1991 as a mixture of the corresponding tetraacetyl derivatives. An attempt at the total synthesis of penaresidin A **52** was made by Reddy et al. through the key fragments **53** and **54** starting from 3,4,6-tri-*O*-benzyl-D-galactal **55** and 1,9-nonanediol **56**. Initially, 3,4,6-tri-*O*-benzyl-D-galactal **55** furnished the corresponding allyl alcohol **57**, which was subjected to Sharpless asymmetric epoxidation procedure using (+)-tartrate to afford



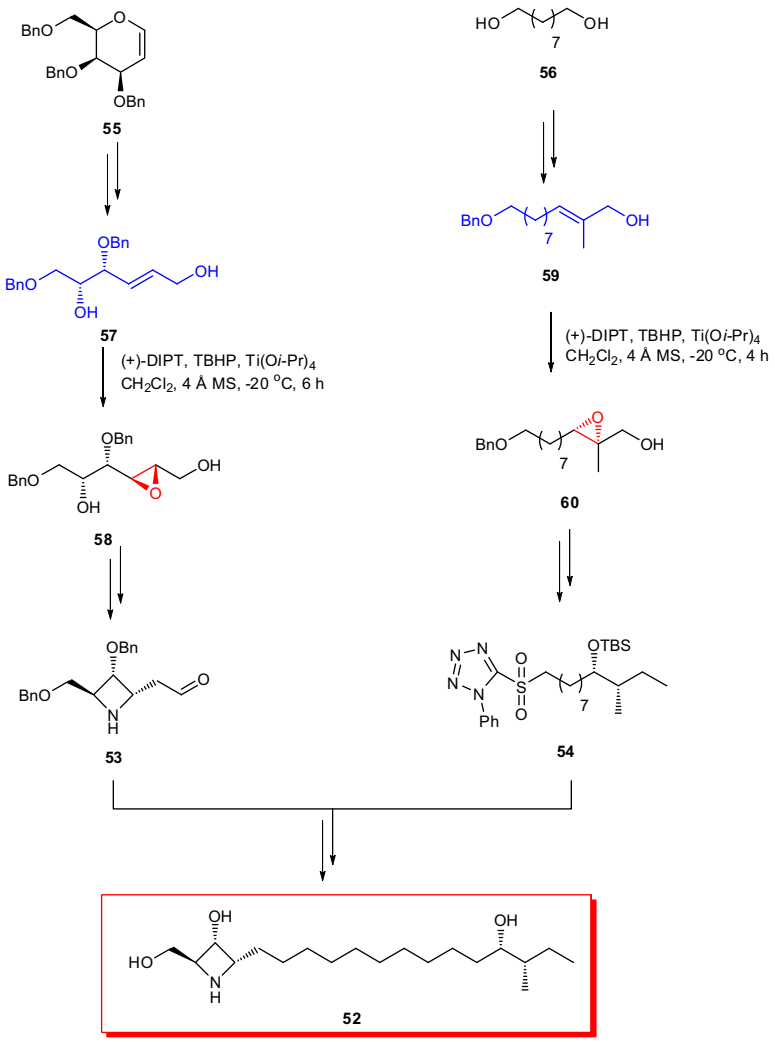
Scheme 15.



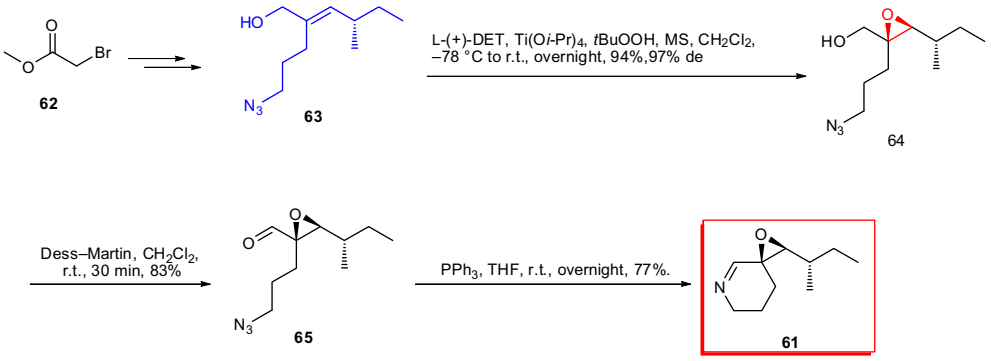
Scheme 16.

epoxy alcohol **58**, which via a twelve step reaction eventually produced aldehyde **53**. Another important segment **54** was provided from 1,9-nonanediol **56** through allyl alcohol **59**, which was then subjected to Sharpless asymmetric epoxidation conditions in the presence of (+)-tartrate to give the epoxy alcohol **60**. Five other steps transformed the epoxy alcohol **60** into sulfone **54**. With both aldehyde **53** and sulfone **54** fragments available, penaresidin A **52** was synthesized in four steps (Scheme 17).[39]

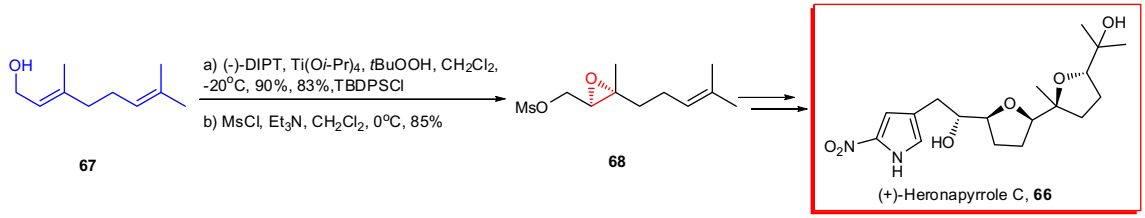
The new piperideine alkaloid cicindeloine **61** was first isolated from the pygidial glands of the beetles *Stenus cicindeloides* and *Stenus solutus*. Muller et al. reported the first total synthesis of cicindeloine. Their strategy began with primary alcohol (*S*)-**62**,



Scheme 17.



Scheme 18.



Scheme 19.

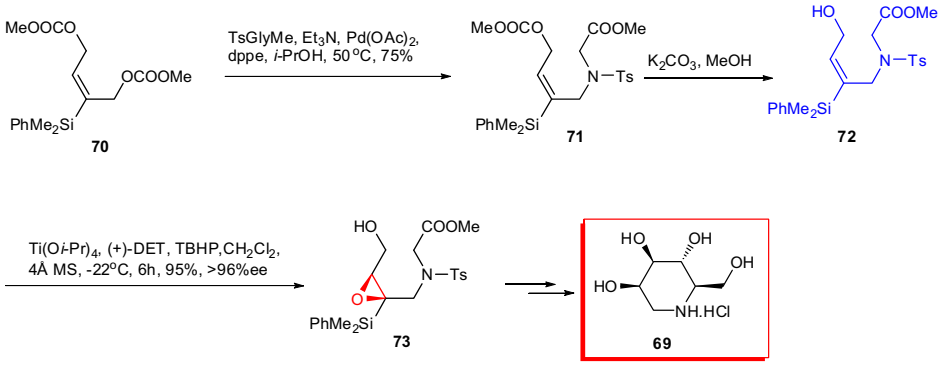
which converted into terminal azide **63** in 9 steps involving different functional group transformations. The synthesis was continued again by a Sharpless asymmetric epoxidation (94%, 97% de) of (*S*,*E*)-**63** followed by the oxidation of the formed epoxy alcohol **64** by Dess–Martin periodinane to give epoxy aldehyde **65** in high yields. Eventually the aza-Wittig reaction afforded the desired target compound **61** (77%) (Scheme 18).[40]

Heronapyrroles C **66** was isolated from a *Streptomyces* sp. (CMB-M0423) culture collected nearby Heron Island, Australia in 2010. These compounds are related to nitropyrrole natural products, and are among the first recognized examples of natural products involving a 2-nitropyrrole ring.[41]

Initially the key sulfone coupling partner was synthesized from geraniol **67** upon Sharpless asymmetric epoxidation with (−)-DIPT followed by mesylation to provide epoxy mesylate **68** as a pure stereoisomer in excellent yields in two steps (Scheme 19). The latter was then converted into the desired natural products in several steps.[42]

Deoxynojirimicin **69** was isolated in the 1970s. Since then the total synthesis of this potent glycosidase inhibitors has attracted much attention.[43] In 2011, Lamas et al. reported a pathway to its total synthesis.

The reaction of bis-allylic dicarbonate **70** with *N*-tosylglycine methyl ester mediated by palladium(0) in *i*PrOH led to a highly regio- and stereoselective substitution of just one carbonate to afford allylic amine **71** in 75% yield. Treatment of the latter with a catalytic amount of K_2CO_3 afforded the corresponding allylic alcohol **72**. The latter was subjected to Sharpless asymmetric epoxidation using (+)-DIPT to give (+)-**73** with an enantiomeric ratio (er) of 98:2. It is worthwhile to discuss this specific Sharpless asymmetric epoxidation strategy regarding its precursor in more detail. Notably, the Sharpless asymmetric epoxidation of alkenes bearing both amine and alcohol functions in the allylic positions have largely been overlooked, probably due to challenging substrates. They only submitted to Sharpless asymmetric epoxidation protocol using a stoichiometric amount of Ti(O*i*Pr)$_4$ along with long reaction times. Since precursor **72** has a double bond bearing three substituents, it can be considered to be relatively hindered and more challenging and tedious conditions are expected. However, the reaction occurred and gave an average yield of 80% upon purification. Under the optimal conditions using (+)-DIPT, an enantiomeric ratio (er) of 98:2 was observed for (+)-**73**. Starting from the latter, 9 more steps should be needed to achieve the target compound (Scheme 20).[44]



Scheme 20.

2.2. Lactones

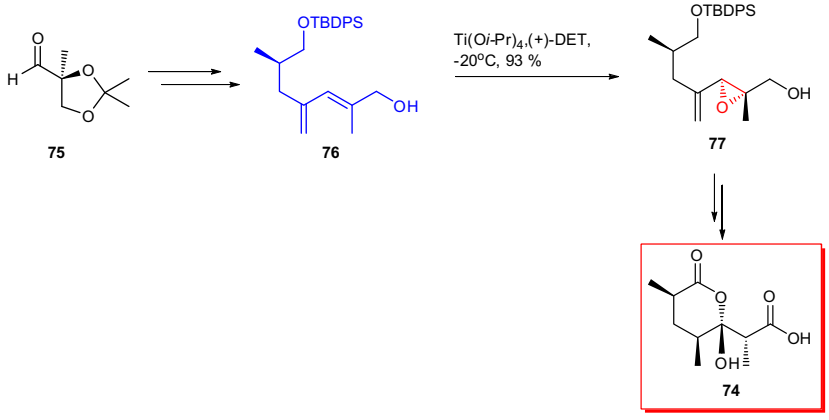
The (+)-Prelog–Djerassi lactonic acid **74** was isolated and reported independently by Prelog and Djerassi in 1956. This compound is an oxidative degradation product of the macrolide antibiotics narbomycin and pikromycin and some other antibiotics.[45] Rickards and Smith disclosed the structure of (+)-Prelog–Djerassi lactonic acid in 1970.[46]

The homochiral aldehyde **75** was subjected to six successive stages to afford allylic alcohol **76**. Next was the key step, the Sharpless asymmetric epoxidation, which asymmetrically gave epoxy alcohol **77** in 93% yields. The obtained compound underwent seven other reactions to afford the target natural product (+)-Prelog–Djerassi lactonic acid **74** (Scheme 21).[47]

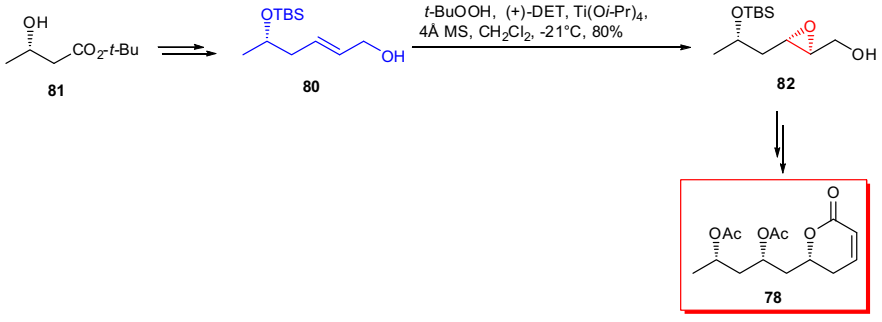
α,β-Unsaturated δ-lactones **78** and **79** were isolated from *Cryptocarya latifolia* in South Africa[48] and has been synthesized by Suenaga et al. Sharpless asymmetric epoxidation plays a key role in this total synthesis which includes Sharpless asymmetric epoxidation of an allylic alcohol followed by stereoselective addition of an allyl moiety to the epoxy aldehyde, with subsequent regioselective reduction of the epoxy ring to form the α,β-unsaturated δ-lactone. First, allyl alcohol **80** was synthesized from commercially available (*S*)-*t*-butyl-3-hydroxybutyrate **81** in several steps. The next step was treating the allylic alcohol **80** using a Sharpless asymmetric epoxidation protocol using (+)-DET to afford the epoxide **82** in 80% yield. Finally, epoxide **82** produced the target compound **78** via 10 more reactions (Scheme 22).[49]

The synthesis of the α,β-unsaturated δ-lactone **79** having a triacetate was accomplished starting from (*S*)-*t*-butyl-3-hydroxybutyrate **81**, which went through several steps to afford the α,β-unsaturated ester **83**. DIBAL-H reduction of the latter compound gave allylic alcohol **84**, which upon Sharpless asymmetric epoxidation employing L-(+)-DET afforded epoxide **85** stereoselectively. After 10 more steps, target compound **79** was obtained from the epoxide **85** (Scheme 23).[49]

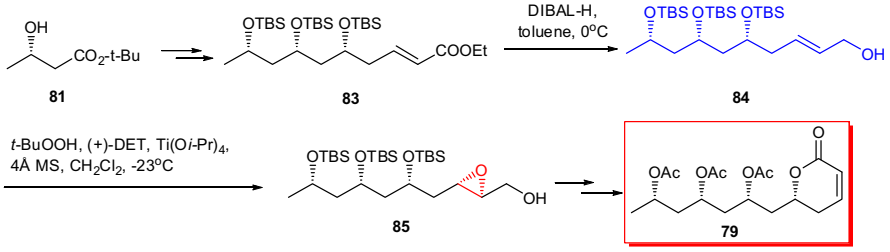
Altholactone **86** and isoaltholactone **87**, furanopyrones of the styryllactone family, were isolated from *Polythea* (Annonacae) species[50] and from various *Goniothalamous*.[51]



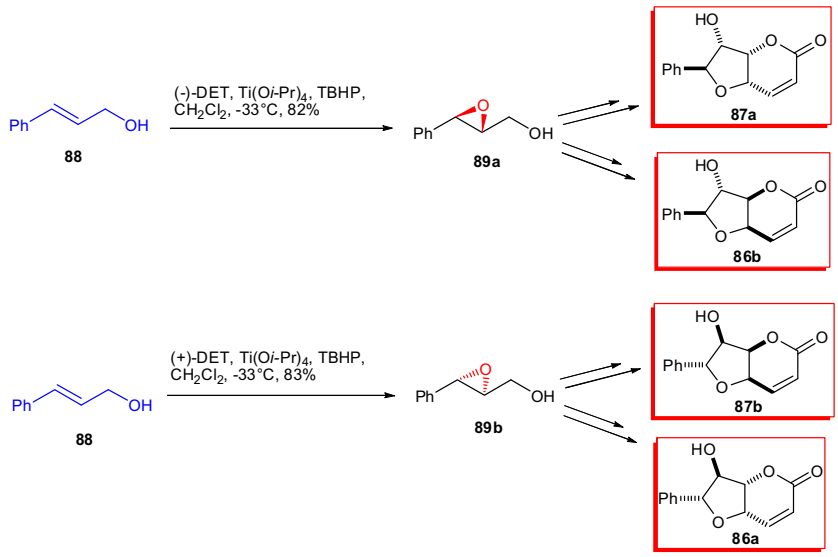
Scheme 21.



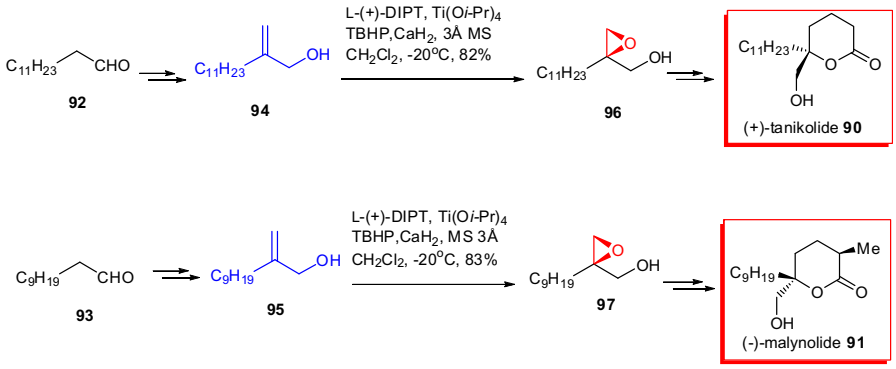
Scheme 22.



Scheme 23.



Scheme 24.



Scheme 25.

The total syntheses of both enantiomers of altholactone **86** and isoaltholactone **87** were achieved in reasonable yields from commercially inexpensive accessible cinnamyl alcohol **88**. The total synthesis of the targets started from the Sharpless asymmetric epoxidation of cinnamyl alcohol **88** to give **89a** and **89b** depending on use of an appropriate DET, in 82% and 83% yields, respectively. These epoxy alcohols **89a** and **89b** were then transformed into the desired natural products **86a,b** and **87a,b** in 9 and 8 steps, respectively (Scheme 24).[52]

Naturally occurring δ-lactonic bioactive compounds[53] (+)-tanikolide **90**[54] and (−)-malyngolide **91**[55] have been isolated from the lipid extract of the marine cyanobacterium *Lymgbia majuscule*.

A similar strategy was used for the synthesis of both compounds **90** and **91**. Aldehydes **92** and **93** were then subjected to two successive reactions to produce the allylic alcohols **64** and **95**, respectively. The Sharpless asymmetric epoxidation of allylic alcohols **94** and **95** using L-(+)-DIPT gave epoxides **96** and **97** in 82% and 83% yields, respectively. The aforementioned epoxides were subsequently converted into the desired natural products **60** and **91** in six steps (Scheme 25).[53]

Nishiyama et al. introduced a new method for the total synthesis of (+)-tanikolide **90**. Allyl alcohol **98** was used as the starting material, which after 8 steps led to compound **99**. The asymmetric epoxidation of allyl alcohol **99** was achieved using the general protocol of the Sharpless asymmetric epoxidation to afford epoxy alcohol **100** in 99% yield with 92–94% ee. The latter was then transformed into the (+)-tanikolide **90** via a four-step organic reaction (Scheme 26).[56]

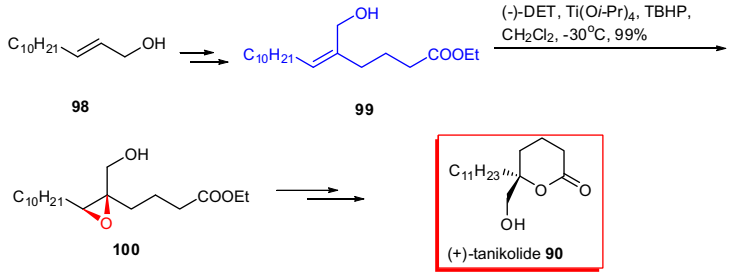
Rubrenolide **101** is a natural product which has been isolated from trunk wood of the Amazonian tree *Nectandrarubra* of the Lauraceae family. Its structure was first determined and revealed in 1971.[57]

The total synthesis of Rubrenolide **101** started with decane-1,10-diol **102** which was converted into allylic alcohol **103** in four steps. The desired (4*R*)-configuration in the natural product had to be induced by choosing the correct chiral inductor in the Sharpless asymmetric epoxidation. Therefore, the allylic alcohol **103** was treated with D-(−)-DET to obtain epoxy alcohol **104** in 69% yield. Several other steps led to target compound **101** through epoxide **104** (Scheme 27).[58]

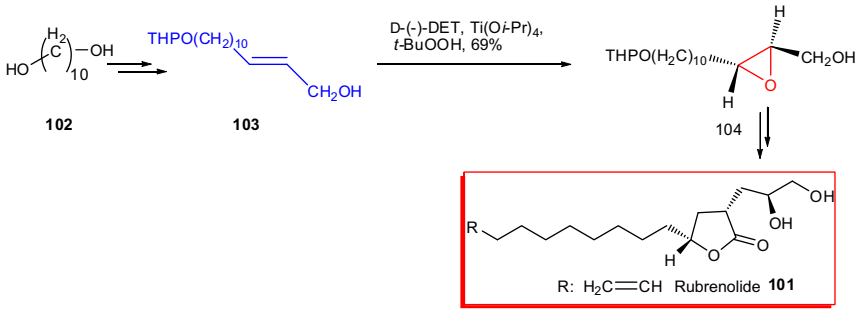
Phomolides can be isolated from leaves of the mangrove species, *Kandeliacandel*, collected in the Fugong Mangrove Conservation Area, Fujian (China).[59]

The total synthesis of Phomolide G **105** and Phomolide H **106** started from (*R*)-epichlorohydrin **107** to obtain allylic alcohol **108**, which was then subjected to Sharpless asymmetric epoxidation using (+)-DIPT to afford epoxy alcohol **109** (82%) in a crucial determining chiral induction. The latter was then converted into the desired natural products **105** and **106** via eight and ten step reactions, respectively, (Scheme 28).[59]

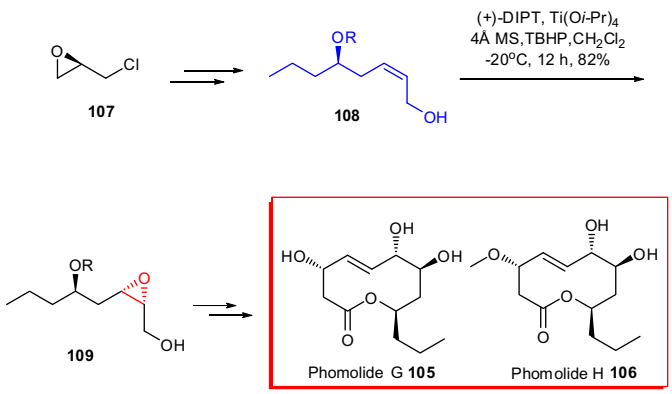
Phomolide B **110** was extracted from the culture of *Phomopsis* sp. *hzla01-1*. The total synthesis of *Z*-isomer of phomolide B **111**



Scheme 26.



Scheme 27.



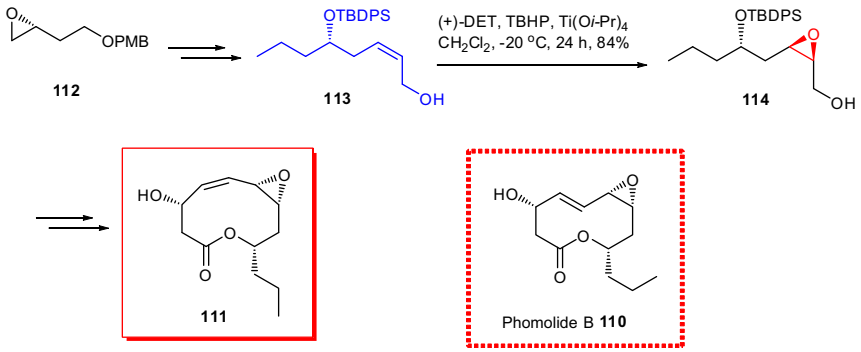
Scheme 28.

was presented using a known chiral epoxide **112** as the starting material, which was transformed into the *Z*-configured allyl alcohol **113**. Upon Sharpless asymmetric epoxidation in the presence of (+)-DET, epoxide **114** was obtained with the required stereoisomer in 84% yield. Six other steps led to the formation of compound **111** (Scheme 29).[60]

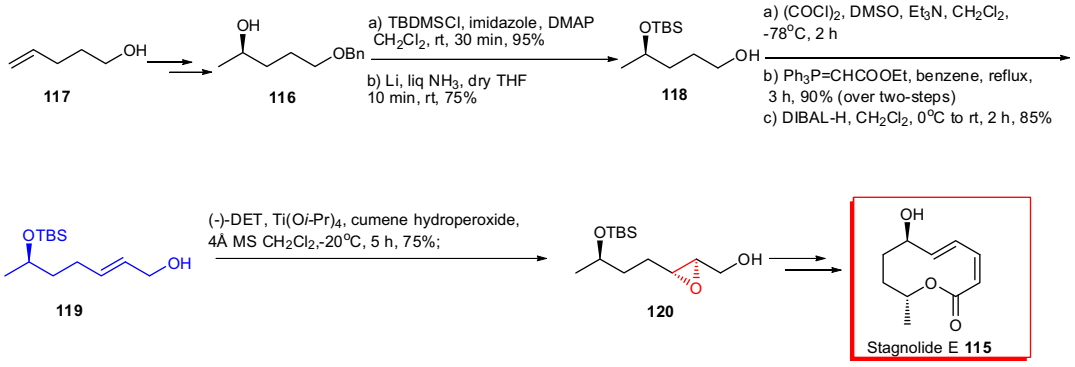
Ten-membered macrolides such as aspinolide A,[61] putaminoxin,[62] and nonenolide[63] have been isolated from fungal sources and are known to possess potent biological properties.

Accordingly, the synthesis of stagonolide E **115** began with the known secondary alcohol **116** prepared from 4-penten-1-ol **117**. Secondary alcohol **116** was protected as the TBS ether and then removal of the benzyl ether provided primary alcohol **118** in 75% yield, which was oxidized into the corresponding aldehyde. The aldehyde was homologated by a two-carbon Wittig ylide to furnish the α,β-unsaturated ester and then the ester group was reduced to alcohol **119** in 85% yield. Sharpless asymmetric epoxidation of **119** using (−)-DET afforded epoxy alcohol **120** in 75% yield (95% ee). The epoxy alcohol went through 9 steps to afford stagonolide E **115** (Scheme 30).[64]

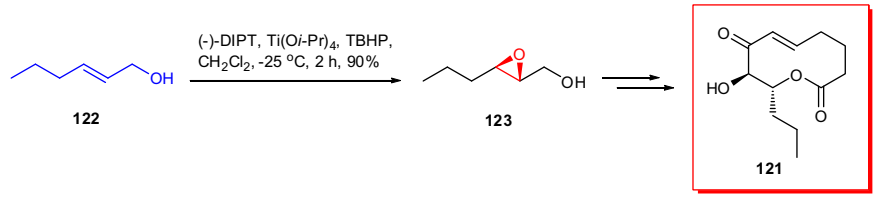
Stagonolides have recently been isolated from the fungus *Stagonospora cirsii*. The total synthesis of (−)-stagonolide A **121** has been reported by Srihariand et al. Initially they started with the commercially available *trans*-2-hexenol **122**. Sharpless



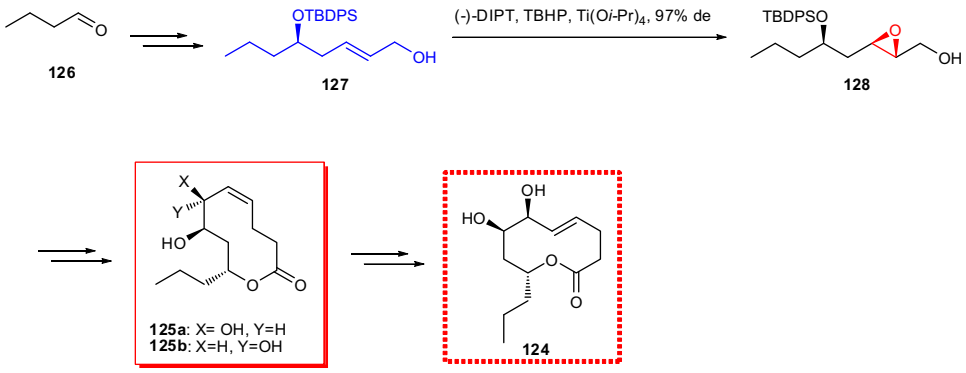
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

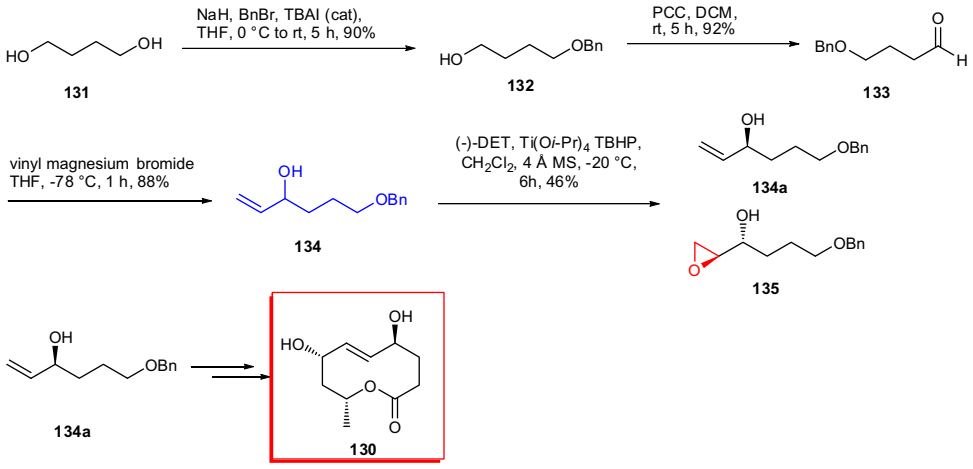
asymmetric epoxidation of **122** produced epoxy alcohol **123**. In continuation, (−)-stagonolide A **121** was prepared from epoxy alcohol **123** in fifteen steps (Scheme 31).[65]

Nonenolides which are 10-membered lactonic compounds with appealing structural features and inspiring bioactivity have been obtained from natural sources.[66] A new phytotoxic nonenolide, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **124** has been extracted from solid cultures of the endophytic fungus *Phomopsis* sp. HCCB03520.[67] Das et al.'s efforts for the synthesis of **94** have led to the synthesis of its (*Z*)-isomer **125a** and the C-6 epimer of its (*Z*)-isomer **125b**. In the present attempt, butyraldehyde **126** gave the respective allylic alcohol **127** which then underwent Sharpless asymmetric epoxidation conditions in the presence of (−)-DIPT to give epoxy alcohol **128** (de 96%). Compounds **125a** and **125b** were synthesized from the corresponding epoxy alcohol **128** in eight steps (Scheme 32).[68]

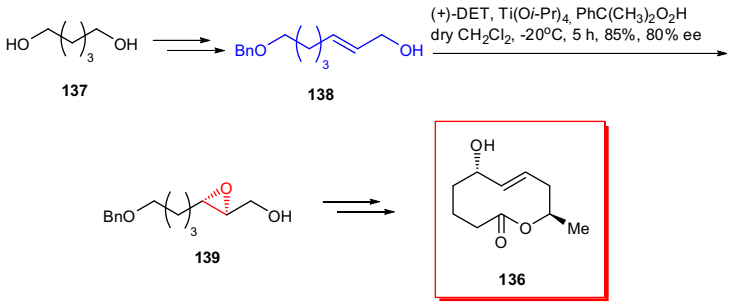
Nonenolides have been isolated as secondary metabolites of terrestrial and marine organisms. Venkatesham et al. reported a strategy for the synthesis of stagonolide C as a member of the nonenolides. One of the key fragments of the target molecule, was synthesized by starting from 1,4-butane diol **131**, which was protected with NaH and BnBr to give mono-benzyl ether **132** in 90% yield. The primary alcohol of **132** was oxidized with PCC to afford aldehyde **133** in 92% yield. Vinylation of aldehyde **133** afforded *rac*-vinyl carbinol **134** in 88% yield. The *rac*-vinyl carbinol **134** upon Sharpless kinetic resolution using (−)-DET afforded the enantiomerically enriched allylic alcohol **134a** with 97% ee and 46% yield, which was separated from the epoxy product **135** by column chromatography. In this way one of the stereogenic centers of the target molecule was achieved (Scheme 33).[69]

The nonenolide (5*S*,9*R*)-5-hydroxy-9-methyl-6-nonen-9-olide, stagonolide-F **136**, a diastereomer of aspinolide,[70] is a 10-membered-ring containing macrolides that display potent biological activity and has been isolated from *Stagonospora circii*, a fungal pathogen isolated from *Cirsium arvense*.[71] The total synthesis of stagonolide-F **136**, reported by Rao et al., initiated from commercially available 1,5-pentanediol **137**. The prepared allylic alcohol **138** was then transformed into epoxy alcohol **139** on Sharpless asymmetric epoxidation, which afforded stagonolide-F **136** through seven reaction steps (Scheme 34).[72]

Nonenolide, a medium-sized macrolide, was recently isolated as a white solid from *C. militaris BCC* 2816, and showed antimalarial activity.[73] The total synthesis of the *Z*-isomer of nonenolide **140** and the *Z*-isomer of desmethyl nonenolide **141** has been reported



Scheme 33.



Scheme 34.

by Sabitha et al. The total synthesis of **140** initiated from 4-pentene-1-ol **142**, which gave allylic alcohol **143**. Sharpless asymmetric epoxidation of **143** produced epoxy alcohol **144** in 75% yield. Continuing the procedure through seven steps resulted in compound **140**.[74]

In another strategy, commercially available 1,4-butane diol **131** was transformed into allylic alcohol **145** which upon Sharpless asymmetric epoxidation produced epoxy alcohol **146** in 75% yield. To complete the synthesis, epoxy alcohol **146** was converted into compound **141** in seven steps (Scheme 35).[74]

The α,β-lactone (−)-tetrahydrolipstatin (THL) **147** is a potent irreversible inhibitor of pancreatic lipase. It is also the saturated analogue of lipstatin isolated from *Streptomyces toxytricini* in 1987.[75]

Yadav et al. reported the total synthesis of (−)-tetrahydrolipstatin **147** starting from dodecanal **148**. Wittig olefination of the latter followed by reduction with DIBAL-H in DCM afforded allyl alcohol **149**. Sharpless asymmetric epoxidation of **159** using D-(−)-DET produced epoxy alcohol **150** in high yields, which was then converted into target molecule **147** (Scheme 36).[76]

The natural product ilexlactone **151**,[77] isolated from *Ilex aquifolium* with a structure defined as a 3-(3′-hydroxycyclopent-1-enyl)-*Z*-propenic acid-1,5′-lactone, is attractive as an interesting synthetic target.[78]

The synthesis started with known allylic alcohol **152**, which was subjected to Sharpless asymmetric epoxidation using (−)-DIPT to afford epoxy alcohol **153a**. The latter was then transformed into ilexlactone **151** through thirteen steps (Scheme 37).[78]

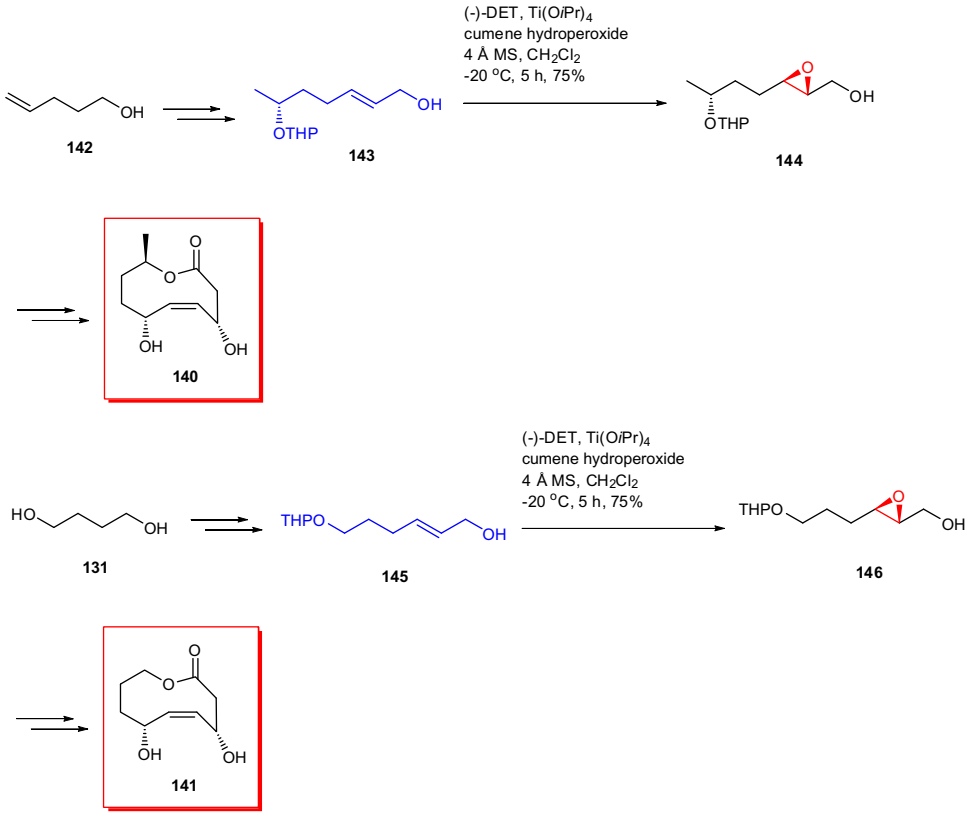
Decarestrictines are members of a family of novel 10-membered lactones, which are secondary metabolites isolated from various *Penicillium* strains.[79]

The synthesis of decarestrictine O **154** reported by Krishna et al began with allylic alcohol **155** which underwent Sharpless asymmetric epoxidation using (+)-DIPT to afford epoxy alcohol **156** (75%). The latter was converted into decarestrictine O **154** in several steps (Scheme 38).[80]

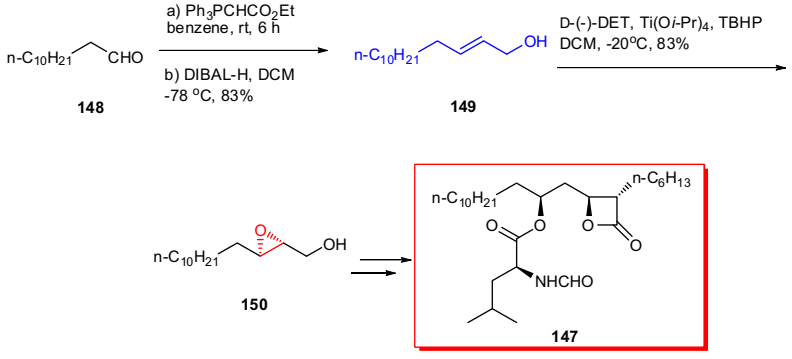
Decarestrictine I **157** was synthesized starting from propylene oxide **158** which was converted into propargylic alcohol **159** according to the literature.[81] The *cis*-allylic alcohol **160** was produced from propargylic alcohol **150** in 67% yield via partial reduction with $Ni(OAc)_2{\cdot}4H_2O$–$NaBH_4$ in ethanol under an H_2 atmosphere. Allylic alcohol, **60** upon Sharpless asymmetric epoxidation by (−)-DIPT gave epoxy alcohol **161**, (93%) which was then transformed into decarestrictine I **157** in six steps (Scheme 39).[82]

The synthesis of decarestrictine J **162** began by the reaction of (*R*)-(+)-propylene oxide **158** and propargyl tetrahydropyranyl ether **163** in the presence of lithium amide in liquid ammonia, which afforded the protected alcohol **164** in 60% yield. Benzylation of alcohol **164**, THP group deprotection, and reduction of the triple bond using lithium aluminum hydride gave the corresponding (*E*)-allylic alcohol **165**. Asymmetric Sharpless asymmetric epoxidation with L-(+)-diethyl tartrate gave (2*S*,3*S*)-epoxy alcohol **166** in >95% de. The total synthesis was completed by converting (2*S*,3*S*)-epoxy alcohol **166** into decarestrictine J **162** through eleven successive reactions (Scheme 40).[83]

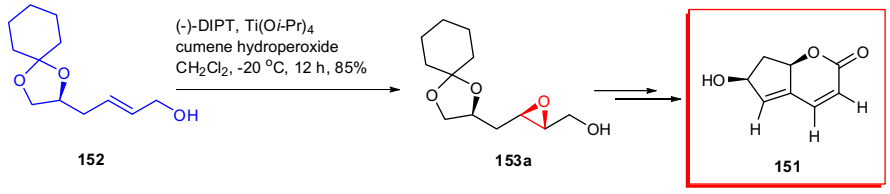
(−)-Decarestrictine D **167** was isolated from different strains of *Penicillium* (*P. orylophilum*, *P. simplicissimum*). Due to its selective biological activity, (−)-decarestrictine D **167** has attracted the attention of many research groups as an interesting synthetic target to complete the total synthesis of a new cholesterol-lowering agent. Accordingly, the total synthesis of **167** and its secoacid have been attempted by various research groups interested in macrolactonization protocols or C–C cyclization.[84]



Scheme 35.



Scheme 36.

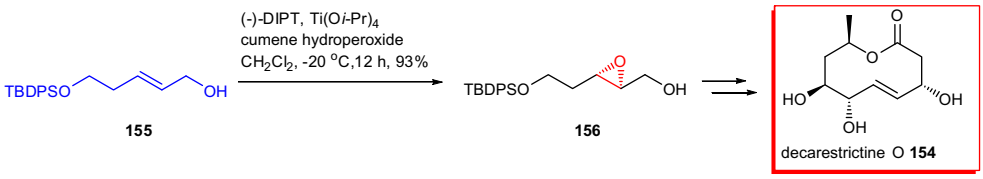


Scheme 37.

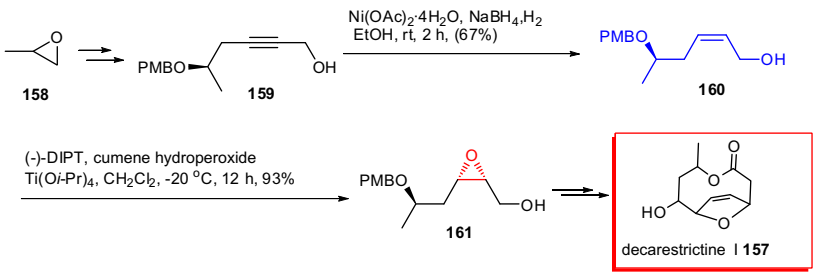
In 2006, Krishna et al. accomplished a stereoselective total synthesis of (−)-decarestrictine D **167**. The synthesis started with alcohol **168**, which was converted into allylic alcohol **152** through three steps. Exposure of the ensuing allylic alcohol **93** to Sharpless asymmetric epoxidation with (+)-DIPT afforded epoxy alcohol **153b** in 85% yield. The total synthesis of (−)-decarestrictine D **167** was completed by directing the epoxy alcohol **153b** to an eighteen step reaction (Scheme 41).[85]

Mohapatra et al. described the total synthesis of decarestrictines C_1 **169a** and C_2 **169b**.[86]

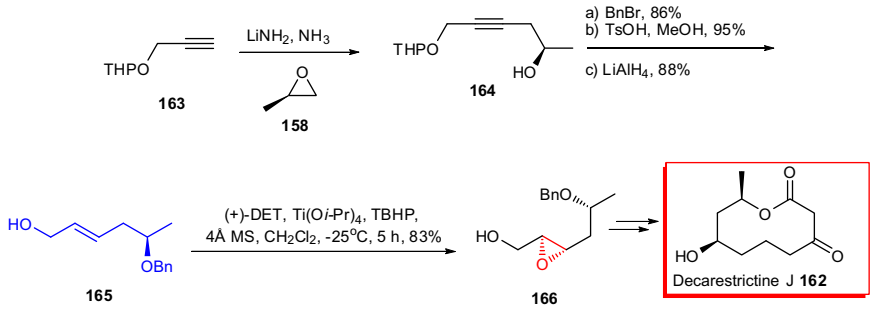
In their strategy, allylic alcohol **152** was prepared following a known protocol using commercially available L-(−)-malic acid



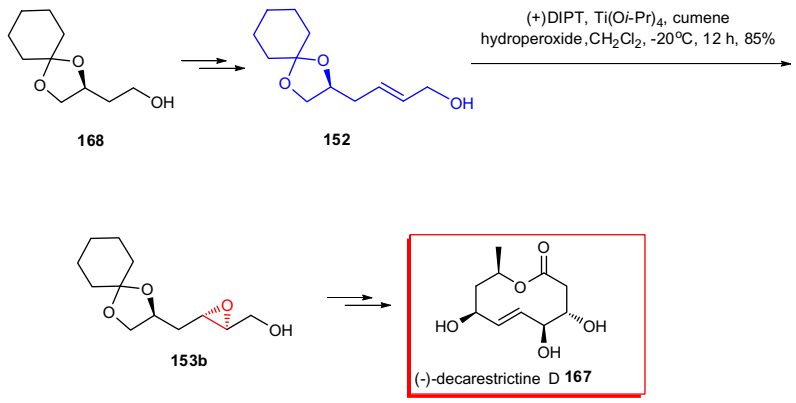
Scheme 38.



Scheme 39.



Scheme 40.

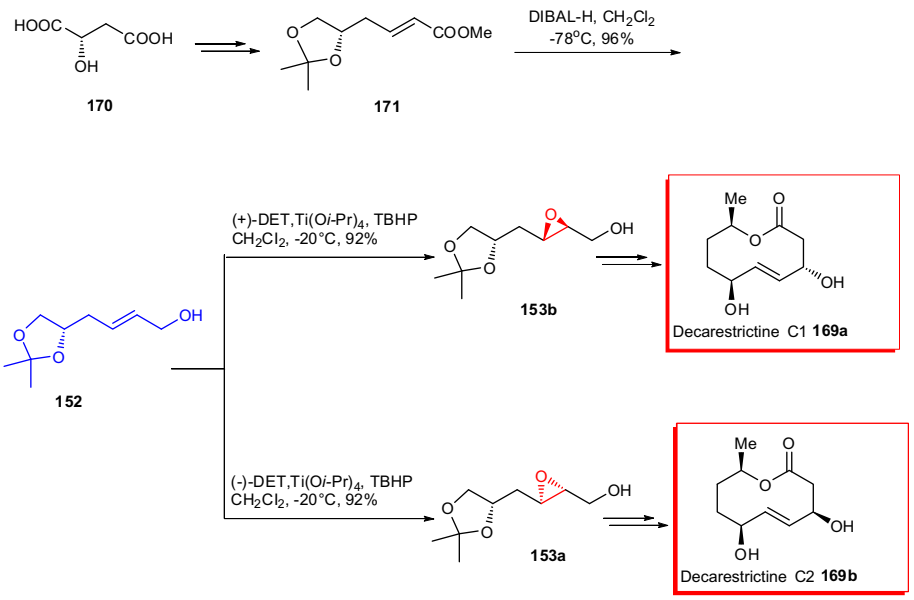


Scheme 41.

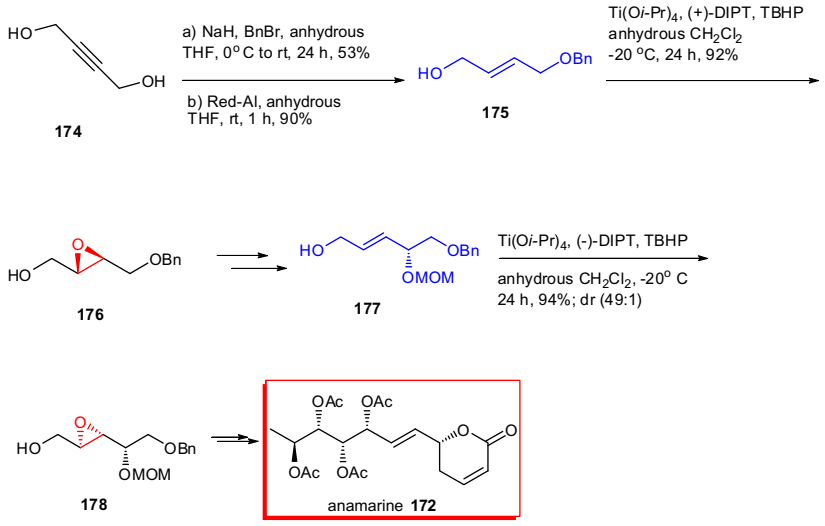
170 as the starting material to achieve *trans*-α,β-unsaturated ester **171**. The latter was selectively reduced to allylic alcohol **152** using DIBAL-H in CH_2Cl_2 at −78 °C. Incorporation of the required chirality was achieved by employing appropriate DET in Sharpless asymmetric epoxidation of the allylic alcohol **152**. Accordingly, the allylic alcohol **152** was treated with Ti(O*i*Pr)$_4$ and *t*-BuOOH in the presence of (+)-DET or (−)-DET to obtain (*S*,*S*)- or (*R*,*R*)-epoxide **153b** and **153a**, respectively.[87] The total synthesis of decarestrictines C_1 and C_2 **169a** and **169b** was achieved using the obtained epoxides **153b** and **154a** in the same sequence of nine reactions (Scheme 42).[86]

In recent years, naturally occurring six-membered α,β-unsaturated δ-lactones substituted with a polyoxygenated chain have gained the interest of synthetic and bioorganic chemists, due to their interesting structures and important biological potencies.[88] Representative examples of this class of molecules are anamarine **172**[89] and synrotolide **173**.[90]

The synthesis of anamarine **172**, a member of the polyoxygenated 5,6-dihydro-2*H*-pyran-2-one was first reported by Sabitha et al.[90] Accordingly, the synthesis of anamarine **172** started with the readily available 2-butyn-1,4-diol **174**, which was subjected to selective monobenzylation followed by partial reduction



Scheme 42.



Scheme 43.

using Red-Al in THF to afford allylic alcohol **175**. Allylic alcohol **175** was then exposed to Sharpless asymmetric epoxidation with (+)-DIPT to produce epoxy alcohol **176**. In continuation of this total synthesis, epoxy alcohol **176** was transformed into olefin **177**, which upon Sharpless asymmetric epoxidation using (−)-DIPT, furnished the desired epoxy alcohol **178** in 94% yield (de 49:1). Anamarine **172** was obtained from epoxy alcohol **178** after thirteen steps (Scheme 43).[90]

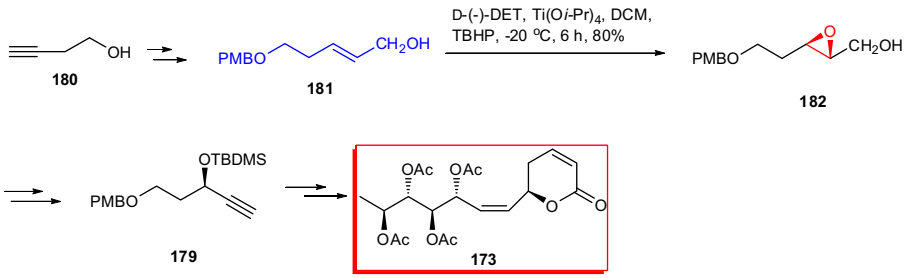
One of the important intermediates for the synthesis of synrotolide **173** is *tert*-butyldimethylsilyl ether **179**. For the synthesis of **179**, 3-butyn-1-ol **180** was employed as the starting material which after three steps afforded allyl alcohol **181**. Sharpless asymmetric epoxidation of allyl alcohol **182** using D-(−)-DET yielded the epoxy alcohol **182** which underwent three other reactions to give *tert*-butyldimethylsilyl ether **180**. Synrotolide **173** was obtained from **179** in several steps (Scheme 44).[91]

The first stereoselective total synthesis of synargentolide A **183**, isolated from *Syncolostemon argenteus*, began with the commercially available (*R*)-benzyl glycidyl ether **184**. Accordingly the ring opening of the epoxide, protection, oxidation, and then a Wittig reaction led to allylic alcohol **185**. Sharpless asymmetric epoxidation of allylic alcohol **185** gave epoxy alcohol **186** in 98% yield as a single diastereomer which started a twelve steps reaction to give the desired target compound **184** (Scheme 45).[92]

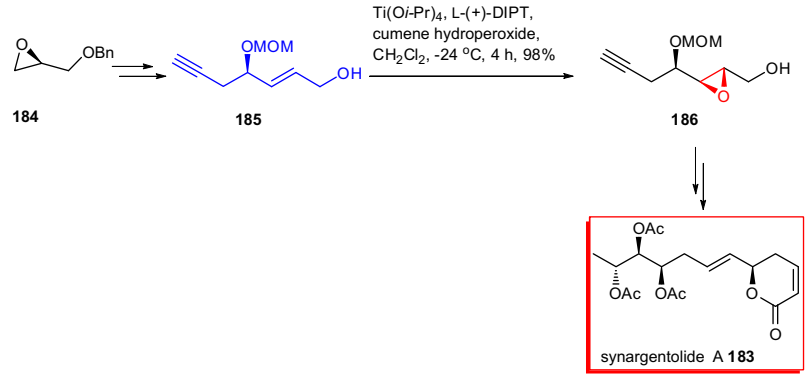
The genus *Goniothalamus* (Annonaceae) involves 115 species and covers entire tropics and subtropics.[93] Most of the identified styryl lactones are extracted from the genus *Goniothalamus*.[94] The selected strategy for the total synthesis of Leiocarpin C **187** and (+)-Goniodiol **188** began with Sharpless asymmetric epoxidation of cinnamyl alcohol **88** using D-(−)-DET, to afford the appropriate epoxy alcohol **89a** in high yields. The obtained epoxy alcohol **89a** was first converted into Leiocarpin C **187**, which was subsequently transformed into (+)-Goniodiol **188** via four further reactions (Scheme 46).[95]

Botryolide B **189** was isolated by Gloer et al. in 2007 from the cultures of a fungicolous isolate of *Botryotrichum* sp.[96]

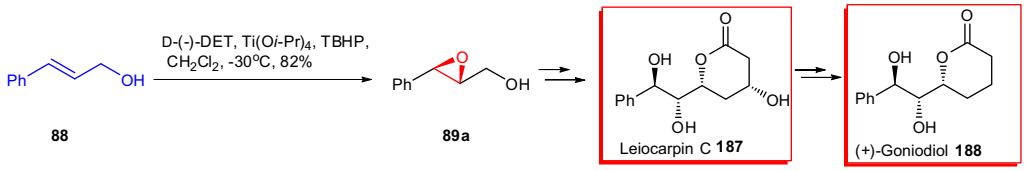
The synthesis began with epoxide **158** to give propargyl alcohol **190** which upon treatment with $Ni(OAc)_2$, $NaBH_4$, and



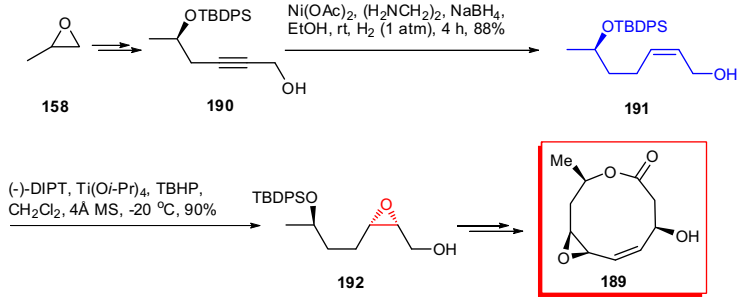
Scheme 44.



Scheme 45.



Scheme 46.



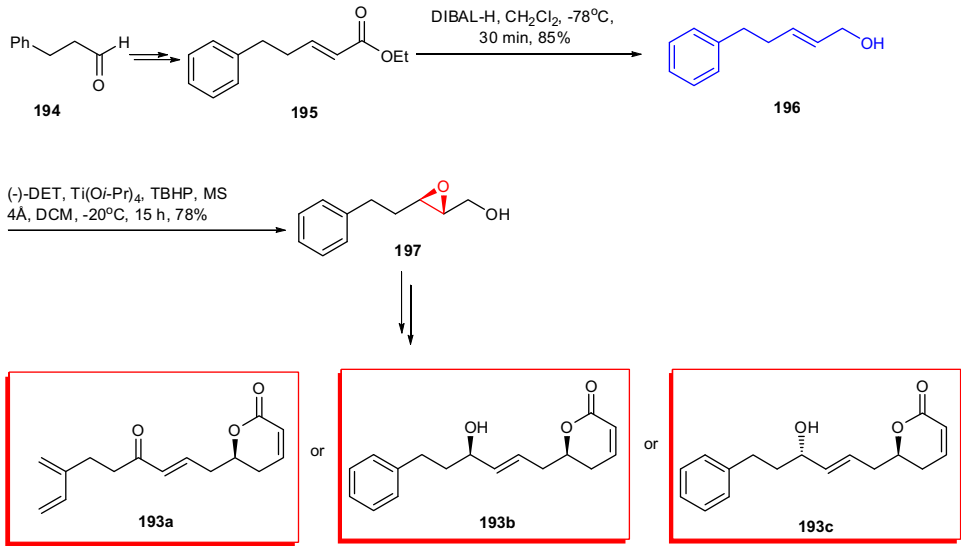
Scheme 47.

ethylenediamine in ethanol at ambient temperature under H_2 (atm) for 4h gave allylic alcohol **191** in high yields, which was subsequently transformed into epoxy alcohol **192** (90%, >20:1 de) via Sharpless protocol. Epoxy alcohol **192** was then converted into Botryolide B **189** through multi step reactions (Scheme 47).[97]

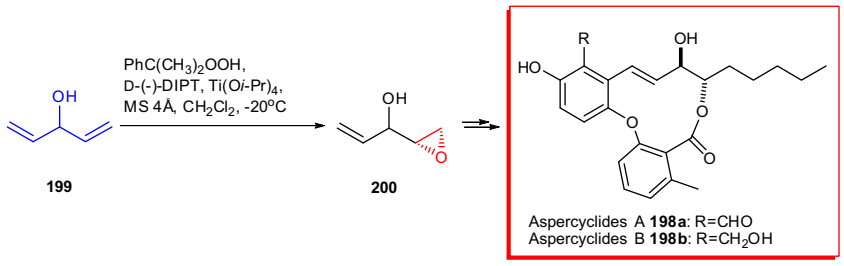
6-(4-Hydroxy-6-phenyl-hex-2-enyl)-5,6-dihydro-pyran-2-one, (*R*)-rugulactone **193a**, was isolated from Cryptocarya *rugulosa* by Cardellinah and identified. Starting from 3-phenylpropanal **194**, ester **195** was obtained, which was then reduced with DIBAL-H in CH_2Cl_2 at 0 °C to allylic alcohol **196** in high yields. Allylic alcohol **196** was then subjected to Sharpless asymmetric epoxidation with (−)-DET to give the corresponding epoxy alcohol **197**. The target, pyrones **193a**–**c** were then produced from compound **196** through several other reactions (Scheme 48).[98]

In 2004, Singh et al. isolated and identified aspercyclides A and B **198a**,**b** from the fermentation broth of *Aspergillus* sp. Aspercyclide A **198a**.[99]

Sato et al. described an effective method for the total synthesis of the 11-membered cyclic aspercyclides A and B **198a**,**b** from diene **199**. In the first step, Sharpless asymmetric epoxidation of



Scheme 48.



Scheme 49.

diene **199** with D-(−)-DIPT gave epoxy alcohol **200**. The following aspercyclides A and B **198a**,**b** were obtained from epoxy alcohol **200** in several steps (Scheme 49).[100]

Two Japanese groups independently reported[101] the isolation and characterization of Pironetin (PA-48153C) from the fermentation broths of *Streptomyces prunicolor* PA-48153 and *Streptomyces sp*. NK 10958. Pironetin **201** acts as the plant growth regulator as well as showing immunosuppressive activity.[102]

Enol **202** was successfully oxidized, olefinated, and reduced to provide allylic alcohol **203**. The Sharpless asymmetric epoxidation employing (−)-DIPT afforded the corresponding epoxide derivative **204**. Subsequently **204** was reacted with Me_2CuLi in ether at −78 °C to afford **205** (20:1); its hydroxyl group was initially protected as TBS-ether followed by methylation and deprotection to afford **206** in high yields. Transformation of **206** into **207** was performed nearly by the same sequence as above for compound **203**. The Sharpless asymmetric epoxidation of **207** using (+)-DIPT as a chiral auxiliary gave **208** in high yields and with excellent de (92%). From this point eleven steps were required for the complete total synthesis of Pironetin **201** (Scheme 50).[103]

A couple of years later, Kitahara et al. synthesized pironetin **201** using *trans*-2-pentenol **209** which was converted into chiral epoxide **210a** via an asymmetric Sharpless asymmetric epoxidation. Pironetin **201** was then obtained from chiral epoxide **210a** through several other steps (Scheme 51).[104]

Leustroducsins, isolated from the culture broth of *Streptomyces platensis* SANK 60191 in 1993,[105] has important biological activities.

The precursor of an ethyl substituted γ-lactone structure in this natural product, was prepared by a sequential Sharpless asymmetric epoxidation and an epoxide cleavage reaction using an organometallic reagent as the decisive steps to control the stereochemistry. In the first step of this total synthesis, optically active epoxide **210b** was synthesized via Sharpless asymmetric epoxidation of *trans*-2-pentenol **209**. Epoxide **210b** in 26 more steps led to the synthesis of target product **211** (Scheme 52).[106]

Korormicin **212** was isolated from the culture filtrate of marine bacterial strain *Pseudoalteromonas* sp.[107]

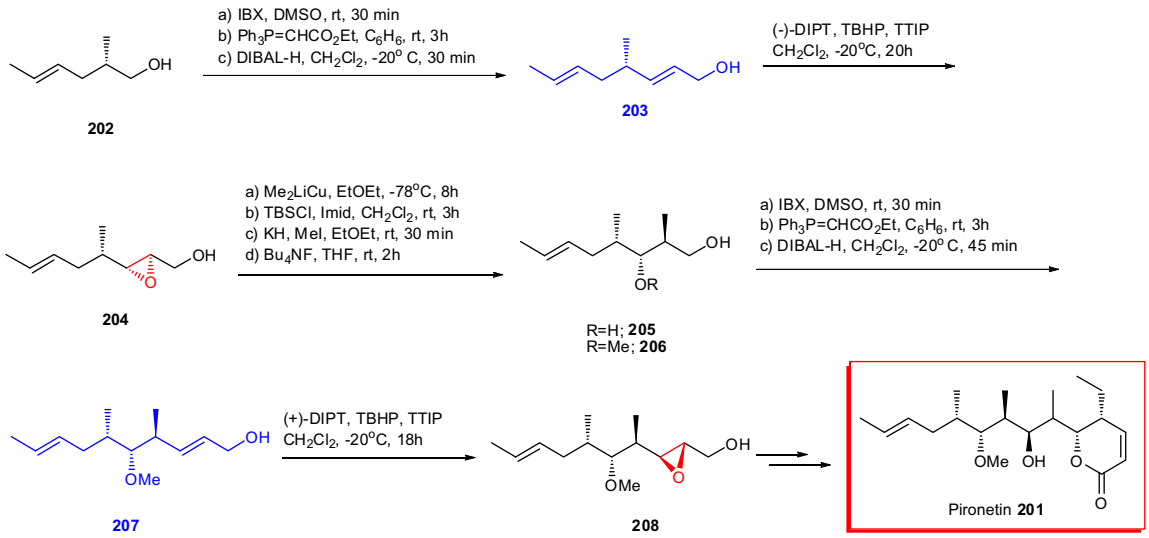
An important part of this total synthesis, the Sharpless asymmetric epoxidation of allylic alcohol **213** was performed using (+)-DIPT.[7b] The resulting epoxy alcohol **214** was subjected to 5 more steps to afford the desired target korormicin **212** (Scheme 53).[108]

As a relatively new compound[109] to the family of cyclic enediynes, kedarcidin chromophore **215**[110] was placed in a class of antitumor natural products[111] structurally inclined toward DNA recognition and cleavage.[112]

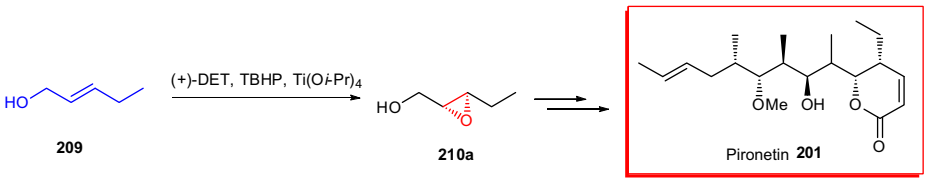
The total synthesis of the latter began from aldehyde **216**, which was added to an already prepared cooled anionic solution (KHMDS, DME) of the *N*-phenyltetrazolylsulfone **217**, which gave *trans*-alkene (*E*)-**218** selectively in good yields. Starting from (*E*)-**219**, 2,3-epoxy carbamate **219** was synthesized from the silyl deprotected allylic alcohol **220** via a highly diastereoselective Sharpless asymmetric epoxidation using L-(+)-diethyltartrate. In four more steps, the 2-deoxypyranosides **221** related to the sugar part of the kedarcidin chromophore was obtained in multi-gram quantity in an overall yield of 48% (Scheme 54).[113]

Nafuredin **222**[114] was isolated from the fermentation broth of a fungal strain, *Aspergillus niger* FT-0554.[114]

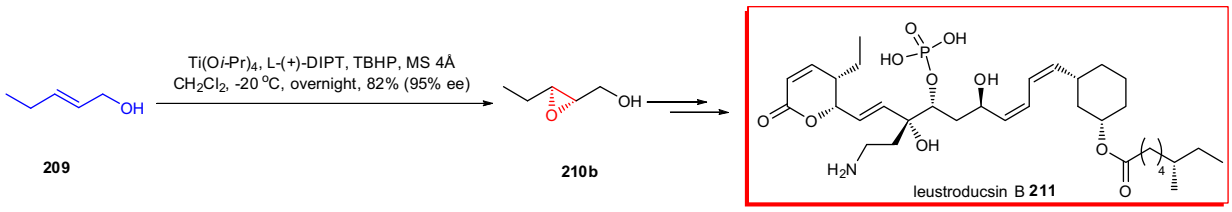
During the course of a series of synthetic studies, it was revealed that under mild basic conditions, nafuredin **222** can be converted into γ-lactone derivative **223**, which exists as a mixture



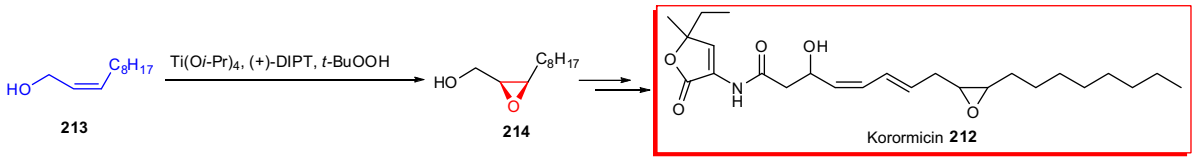
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

of keto–enol tautomers (Scheme 55).[115] This γ-lactone derivative **223** was named nafuredin-γ.[116]

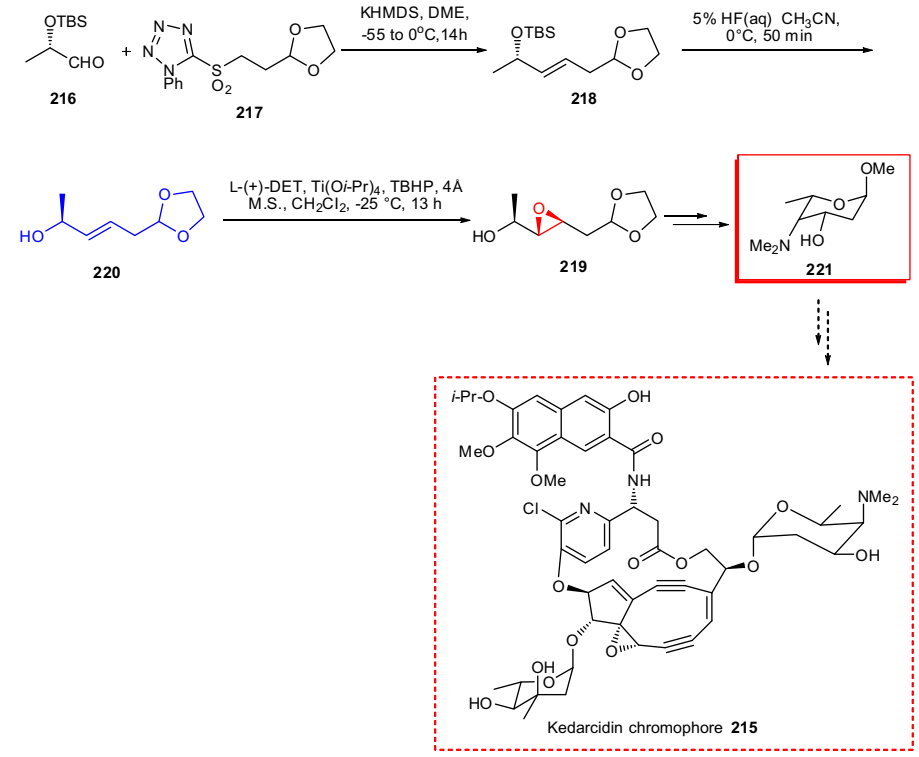
Diol **224** (97% ee) was employed as the precursor which after five steps, involving successive acetalization, oxidation, and Horner–Wadsworth–Emmons reaction gave allylic alcohol **225**. Using a Sharpless protocol employing (+)-DET, oxirane **226** was obtained and subjected to 9 more reactions to give Nafuredin-γ **223** (Scheme 56).[116]

The same strategy starting from **226** resulted in compounds **227** and **228** which are analogues of Nafuredin-γ (Scheme 57).[116]

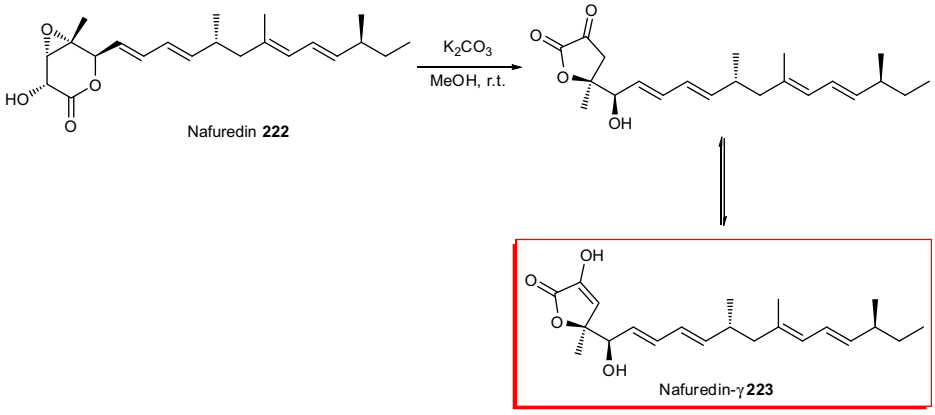
The synthesis of the C4-epimer **229** started from methallyl alcohol **230**, which was easily transformed into the allyl alcohol **231** after seven steps. Sharpless asymmetric epoxidation of **232** with (+)-diethyl tartrate afforded the corresponding epoxy alcohol **153a**, which underwent 11 more steps to afford the Nafuredin analogue **229** (Scheme 58).[116]

Leinamycin **233** is known to be a highly potent macrocyclic anticancer antibiotic containing a spiro-1,3-dioxo-1,2-dithiolane moiety.[117]

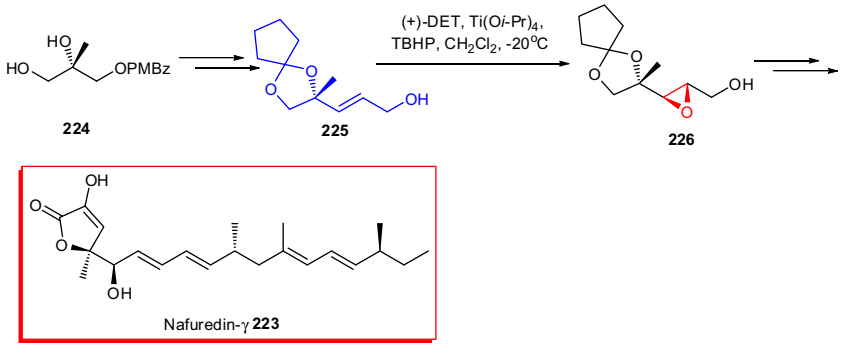
Geraniol **234** was selected as a staring material, which after five steps, was converted into the corresponding allyl alcohol **235**. Sharpless asymmetric epoxidation of racemic allyl alcohol **235** employing (−)-DIPT and *t*-BuOOH was accomplished with a high enantio- (98%) and diastereoselectivity (98%) to give



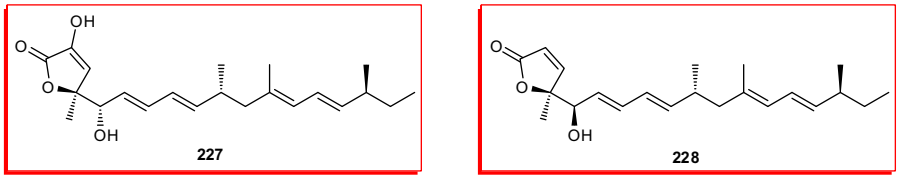
Scheme 54.



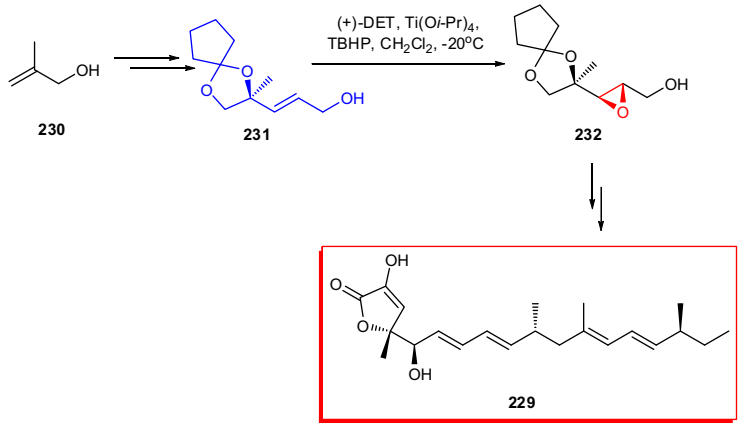
Scheme 55.



Scheme 56.



Scheme 57.



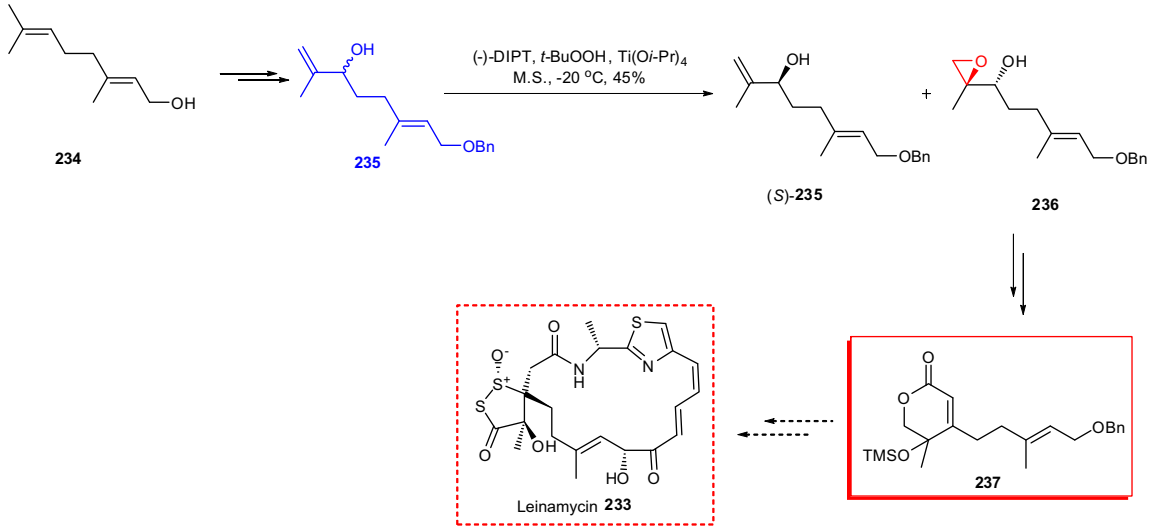
Scheme 58.

hydroxyepoxide **236** with 45% yield and as expected, predominantly the (*S*)-allyl alcohol (*S*)-**235** was recovered. Compound **235**, as the key intermediate in the synthesis of DNA damaging fragment of leinamycin **233** (Scheme 59) was obtained after six more different steps.[118]

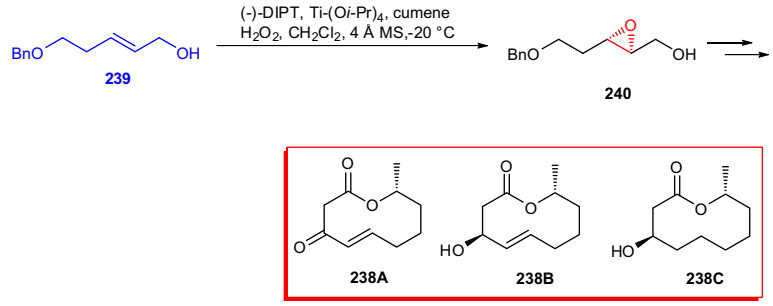
Diplodialides A–C **238 A–C**, the first 10-membered pentaketides, were isolated from the plant pathogenic fungus *Diplodia pinea* (IFO 6472) by Wada and Ishida.[119] For the synthesis of diplodialides A–C **238A–C**, Sharpless asymmetric epoxidation on allylic alcohol **239** afforded successfully the corresponding epoxy alcohol **240** with the creation of two stereogenic centers.[120] Epoxy alcohol **240** was then converted into target compounds **238A–C** through other several steps (Scheme 60).[121]

Peridinin **241** was isolated from the planktonic algae Dinoflagellates,[122] which is associated with the formation of red tides and is part of the pigment that helps photosynthesis in the sea.[12] Katsumura et al. reported the total synthesis of Peridinin **241** using vinyltriflate **242** as the starting material. Enantiomerically pure allylic alcohol **243** was prepared from readily available vinyl triflate **242**. Under Sharpless asymmetric epoxidation conditions, (−)-diethyl-D-tartrate **243** was converted into **244** in 99% chemical yield and with 92% de. The latter can be converted into the desired all-*trans*-peridinin in eighteen steps (Scheme 61).[123]

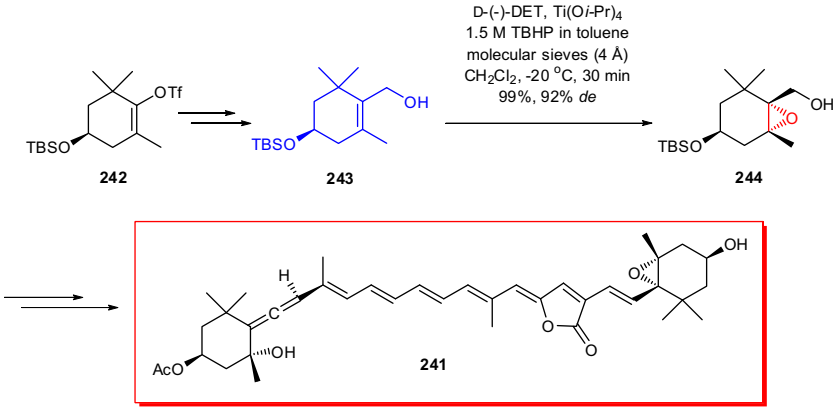
Marine microorganisms have new secondary metabolites with different chemical structures.[124] The total synthesis of Ieodomycin A **245** and B **246** was reported using geraniol **247** as the starting material, which was transformed into the corresponding allylic alcohol **248**. The latter underwent Sharpless asymmetric epoxidation strategy using (−)-DIPT to provide the corresponding



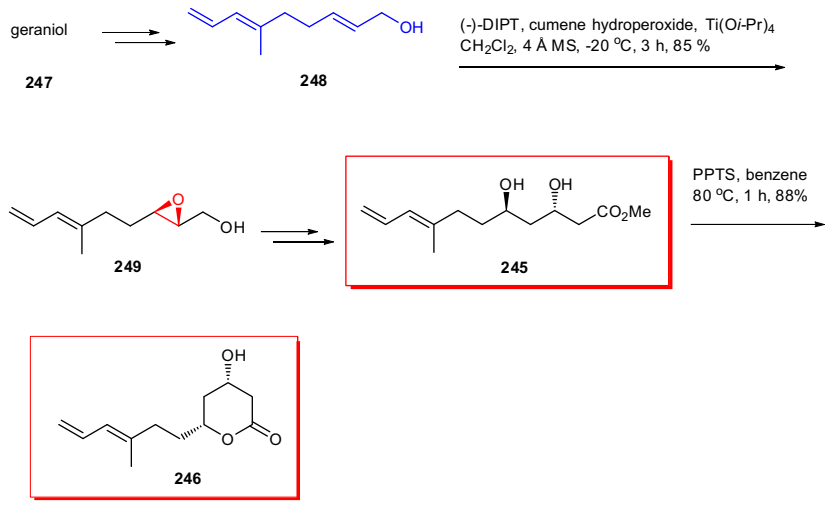
Scheme 59.



Scheme 60.



Scheme 61.

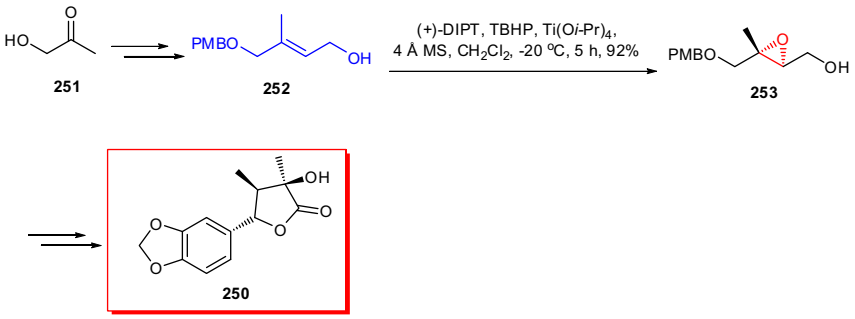


Scheme 62.

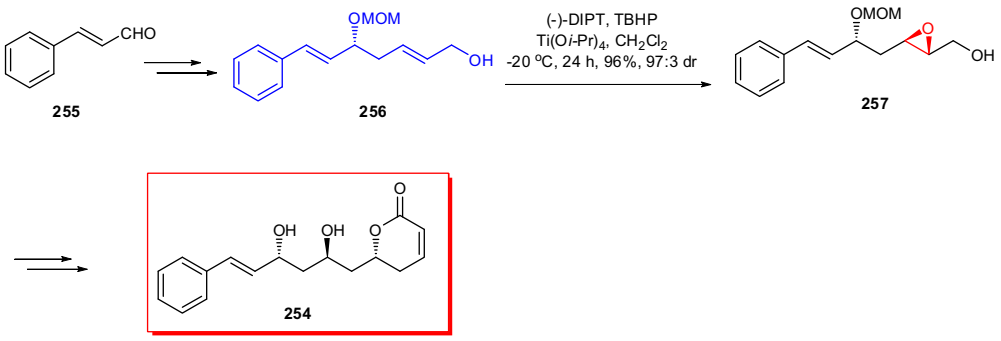
epoxy alcohol **249** in 85% yield with 93% ee. Seven other steps led to the formation of Ieodomycin A **245**. Ultimately, Ieodomycin B **246** was obtained in high yields via refluxing Ieodomycin A **245** in benzene for 1 h mediated by pyridinium-4-tolunesulfonate (PPTS) (Scheme 62).[125]

Nicotlactone A **250**, a lignan derivative was recently isolated from the leaves of Nicotiana tabaccum by Yang et al.[126] The total synthesis of nicotlactone A **250** was achieved using hydroxy acetone **251** as the starting material, which was transformed into the corresponding allylic alcohol **252**. Allylic alcohol **252** was transformed into chiral epoxy alcohol **253** upon Sharpless asymmetric epoxidation conditions in the presence of (+)-DIPT. Seven other steps led to the formation of nicotlactone A **250** (Scheme 63).[127]

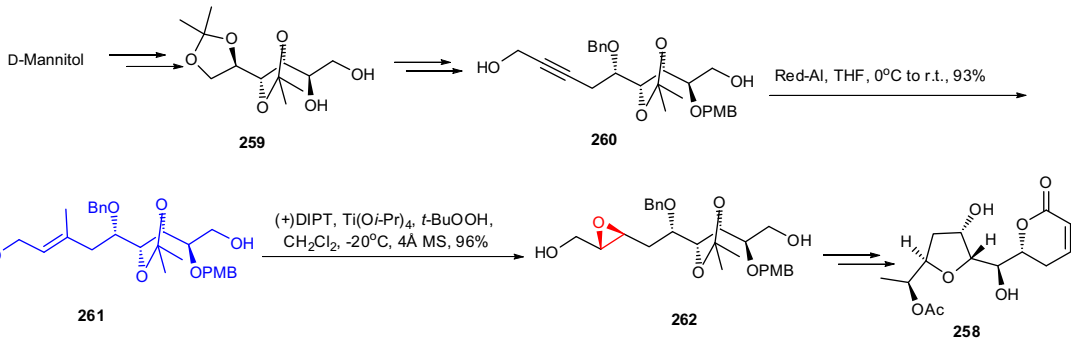
Cryptomoscatone D2 **254** was first isolated from the branch and stem bark of *Cryptocarya moschata*, Lauraceae in 2000 by Cavalheiro and Yoshida.[128] It was synthesized stereoselectively from commercially available *trans*-cinnamaldehyde **255** which was transformed into the corresponding allylic alcohol **256**. The key intermediate, epoxy alcohol **257** was obtained in excellent yields via Sharpless asymmetric epoxidation conditions, imposed to allylic alcohol **256**. Nine more steps required to produced cryptomoscatone D2 **254** from the epoxide **257** (Scheme 64).[129]



Scheme 63.



Scheme 64.



Scheme 65.

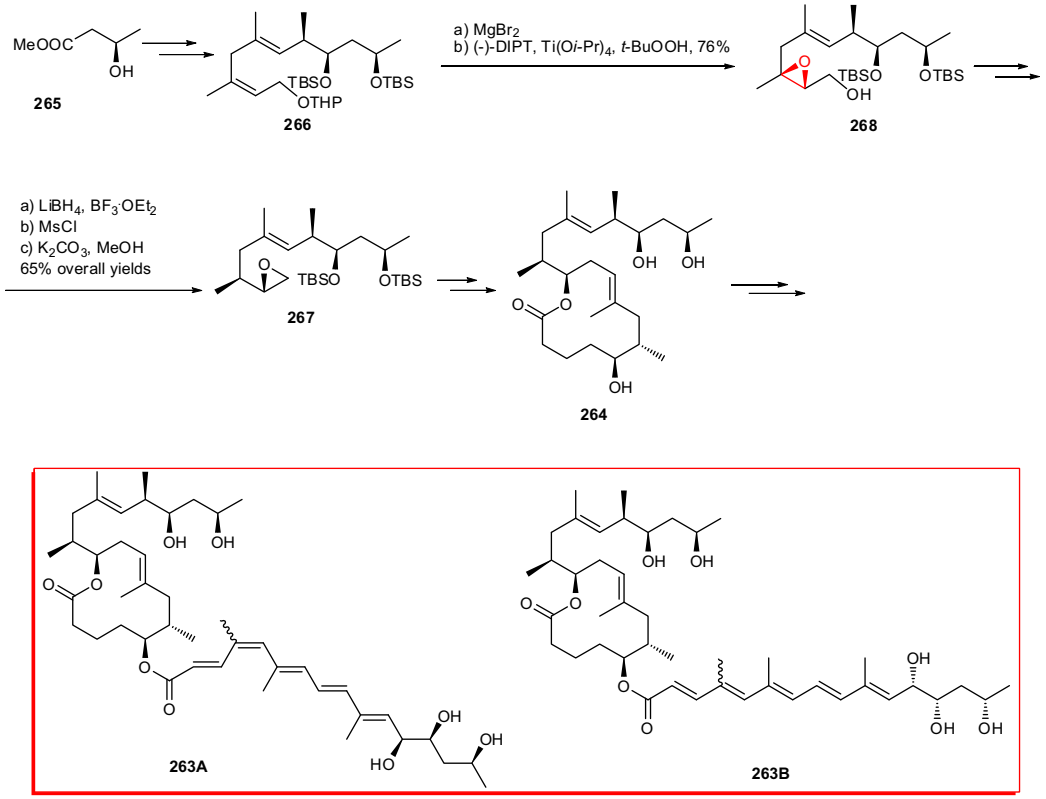
6-Substituted-5,6-dihydro-2*H*-pyran-2-ones (γ-lactone derivatives) isolated from a natural source.[130] In 1996 Rivett et al. isolated three polyhydroxy D-lactones synparvolides A–C from the leaves of *Syncolostemon parviflorus*.

Gowravaram Sabitha et al. reported the synthesis of synparvolides C **258**. The synthetic strategy commenced with diol **259**, which was easily obtained from commercially available D-mannitol. After 10 steps, alkyne **260** was obtained. The triple bond of the latter was reduced to a degree using Red-Al in THF, a selective reducing agent to give homoallylic alcohol **261**, an appropriate precursor for the Sharpless asymmetric epoxidation protocol to afford epoxy alcohol **262** in high yields. The latter was employed in the first step of 11 reactions, which were required to obtain the desired target (Scheme 65).[131]

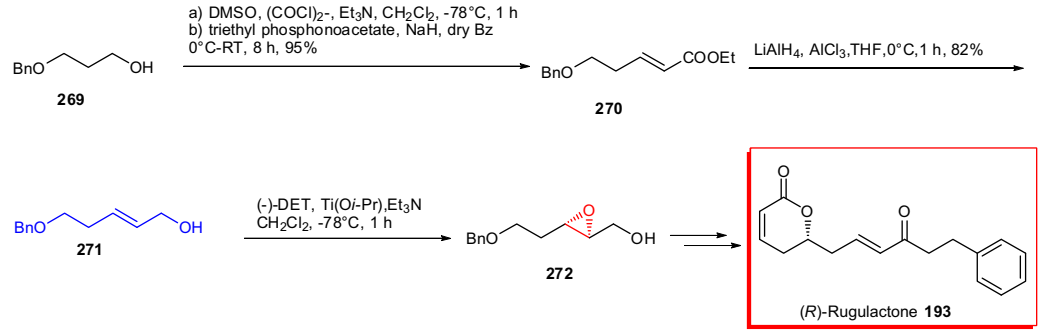
Mycobacterium ulcerans infection has been known for a long time; it was discovered by Sir Albert Cook in 1897. In spite of its early discovery, the first and isolation and determination of Buruli ulcer was not achieved until 1999.[132] Initially, a stereoisomeric mixture of mycolactones A and B was isolated from the West African strain of M. ulcerans.

Mycolactones A **263** and B **263** show high inhibition of interleukin production. Thus attempts toward their chemical synthesis are in much demand. A literature survey showed no records of the total synthesis of mycolactones A and B before 2002 when by Kishi et al. revealed this important but hampered total synthesis.[133]

For the construction of the C1–C20 core **264**, (*R*)-3-hydroxybutyric acid methyl ester **265**, a readily accessible chemical was employed as the starting material. After 6 steps, including common chemical transformations, compound **266** was obtained. In the ultimate functional alterations for transforming **265** into **266**, Sharpless asymmetric epoxidation played a key role. After THP deprotection, compound **266** underwent Sharpless asymmetric epoxidation using (−)-DIPT to provide **267** with excellent enantiomeric purity (98% pure) and good chemical (76%) yields. Subsequent treatment of **267** with $LiBH_4$ and $BF_3{\cdot}OEt_2$ and then selective monomesylation and base-induced epoxidation gave isomerically pure (98%) **268** in 65% yield over two steps. In this way, the C10–C20 segment of 98% isomeric purity was synthesized in 29% overall yield with methyl (*R*)-3-hydroxybutyrate as the starting material (Scheme 66).[134]



Scheme 66.



Scheme 67.

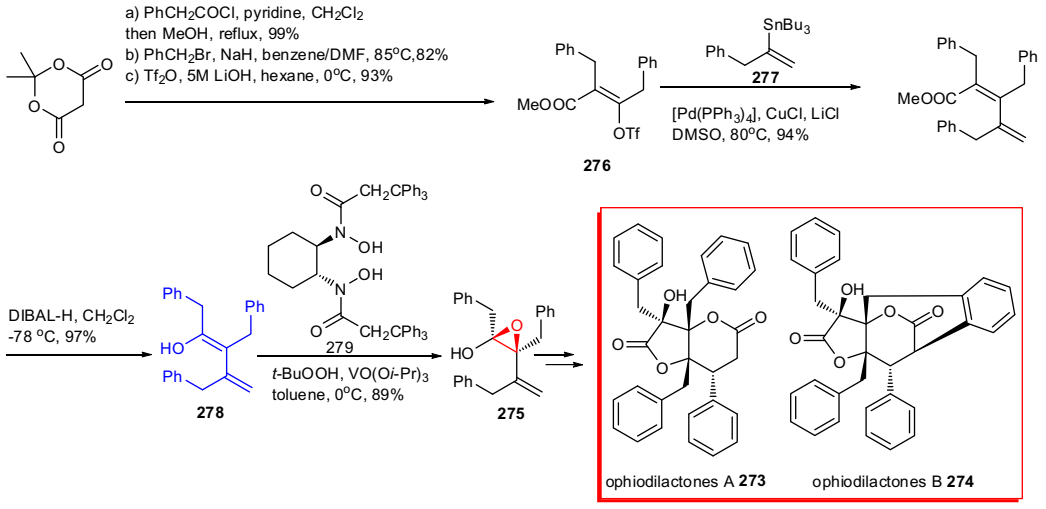
(*R*)-Rugulactone **193** has been isolated via extraction from the evergreen tree *Cryptocarya rugulosa*[135] of Lauraceae family. The synthetic protocol started from 3-benzyloxypropanol **269**. The primary alcohol of the latter initially was oxidized by Swern oxidation into the corresponding aldehyde, followed by Horner–Wadsworth–Emmons olefination of aldehyde to give α,β-unsaturated ester **270** in excellent yields. The latter was then reduced to allyl alcohol **271** via reduction using $LiCl/LiAlH_4$ conditions. Allyl alcohol **271** subsequently underwent Sharpless asymmetric epoxidation to give epoxy alcohol **272** in high yields. After 8 more steps, the target molecule was obtained (Scheme 67).[136]

The extraction and structural elucidation of ophiodilactones A **273** and B **274** from *Ophiocoma scolopendrina* was achieved by Matsunaga et al. in 2009.

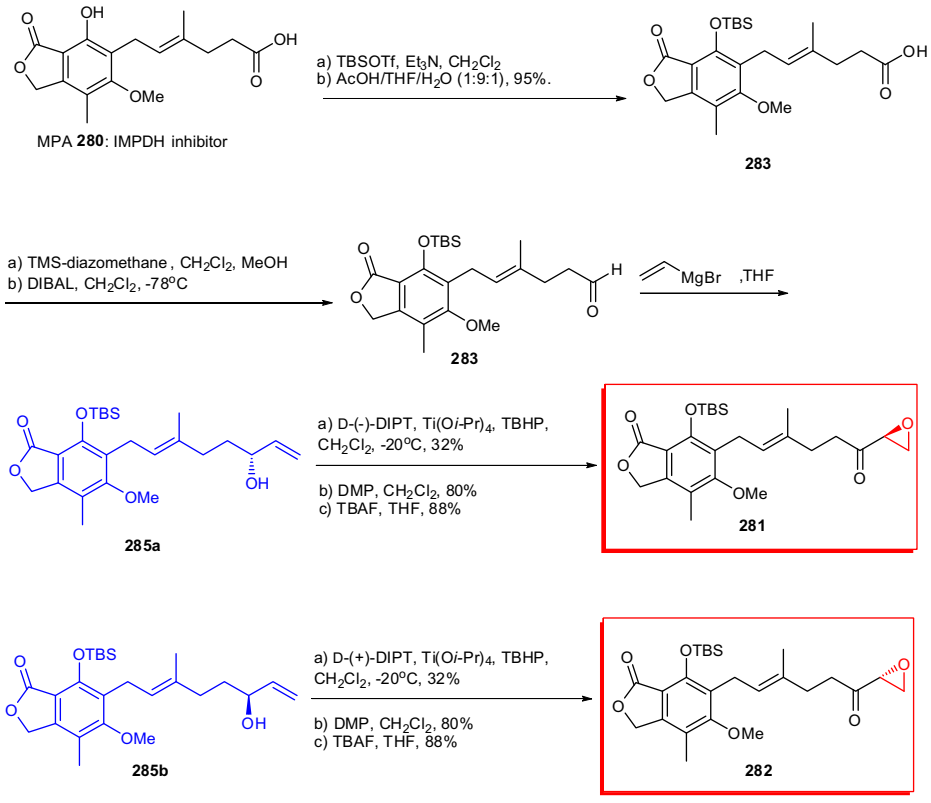
A multi-step synthesis of epoxy **275** from Meldrums acid via Stille coupling of **276** with **277** to give **278** followed by Katsuki/Sharpless asymmetric epoxidation of latter has been reported (Scheme 68). In spite of high diastereoselectivity and good overall chemical yields, its enantioselectivity was inadequately low (35% ee). Therefore, Yamamoto et al. tried to develop the strategy[137] via the synthesis of epoxy alcohol **275** with adequate enantioselectivity and yield although the reaction made progress very slowly. Compound **278** was reacted with *tert*-butyl hydroperoxide using **279** and $VO(OiPr)_3$, to afford **275** with improved 79% ee and chemical 89% yields. In light of this result, a novel total synthesis of (−)-ophiodilactone A **273** and (−)-ophiodilactone B **274** was achieved. The final product was enantiomerically pure and the overall yield in 17 steps was 14% (17 steps) whereas 18 steps were required starting from Meldrum's acid, and 10% yield was obtained (Scheme 68).[138]

Inosine-50-monophosphate dehydrogenase (IMPDH) is an enzyme which catalyzes the NAD-dependent oxidation of inosine monophosphate (IMP) to xanthosine monophosphate (XMP), the first committed and rate-determining step in guanine nucleotide biosynthesis.[139]

In 2013 Sunohara et al. achieved the total synthesis of new Mycophenolic acid **280**, terminus epoxide derivatives **281**, **282**. Initially, 7-O-TBS-mycophenolic acid **283** was synthesized upon



Scheme 68.

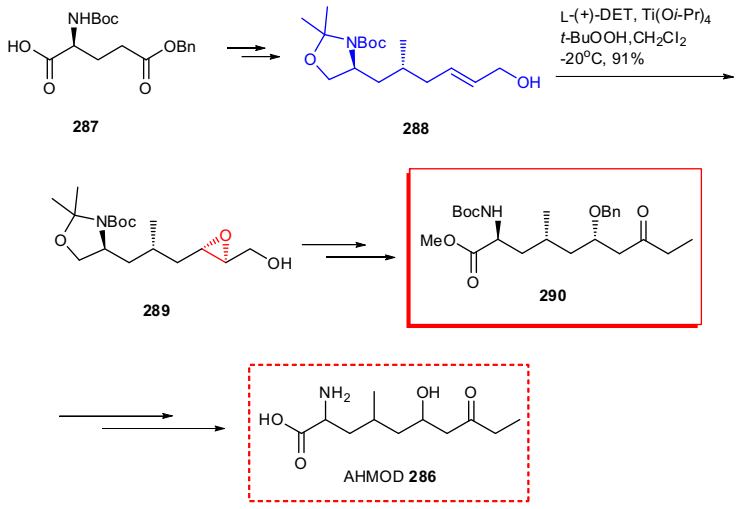


Scheme 69.

treatment of **280** with TBSOTf, with subsequent selective hydrolysis in high yields. Esterification followed by DIBAL-H under common reduction conditions gave **284**, which was transformed into racemic alcohol **285**. Kinetic resolution, that is, Sharpless asymmetric epoxidation, was employed to provide (60*R*,70*S*)-epoxy alcohol. For this purpose, precursor **283** was subjected to Sharpless asymmetric epoxidation using D-(−)-DIPT to make a chiral media. Dess–Martin oxidation was imposed to (60*R*,70*S*)-epoxy alcohol, followed by deprotection promoted by TBAF to afford the desired (70*S*)-epoxyketone **281**. After recrystallization from EtOAc/hexane a pure sample was biologically screened and evaluated. Kinetic resolution of **285b** using D-(+)-DIPT gave the other diastereomer (60*S*,70*R*) epoxy alcohol, which upon Dess–Martin oxidation followed by deprotection of the silyl group provided (70*R*)-epoxy ketone **282** which was purified by recrystallization (Scheme 69).[140]

2.3. Amino acids

More than 850 peptaibiotics have been isolated from fungi over the past few decades.[141]



Scheme 70.

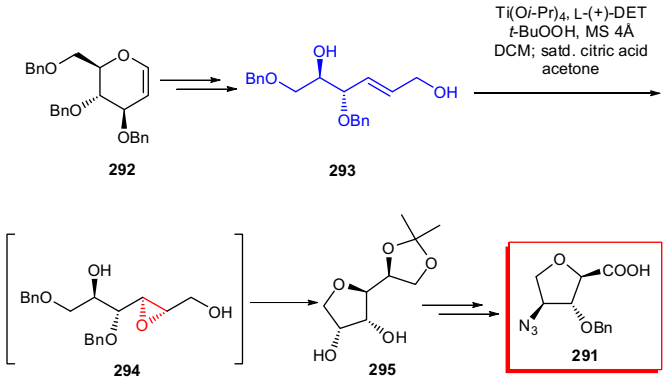
As shown in Scheme 70, the total synthesis of 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD) **286** started from an inexpensive and commercially available glutamate derivative [Boc-Glu(OBn)-OH] **287**. The latter was first converted into the corresponding allylic alcohol in several steps **288**. Allylic alcohol **288** was then subjected to Sharpless asymmetric epoxidation to give the epoxy alcohol **289** in 91% yield as a single diastereomer (confirmed by ^{1}H NMR). Then, the latter via 9 more steps led to (2*S*,4*S*,6*S*)-2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid **290**, the fully protected form of AHMOD **286** (Scheme 70).[141]

Sugar amino acids are considered as an important class of such designer templates that have attracted significant attentions in the field of peptidomimetic research. The development of these molecules as resourceful and multifunctional synthetic building blocks has been previously reviewed.[142]

Furanoid γ-sugar amino acid **291** was prepared by Shaw et al. with ring opening of glycal **292**, with subsequent reduction to afford the corresponding allylic alcohol **293**.[143]

The latter was then subjected to Sharpless asymmetric epoxidation strategy to give the corresponding epoxide **294**. This epoxide was then converted into compound **295** which upon four other reactions produced a tetrahydrofuran core γ-azido acid **291** (Scheme 71).[144]

Several important neurological disorders such as Parkinson's disease and epilepsy have been associated[145] with the deficiency of 4-aminobutanoic acid (γ-aminobutyric acid, GABA). One of the most effective and selective inhibitors of GABA-T is 4-amino-5-hexenoic acid (γ-vinyl GABA, Vigabatrin **296**).[146]



Scheme 71.

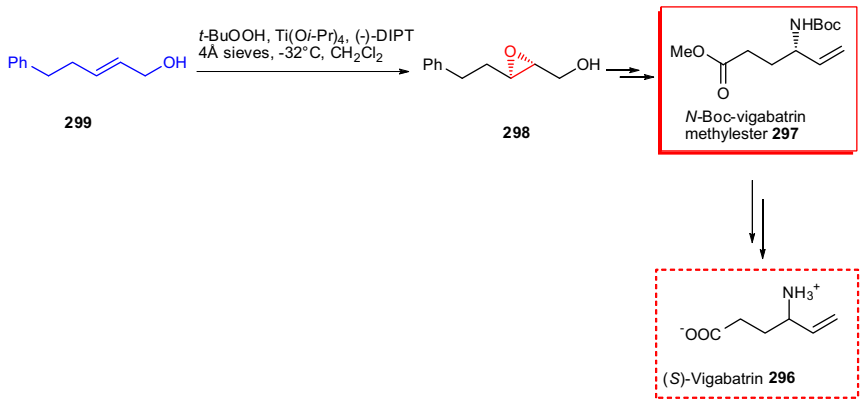
For the stereoselective synthesis of *N*-Boc-vigabatrin methyl ester **297**, (2*R*,3*R*)-5-phenyl-2,3-epoxypentanol **298** is an important building block which was obtained in 77% yield (90% ee) by Sharpless asymmetric epoxidation of the readily available 3-phenyl-2-penten-l-ol **299**. The epoxy alcohol **298** was then treated in 9 more reactions to give *N*-Boc-vigabatrin methyl ester **297**, which is a precursor for the desired Vigabatrin **296** (Scheme 72).[147]

The structural class of β-hydroxy-γ-amino acids has recently been the object of much attention, especially in connection with the development of new pharmaceutics based on protease inhibitors.[148] Statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, is an essential component of pepstatine.[149] The stereoselective synthesis of protected *cis*-γ-amino-β-hydroxy acids **300a**,**b** has been prepared by Moyano et al. using the Sharpless enantioselective epoxidation of allylic alcohols **301a**,**b** in the initial step. Thus, Sharpless enantioselective epoxidation of allylic alcohols **301a**,**b** afforded the corresponding epoxides **302a**,**b**. After eight additional steps the target amino acids **300a**,**b** were achieved (Scheme 73).[150]

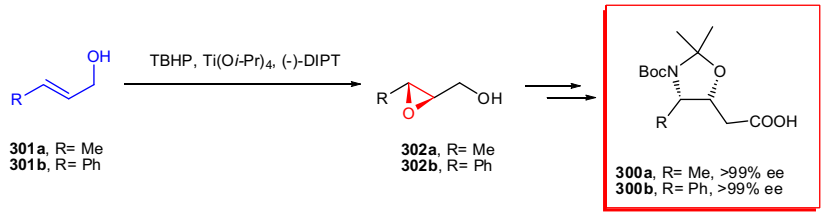
Enantioselective epoxidation of allylic alcohol **303** according to a Sharpless methodology followed by protection with 2-methoxypropene produced (2*R*,3*R*)-epoxide **304** in 77% yield. The epoxide **304** was then converted into (3*R*,4*S*)-epistatine **305** after 6 steps and in a similar way afforded (3*S*,4*S*)-statine **306** (Scheme 74).[151]

Using (*E*)-but-2-en-1-ol **301a** as the starting material, Castejon et al. also synthesized (3*R*,4*S*)-4-(*tert*-butoxycarbonylamino)-3-hydroxypentanoic acid **307** in 7 steps. The first part of this total synthesis was the Sharpless asymmetric epoxidation of but-2-en-1-ol **301a**, which led to (2*R*,3*R*)-2-hydroxymethyl-3-methyloxirane **302a**. Compound **302a** was then converted into the target amino acid **307** through 6 steps (Scheme 75).[150]

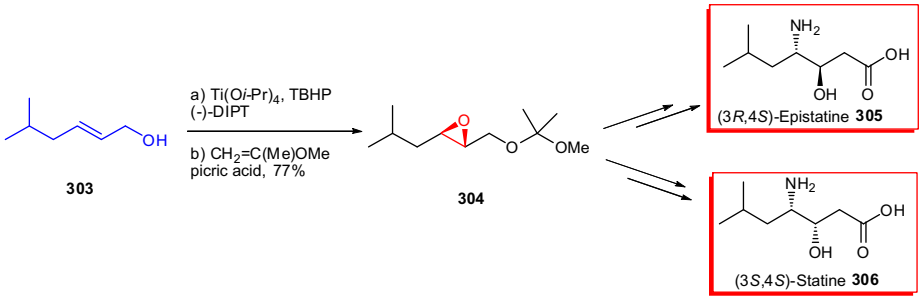
Regioselective ring opening of chiral epoxy alcohols by primary amines to in situ generated (2*R*,3*R*)-2-hydroxymethyl-3-methyloxirane **308** allowed the preparation of multigram amounts of (2*S*,3*S*)-3-benzhydrylamino-1,2-butanediol **309** with 92% enantiomeric excess. Sharpless asymmetric epoxidation of allylic alcohol **301a** using DIPT led to epoxy alcohol **308**, which then via a ring opening afforded aminodiol **308**. Benzhydrylaminodiols like **309** have proved to be valuable starting materials for the preparation of α-amino acids, β-amino acids, azetidines, aziridines and terminal aminoalkyl epoxides (Scheme 76).[152]



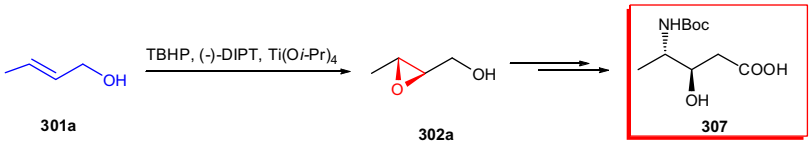
Scheme 72.



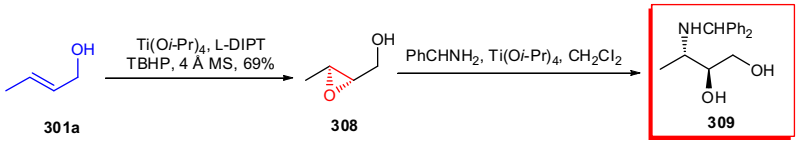
Scheme 73.



Scheme 74.



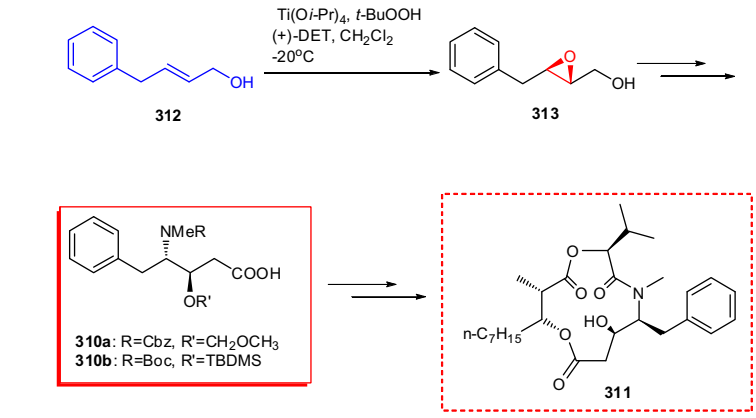
Scheme 75.



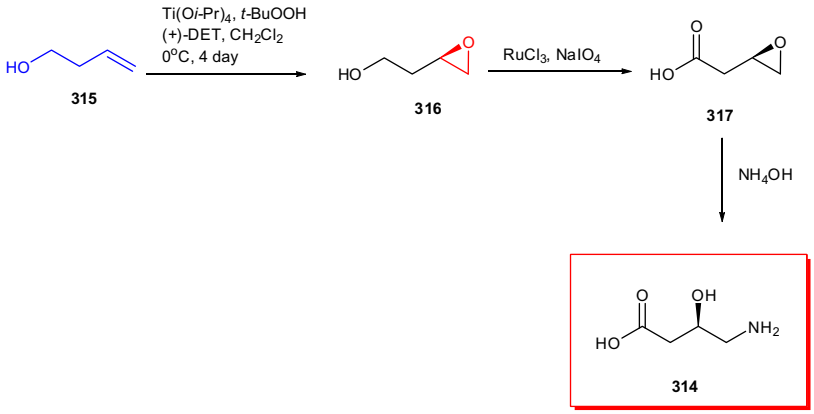
Scheme 76.

Moyano et al.[153] have reported the stereoselective synthesis of protected *N*-methyl-γ-amino-β-hydroxy acids **310a**,**b**, essential components of Hapalosin **311**, a cyclic depsipeptide isolated from the blue-green alga *Hapalosiphon welwitschii*[154] which shows a high multidrug-resistance reversal activity.[155]

The starting material for this synthesis was (*E*)-4-phenyl-2-buten-l-ol **312**, which was transformed into (2*R*,3*R*)-2,3-epoxy-4-phenyl-l-butanol **313** in good yield (88%) and in enantioenriched form (94% ee) through catalytic Sharpless asymmetric epoxidation. Continuing the procedure using epoxy alcohol **313** and after 7



Scheme 77.



Scheme 78.

more steps, led to amino acids **310a,b** which are the protected forms of a basic component of Hapalosin **311** (Scheme 77).[153]

The synthesis of (+)-γ-amino-β(*R*)-hydroxybutyric acid (GABOB) **314**, an antiepileptic and hypotensive drug, has been reported by Sharpless and Rossiter in 1984. The procedure starts with asymmetric epoxidation of homoallylic alcohol **315** using the (+)-diethyl tartrate. Epoxy alcohol **316** was obtained in 55% ee and 15-25% yield can could be readily oxidized to epoxy acid **317** which upon treatment with concentrated NH_4OH produced amino acid **314** in 66% overall yield (Scheme 78).[156]

2.4. Lipids

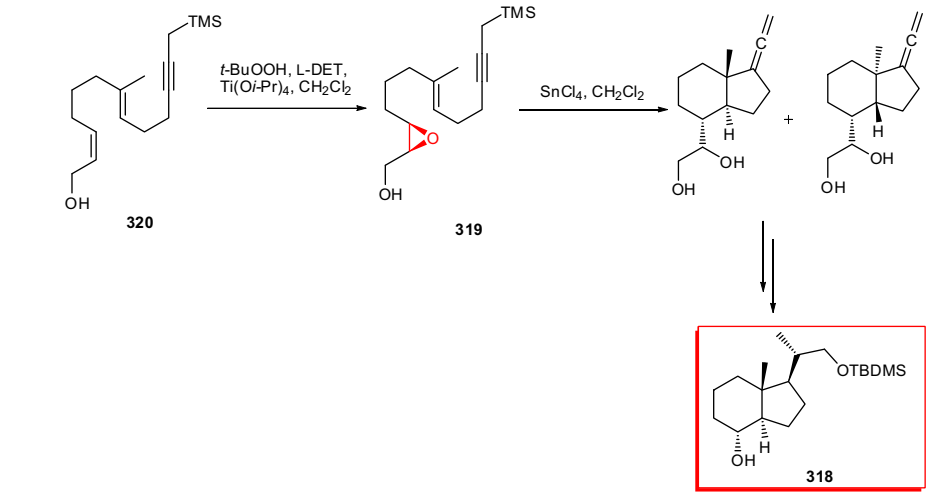
The medicinal importance of vitamin D3 metabolites such as la,25-dihydroxyvitamin D3 **318** has attracted much research attention with their partial and total synthesis.[157]

Takano et al. used a stereoselective epoxy alcohol-initiated cationic polyalkene cyclization, incited by Johnson's biomimetic approach for the synthesis of the Inhoffen–Lythgoe diol **318**. The appropriate epoxy alcohol **319** was synthesized from the corresponding acyclic allylic alcohol **320** via Sharpless asymmetric epoxidation. The subsequent intramolecular nucleophilic opening of the epoxide upon treatment with $SnCl_4$ occurred to afford the bicyclic allene diol with a *trans*-junction.[157b] Notably, cyclization of the (*Z*)-epoxy alcohol gave a higher diastereoselectivity, in comparison with that of the corresponding (*E*)-isomer. The desired hydranol **318** was obtained from **319** via manipulation of different functional group in several steps (Scheme 79).

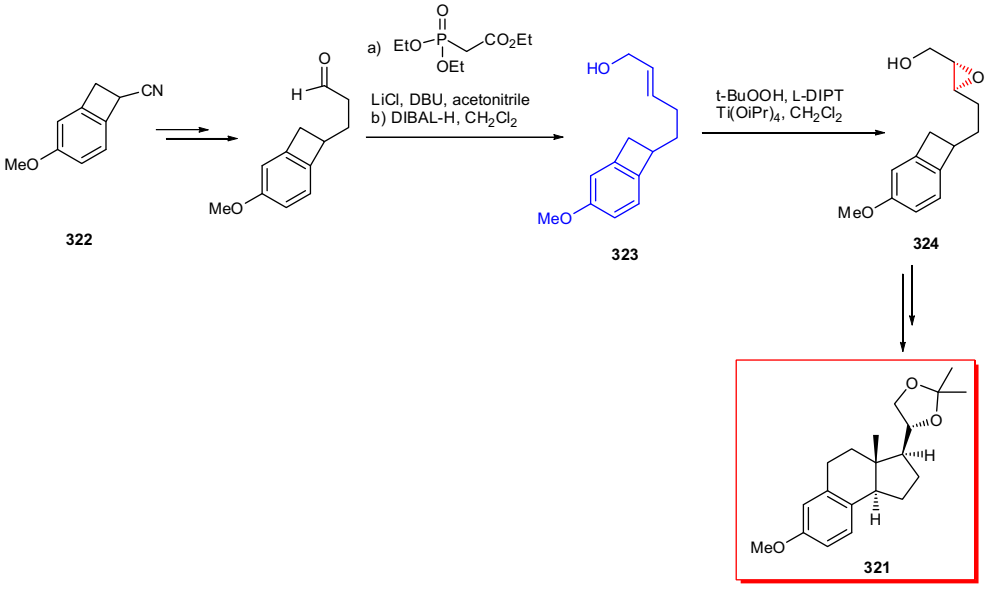
Corticosteroids and their analogues are compounds that lack the common tetracyclic steroid structure are physiologically and clinically important due to their hormonal or antihormonal potencies.[158] The synthesis of the optically active des-AB trienic steroid **321** was accomplished via thermolysis of an enantiomerically pure alkenic benzocyclobutene. Stating from 1-cyano-4-methoxybenzocyclobutene **322**, the *trans*-primary allyl alcohol **323** was synthesized. The latter was then enantioselectively epoxidized following Sharpless strategy to obtain epoxy alcohol **324**. The epoxy alcohol **324** was then converted into target compounds **321** through two more steps (Scheme 80).[159]

Vitamin D and congeners have received much attention since their discovery, due to a broad range of biological potency, being essential for body as well as growing therapeutic applications.[160] An important convergent synthesis of these compounds involves coupling of the pre-prepared ring A and the corresponding ring CD-side chain fragments.[161] Stork et al. reported the total synthesis of calcitriol **325** in 1992, which involved the coupling of the C/D *trans* indanone system with the ring-A moiety. To synthesize the C/D *trans* indanone system, they used enantiomerically pure epoxy alcohol **326**. They applied Sharpless asymmetric epoxidation to allylic alcohol **327**. The epoxy alcohol **326** then underwent several functional manipulated steps to afford the C/D *trans* indanone system which was then coupled to the ring-A moiety to produce calcitriol **325** (Scheme 81).[162]

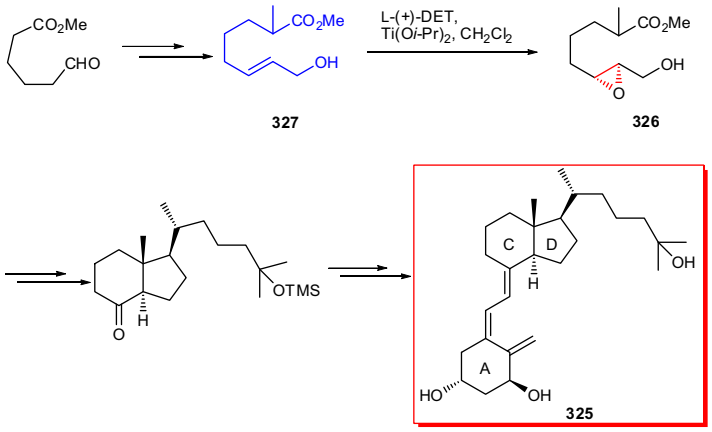
In 1998, Mikami et al. reported the asymmetric synthesis of the A-ring of the 19-nor-22-oxa vitamin D_3 analogue **328**. They employed a regioselective propiolate-ene reaction of a homoallylic



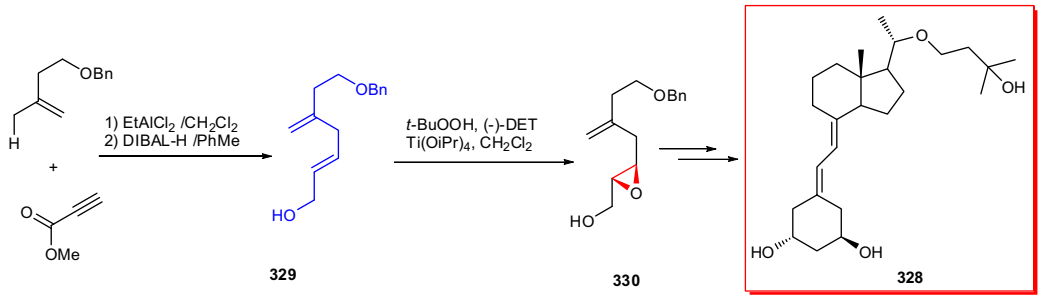
Scheme 79.



Scheme 80.



Scheme 81.



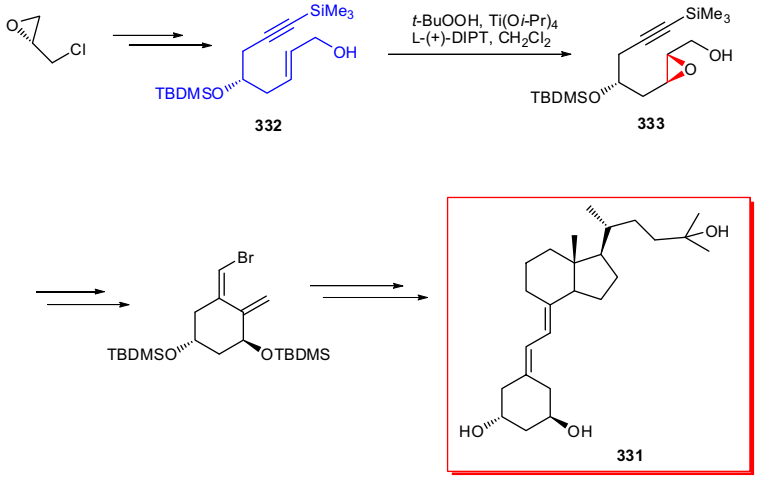
Scheme 82.

alcohol with subsequent catalytic kinetic resolution of the resulting allylic alcohol **329** as depicted in Scheme 4. The epoxy alcohol **330** was then converted into 19-nor-22-oxa vitamin D_3 **328** via several other steps (Scheme 82).[163]

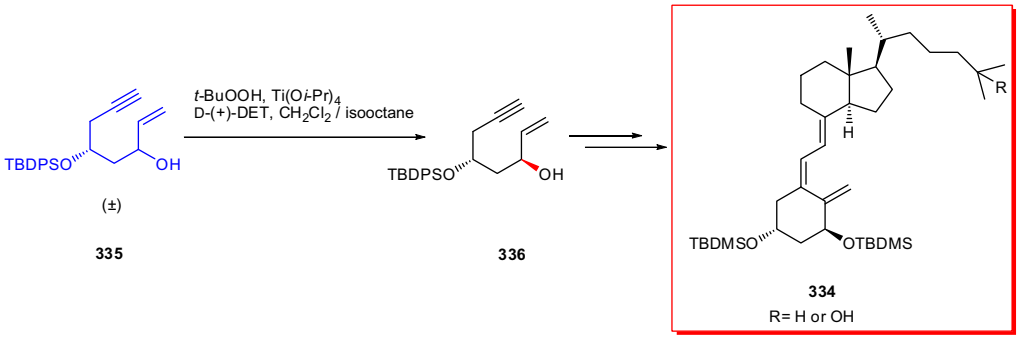
Starting from the optically active epichlorhydrin, Sato et al. synthesized the A-ring precursor of 1α,25-dihydroxyvitamin D_3 **331**. In this total synthesis the 1α-hydroxyl group was introduced in a key step via Sharpless asymmetric epoxidation on allylic alcohol **332** to provide **333**. 1α,25-dihydroxyvitamin D_3 **331** was then synthesized from epoxy alcohol **333** employing a Suzuki–Miyaura coupling strategy, between the corresponding bromodiene A-ring and alkenylboronate CD-ring segments (Scheme 83).[164]

The kinetic resolution of a racemic allylic alcohol using Sharpless asymmetric epoxidation protocol is a helpful and powerful tool to generate a desired stereogenic center.[165] Trost et al reported an original protocol to build, the A-ring and the trienic system of 1α-hydroxyvitamin D_3 **334**, simultaneously. This total synthesis utilized the Sharpless kinetic resolution of the racemic allylic alcohol **335** to achieve the enantiopure starting acyclic enyne **336** (Scheme 84). This synthesis was completed by functional group manipulation in several steps, using a palladium-catalyzed alkylative tandem carbometallation–cyclization of a protected 1,7-enynediol with an (*E*)-vinyl bromide derivative of Windaus–Grundmann as a key step (Scheme 84).[166]

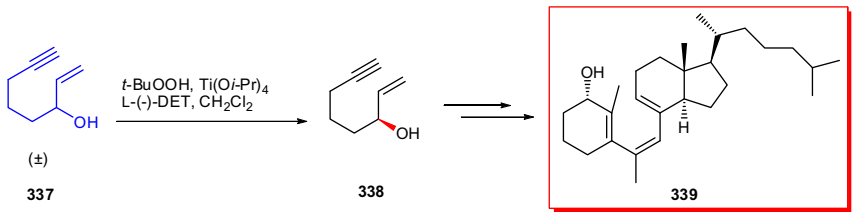
In order to synthesize 6-methyl analogues of vitamin and previtamin D, Mourino et al. used a Sharpless kinetic resolution of the racemic enynol as precursor **337**. After elimination of HI from the resulting optically active enynol **338**, a Negishi-type cross-



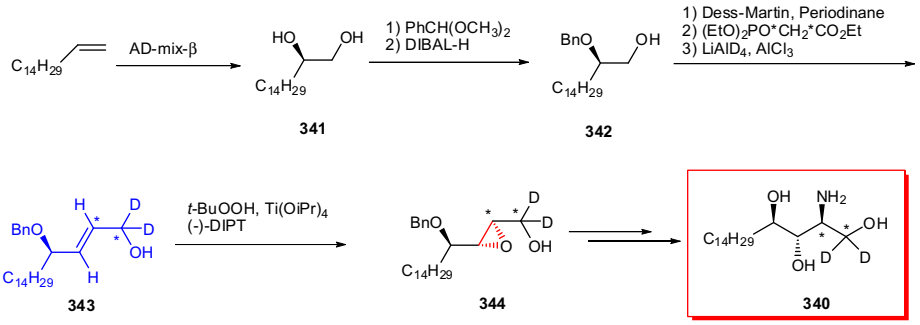
Scheme 83.



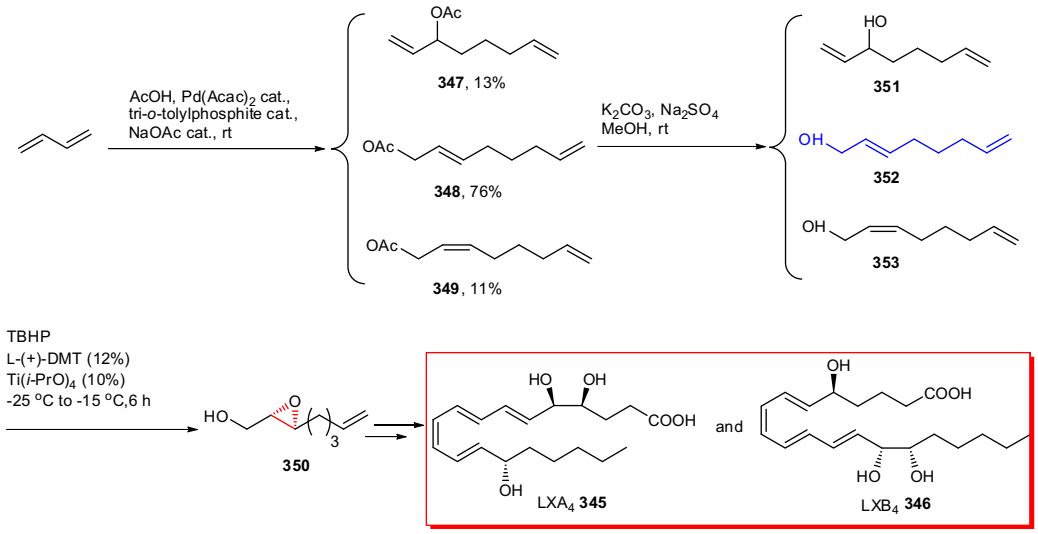
Scheme 84.



Scheme 85.



Scheme 86.

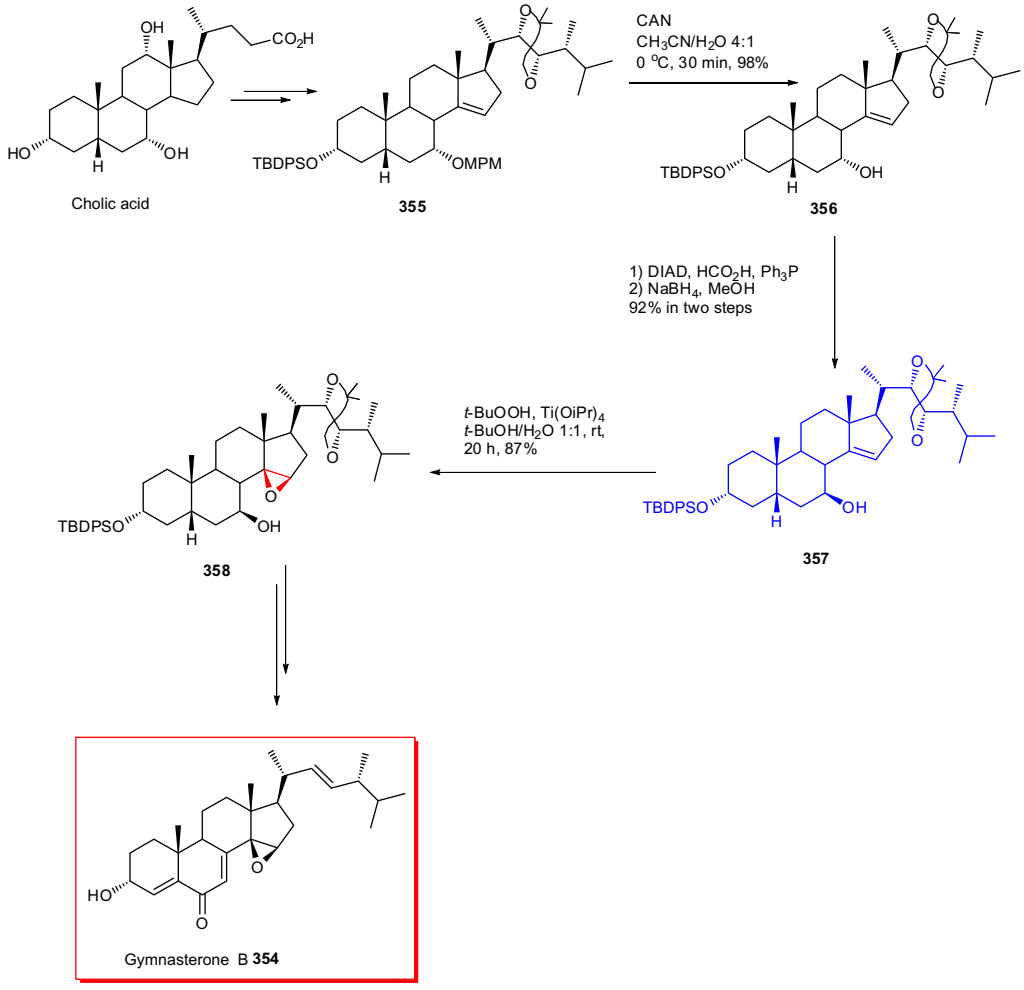


Scheme 87.

coupling of the vinyl iodide with an alkenylzinc reagent bearing the CD-ring-side chain of vitamin D_3 was performed as the key step and afforded the expected triene **339** (Scheme 85).[167]

Sphingolipids are significant structural scaffolds of eukaryotic cell membranes and their metabolites, such as phytosphingosin.[168] Wilson et al. have reported the stereoselective total synthesis of D-*ribo*-[1,1-^{2}H-1,2-^{13}C]phytosphingosine **340**. They started from the asymmetric dihydroxylation of 1-hexadecene with AD-mix-β. A 9:1 mixture of (2*R*)- and (2*S*)-diols **341** was then selectively protected as the 2-benzyl ether **342**. Mild oxidation of the latter using Dess–Martin periodinane with subsequent Horner–Emmons condensation of the product followed by reduction of the resulting α,β-unsaturated ester afforded allylic alcohol **343**. During these reactions the introduction of the isotopic labels was also completed. The two remaining stereogenic centers were generated via Sharpless asymmetric epoxidation of **343**. The resulting epoxide **344** was subjected to five more steps to obtain D-*ribo*-[1,1-^{2}H-1,2-^{13}C]phytosphingosine **340** (Scheme 86).[169]

Lipoxin A_4 **345** and lipoxin B_4 **346** are two metabolites of arachidonic acid that have a conjugated tetraene structure. Spur et al. described the total synthesis of LXA_4 and LXB_4 starting from butadiene. The compatibility of the protocol provides an easy synthesis of the linear eicosanoids. The dimerization of butadiene using acetic acid, catalyzed with $Pd(Acac)_2$ (0.2%), tri-*o*-tolylphosphite (0.2%) and NaOAc (3%) at ambient temperature afforded a mixture of the octadienol acetates **347** (13%), **348** (76%) and **349** (11%) in excellent yields upon distillation (Scheme 9). The chiral scaffold **350** was produced from a mixture of octadienols **351**, **352** and **353** via Sharpless catalytic asymmetric epoxidation, directly (60% isolated yield, 79% based on **352**). The epoxidation of the *trans*-allyl alcohol **352** was favored over the other component, *cis*-**353,** and the 3-hydroxy allyl isomer **351** under



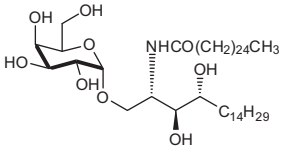
Scheme 88.

Sharpless reaction conditions. Compound **350** was converted into both LXA_4 and LXB_4 through several manipulations of different functional groups (Scheme 87).[170]

Gymnasterone B **354**, a marine natural product, has exhibited a remarkable cytotoxicity versus cultured P388 cells.[171] Li et al. accomplished a stereoselective approach toward Gymnasterone B via a multi-step reaction starting from cholic acid. First, cholic acid (No) was converted into compound **355**, which possessed the desired stereochemistry of the side chain in the target (Scheme 10). Treatment of **355** with *m*-CPBA gave the epoxidation inseparable products, 14β,15β-epoxide. Thus as an alternative, Sharpless asymmetric epoxidation was performed on **355**. However, epoxidation of **356** was unsuccessful by using either D- or L-tartrate as the ligand. Conversion of 7α-OH to 7β-OH via a Mitsunobu reaction[172] gave **357**, which upon Sharpless asymmetric epoxidation easily and smoothly, gave the desired **358** as the sole product. The latter was then transformed into Gymnasterone B **354** through several other steps (Scheme 88).[173]

The synthetic compound, α-galactosylceramide **359** (Fig. 1), is also known as KRN7000 and a-Galcer. Franck et al. synthesized the *C*-glycoside analogue of α-galactosylceramide (KRN7000) **360** in 19 linear steps, using Sharpless asymmetric epoxidation as a key step (Scheme 89).[174]

The known aldehyde **361** was obtained in five steps from commercially available β-D-galactose pentaacetate **362** according to a literature procedure.[175] Homologation of **361** via Horner–Wadsworth–Emmons reaction and DIBAL-H reduction of the

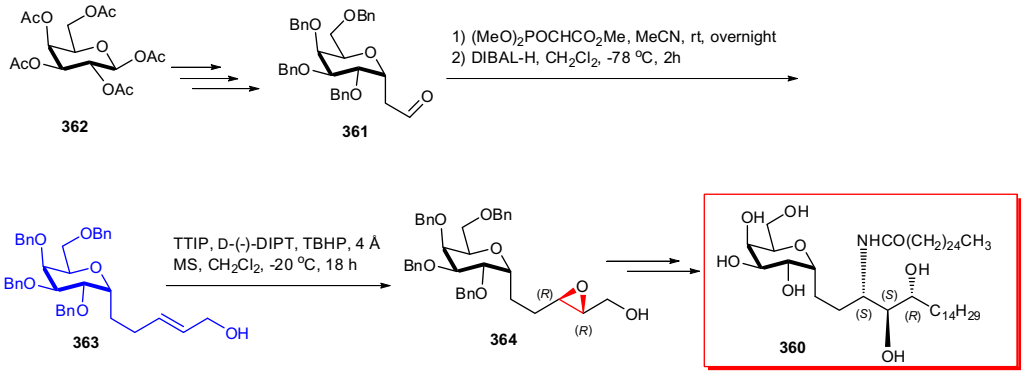


359, α-galactosylceramide
(KRN7000, α-Galcer)

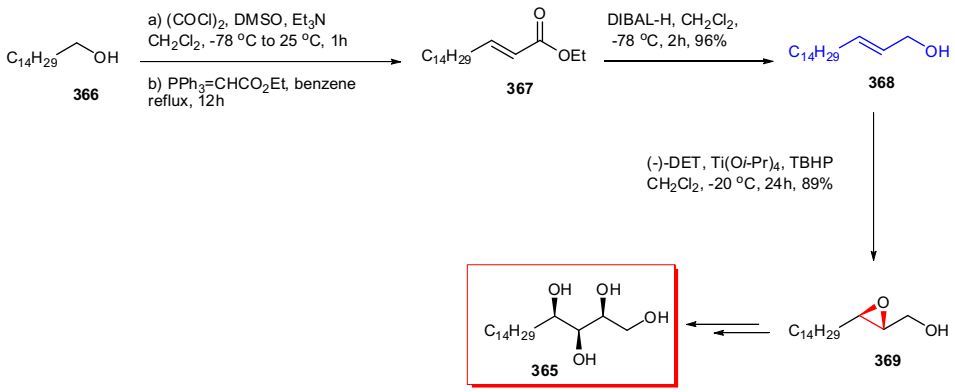
Figure 1.

resulting (*E*)-α,β-unsaturated ester gave (*E*)-allylic alcohol **363**. Sharpless asymmetric epoxidation (Sharpless asymmetric epoxidation) using a substoichiometric amount of catalysts (50 mol % TTIP, 60 mol % D-(−)-DIPT) ensured conversion of **363** to (2*R*,3*R*)-epoxy alcohol **364** with high enantiomeric excess (ee >95%). The epoxy alcohol **364** then afforded the glycoside analogue of KRN7000 **360** in several steps.[174]

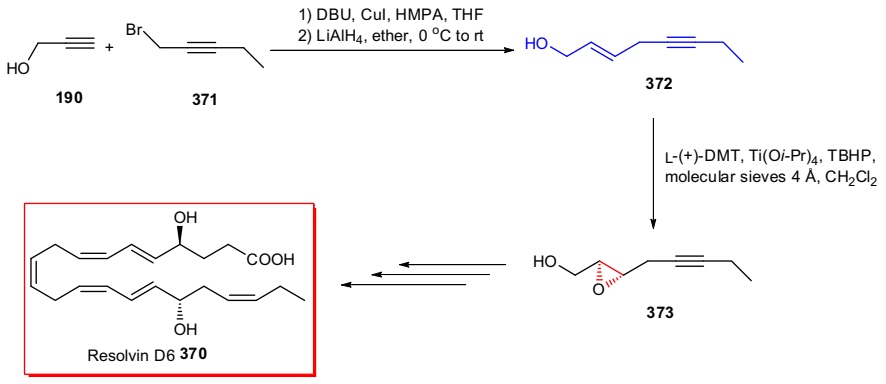
Guggultetrol **365** is a natural lipid, isolated from the gum-resin of the tree *Commiphoru mukul* (*guggul*).[176] An enantioselective total synthesis of guggultetrol **365** has been described by Sudalai et al. starting from the commercially or easily synthesized 1-pentadecanol **366** with an overall yield of 24.1%, employing Sharpless asymmetric epoxidation (Scheme 12). The oxidation of alcohol **366** upon Swern oxidation with subsequent Wittig olefination of the resulting aldehyde afforded (*E*)-α,β-unsaturated ester **367** in



Scheme 89.



Scheme 90.



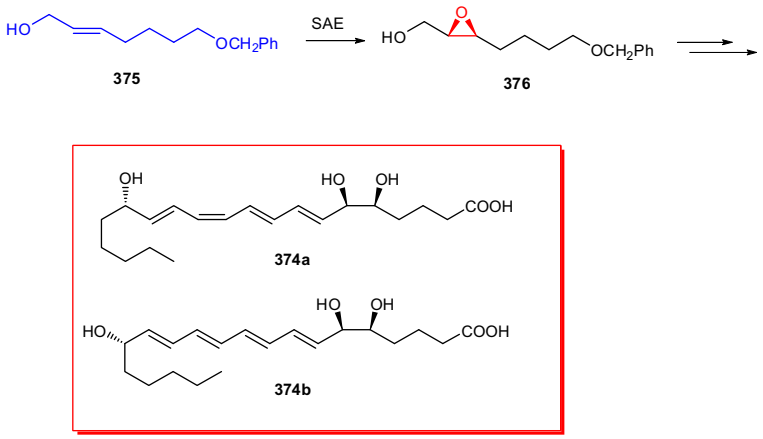
Scheme 91.

excellent yields. The latter was then subjected to reduction using DIBAL-H in CH_2Cl_2 to afford the corresponding allylic alcohol **368** in excellent yields. The latter, upon epoxidation via Sharpless strategy using (−)-diethyl tartrate [(−)-DET], Ti(O-*i*-Pr)$_4$, and anhydrous TBHP as the oxidant afforded the corresponding chiral epoxy alcohol **369** in high yields and with excellent 98% ee. The epoxy alcohol **369** was then converted into guggultetrol **365** through epoxide ring opening and other functional group manipulations (Scheme 90).[177]

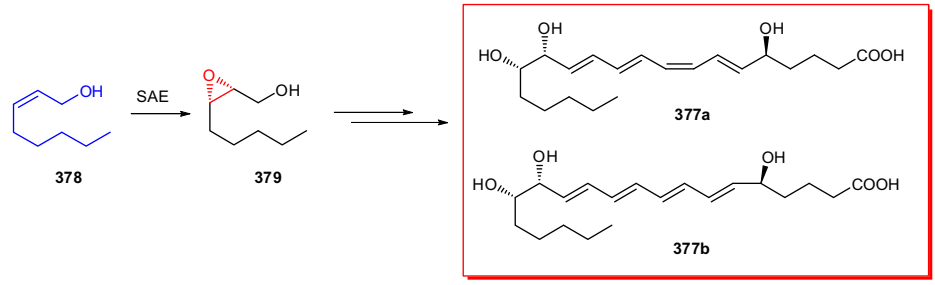
Resolvins are powerful and potent anti-inflammatory and immunoregulatory lipid mediators.[178] To obtain Resolvin D6 **370**, propargyl alcohol **190** and 1-bromo-2-pentyne **371** were treated with CuI, DBU and HMPA in THF.[179] The product was selectively reduced with $LiAlH_4$ in ether to obtain (*E*)-2-octen-5-yn-1-ol **372** in high yields. Sharpless catalytic asymmetric epoxidation of **372** afforded the corresponding epoxy alcohol **373**, which was then converted into Resolvin D6 **370** through a multi-step reaction (Scheme 91).[180]

The lipoxins (LX) show an excellent range of biological activities. The formation of lipoxins has been found to be associated with bronchoalveolar lavage fluids.[181] The total synthesis of (5*S*,6*R*,15*S*) lipoxin A **374a** and its all-*trans* isomer **374b** has been reported, starting from allylic alcohol **375**, which was subjected to Sharpless asymmetric epoxidation to give epoxide **376**. The latter was transformed into the desired natural product **374a** and **374b** in fifteen consecutive steps (Scheme 92).[182]

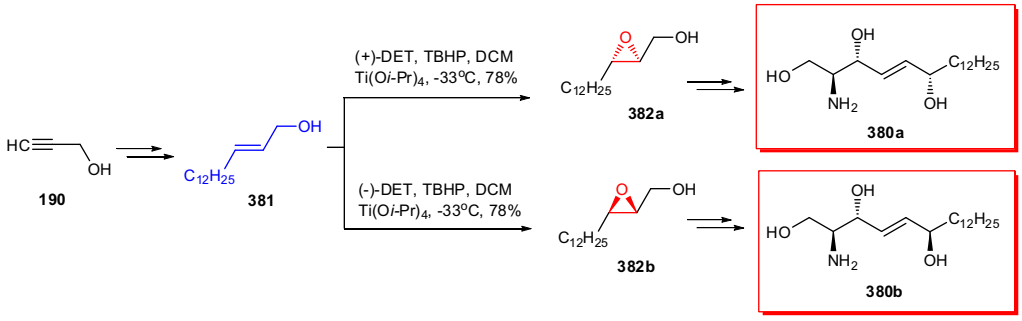
Lipoxin B_4 **377a** and 8-*trans*-LXB_4 **377b** were synthesized starting from allylic alcohol **378**, which was submitted to Sharpless



Scheme 92.



Scheme 93.



Scheme 94.

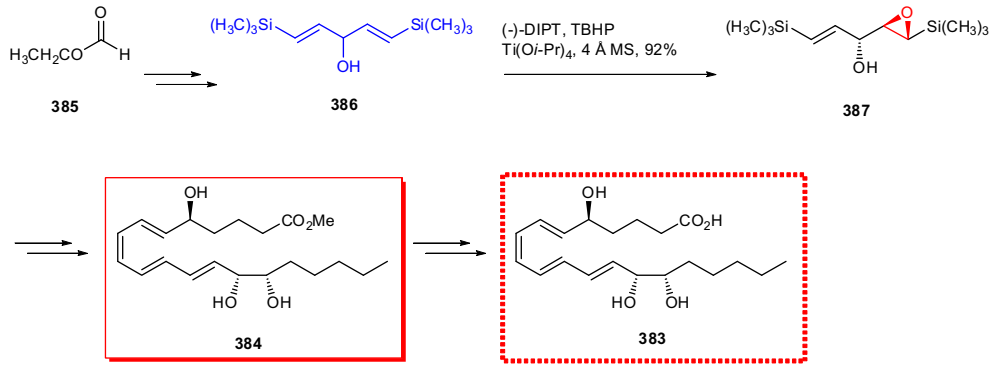
asymmetric epoxidation protocol to give epoxide **379**. Twelve more steps are required to achieve target **377a**,**b** (Scheme 93).[183]

Ceramides are in the class of sphingolipids, which comprise a wide range of biologically active compounds. The total synthesis of 6-hydroxy-4*E*-sphingenines **380a** and **380b** used commercially available propargyl alcohol **190** as a starting material. The latter was converted into the *E*-allyl alcohol **381**, which underwent Sharpless asymmetric epoxidation protocol in the presence of both (+)-DET and (−)-DET to produce the corresponding epoxy alcohols **382a** and **382b**, respectively. The corresponding epoxy alcohols **382a** and **382b** were converted in six steps into 6-hydroxy-4*E*-sphingenines **380a** and **380b**, respectively (Scheme 94).[184]

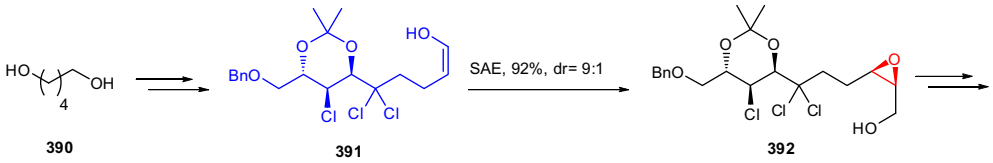
Lipoxin B **383** is a member of a group of linear oxygenated metabolites of arachidonic acid.[185] The important synthesis of Nicolaou's lipoxin B intermediate **384** was reported by Nicolaou using ethyl formate **385** as the starting material, which was converted into 1,5-bis(trimethylsilyl)-1,4-pentadien-3-0l **386**. Under Sharpless asymmetric epoxidation conditions the latter provided epoxide **387** in 92% yield. Nine other steps manipulating different functional group transformations, led to the formation of intermediate **384** (Scheme 95).[186]

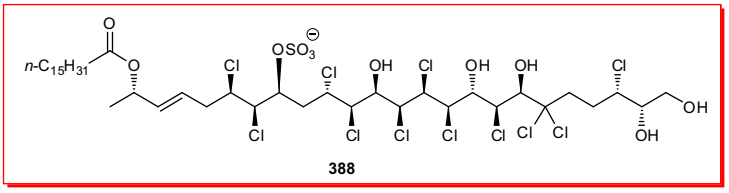
Chlorosulfolipids (CSLs), first isolated in 1962 from *Ochromonas danica* by Haines et al., include mytilipin B **388** and danicalipin A **389**.[187] The total synthesis of mytilipin B **388** was accomplished using 1,5-pentanediol **390** as the starting material. The latter was transformed into the respective allylic alcohol **391**. The latter in turn was subjected to Sharpless asymmetric epoxidation conditions to give the respective epoxide **392** which in fourteen steps was transformed into the desired compound **388** (Scheme 96).[188]

The total synthesis of danicalipin A **389** was achieved starting from readily available (*Z*)-2-nonene-1-ol **393**. This was initially transformed into epoxy alcohol **394** through Sharpless asymmetric epoxidation conditions using an appropriate DIT. Thirteen steps gave the desired compound **389** (Scheme 97).[188b,189]

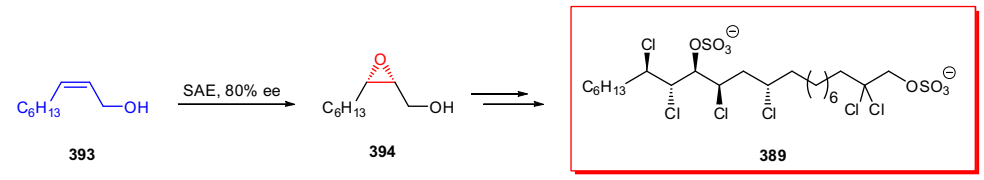


Scheme 95.

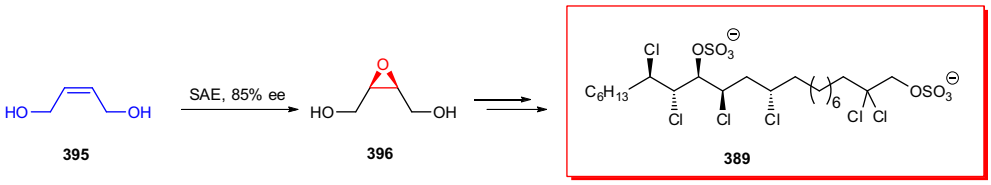




Scheme 96.



Scheme 97.

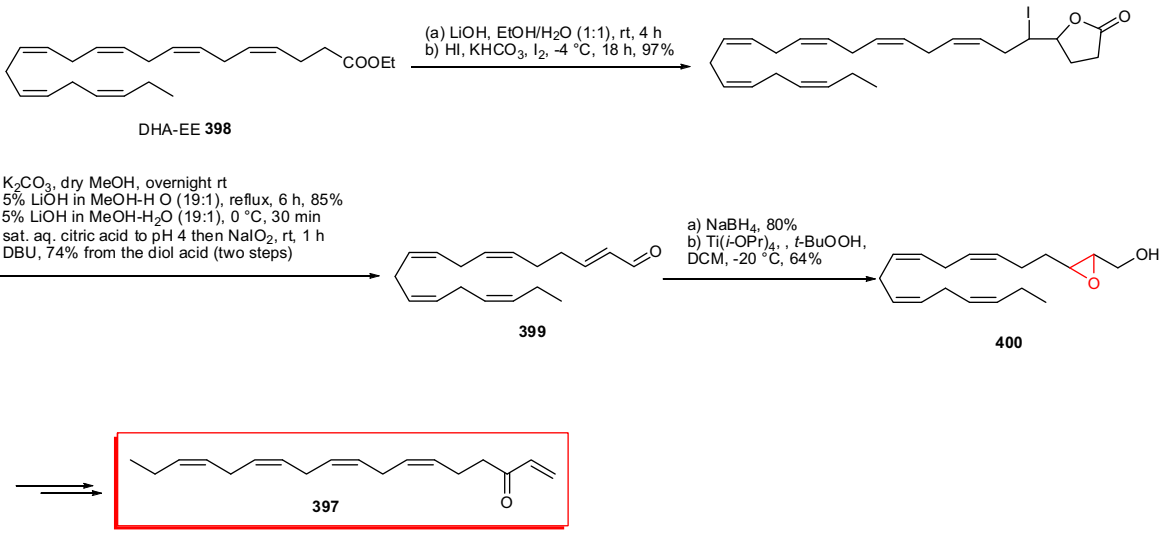


Scheme 98.

Another total synthesis of danicalipin A **389** was reported using (*Z*)-2-butene-1,4-diol **395** as the starting material, which was transformed into the epoxy alcohol **396** through Sharpless asymmetric epoxidation conditions using an appropriate DET to induce the desired stereoselectivity to **396**. Eighteen more steps gave the desired compound **389** (Scheme 98).[188b,190]

Polyunsaturated lipids have been of interest since several of them have been isolated and characterized as secondary metabolites from marine sources, over the years.[191] Many of them show significant biological activities and have attracted much attention for total synthesis. Among them, (6*Z*,9*Z*,12*Z*,15*Z*)-octadecapentaen-3-one **397** was isolated from an Australian marine sponge Callyspongia sp by Urban and Capon.[192]

The total synthesis began from DHA **398** by employing a modified iodolactonization/oxidative cleavage, with subsequent DBU-induced isomerization of the β,γ-double bond, and gave conjugated aldehyde **399** in good overall yields. The corresponding alcohol obtained from compound **399** was subjected to Sharpless asymmetric epoxidation to provide **400**. Protection of the latter, epoxide ring opening and several functional group manipulations were successfully attempted to achieve the fruitful total synthesis of (6*Z*,9*Z*,12*Z*,15*Z*)-octadecapentaen-3-one **397** (Scheme 99).[193]

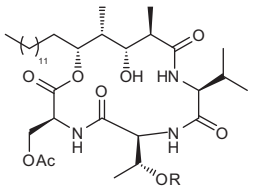


Scheme 99.

2.5. Lactam

Stevastelins **401a,b** (Fig. 2), which were first isolated from the culture broths of *Penicillium* sp. NK374186,[194] include a family of [13]- and [15]-membered cyclic depsipeptides with significant immunosuppressive pontensy.[195]

A synthetic pathway to the epoxy analogue of stevastelin B **402** was achieved by Sarabia et al. using the macrolactamization route as the key step.[196] The synthesis began with the reaction of aldehyde **403**[197] with methyl (triphenylphosphoranylidene)acetate



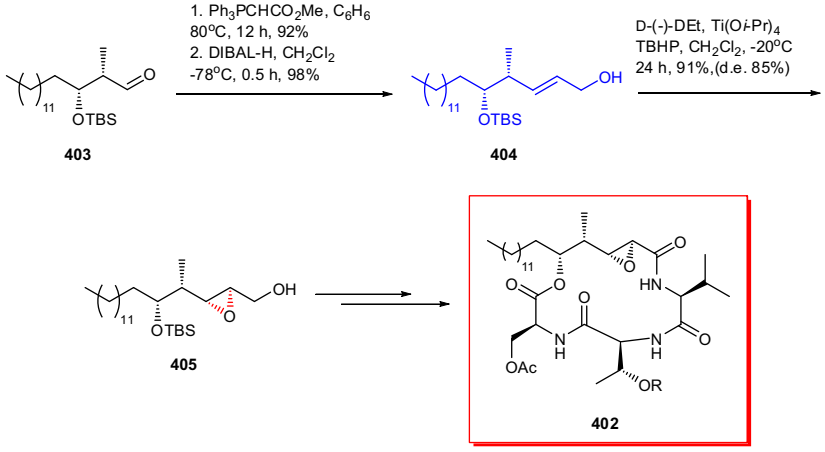
Stevastelin A **401a**: R= SO_3H
Stevastelin B **401b**: R= H

Figure 2.

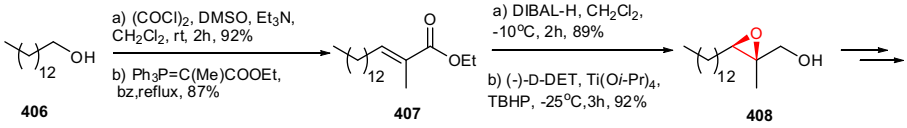
followed by reduction with DIBAL-H to give the *E*-allyl alcohol **404**. Asymmetric Sharpless asymmetric epoxidation of **404** using (−)-DET provided epoxide alcohol **405** in very good yield (91%) but with a moderate diastereomeric excess of 85%. Employing ten other functional group manipulations produced the epoxy analogue of stevastelin B **402** from epoxy alcohol **405** (Scheme 100).[196]

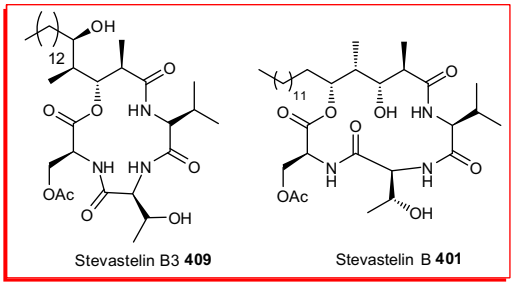
Another successful endeavor for the formal total synthesis of stevastelins was reported by Jhillu et al. very recently, in 2014. In this total synthesis commercially available tetradecan-1-ol **406** was transformed into epoxy alcohol **407**. Upon initial Swern oxidation followed by C2-Wittig reaction, **406** was converted into α,β-unsaturated ester **408**. Under reduction conditions using DIBAL-H, followed by Sharpless asymmetric epoxidation **408** was transformed into **407**. The latter was subjected to several different reactions to afford stevastelins B **401** and B3 **409** (Scheme 101).[127]

(20*S*)-Camptothecin **410** (Fig. 3) is an important moiety of an established class of anticancer agents. In 1997, Lavergn et al. reported a semi-synthetic pathway for the total synthesis of racemic homocamptothecin **411** (Fig. 3) from camptothecin **410**. They also reported that this *E*-ring expanded analogue was more active than camptothecin in a number of different of assays.[198] On the other hand, the synthesis of a diverse assortment of 7-silylcamptothecins (or silatecans) **412** (Fig. 3) was also carried out[199] and



Scheme 100.





Scheme 101.

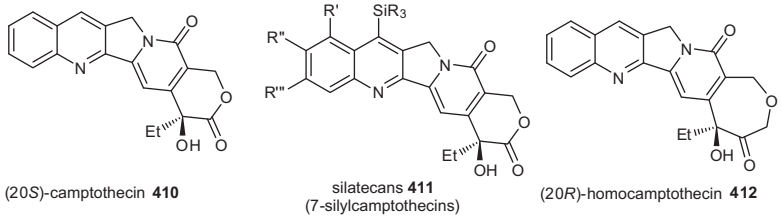


Figure 3.

some of them were appropriate candidates in cancer chemotherapy.[200]

To develop this area, Curran et al. attempted the asymmetric synthesis of (20*R*)-homocamptothecin **412** and a number of known and new homosilatecan analogues **413a–e**. The synthesis commenced from iodoformyl pyridine **414**, which in four subsequent reactions led to the formation of (*E*)-allylic alcohol **415**. In continuation, the (*E*)-allylic alcohol **415** submitted to Sharpless asymmetric epoxidation to afford *trans*-epoxide **416** in high yields and excellent ee. The *trans*-epoxide **416** was used as a key intermediate to prepare (20*R*)-homocamptothecin **412** and homosilatecan analogues **413a–e** in eight and nine steps, respectively, (Scheme 102).[201]

One of the first members of the isolated oxazolomycin natural product family is neooxazolomycin **417**. It was isolated in 1985 from strains of *Streptomyces* and characterized by Uemura et al.[202]

In 2011, the first total synthesis of neooxazolomycin **417** was reported by Taylor et al. The (*E*)-tri-substituted alkene **418**, which is readily synthesized in two-steps from (trimethylsilyl)propargyl alcohol,[203] was used as the starting material. Sharpless asymmetric epoxidation of alkene **418** using (+)-DIPT, produced epoxide **419** in high yields and excellent er. Twenty more steps led to intermediate **420**[204] which could be transformed into the desired neooxazolomycin **417**[205] through two further steps (Scheme 103).

Lactacystin **421** is an important biologically well-established pyrrolidinone-based secondary metabolite which was isolated from the culture broth of *Streptomyces* sp. OM-6519.[206] This compound showed remarkable neurotrophic activity due to its potency to inhibit mammalian 20S proteasomes[207] which have led to assumption that lactacystin may have a remedial use in the treatment of incapacitating conditions such as arthritis, asthma, and Alzheimer's disease.[208] Thus, lactacystin has become a target for synthetic organic chemists.

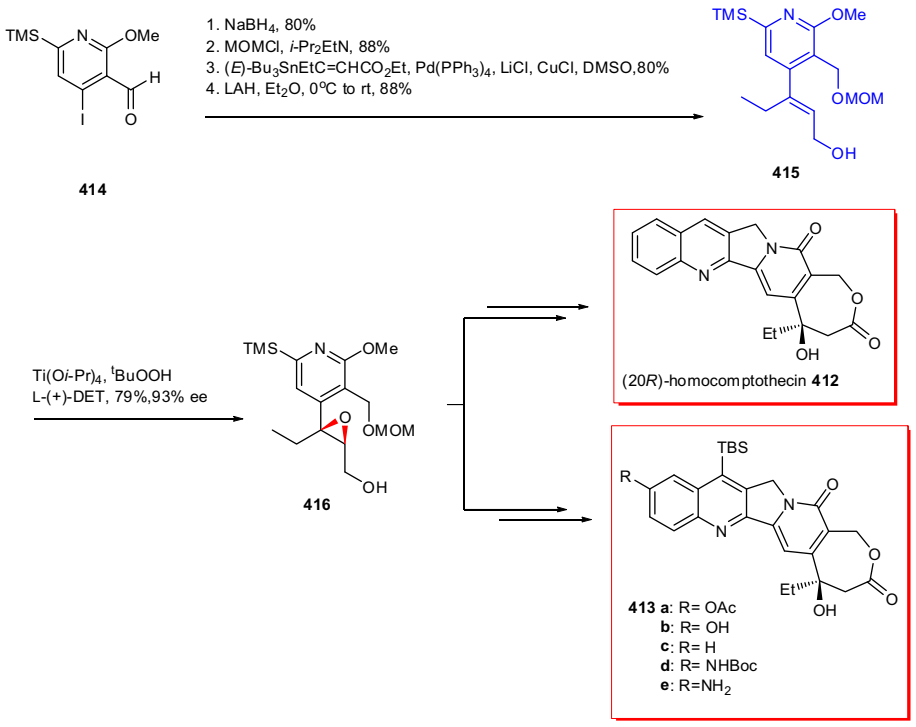
Pattenden et al. reported a synthetic pathway to lactacystin **421** based on a 5-*exo*-dig radical cyclization of a chiral ethynyl substituted serine derivative. In the first step of this multi-step synthetic approach, a Sharpless asymmetric epoxidation of the 2-ethynylpropenol **422** employing (+)-DIPT afforded the chiral epoxide **423** (66% and 90% ee), which was then transformed into pyrrolidinone derivative **424s**, a crucial intermediate in total synthesis of (+)-lactacystin **421**, through fourteen steps. Finally, lactacystin **421** was synthesized from pyrrolidinone **424** via seven further reactions (Scheme 104).[209]

Macbecin I **415** is a recently established antitumour antibiotic which was isolated from the fermentation broth of *Nocardia* sp. (No. C-14919).[210] Baker et al. reported their protocol for the first total asymmetric synthesis of (+)-macbecin I, in 1990.[211]

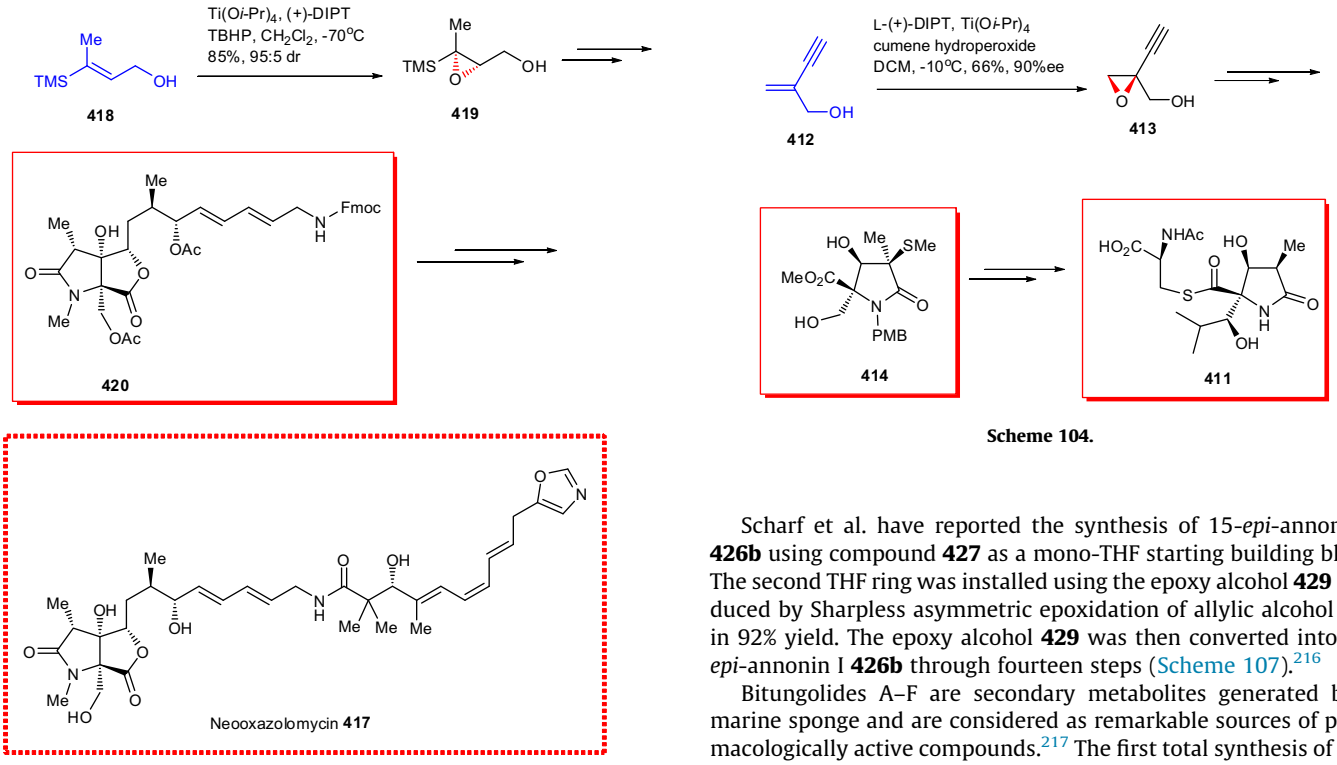
The starting materials for this strategy were diethyl methylmalonate **416** and *p*-methoxyphenol **417**, which were converted into propionyloxazolidinone **418** and 2,5-dimethoxy-3-nitrobenzaldehyde **419**, respectively, via multi-step synthesis. These compounds were used to prepare the secondary (*E*)-allylic alcohol **420**, which is a suitable precursor for Sharpless asymmetric epoxidation, using (+)-DIPT to afford the epoxide **421** in 96% yield and 95:5 diastereomeric ratio. Finally, macbecin I **415** was prepared from epoxide **421** through twenty one steps (Scheme 105).[211]

The Isobe synthesis is another approach toward the total synthesis of maytansinoid **422** which takes advantage of the Sharpless asymmetric epoxidation strategy. Isobe et al. used a chiral carbohydrate precursor, D-mannose **423** to prepare the allylic alcohol **424**. Sharpless asymmetric epoxidation of the latter gave epoxide **425** in 70% yield. Epoxide **425** was subjected to eleven further reactions to produce the desired maytansinoid **422** (Scheme 106).[212]

The annonaceous acetogenins of polyketide origin have shown a wide range of biological and pharmacological activities such as



Scheme 102.



Scheme 103.

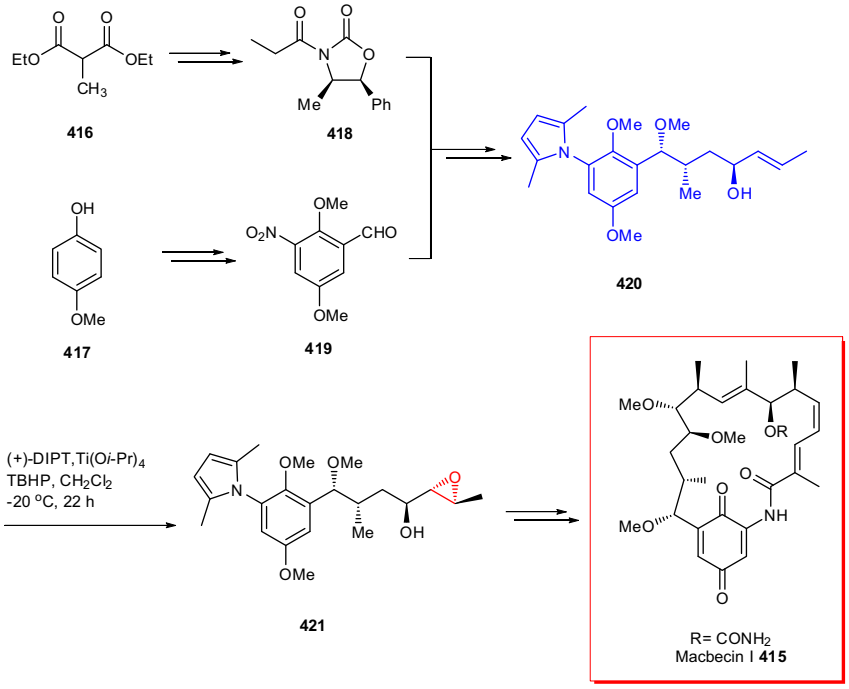
Scheme 104.

cytotoxic, antitumor, fungicidal, pesticidal, and insecticidal properties[213] and have also shown effective inhibition of mitochondrial NADH-ubiquinone reductase.[214] Annonin I **426a** (Fig. 4) belongs to the Annonaceous acetogenin family and has been found to possess cytotoxic and insecticidal effects.[215]

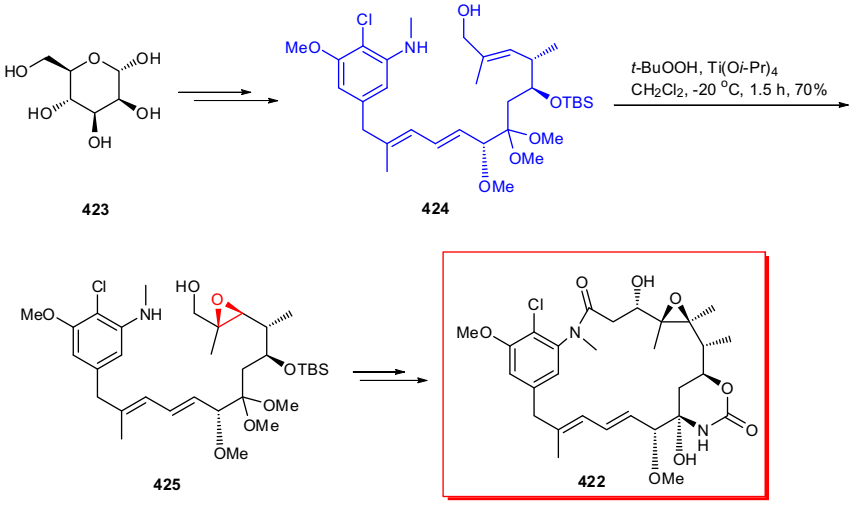
Scharf et al. have reported the synthesis of 15-*epi*-annonin I **426b** using compound **427** as a mono-THF starting building block. The second THF ring was installed using the epoxy alcohol **429** produced by Sharpless asymmetric epoxidation of allylic alcohol **428** in 92% yield. The epoxy alcohol **429** was then converted into 15-*epi*-annonin I **426b** through fourteen steps (Scheme 107).[216]

Bitungolides A–F are secondary metabolites generated by a marine sponge and are considered as remarkable sources of pharmacologically active compounds.[217] The first total synthesis of (−)-bitungolide E **430** was reported by Ghosh et al. using Sharpless asymmetric epoxidation as the key step. The synthesis started from (−)-(*R*)-Roche ester **431**, which was transformed into allylic alcohol **432**. The latter was subjected to Sharpless asymmetric epoxidation, giving epoxy alcohol **433**. The latter was transformed into (−)-bitungolide E **430** via eleven more steps (Scheme 108).[218]

The synthesis of an advanced intermediate of macrosphelide A **434**,[219] a highly potent antitumor polyketide,[220] was reported by Chakraborty et al. This strategy started from aldehyde **435** which



Scheme 105.



Scheme 106.

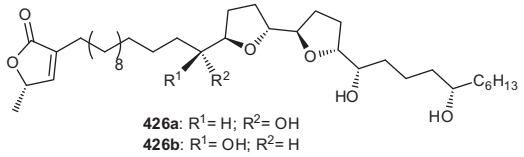


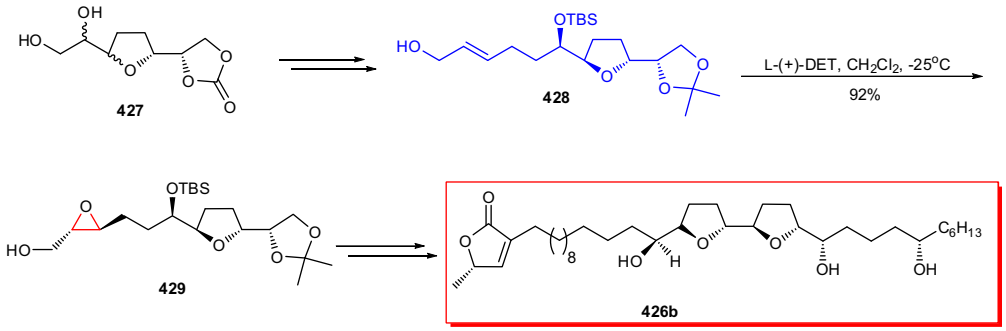
Figure 4.

was transformed into the corresponding allylic alcohol **436**. Treating allylic alcohol **436** with (+)-DET and Ti(O-^{i}Pr)$_4$ with a Sharpless asymmetric epoxidation strategy led to the chiral epoxy alcohol **437** in 40% yield and 94% ee. Epoxy alcohol **437** was transformed into compound **438** via five steps, to the desired macrosphelide A **434** (Scheme 109).[221]

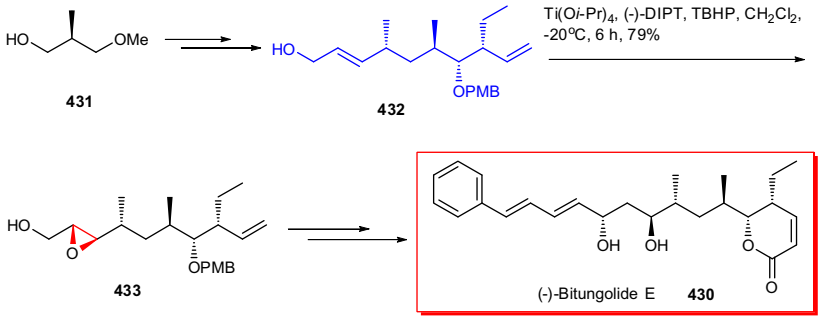
Leptomycin B **439** was first isolated as an antifungal antibiotic from *Streptomyces* sp.[222] Kobayashi et al. reported a total synthesis of leptomycin B **439** using *trans*-crotyl alcohol **301** as the starting material. Sharpless asymmetric epoxidation of alcohol **301** upon treatment with TBHP, (+)-DEPT gave epoxide **302** in 75% yield and 96% ee. The resulting epoxide **302** was then converted into leptomycin B **439** in thirty six steps (Scheme 110).[223]

Macrolide antibiotics antascomicin A **440** were obtained from a fermentation broth of a strain of Micromonospora, which was isolated from a soil sample collected from China.[224] Antascomicin A **440** showed potent antagonize. An asymmetric synthesis of the C18–C34 fragment of antascomicin A was accomplished by Fuwa et al. This fragment is an important and key intermediate for the total synthesis of antascomicin A.[225]

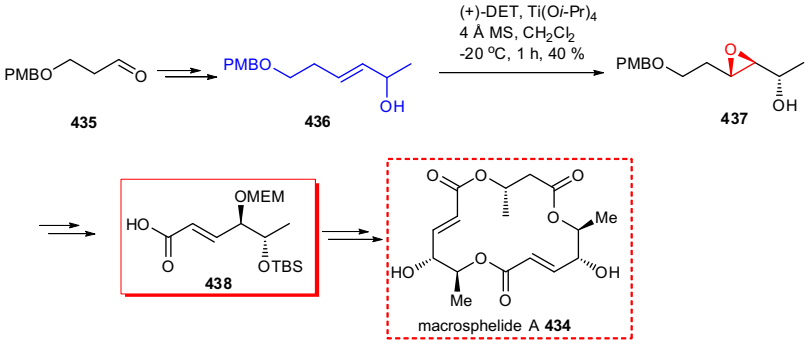
The synthesis of the C18–C34 fragment **441** started from tri-*O*-acetyl-D-glucal **442**, which after 14 steps gave allylic alcohol **443**.



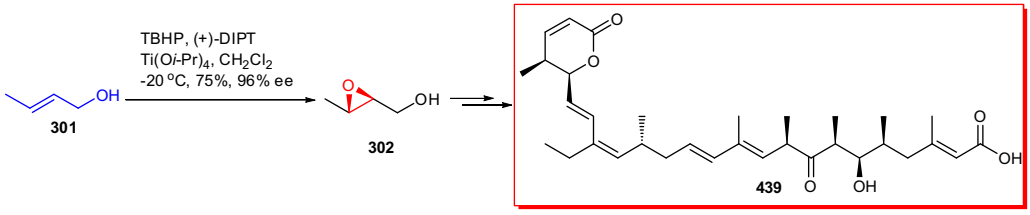
Scheme 107.



Scheme 108.



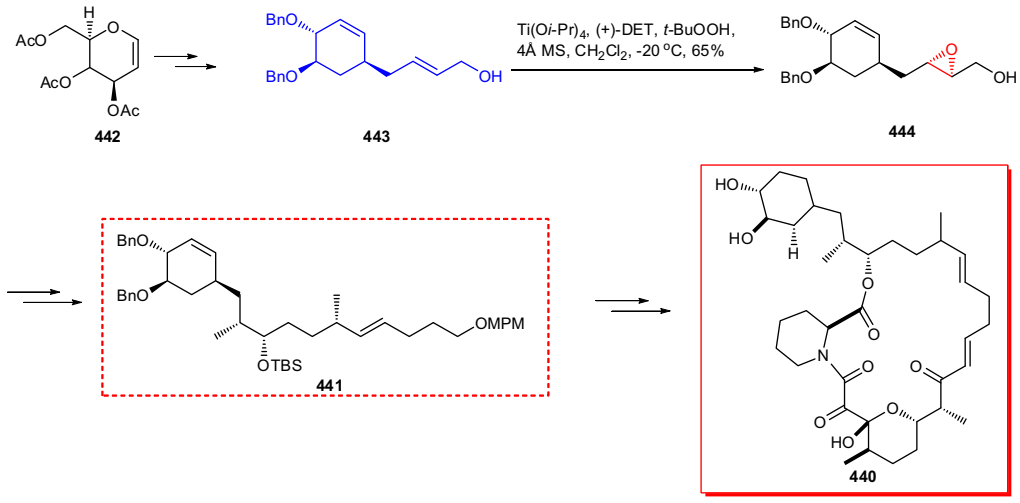
Scheme 109.



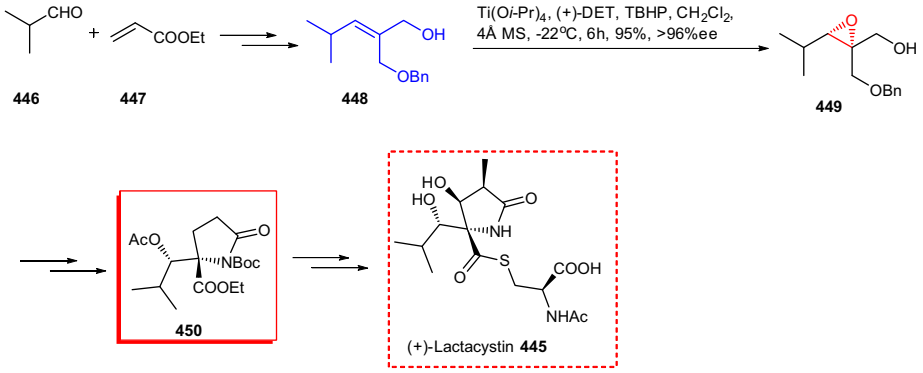
Scheme 110.

The latter then underwent Sharpless asymmetric epoxidation by employing (+)-DET as a chiral auxiliary to give hydroxyl epoxide **444**. Several more steps were still required to obtain the target natural product **441** (Scheme 111).[225]

Lactacystin **445**, a new anti-microbial natural product, inhibits cell cycle progress. For the total synthesis of the target **445**, isobutyraldehyde **446** and ethyl acrylate **447** were employed as starting materials, After 5 steps the desired allylic alcohol **448** was obtained to be used for further stereoselective transformation via Sharpless asymmetric epoxidation strategy which in this case (+)-diethyl tartrate was used to provide a chiral media. As a result the desired chiral epoxy alcohol **449** was obtained in 95% yield and



Scheme 111.



Scheme 112.

with 96% ee conducting 10 more reactions led to ethyl ester **450**, a key intermediate for the total synthesis of Lactacystin **445** (Scheme 112).[226]

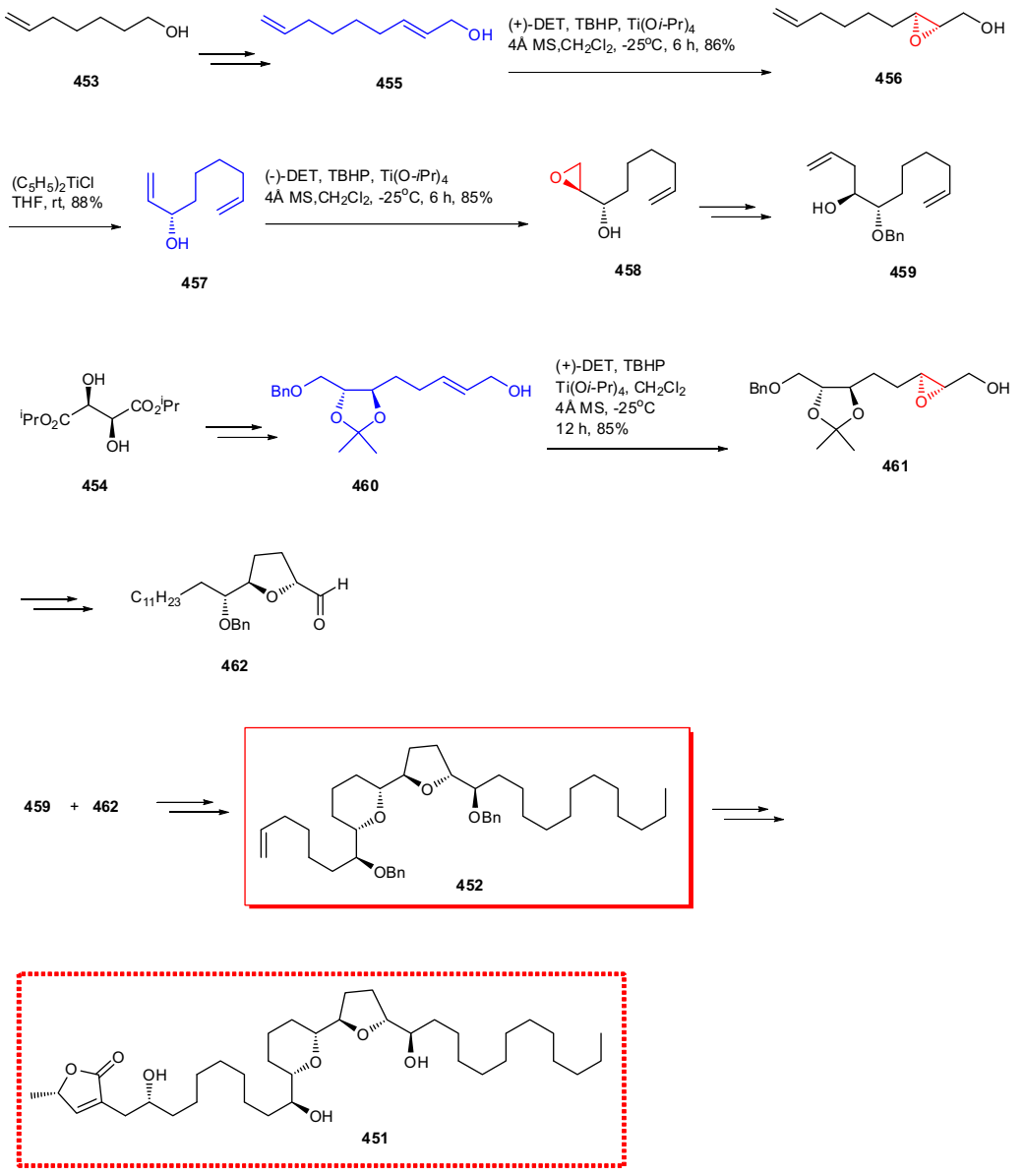
2.6. Polyketide

The synthesis of the THP–THF core **452** of (+)-muconin **451** was achieved using hepta-6-ene-1-ol **453** and (−)-diisopropyl tartrate **454** as starting materials. First, hepta-6-ene-1-ol **114** was converted into the respective allylic alcohol **455**, which underwent Sharpless asymmetric epoxidation conditions in the presence of (+)-DET to afford the corresponding chiral epoxy alcohol **456** with 96% ee in 86% chemical yield. Regioselective ring opening of epoxide **456** upon reduction using titanium(III) in THF provided the appropriate allylic alcohol **457** in 88% yield which upon submission to Sharpless asymmetric epoxidation conditions, in the presence (−)-DET furnished the epoxy alcohol **458** in 92% de in 85% chemical yield. Subsequently, the epoxy alcohol **458** afforded the homoallylic alcohol **459** in two steps. On the other hand, (−)-diisopropyl tartrate **454** was converted into allylic alcohol **460** which was further transformed into chiral epoxy alcohol **461** in high yields under Sharpless asymmetric epoxidation conditions in the presence of (+)-DET. After eight steps, aldehyde **462** was obtained from epoxy alcohol **461**. The reaction of homoallylic alcohol **459** and aldehyde **462** led to the formation of THP–THF core **452** of (+)-muconin **451** (Scheme 113).[227]

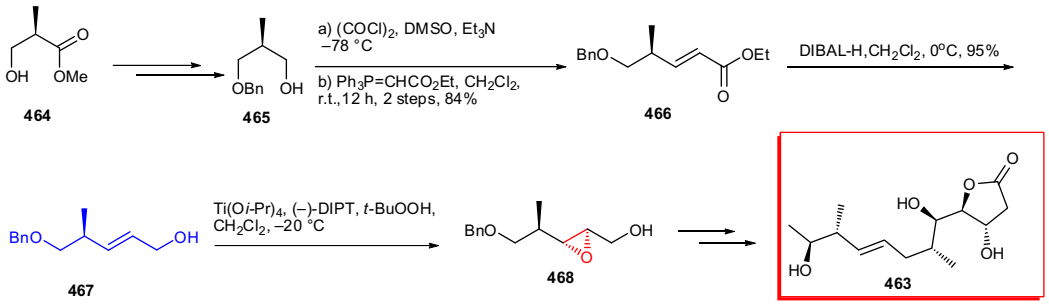
Mupirocin was isolated from naturally occurring polyketides, which in turn was isolated from *Pseudomonas fluorescens*. One reported total synthesis involves the initial conversation of commercially available (+)-(*R*)-Roche ester **464** into monoprotected diol **465**. The latter was submitted to a sequential protection of the alcohol, reduction of the ester, Swern oxidation of the primary alcohol, two-carbon Wittig elongation to yield intermediate a,β-unsaturated ester **466**, which upon chemoselective reduction employing DIBAL-H (diisobutylaluminum hydride) provided the corresponding allylic alcohol, that is, **467** in excellent yields, as an appropriate precursor Sharpless asymmetric epoxidation protocol which in this case using (−)-DIPT afforded a mixture of diastereomeric epoxy alcohols **468**, which was inseparable and used as obtained in a multi-step reaction to give the mupirocin H **463** (Scheme 114).[228]

Bitungolides A–F are secondary metabolites generated by a marine sponge and are considered to be remarkable sources of pharmacologically active compounds.[5] The first total synthesis of (−)-bitungolide E **469** was reported by Ghosh et al. using Sharpless asymmetric epoxidation as a key step. The synthesis commenced from (−)-(*R*)-Roche ester **470**, which was transformed into allylic alcohol **471**. The latter was subjected to Sharpless asymmetric epoxidation, as a crucial step to give epoxy alcohol **472**. The latter was transformed into (−)-bitungolide E **469** via eleven more steps (Scheme 115).[6]

The synthesis of an advanced stage intermediate of macrosphelide A **473**,[7] a highly potent antitumor polyketide,[8] was reported by Chakraborty et al. This strategy started from aldehyde **474** which was transformed into the corresponding allylic alcohol **475**. Treating allylic alcohol **475** with (+)-DET via a Sharpless



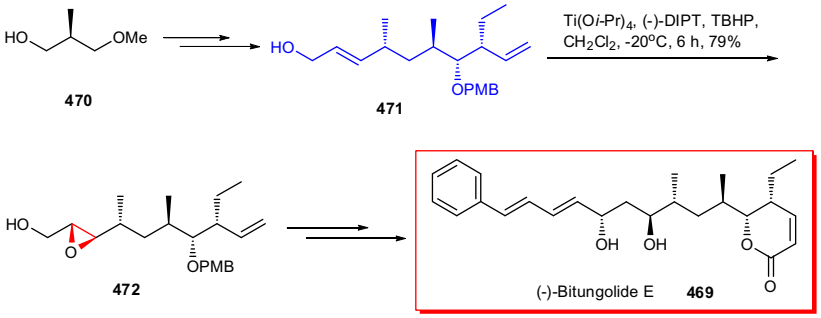
Scheme 113.



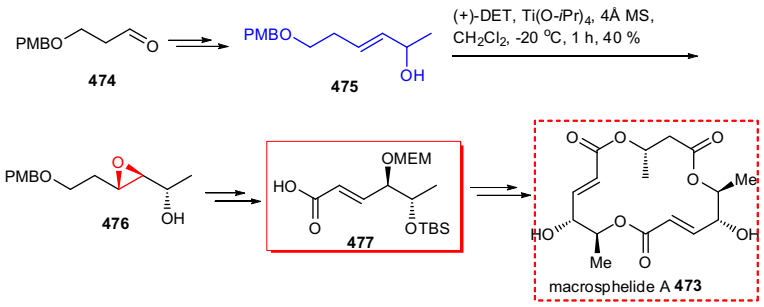
Scheme 114.

epoxidation strategy led to the chiral epoxy alcohol **476** in 40% yield and with 94% ee. Epoxy alcohol **476** was then transformed into compound **477** via five steps to give the desired macrosphelide A **473** (Scheme 116).[229]

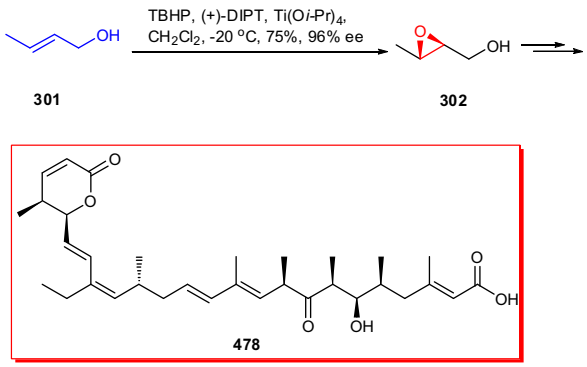
Leptomycin B **478** was first isolated as an antifungal antibiotic from *Streptomyces* sp.[221] Kobayashi et al. reported a total synthesis of leptomycin B **478** using *trans*-crotyl alcohol **301** as the starting material (Scheme 117). Sharpless asymmetric epoxidation of



Scheme 115.



Scheme 116.



Scheme 117.

alcohol **301** upon treatment with TBHP, (+)-DIPT and Ti(O-*i*Pr)$_4$ gave epoxide **302** in 75% yield and with 96% ee. The resulting epoxide **302** was then converted into leptomycin B **478** through thirty six steps (Scheme 122).[223]

Phorboxazoles A **479a** and B **479b** are marine natural products isolated from a recently discovered species of Indian Ocean sponge (Genus *Phorbas* sp.) A strategy for the synthesis of the C20–C28 moiety of phorboxazoles **480** has been described starting from *N*-propanoyloxazolidinethione **481**. Compound **481** furnished *E*-allylic alcohol **482**, which was then subjected to Sharpless asymmetric epoxidation using (−)-diisopropyltartrate (DIPT) in the presence of Ti(O*i*Pr)$_4$ and *tert*-butylhydroperoxide (TBHP) and 4 Å molecular sieves in CH_2Cl_2 at −20 °C to furnish the desired epoxy alcohol **483** in 81% isolated yield and 83% de. Twelve more steps led to the formation of the desired product **480** (Scheme 118).[21]

2.7. Cyclic ether

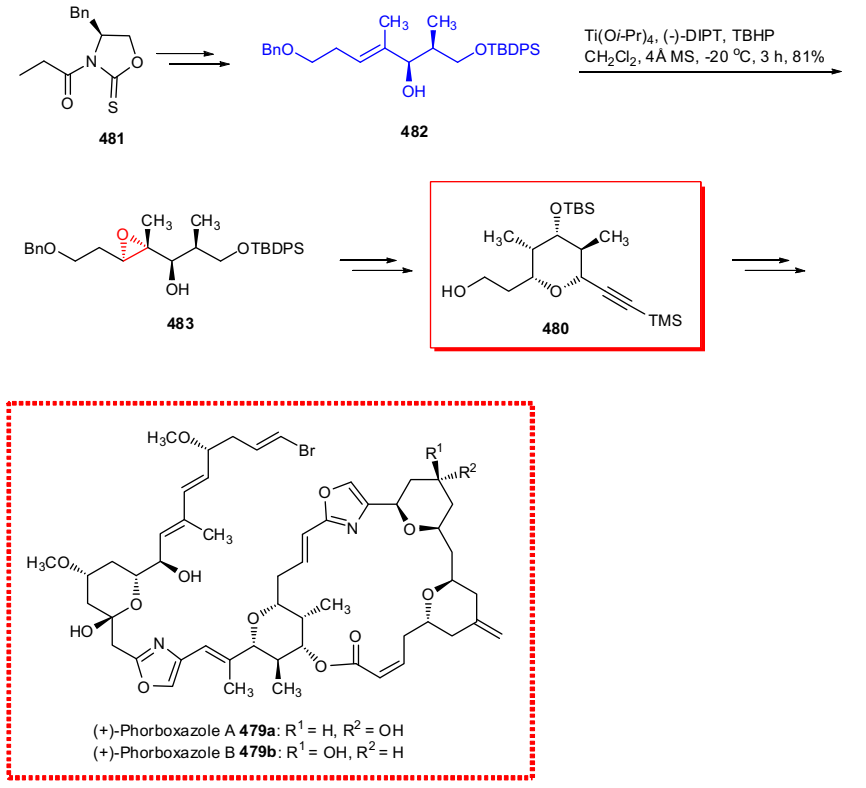
Ebivolol **484** is a potent and selective β1-adrenergic blocker with antihypertensive activity.[230] The beneficial hemodynamic profile of racemic nebivolol has been mainly ascribed to the L-enantiomer, which is devoid of β-adrenoceptor blocking properties as therapeutic doses. The synthesis began from commercially available *p*-fluorophenol **485**. After 5 steps, allyl alcohol **486** was obtained and subjected to Sharpless asymmetric epoxidation. The two requisite epoxy alcohol **487** and **488** were obtained from **486** in 'one pot' upon treatment with (−)-DET and (+)-DET, respectively, followed by sodium hydroxide work-up. The commercial availability of Sharpless asymmetric epoxidation reagents and easy preparation of allyl alcohols makes this approach most attractive for the synthesis of other possible isomers and analogues (Scheme 119).[231]

Saturated oxygen heterocycles are important structural moieties of a large number of organic natural products.[232] The total synthesis of these natural products depends largely on the efficient stereoselective construction of these essential cyclic components.[233]

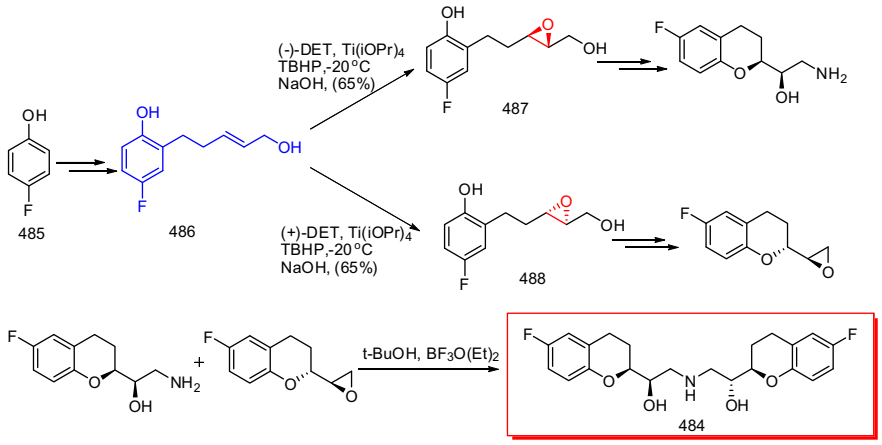
A new strategy for the synthesis of highly substituted tetrahydro 2*H*-pyrans[234] **489** to **493** has been described starting from a common intermediate, a propionate-derived polyketide unit. Compound **489** constitutes the C20–C28 moiety of phorboxazoles,[235] cytotoxic natural products that have attracted the attention of synthetic chemists.[236]

The asymmetric aldol addition of titanium enolate derived from the *N*-propanoyl oxazolidinethione **494**, to aldehyde **495** gave the non-Evans *syn*-aldol product **496** as the only isolable diastereomer in 78% yield.

Reductive removal of the chiral auxiliary using $NaBH_4$ gave an intermediate diol that was selectively protected at its primary hydroxyl as *tert*-butyldiphenylsilyl (TBDPS) ether to furnish **497** in 68% yield from **496**. The *E*-allylic alcohol **497** was then subjected to Sharpless asymmetric epoxidation using 2-diisopropyl tartrate (DIPT) to furnish the desired epoxy alcohol **498** in 81% isolated yield and 83% de, as determined by ^{1}H NMR studies of the crude product. With the trisubstituted chiral epoxide in hand, highly substituted tetrahydro-2*H*-pyrans **489** was subjected to further reactions to give **493** (Scheme 120).[237]



Scheme 118.



Scheme 119.

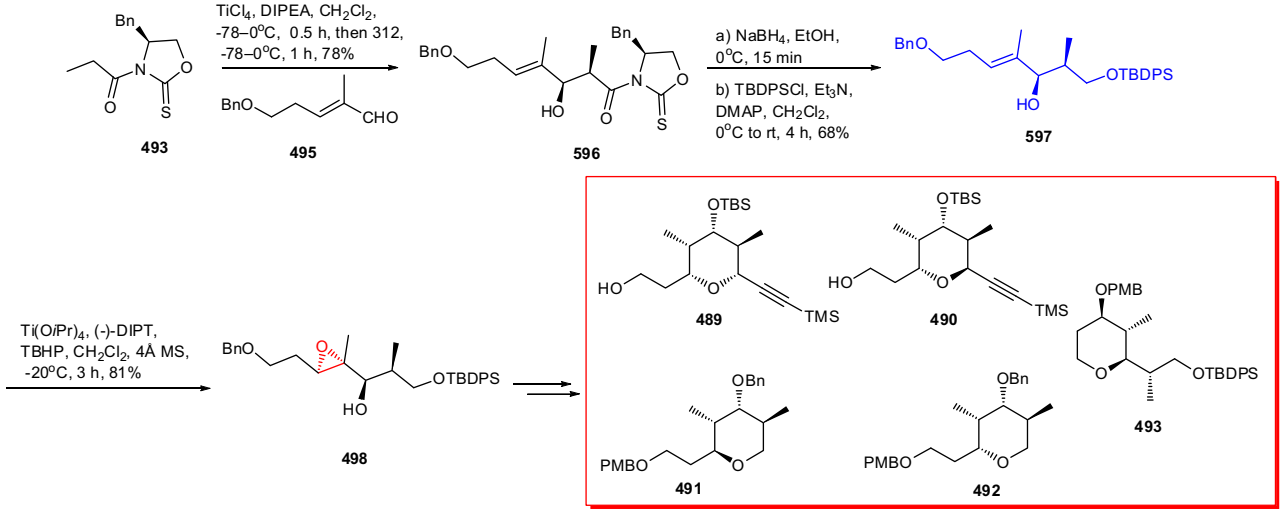
Sponges of the genus *Jaspis* (family Coppatiidae) have received considerable attention from scientists because of the interesting pharmacological properties of its chemical components.[238] The synthesis of pachastrissamine (jaspine B) **499** from (*R*)-glycidol as the chiral starting material was reported by Ribes et al.

The synthesis of **499** is illustrated in Scheme 121. Commercial (*R*)-glycidol **500** was transformed into its known TPS ether. The epoxide opening in **500** with an *n*-tridecyl cuprate reagent afforded alcohol **501**, which was then protected as its MOM derivative **502**. Desilylation of the latter with TBAF furnished alcohol **503**, which was transformed into the (*E*)-unsaturated ester **504** as reported by sequential Swern oxidation and olefination. DIBAL reduction of **504** to (*E*)-allylic alcohol **505** followed by Sharpless asymmetric epoxidation with (−)-DET provided epoxy alcohol **506**. Then after 7 more reactions, jaspine B was obtained (Scheme 121).[239]

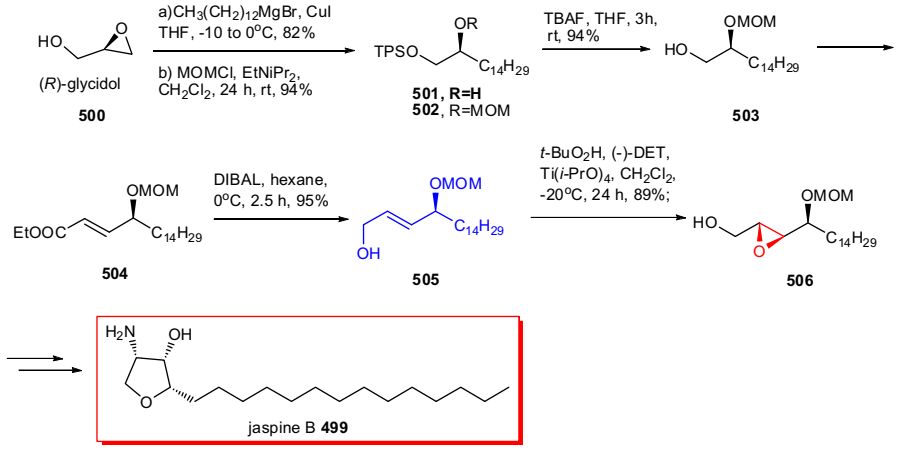
Sphingoid bases are long-chain (typically C18) aminopolyols that constitute the backbone of sphingolipids, ubiquitous components of eukaryotic cell membranes.[240]

Genisson et al. reported the total synthesis one of the analogues of jaspine **507**. The starting allylic alcohol **508** was readily obtained by monobenzylation of butyne-1,4-diol **509** followed by LAH reduction. This was then subjected to Sharpless asymmetric epoxidation to yield **510**. The latter was further transformed into an original C12 analogue of jaspine B **507** through a concise eight-step sequence (Scheme 122).[241]

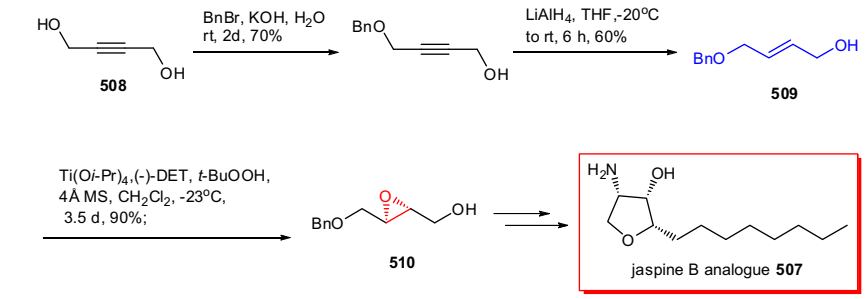
Red algae of the genus *Laurencia*, particularly *Laurencia nipponica*, produce a wide variety of medium-sized cyclic ethers as distinctive members of marine natural products.[242] Saitoh et al. reported the total synthesis of (+)-laurallene **511** which is a member of the laurenan compounds. Diol **512**, prepared from D-(+)-



Scheme 120.



Scheme 121.

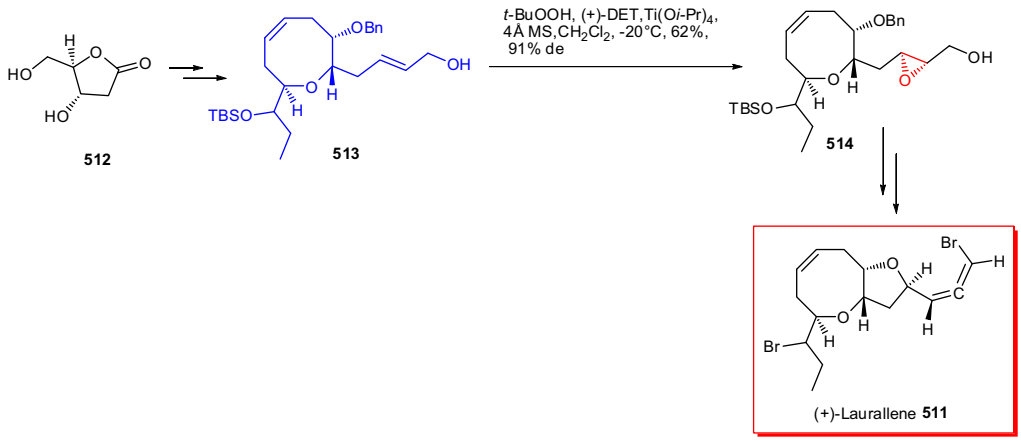


Scheme 122.

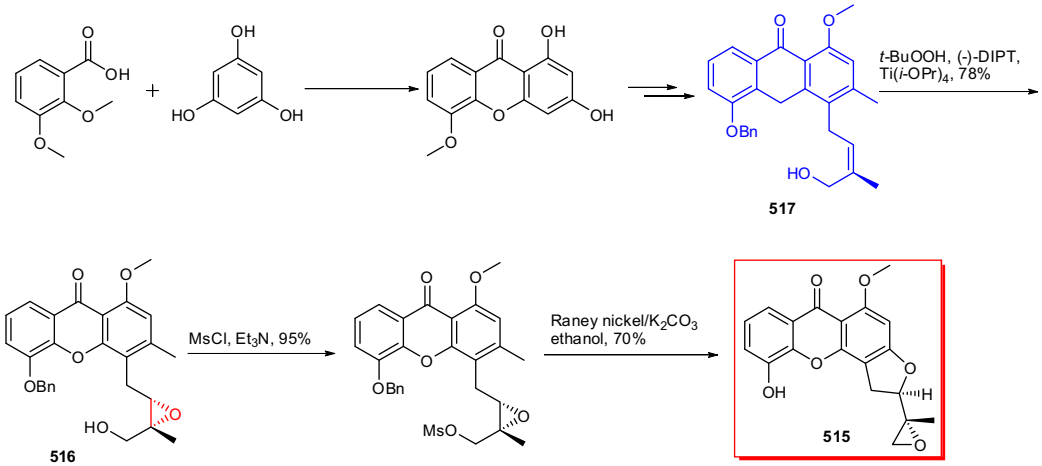
ribonic γ-lactone according to the Chen procedure,[243] was used as a precursor. It underwent 27 reactions to give **513**. Diastereoselective epoxidation of **513** by the Sharpless protocol provided the desired epoxide **514** (62%, 91% de). After 12 steps (+)-Laurallene **511** was obtained (Scheme 123).[244]

Psorospermin **515** is a xanthone natural product first isolated by Kupchan et al. from the bark of the African plant *Psorospermum febrifugum*.[245] The absolute stereochemistry was later determined by Cassady et al.[246] Psorospermin has been of great interest for the past three decades because of its unique structure and novel antineoplastic properties.[247]

The synthesis began with the construction of the xanthone skeleton as reported by Grover et al. and a further nine steps were needed to achieve the allylic alcohol **516**. Sharpless asymmetric epoxidation proceeded smoothly with stoichiometric addition of reagents and powdered sieves. Thus, epoxide **517** obtained in



Scheme 123.



Scheme 124.

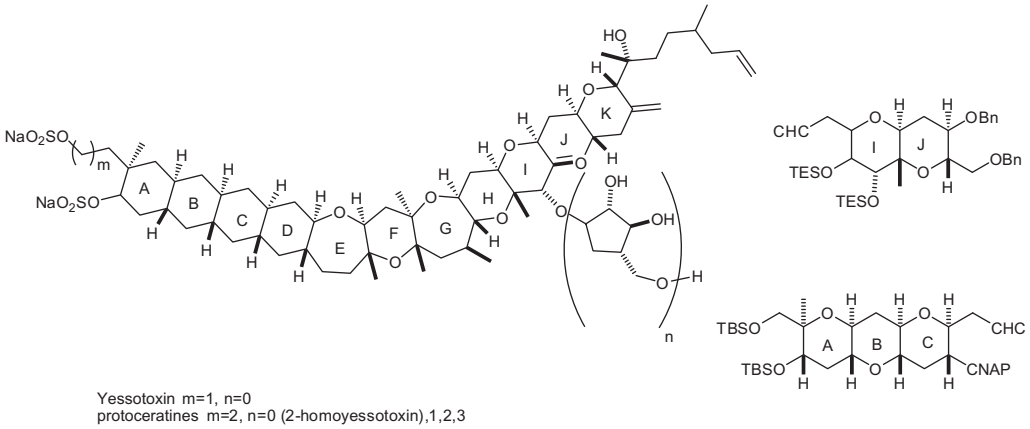
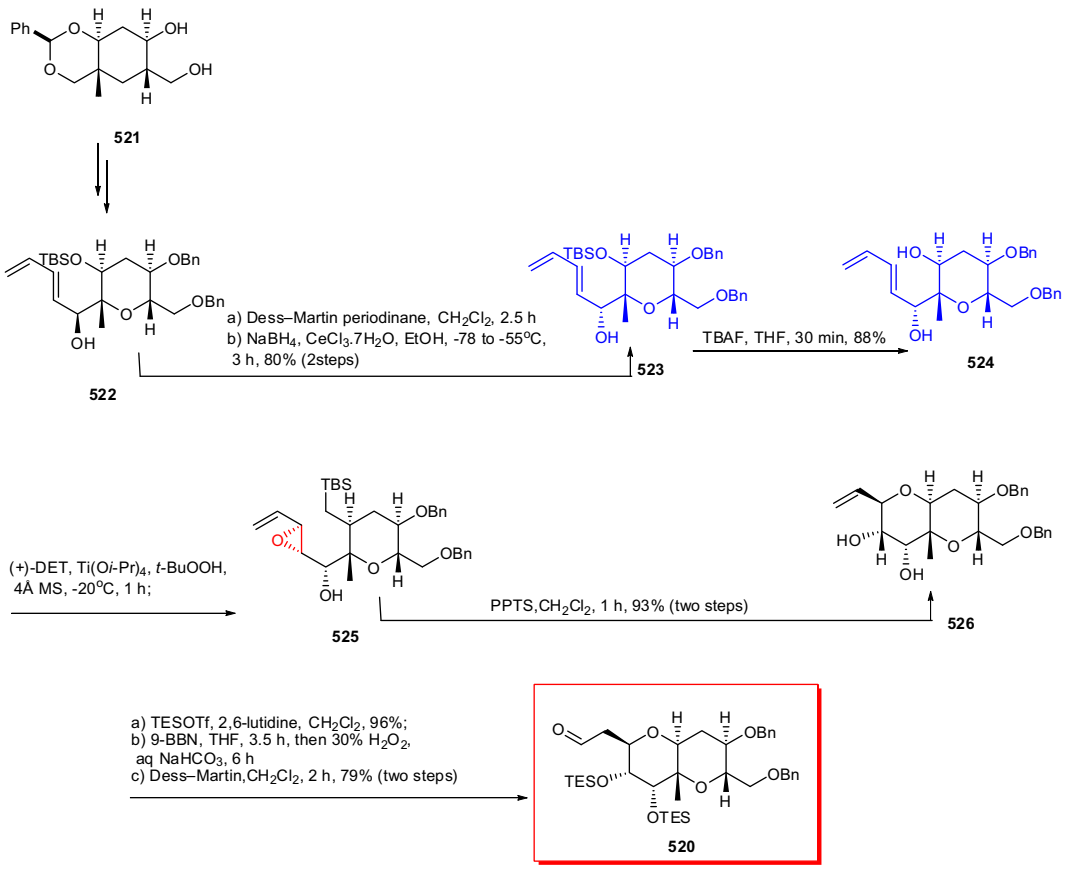


Figure 5.

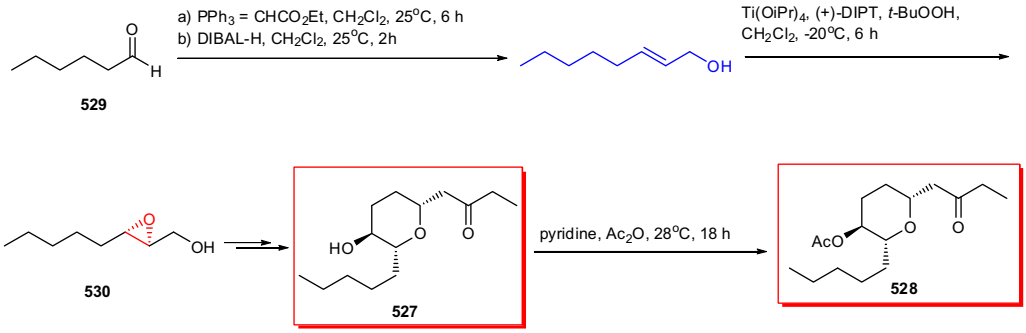
78% yield with 70% ee. The final step involved the selective reduction of the 3-and 5-benzyl protecting groups and a zipper-type cyclization (Scheme 124).[248]

Yessotoxin **518**[249] is a marine polyether toxin produced by the dinoflagellate Protoceratium species (Fig. 5).[250] Recently, glycoside analogues of **518**, protoceratins **519**, which show potent cytotoxicity against human tumor cell lines, have been isolated from this organism.[251] Due to their biological activity, coupled with their arched molecular structure, **518** and its analogues have attracted the attention of synthetic chemists.[252]

The synthesis of the IJ ring fragment **520**, started with the tetrahydropyran derivative **521**, which is a common intermediate with the A ring. Six steps of protecting of the diol, hydrolysis, bis-TBS ether formation, and subsequent selective hydrolysis



Scheme 125.



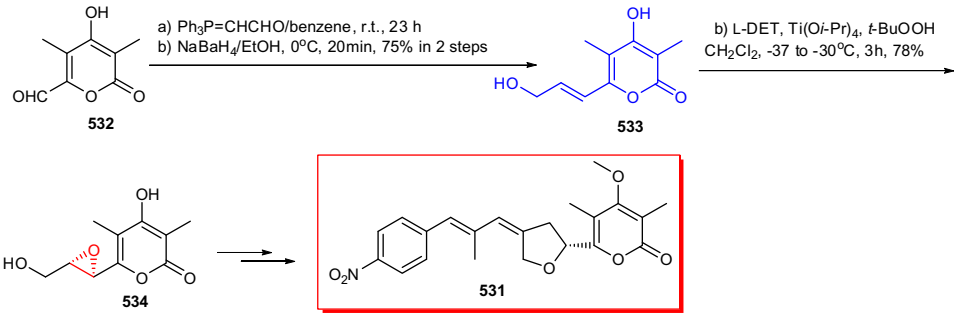
Scheme 126.

furnished primary alcohol. Swern oxidation followed by treatment of the resulting aldehyde with (*E*)-1-lithio-1,3-butadiene afforded a mixture of alcohol **522** and its epimer **523** in a 1:2 ratio, which was separated by silica gel chromatography. The undesired **339** was converted into **340** via an oxidation and Luche reduction sequence. Removal of the TBS group led to **524** and subsequent Sharpless asymmetric epoxidation using L-(+)-diethyl tartrate yielded hydroxyl epoxide **525**. Under the reaction conditions described, partial cyclization occurred to give an inseparable mixture of **7** and pyranopyran **526** (1.5:1), which was treated with PPTS to give **343** in 93% yield for two steps. Protection of diol **526** as a bis-TES ether, followed by hydroboration and Dess–Martin oxidation, afforded the IJ ring fragment **520** (Scheme 125).[253]

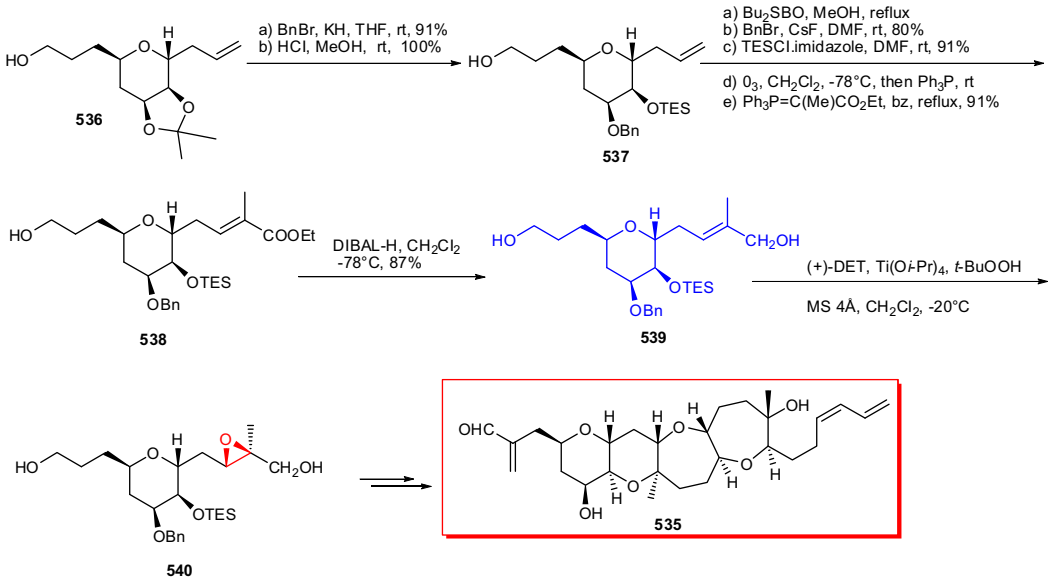
Decytospolides A **527** and B **528** were recently isolated from Cytospora sp.[254] The synthesis began from *n*-hexanal **529**. Accordingly, *n*-hexanal **529** was converted into epoxide **530** in three steps using a Wittig reaction and reduction and finally Sharpless asymmetric epoxidation in the presence of (+)-DIPT. The resulting epoxy alcohol **530** was then converted into compound **527** through other more steps, to finally give compound **528** (Scheme 126).[255]

Lsoaureothm **531**, is a toxic metabolite and has a nitro group, and was first isolated by Maeda et al. from the mycelium of Streptomyces thioluteus; its structure was elucidated by Hirata et al in 1961.[256]

The known 3,5-methyl-6-formyl-4-methoxy-2-pyrone **532** was subjected to Wittig reaction followed by $NaBH_4$ reduction to afford



Scheme 127.



Scheme 128.

allyl alcohol **533** in good yields, which was further subjected to Sharpless asymmetric epoxidation to give rise to the (+)-epoxide **534** in 78% yield (>99% ee), as shown in Scheme 127. The epoxy alcohol **534** was finally converted into the desired compound **531** through more steps (Scheme 127).[257]

Hemibrevetoxin B **535**, isolated from cultured cells of the red tide organism Gymnodinium breve by Prasad and Shimizu in 1989[258] has a 6,6,7,7-tetracyclic ether skeleton and contains 10 stereocenters (Scheme 10). Much attention has been paid to the synthesis of polycyclic ethers including hemibrevetoxin B due to their unusual structural framework, novel functionalities, and biological activities.[259]

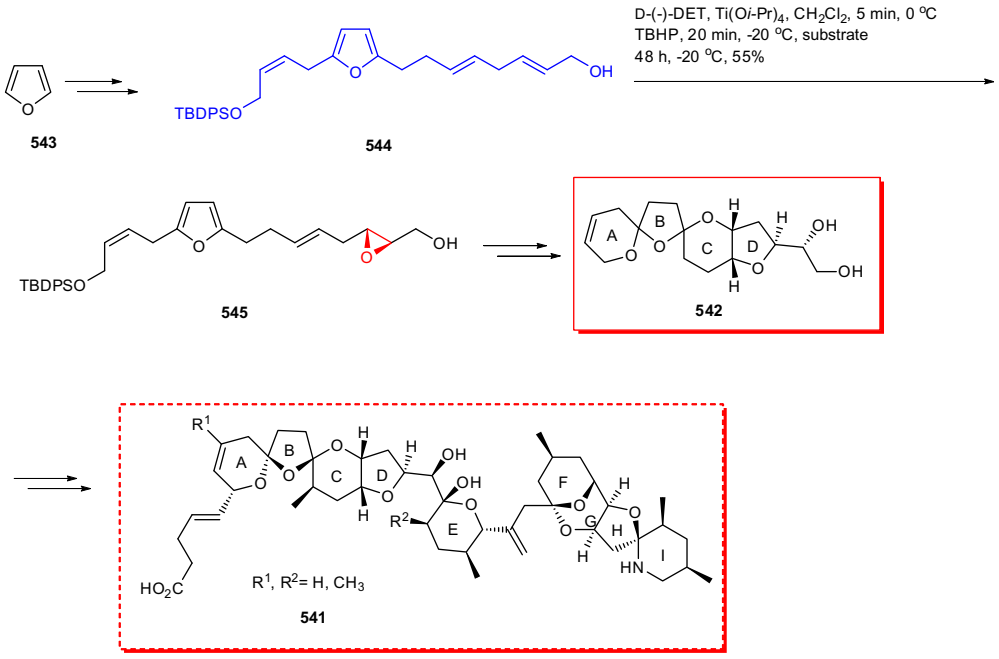
The preparation of the 6,6-ring system was carried out primarily based on the modified Nicolaou's method (Scheme H). The mannose-derived starting material **536** was converted into **537** by benzylation followed by removal of the acetonide protection and selective elaboration of the liberated diol using Bu_2SnO/BnBr and TESCI/imidazole. Ozonolysis of the double bond followed by treatment of the resulting aldehyde with a Wittig reagent afforded **538** in 91% yield. Reduction with diisobutylaluminum hydride gave allylic alcohol **539** in 87% yield, which was converted into the epoxide **540** upon treatment with the Sharpless asymmetric epoxidation reagent. After 23 steps, the target Hemibrevetoxin B **535** was obtained (Scheme 128).[260]

Several natural products such as azaspiracids **541**,[261] contain a *bis*-spiroketal moiety.[262] Due to promising results from screening, acting as anti-cancer, these molecules have attracted much attention. The azaspiracids **541** have exhibited a broad range of interesting biological potencies[263] involving the recently explored inhibition of the hERG ion channel.[264]

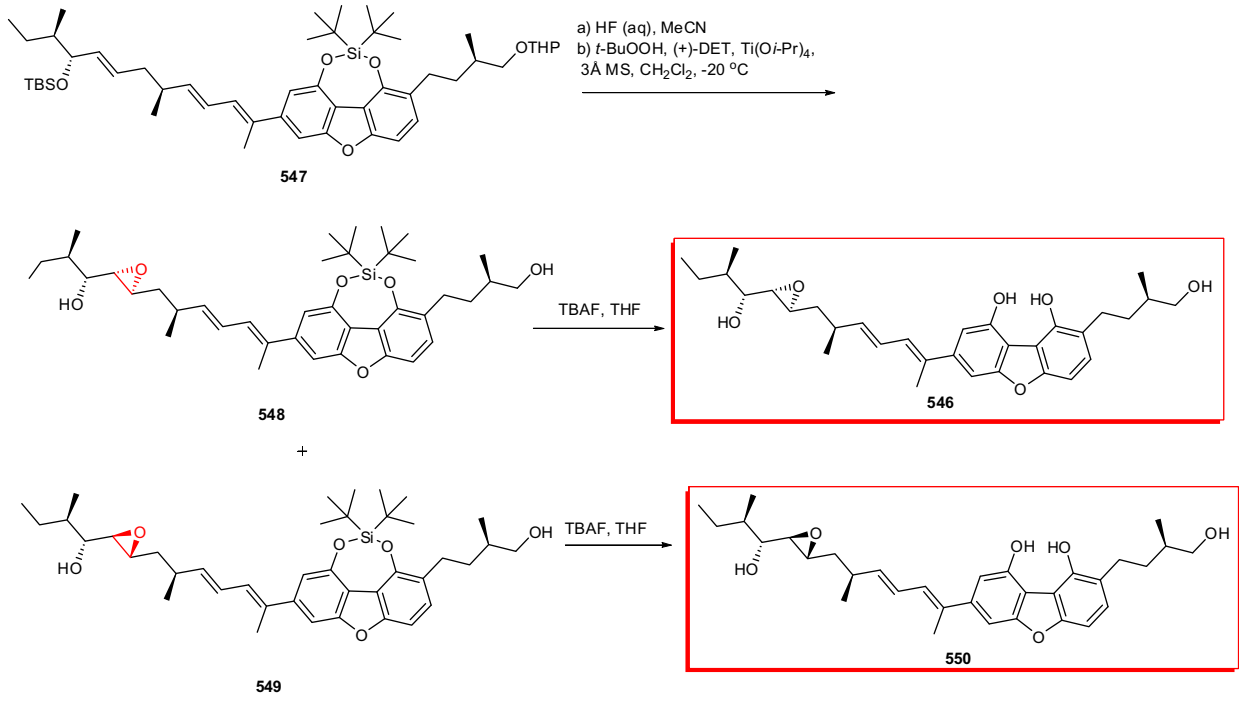
The ABCD-ring scaffold of azaspiracids **542** was synthesized from furan **543** through allylic alcohol **544**. The latter was subjected to Sharpless asymmetric epoxidation conditions to afford the corresponding epoxide **545** which in turn was converted into the desired [6,5,6]-*bis*-spiroketal **542** in four steps (Scheme 129).[265]

The isolation and characterization of natural product (+)-fulicineroside from the slime mold Fuligo cinerea collected in the Czech republic was reported in 2005.[266] In the total synthesis of the aglycone fulicinerine **546**, allylic alcohol **547** underwent Sharpless asymmetric epoxidation. In this system (+)-(DET, favors the *erythro*-product **548**. By using (−)-DET, product **549** was obtained with 9:1 selectivity (matched case). To obtain the *threo*-product, the mismatched case using (+)-DET was studied, obtaining a 1:1 mixture of both diastereomers **548** and **549**, which are separable by HPLC. Epoxidation led to a 6:1 ratio with the *erythro*-product as the major product. The final TBA catalyzed deprotection of the di-*tert*-butylsilene group afforded the postulated structure of fulicinerine **546** and its epoxy diastereomer **550** (Scheme 130).[267]

Spiroketal bearing natural products constitute an important family of bio-active molecules due to their significant and miscellaneous biological potencies.[268]



Scheme 129.

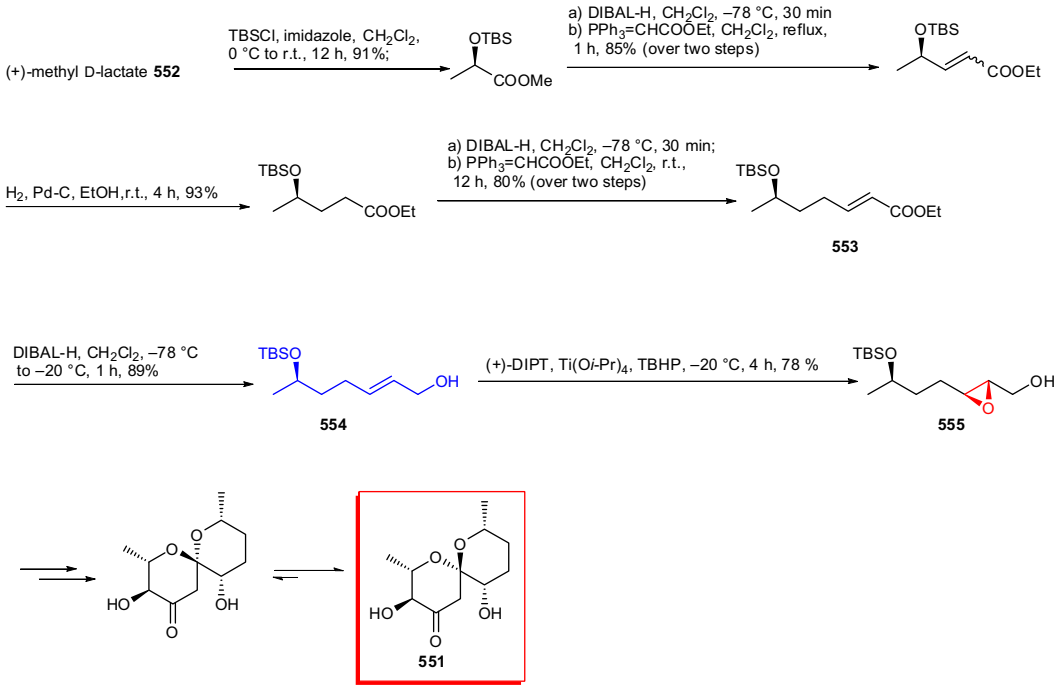


Scheme 130.

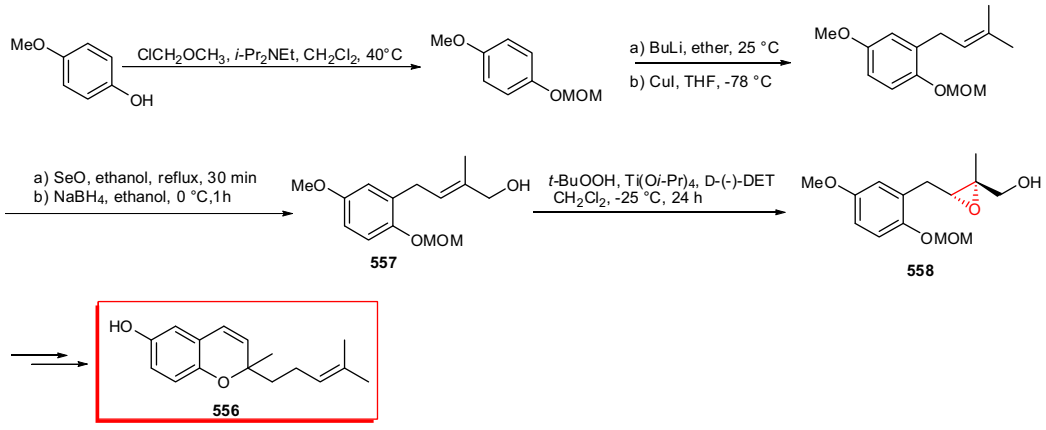
For the total synthesis of **551**, methyl (+)-D-lactate **552** was used as starting materials which after 5 steps gave ester **553**. The ester motif in **553** was subjected to selective reduction to afford allylic alcohol **554** in 89% yield, using a common reductive agent, DIBAL-H in dichloromethane. The latter in this stage was subjected to Sharpless asymmetric epoxidation to obtain the required chiral epoxide using (+)-diethylisopropyl tartrate to yield **555** in good yields but high diastereoselectivity (de 95:5). After 8 more steps, the desired target molecule was obtained (Scheme 131).[269]

Cordiachromen **556** was initially isolated and characterized[270] from *Cordia alliodora*, by acetone extraction.

An enantioselective synthesis of **114** was first reported by Samir Bouzbouz. The pathway started from *p*-methoxyphenol as the starting material. After five steps, the required allylic alcohol **557** was achieved. The key step in this total synthesis, is the induction of chirality which is achieved by the well established Sharpless asymmetric epoxidation on the allylic double bond, to obtain an (*R,R*)-epoxy alcohol **558**, which was isolated in high yields. The



Scheme 131.



Scheme 132.

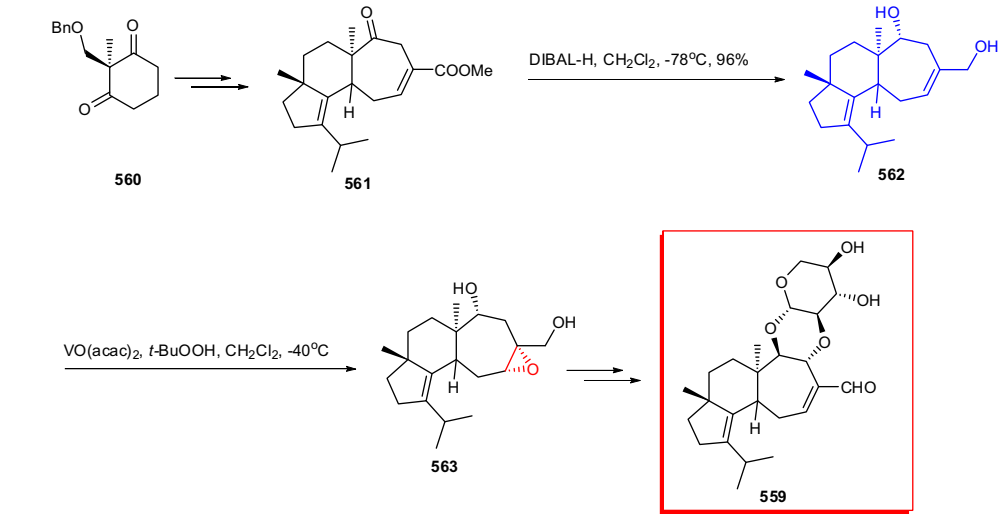
epoxide was then opened regioselectively with lithium aluminum hydride, which can be turned into the target compound after 10 steps (Scheme 132).[271]

After the isolation and characterization of the first cyathins from bird nest fungi by Ayer et al., several structurally similar compounds have been isolated and their structures elucidated. A few members of this numerous family of natural products illustrated high antibiotic potencies, and erinacines **559** and scabronines were found to show strong stimulating potency toward nerve growth factor (NGF) synthesis.[272]

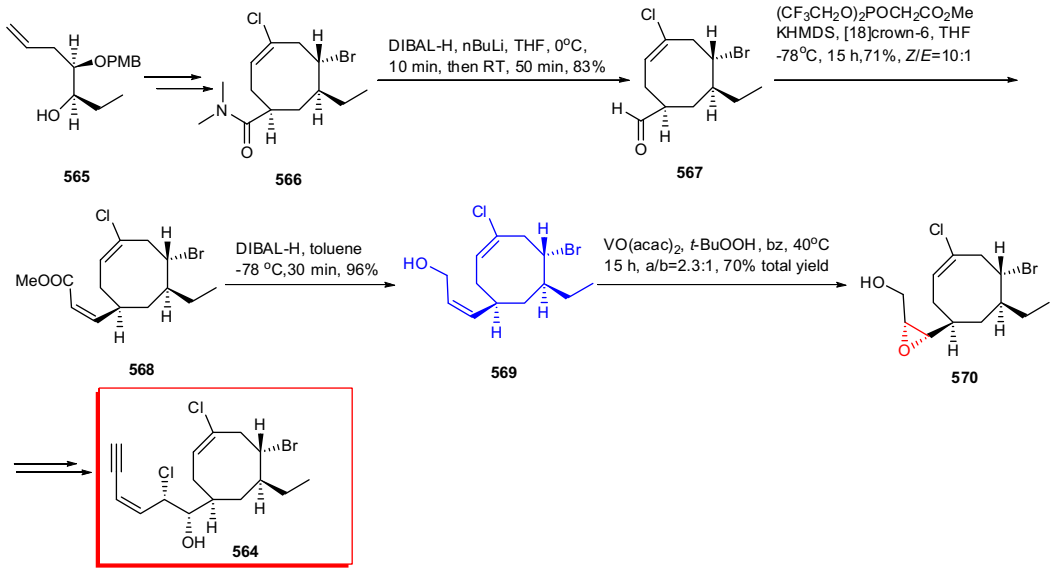
For the total synthesis of (−)-erinacine B **559**, a potent member of this family, compound **560** was selected as the starting material, which after several modifications provided ester **561**. Upon DIBAL-H reduction, the latter was converted the desired diol **562**, as the sole product. The latter was then subjected to Sharpless asymmetric epoxidation conditions [TBHP/VO(acac)$_2$] as a key step to provide the desired epoxide **563** of course as a single stereoisomer. Then after 10 more steps, the total synthesis of (−)-erinacine B was accomplished (Scheme 133).[273]

Red algae of the genus *Laurencia* gives a miscellaneous series of halogenated secondary metabolites.[274] In 1982, (+)-Bermudenynol **564** was isolated from the red alga *Laurencia intricata*, found in Castle Harbour, Bermuda and isolated by Meinwald et al.[275]

The asymmetric total synthesis of (+)-bermudenynol **564**, containing several halogen atoms was difficult and was accomplished in 21 steps. It began from easily available *syn*-diol intermediate **565**. 13 steps were required to obtain compound **566**. Upon reduction of oxocene amide **566**, the corresponding aldehyde **567** was obtained in good yields.[276] Compound **15** was then converted into the essential (*Z*)-enoate **568** with good *Z*-/*E*-selectivity (10:1) via a Still–Gennari olefination in fair yields.[277] (*Z*)-Allylic alcohol **569** was synthesized upon DIBAL-H reduction of (*Z*)-enoate **568** in excellent yields. Treatment of (*Z*)-allylic alcohol **569** with VO(acac)$_2$ under Sharpless asymmetric epoxidation conditions



Scheme 133.



Scheme 134.

gave the desired *cis*-aepoxide **570** a moderate level of selectivity (a/b = 2.3:1, 70% total yield).[278] The latter after 4 more steps afforded (+)-bermudenynol **564** (Scheme 134).[279]

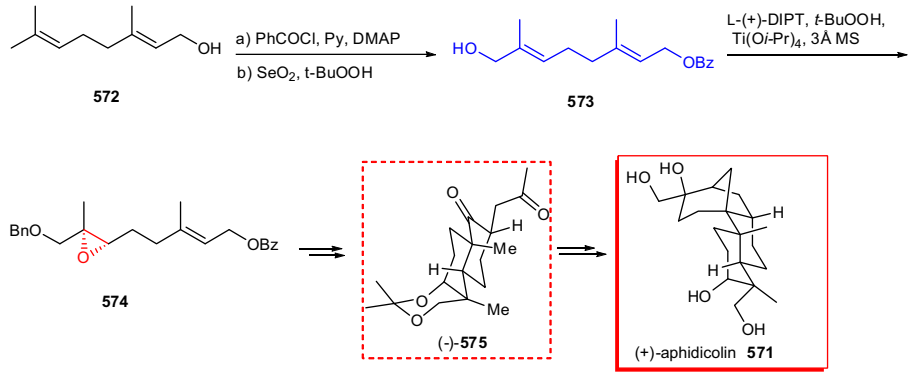
2.8. Terpens

Tanis et al. reported a new method for the synthesis of the AB *trans*-ring system of aphidicolin (+)-**571**. Benzoylation of geraniol **572** followed by catalytic allylic hydroxylation gave 8-hydroxygeranyl benzoate **573**. Sharpless asymmetric epoxidation provides the corresponding epoxy alcohol **574**, whose enantiomeric purity is judged to be ⩾95% ee by HPLC analyses of its Mosher ester.[280] 13 more steps were needed to achieve the desired dione **575**. Since (±)-**575** had been converted into (±)-aphidicolin **571** by McMurry et al., the preparation of (−)-**575** provided a formal synthetic route to (+)-aphidicolin **571** (Scheme 135).[281]

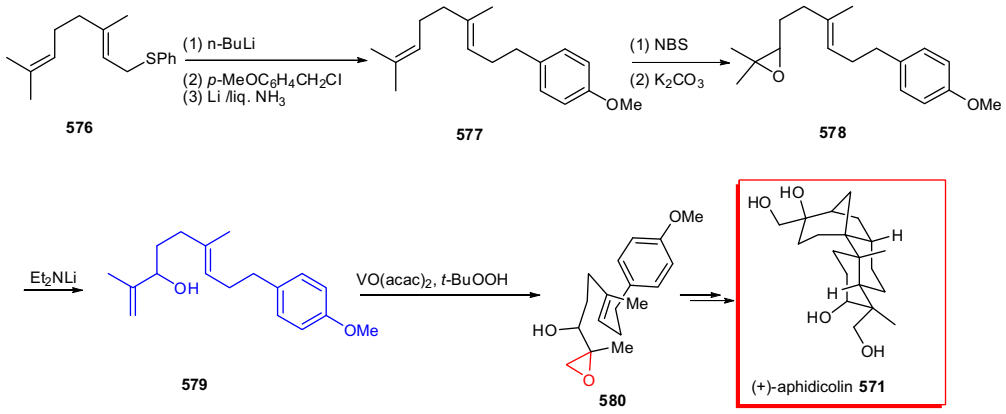
Van Tamelen[282] et al. also made use of polyene cyclization reaction as a key step. Treatment of phenylgeranyl thioether anion **576** with *p*-methoxybonzyl chloride, followed by reductive desulfurization, afforded diene **577**. Regioselective epoxidation of the terminal olefin is achieved in 2 steps through bromohydrin formation. Basic treatment of the resulting epoxide **578** yielded the allylic alcohol **579**, which was subjected to Sharpless asymmetric epoxidation and O-benzylation to give rise to compound **580**. The desired compound **571** was then obtained from compound **580** through other steps (Scheme 136).[281]

Methyl sartortuoate **581** is a tetracyclic tetraterpenoid isolated from the *Sarcophyton tortuosum* tixier-durivault by Su et al.[283] The novelty and challenge of its structure as well as the potential bioactivity have attracted much attention and toward it total synthesis. Gao et al. reported a method for the synthesis of the 2,3,3,6-tetrasubstituted D-ring segment **582**.

The coupling of **583** and **584** was carried out by using *n*-BuLi as the base and $BF_3{\cdot}Et_2O$ as the Lewis acid at −78 °C. The desired product, after desulfonylation and protection of the tertiary hydroxyl group, and selective allylic oxidation with SeO_2/TBHP afforded the allylic alcohol **585**. Sharpless asymmetric epoxidation of **585** smoothly produced the required epoxy alcohol

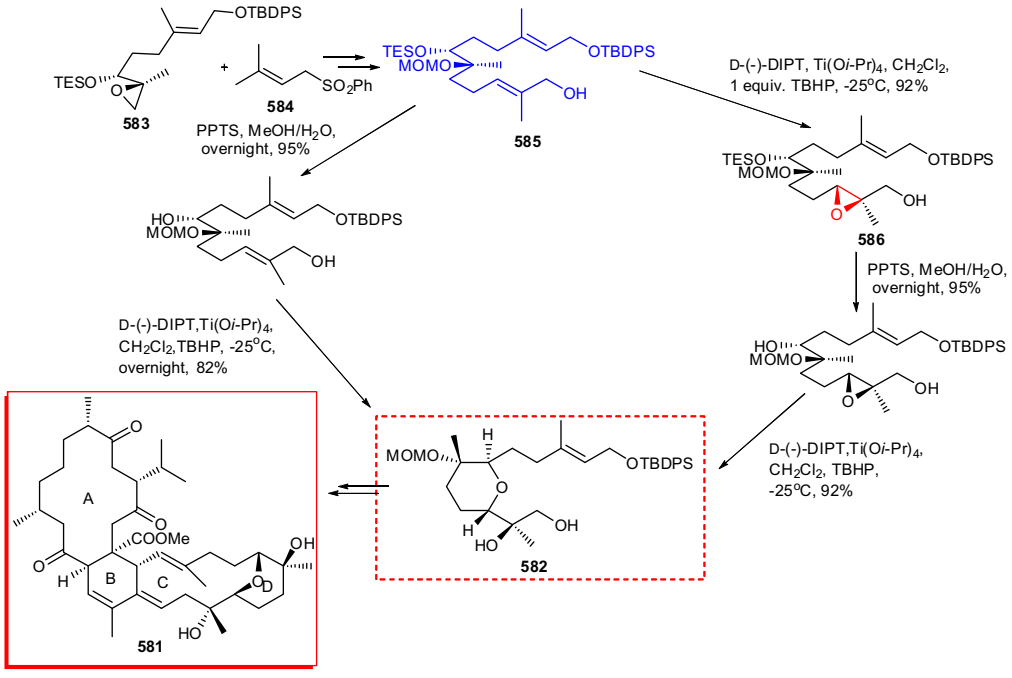


Scheme 135.

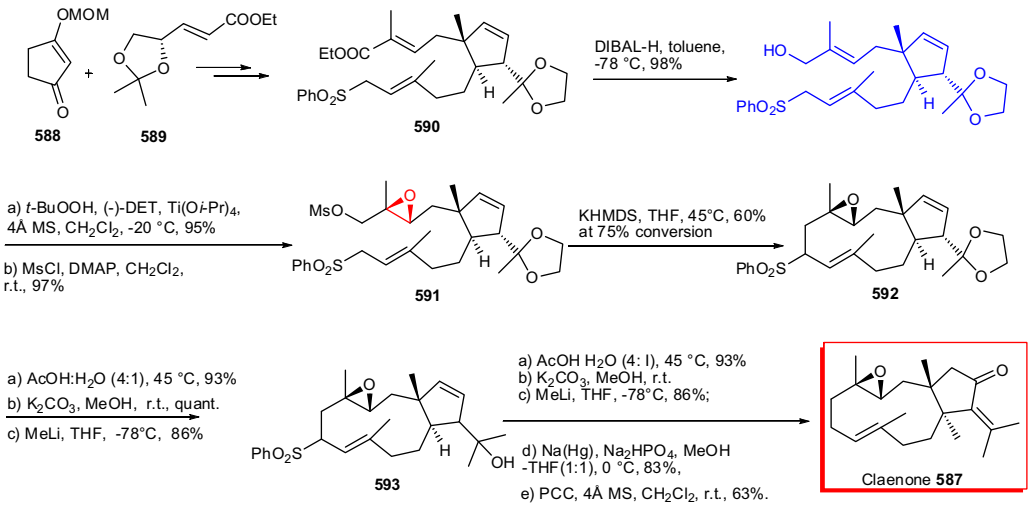


Scheme 136.

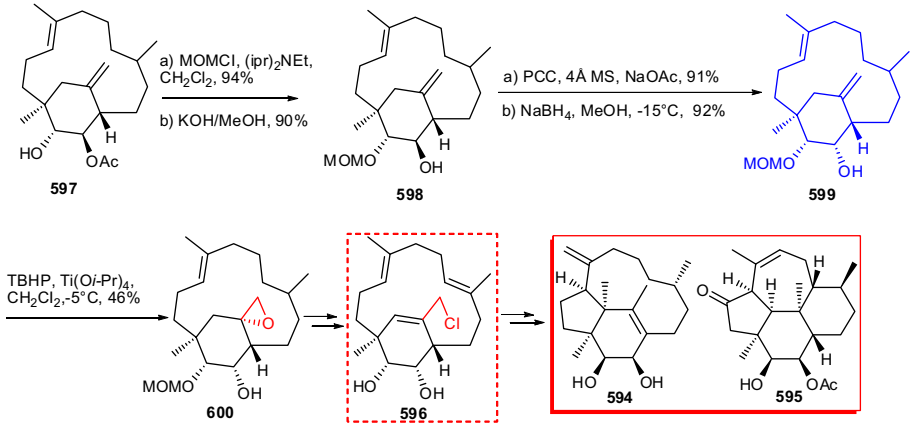
586 in 92% yield, then selective desilylation and treatment with Ti(O-*i*-Pr)$_4$ in refluxing benzene gave the desired 2,3,3,6-tetrasubstituted D-ring segment **582** in 85% yield. Alternatively, the TES ether moiety of compound **585** was removed first, then Sharpless asymmetric epoxidation of the resulting product afforded the same compound **582** in 82% yield. The desired compound **581** could be obtained from compound **582** through other steps (Scheme 137).[284]



Scheme 137.



Scheme 138.



Scheme 139.

Dolabellane diterpenoids, characterized by ordinary *trans*-bicyclo[9. 3. 0]tetradecane, are obtained primarily from marine sources.[285]

The methodology began with the Michael reaction of enone **588** with chiral α,β-unsaturated ester **589** to afford bicyclo[2.2.1]heptane, which after 13 steps turned into compound **590**. Using DIBAL-H, **590** underwent reduction to the allylic alcohol and with Sharpless asymmetric epoxidation of it, epoxide compound **591** was achieved. Mesylation and regioselective macrocyclization of the resulting epoxide gave **592** as the sole product. Compound **592** was converted into allylic alcohol **593** in three steps: (1) hydrolysis of the acetal, (2) isomerization of the olefin to the enone; and (3) methylation by MeLi. Finally, the phenyl sulfonyl group of compound **593** was removed by treatment with Na–Hg and oxidation of the tertiary allylic alcohol with PCC to afford claenone **587** (Scheme 138).[286]

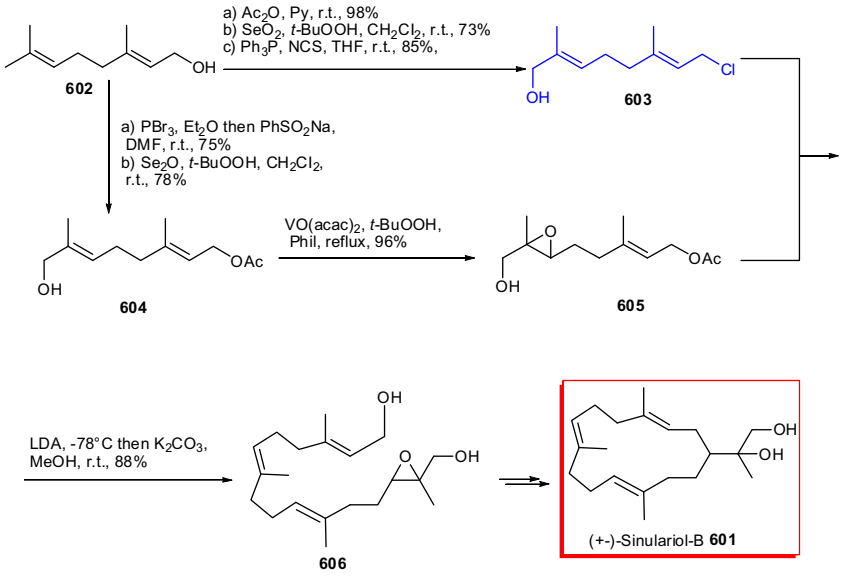
Unusual bioactive terpenoids have been isolated from termite soldiers[287] and their roles are clarified as the defense chemicals in termite society. Examples of these polycyclic diterpenes are **594** and **595** which can be biosynthesized from cembrene.[288] The tricyclic **594** and tetracyclic **595** diterpenes belong to trinervitane and kempane type skeletons, respectively.

Synthetic studies of tricyclic and tetracyclic compounds **594** and **595** showed that both skeletons corresponding to **594** and **595** are constructed from the common intermediate **596**.[289]

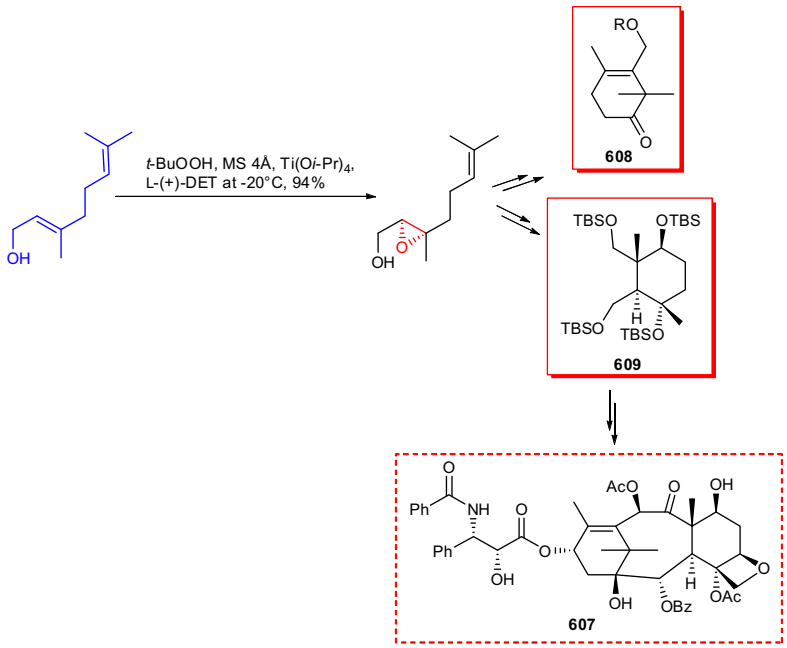
The common intermediate **596** was prepared from (±)-**597** by the improved route shown in Scheme 139. The configuration of 2[3-hydroxy group of **598** was first converted into isomer **599**, which provided epoxide **600** under Sharpless asymmetric epoxidation conditions. The α-isomer **598** afforded no epoxide under the employed conditions due to the equatorial nature of the β-hydroxy group of **598**. The epoxide **600** was then converted into the common intermediate **596** to give the desired compound **594** and **595** (Scheme 139).[289]

Cerbanoids, a 14-membered cyclic diterpene family are of interest to synthetic chemists and biologists because of their unusual structures and wide range of biological activities[290] Sinulariol-B **601**,[291] a marine cembranoid, was isolated in 1987 from the southern Japan soft coral *Sinularia mayi*.

The synthesis began with *E*-geraniol **602**. Acetylation of *E*-geraniol **602** with Ac_2O in pyridine gave acetate in 98% yield, which was then converted into alcohol in 73% yield. Reaction of the alcohol with the insoluble complex of NCS and Ph_3P in dry THF yielded allylic chloride **603**. On the other hand, sulfonyl alcohol **604** was prepared from *E*-geraniol **602** using the Grieco procedure and selective oxidation with SeO_2/*t*-BuOOH. Epoxidation of the sulfonyl alcohol **603** with *t*-BuOOH in the presence of $VO(acac)_2$ gave epoxide **605** in 96% yield. Alkylation of the anion of sulfone **605** with allylic chloride **603** took place smoothly in dry THF at −78 °C to give compound



Scheme 140.



Scheme 141.

606 after which 6 more steps were needed to achieve Sinulariol-B **601** (Scheme 140).[292]

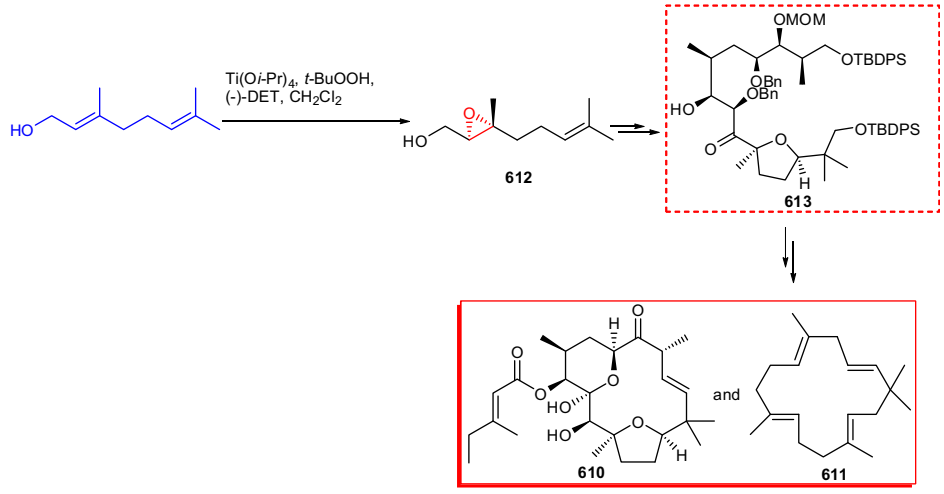
The unique diterpenoid taxol **607**, isolated from the western yew Taxus brevijolia,[293] has potent anticancer and antileukemic properties.

As Takaha et al. reported in 1997, toward the stereoselective synthesis of the A-ring **608** and the C-ring **609** as a synthetic intermediate for taxol **607**. The first step is the Sharpless asymmetric epoxidation of geraniol using L-(+)-DET in high yields. The resulting epoxide as then converted into intermediates **608** and **609** through two distinct ways, which can then be transformed into the desired compound **607** through other more steps (Scheme 141).[20]

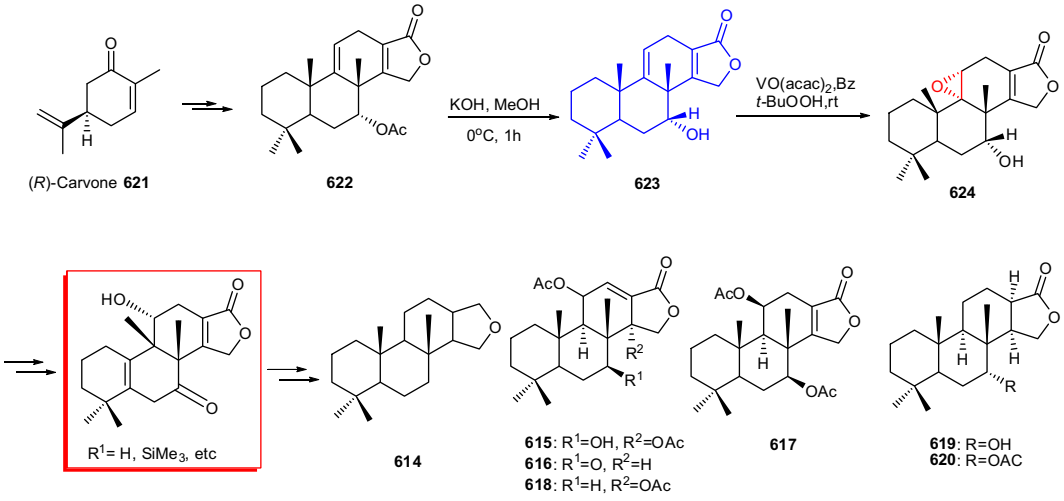
In 1997, Jakupovic and Jeske isolated a new diterpenoid from the endemic Mexican plant *Stillingia sanguinolenta* with an unknown absolute stereochemistry and named it tonantzitlolone **610**.[294] Besides flexibilene **611**,[295] it is the only 15-membered macrocyclic diterpene found in Nature so far.

In order to achieve one of the key fragments of **610**, Wittenberg et al. started from geraniol as the starting material. The Sharpless asymmetric epoxidation of geraniol using (−)-DET led to epoxide **612** which after more steps gave **613** as a possible intermediate for achieving tonantzitlolone **610** (Scheme 142).[296]

A wide range of diterpenes with the spongiane tetracyclic skeleton **614** has been isolated from various species of sponges.[297]



Scheme 142.



Scheme 143.

Such is the case of dorisenones A **615**, B **616**, C **617** and D **618**, four spongiane diterpenoids recently isolated together with other related saturated compounds, for example, **619** and **620** from the Japanese marine mollusk *Chromodoris obsoleta* (Chromodoridiidae). These dorisenones showed strong cytotoxicity against several cell lines.[298]

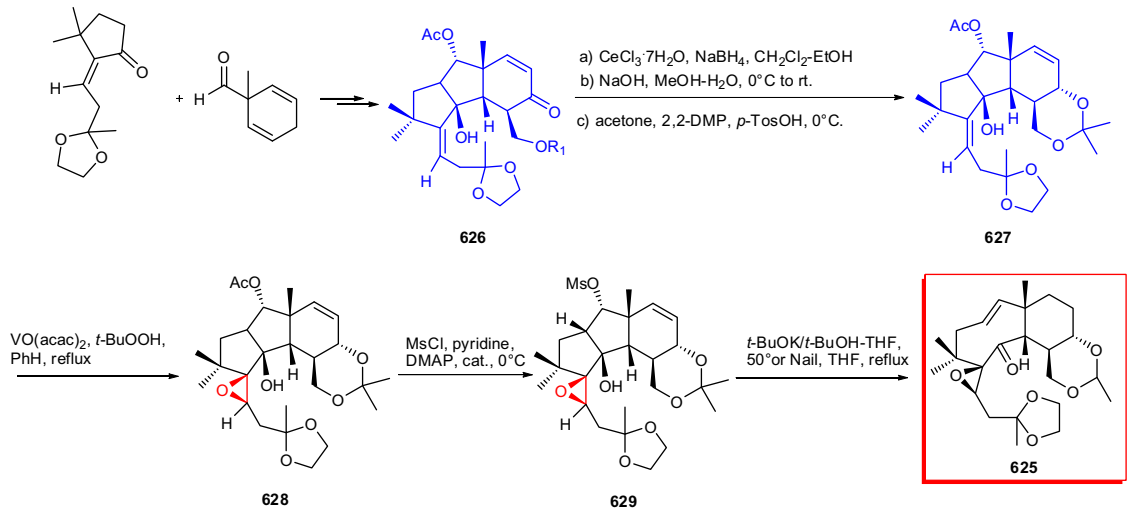
Abad et al. tried to find an efficient approach for preparing the spongiane framework in enantiomerically pure form. Hence (*R*)-carvone **621** was used as a precursor and several procedures were carried out to produce unsaturated γ-lactone **622**. Using methanolic KOH, lactone **622** was hydrolyzed to **623**.[299]

In the next step, catalytic non-asymmetric Sharpless asymmetric epoxidation conditions were employed to gain epoxy alcohol **624** which has a tetracyclic natural spongiane shape frame. Treatment of **624** with BF_3–etherate in benzene resulted in a smooth reaction to give, after 8 h, a 7:3 mixture of two chromatographically homogeneous products in 88% yield; the major product of this mixture was the ketone **625** which possibly will turn in to dorisenones A–D and other related saturated compounds (Scheme 143).[299]

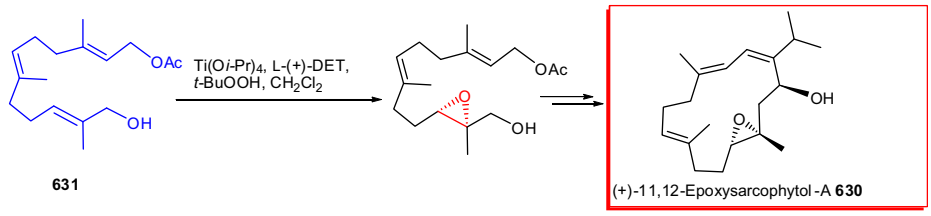
Arseniyadis et al. in 1998 were concerned with the development of a strategy for the synthesis of the bridged-fused tricyclic diterpene skeleton I. They presented an aldol-annelation-fragmentation method for the stereoselective synthesis of A-seco taxane framework **625** in 12 steps.[300]

Aldol **626** was obtained in enantiomerically pure form through a resolution sequence. Enone reduction with $NaBH_4$, in the presence of $CeCl_3$ and subsequent treatment with 2,2-dimethoxy propane (DMP), and a catalytic amount of *p*-TsOH furnished the corresponding acetonide **627** (98%). The introduction of the C-1 stereogenic center required chemo- and stereoselective epoxidation of the C1–C14 double bond. This was achieved by using Sharpless conditions to afford target compound **628** in over 98% isolated yield. From **628**, a straightforward functional group manipulation completed the synthesis of **625**. Acetate hydrolysis at C-9 followed by mesylation set the stage for the introduction of the requisite leaving group. With mesylate **629** in hand, all that remained in the synthesis of the target molecule **625** was the C2–C10 cleavage, which was achieved by treating mesylate **629** with either *t*BuOK or *t*BuOH to afford a 72% isolated yield of the desired eight-membered ring containing BC-subunit **625** along with unreacted mesylate **629** (Scheme 144).[301]

Cembranoids, a family of 14-membered cyclic diterpenoid natural products existing in terrestrial, and especially in marine



Scheme 144.



Scheme 145.

organisms,[302] are of great interest to synthetic organic chemists and biologists because of their unique structures and wide range of biological activities.[303]

(+)-11,12-Epoxysarcophytol A **630**, an epoxy cembrane diterpene, was first isolated by Bowden et al. in 1983 from an Australian marine soft coral *Lobophytum* sp. and characterized spectroscopically and chemically as (1*Z*,3*E*,7*E*)-14-hydroxyl-11,12-epoxycembra-1,3,7-triene.[304]

The synthesis started with *trans*, *trans*-farnesol derivative **631** as a precursor. In the first step, Sharpless asymmetric epoxidation conditions were used to add an epoxide to the precursor enantioselectively. After 5 more reactions the target molecule was obtained with an overall yield of ca. 42% (Scheme 145).[305]

Naturally occurring cembranoid epoxides (cembranoxides) have been found as chemical components of various tropical marine soft corals and represent a class of oxidative metabolites of cembrane diterpenes. (+)-11,12-Epoxycembrene-C **632**, another cembrane epoxide, was first isolated in 1978 by Bowden et al.[306] from the Australian soft coral *Sinularia grayi*, which has subsequently been found in various marine soft corals, that is, *Nephthea* sp.[307] *Lobophytum* sp.,[308]and *Sinularia* sp..[309]

Starting from readily available geranyl acetate **633**, several reactions were needed to obtain ester **634**. Reduction of ester **634** gave allylic alcohol **635** in 92% yield, which was epoxidized under Sharpless asymmetric epoxidation conditions with D-(−)-DET to afford epoxy alcohol **636** in 85% yield and with 95% ee. Standard iodination of **636** and subsequent reductive dehalogenation of the corresponding intermediary iodide with $NaBH_3CN$ furnished the title compound **632** (Scheme 146).

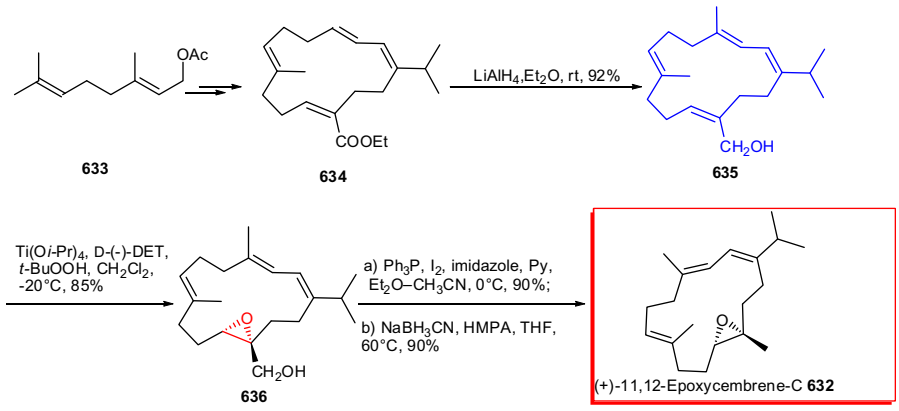
Kalihinane-type diterpenoid possessing either *cis*- or *trans*-decalin and tetrahydropyran or tetrahydrofuran as its basic skeleton, is a highly functionalized marine diterpenoid, bearing isocyano, sothiocyanato, formamide, hydroxy, and/or chlorine groups.[310]

Kalihinene X **637**, isolated from the Japanese marine sponge, Acanthella cavernosa, by Fusetani in 1995, is a kalihinane-type diterpene formamide with *cis*-decalin and chlorinated tetrahydropyran moieties.[311]

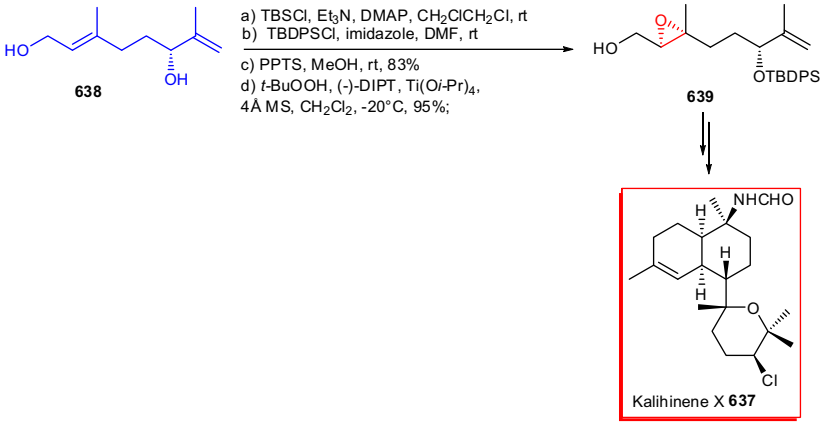
The synthesis of kalihinene X **637** was conducted starting from the known (*E*,*R*)-3,7-dimethylocta-2,7-diene-1,6-diol **638** (97% ee) (Scheme 2). The primary hydroxyl group in diol **638** was protected as the TBS ether and the secondary hydroxy group, as TBDPS ether. Selective methanolysis of TBS ether afforded allylic alcohol. Epoxidation of the allylic alcohol according to the Sharpless procedure gave epoxide **639** as a diastereomeric mixture (10:1). Ten more steps were required to obtain target compound **637** (Scheme 147).[312]

Aromadendranes are a family of hydroazulenes and the related sesquiterpenoids (−)-epiglobulol **640a**, (−)-4α,7α-aromadendranediol **640b**, and (−)-4β,7α-aromadendranediol **640c** are prevalent in plant species.[313] Echavarren et al. reported the synthesis of aromadendranes **1a–c** from (*E*,*E*)-farnesol **641**. The first step involved Sharpless asymmetric epoxidation on (*E*,*E*)-farnesol **641** to provide the epoxide (*S*,*S*)-**642** (88% yield, 91:9 er). Three independent pathways, each containing six steps, led to the formation of aromadendranes **1a–c** (Scheme 148).[314]

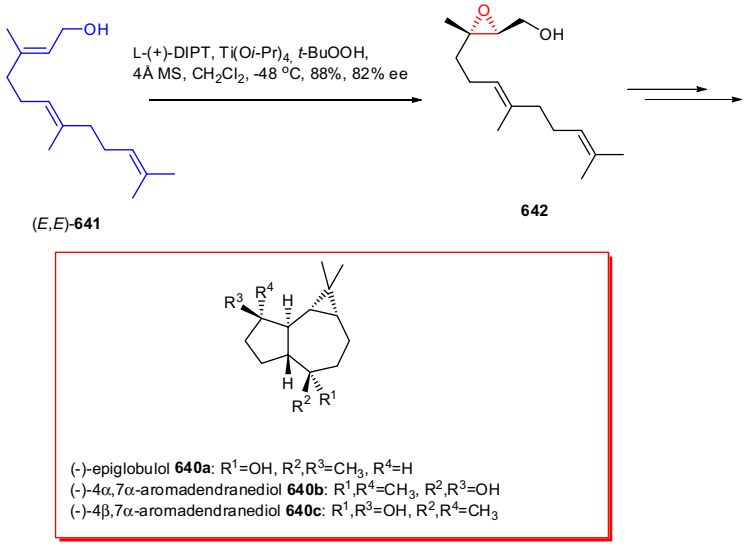
The sclerophytins are classified as polyoxygenated diterpenes of the cladiellin family of marine natural products.[315] In 1989 Alam et al. reported the isolation of sclerophytin F **643** from the soft coral *Sclerophytum capitalis*. This report also includes the date concerning the elucidation of its structure.[316] Encouraged by this success, Clark et al. attempted the total synthesis of **643** using alcohol **644** as the starting material. First, the latter was converted into allylic alcohol **645**, which afforded the epoxide **646** upon exposure to Sharpless asymmetric epoxidation conditions. DIBAL-H reductive opening of this epoxide at the expected terminal position afforded sclerophytin F **643** (Scheme 149).[317]



Scheme 146.

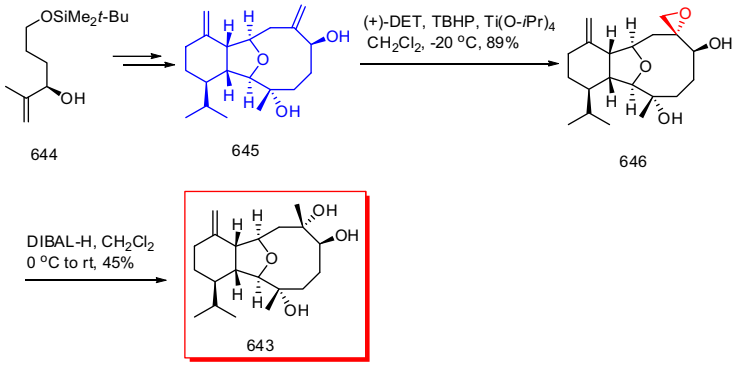


Scheme 147.



Scheme 148.

Extracts from the *Schisandra* genus of herbal plants are used in Chinese herbal medicines and are recommended by Chinese medicos. Three examples are lancifodilactone I **647** and rubriflordilactones A **648** and B **649**. The synthesis of the AB ring system in compound **650**, that is in the majority of *Schisandra* nortriterpenoid natural products has been reported by Anderson et al. Their pathway started with but-2-yne-1,4-diol **651**, which was converted into allylic alcohol **652**. The latter was subjected to Sharpless

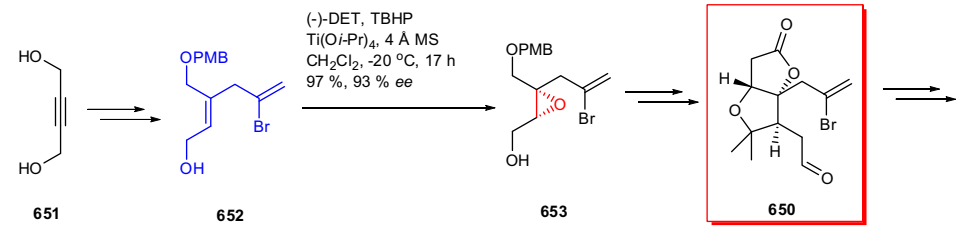


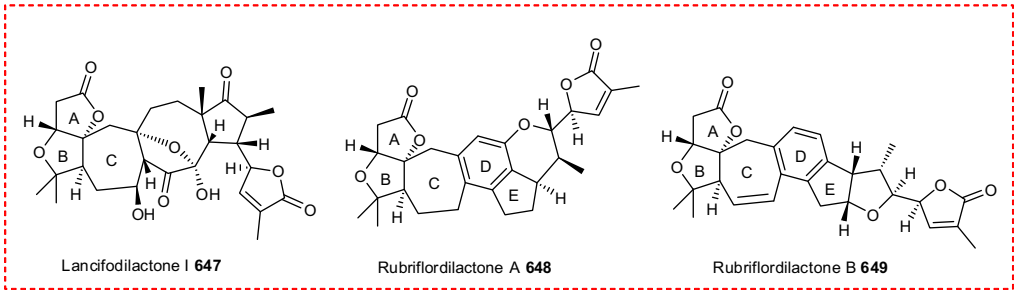
Scheme 149.

asymmetric epoxidation conditions in which epoxide **653** was obtained. The latter after twelve steps produced the desired compound **650** (Scheme 150).[318]

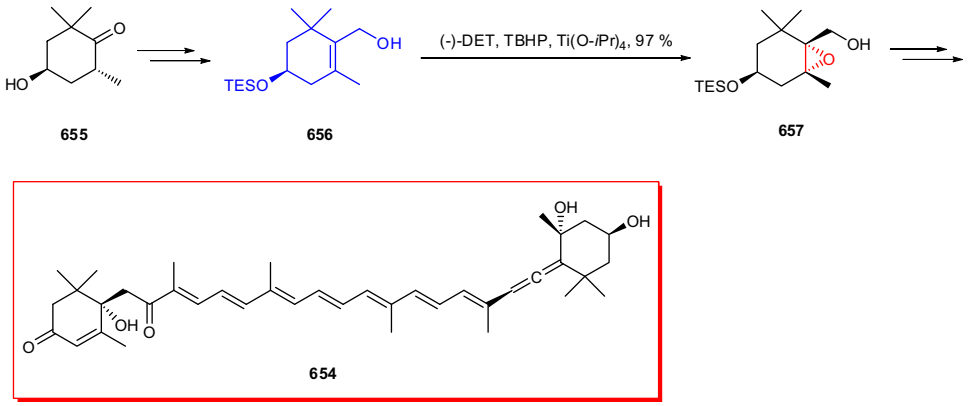
Amarouciaxanthin A **654**, which has a novel γ-hydroxy cyclohexenone moiety, was first isolated from the tunicate *Amaroucium pliciferum*.[319] Amarouciaxanthin A **654** showed remarkable suppress adipocyte differentiation.[320] Yamano et al. reported the total synthesis of amarouciaxanthin A **654** starting with (−)-actinol **655** which was transformed into allylic alcohol **656**. The latter upon Sharpless asymmetric epoxidation conditions produced epoxide **657**, which after ten steps led to the formation of the desired amarouciaxanthin A **645** (Scheme 151).[321]

Indole terpenoids have been of interest from a chemical, biological, and biosynthetic point of view. Sespenine **658** is an

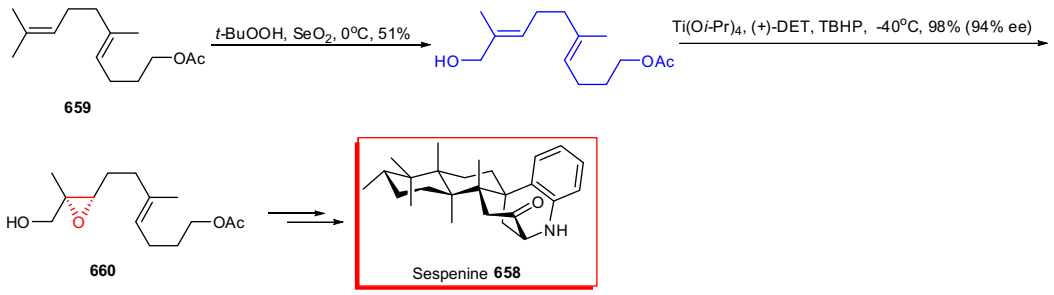




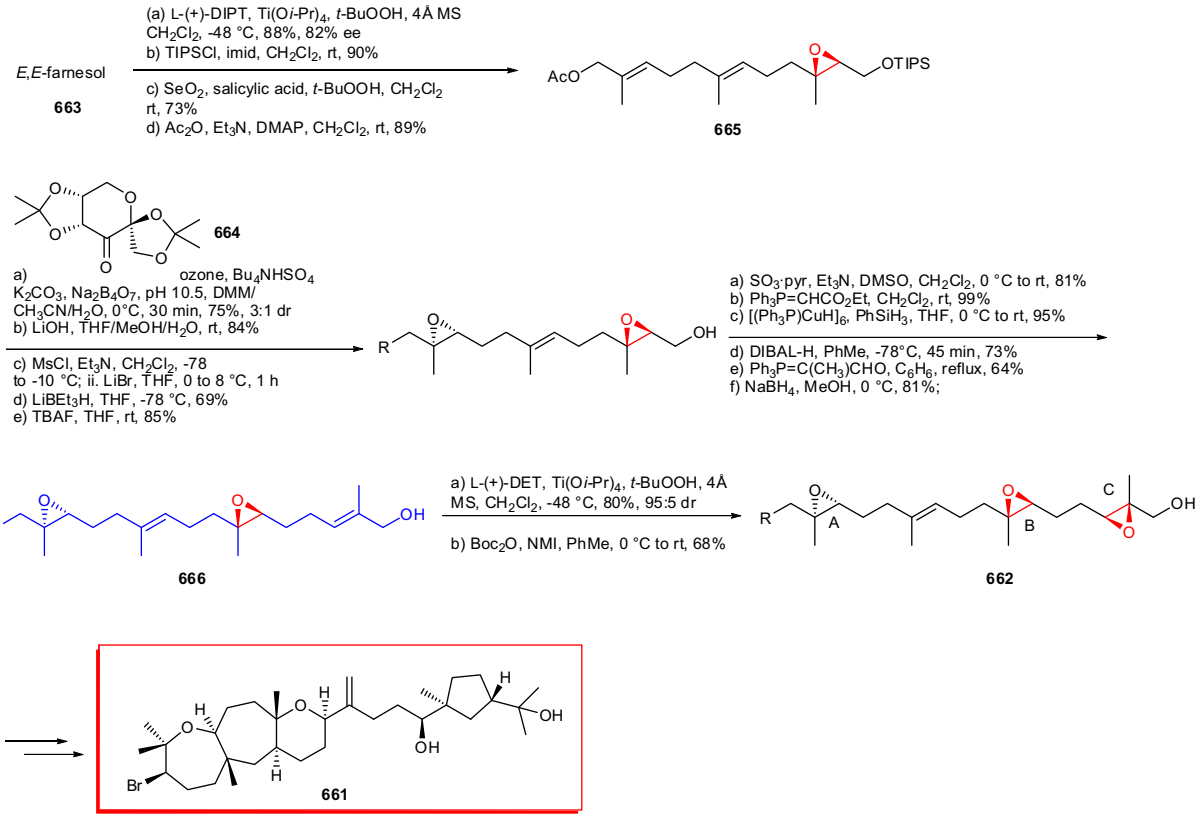
Scheme 150.



Scheme 151.



Scheme 152.



Scheme 153.

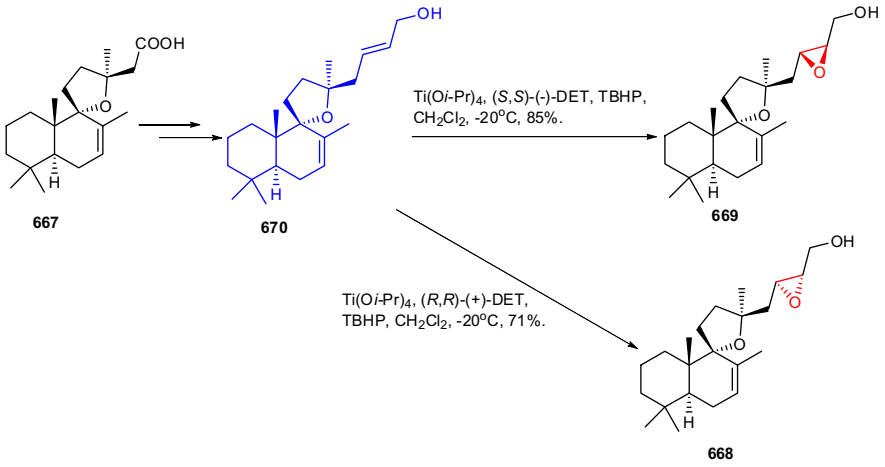
indolosesquiterpenoid derivative. In 2011, it first was isolated from an endophytic *Streptomyces*.[322] It contains a spiro-tetrahydroquinoline[323] backbone attached to a cyclic ketone bridge, which is remarkably similar to the fungal (*Aspergillus*) metabolite aspernomine.[324]

Its total synthesis started from allylic oxidation of the already known compound **659** which was subjected to Sharpless asymmetric epoxidation to give the epoxy alcohol **660** in 50% overall yield and with excellent 94% ee. Several more steps involving the indosespene-type intermediates, including a titanium-(III)-catalyzed radical cyclization followed by acid-promoted indole conjugate addition were required to afford the Sespenine **658** (Scheme 152).[325]

Dioxepandehydrothyrsiferol1 **661**, is classified as squalene-derived bromotriterpenes which is isolated from the red algae of the genera *Laurencia* and *Chondria*.[326] The latter has a unique structural motif, a *trans–anti–trans* topography, instead of the more frequently observed *trans–syn–trans* at junctions between fused oxygen heterocycles.[327]

The synthesis of the left-hand triepoxide segment **662** started by the fixing of epoxide B via Sharpless asymmetric epoxidation of (*E,E*)-farnesol **663**. Regio-selective assembly of epoxide provided **664** via transforming the C2–C3 alkene to an allylic acetate **665**. A two-carbon Wittig homologation, followed by 1,4-reduction of the obtained α,β-unsaturated ester, with subsequent reduction of the ester to the aldehyde opened a route for a second Wittig homologation, which upon 1,2-reduction formed allylic alcohol **666**. Then epoxide C was fixed by another Sharpless asymmetric epoxidation, and a well-recognized terminating nucleophile in acid-promoted cascades such as a *tert*-butyl carbonate was attached, to afford **662** (Scheme 153).[328]

Reta et al. created a small library of new derivatives from the labdane-type diterpene grindelic acid **667**. Compound **667** was selected as a starting material for the synthesis of a series of thirty-six derivatives. Many oxygenated compounds can be obtained by this method by manipulating the carboxylic acid motif. The synthesis of epoxides **668** and **669** was accomplished



Scheme 154.

via a modified K-Sharpless asymmetric epoxidation of the allylic alcohol **670** using (*R*,*R*)-(+)-DET and (*S*,*S*)-(−)-DET, respectively (Scheme 154).[329]

Aromadendranes **671a–c** are a family of hydroazulenes named after (+)-aromadendrene, which is the major constituent in the essential oil from *Eucalyptus* trees. The related sesquiterpenoid (−)-epiglobulol **671a** is prevalent in plant species[313] and has potential as antifungal,[330] antibacterial,[331] antiviral,[332] cytotoxic,[333] and also shows other activities.[334]

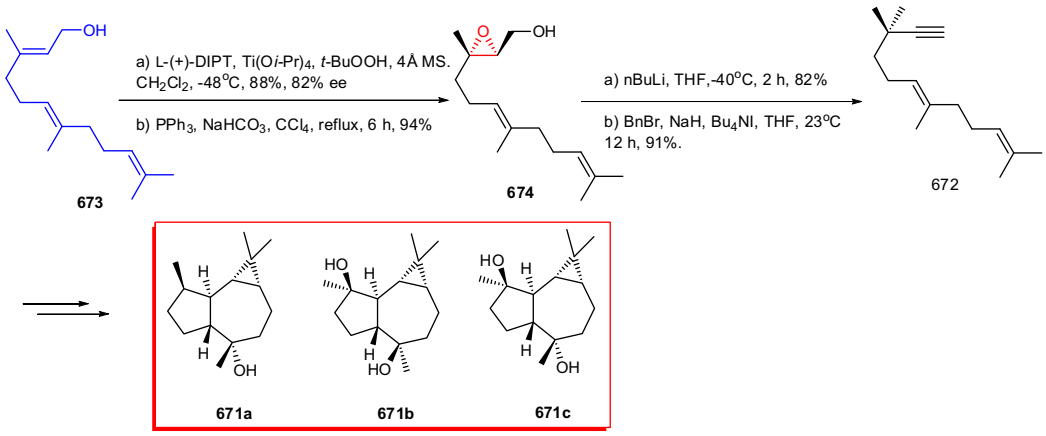
Dienyne (*S*,*E*)-**672** (R = Bn) was contemplated as an appropriate precursor for the total synthesis of Aromadendranes **671a–c**. Compound **672** was synthesized in four steps. In a key step in this transformation, (*E*,*E*)-farnesol **673** was subjected to Sharpless asymmetric epoxidation (88% yield, 91:9 er) to afford **674**. The latter was then treated with *n*-BuLi to give the propargylic alcohol which upon benzylation under typical reaction conditions provided (*S*,*E*)-**672**. Several more steps are required to obtain the target **671a–c** (Scheme 155).[335]

2.9. Macrolide

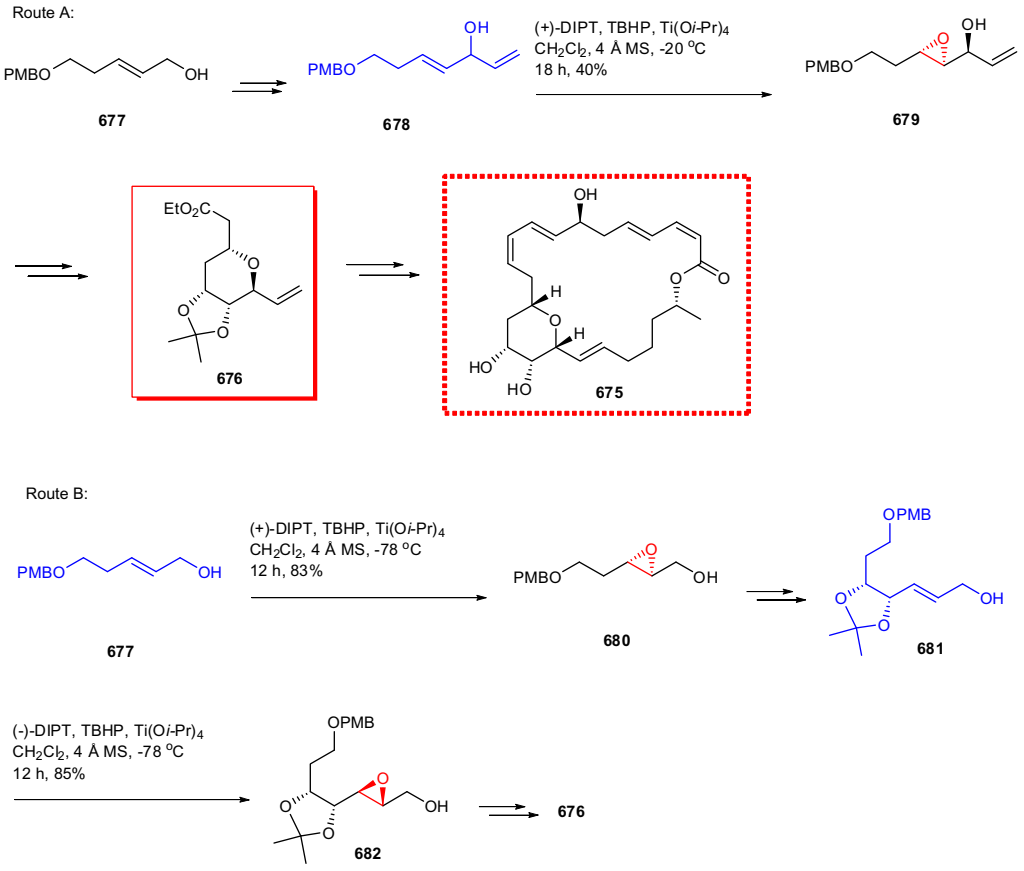
A protocol, consisting of two routes, toward the synthesis of the pyran core of macrolactin **676** was accomplished in the Palakodety Radha Krishna laboratory. Both routes commenced from the known allyl alcohol **677**. In route A, the corresponding allyl alcohol **677** was converted into the racemic divinyl methanol **678** which underwent Sharpless asymmetric epoxidation conditions to give the respective epoxy allyl alcohol **679**. The *trans*-pyran **676** was prepared from the epoxy allyl alcohol **679** in nine steps. In route B, the allyl alcohol **677** as subjected to Sharpless asymmetric epoxidation to form the epoxy alcohol **680** in 83% yield. The epoxy alcohol afforded allylic alcohol **681** in eight steps, which was subsequently transformed into chiral epoxy alcohol **682** under Sharpless asymmetric epoxidation conditions. Eight subsequent reaction steps resulted in the formation of compound **676** from the already provided epoxy alcohol **682** (Scheme 156).[336]

Marine natural products have become a major source of potently suppress molecular targets.[337] Caylobolide A **683** is one such natural product, which was extracted from the Bahamian cyanobacterium *Lyngbya majuscula* by Molinski and MacMillan.[338] It shows potent cytotoxicity toward a specific human colon tumor cell. Stereoselective synthesis of the C21–C40 core fragment of caylobolide A **684** was successfully accomplished following a pathway starting from alcohol **685**, which was transformed into the corresponding allylic alcohol **686**. The latter was then subjected to Sharpless asymmetric epoxidation conditions in the presence of (−)-DET to give epoxide **687** in high yields. Three more steps led to the formation of desired target **684** (Scheme 157).[339]

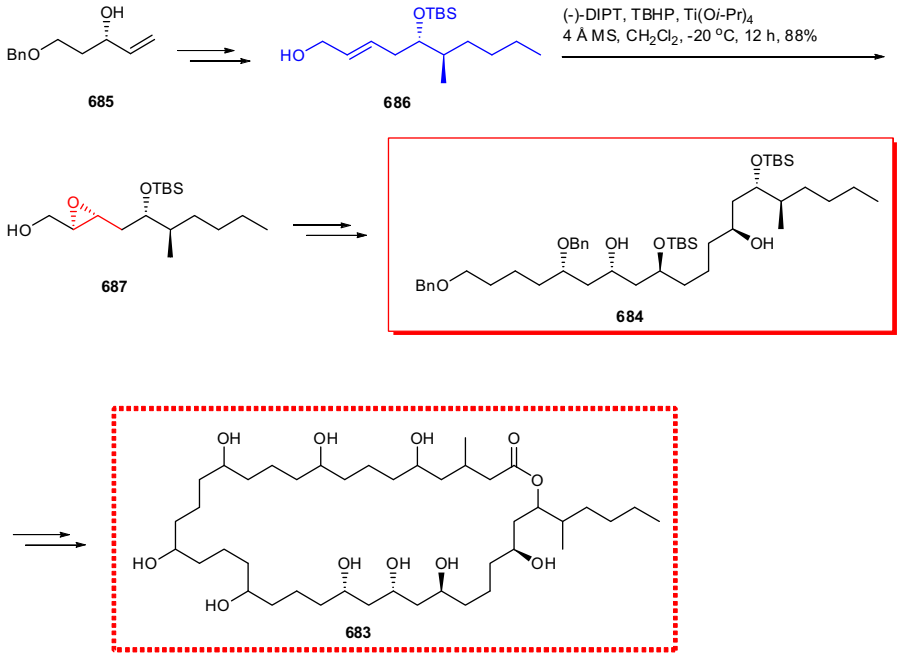
Epothilones A **688** and B **689** are examples of macrocyclic lactones.[340] For the synthesis of the macrolide epothilone B **688**, the protected derivative of C(11)–C(20) fragment **690** of epothilone B was synthesized via 10 stages starting from (*S*)-malic acid **691** in 13% overall yield. Compound **692** was synthesized from (*S*)-malic acid in several steps. The reduction of **692** led to (*Z*)-allylic alcohol



Scheme 155.



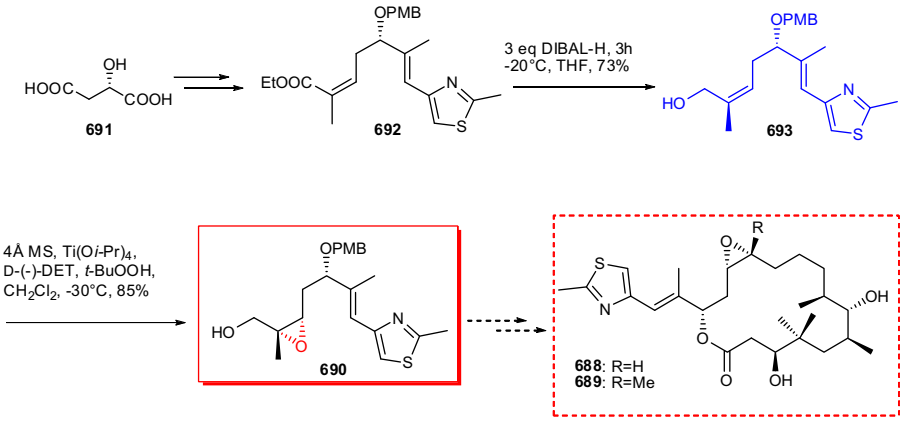
Scheme 156.



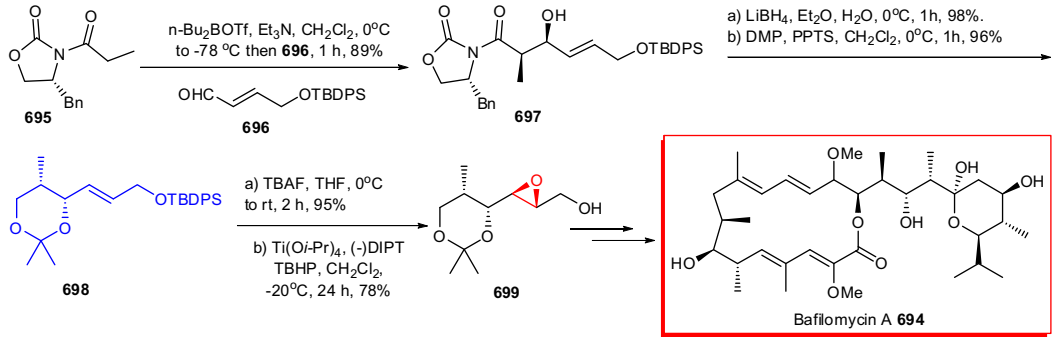
Scheme 157.

693 in 73% yield, which was then subjected to an asymmetric Sharpless asymmetric epoxidation using D-(−)-DET reagent to produce the epoxy alcohol **690** in 85% yield (Scheme 158).[341]

Bafilomycin A **694** is a 16-membered macrolide, which was first isolated from a culture of Streptomyces griseus sp. by Werner et al. in 1983.[342] Four total syntheses[343] and several partial



Scheme 158.



Scheme 159.

contributions[344] of bafilomycin A **694** have been reported by various research groups so far.

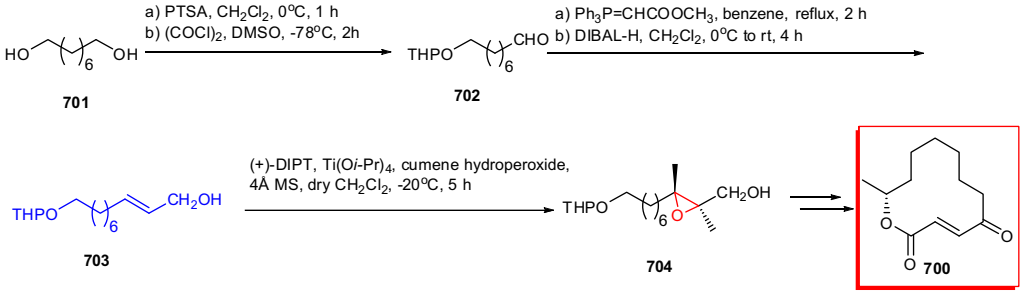
The synthesis was developed on the basis of Evans asymmetric aldol reaction. Thus, the asymmetric aldol reaction of oxazolidene **695** with aldehyde **696** provided *syn*-aldol product **697** in 82% yields as a single diastereoisomer. After reduction with $LiBH_4$, the diol was converted into the corresponding acetonide **698** in 98% overall yield over two steps. Desilylation with TBAF and then exposure of the resulting alcohol to Sharpless asymmetric epoxidation conditions afforded diastereomeric epoxy alcohol **699** in 78% yield.[345] Several more steps were required to obtain Bafilomycin A **694** (Scheme 159).[346]

Patulolides A **700**, isolated from *Penicillium urticae* S11R59, have shown antifungal, antimicrobial, and anti-inflammatory, activity and were characterized by Yamada et al.[347]

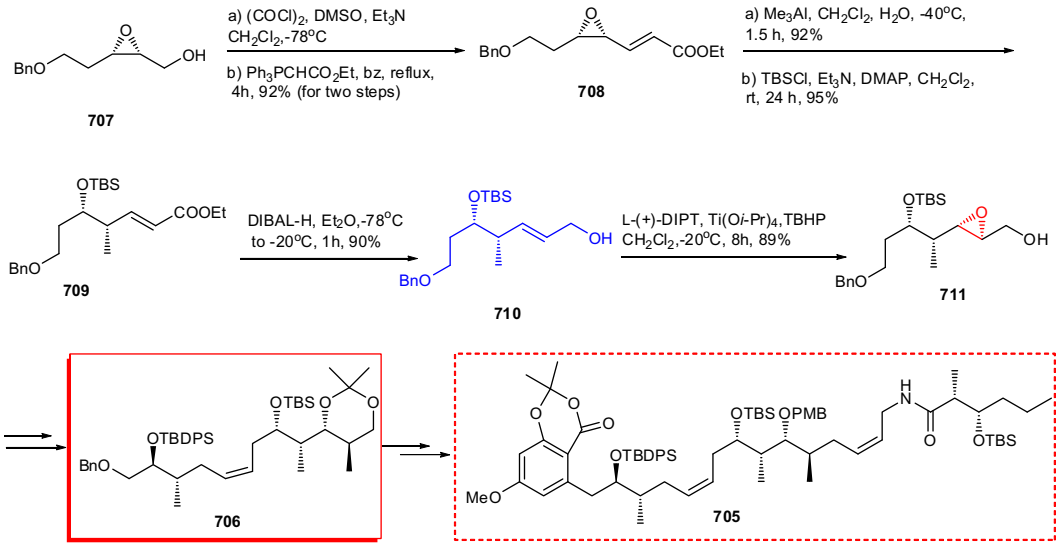
The synthesis of patulolide was initiated from commercially available 1,8-octane diol **701**. Selective monoprotection of **701** with 2,3-dihyropyran gave THP–ether in 82% yield, which upon oxidation under Swern conditions gave the corresponding aldehyde **702**. Wittig olefination of **702** furnished the α,β-unsaturated ester in 91% yield, which was reduced with DIBAL-H to allylic alcohol **703** in 81% yield. Sharpless asymmetric epoxidation of allylic alcohol **703** with (+)-DIPT afforded **704** (90%). Patulolides A **700** was obtained using 12 more steps (Scheme 160).[348]

Cruentarens A and B **705** are cytotoxic macrolides isolated from myxobacterium, *Byssovorax cruenta*. Considering their novel structures and the biological activities[349] of cruentarens, many groups focussed their attention toward the synthesis of these targets. Prasad et al. reported the synthesis of the C8–C19 segment of cruentarens A and B **706** in which the key steps involve radical cyclization, epoxide opening with trimethyl aluminum, methyl lithium and a *cis*-Wittig olefination.[350]

The synthesis began with the known *cis*-epoxy alcohol **707** (Scheme 161). The hydroxyl group was oxidized using Swern conditions to afford an aldehyde which upon Wittig olefination with the stable ylide carboethoxymethylenetriphenylphosphorane produced γ,δ-epoxy acrylate **708** in 92% yield over two steps. Upon treatment of **708** with an excess of trimethyl aluminum in the



Scheme 160.



Scheme 161.

presence of water in dichloromethane, methylation took place at the γ-position with complete regio- and stereoselectivity to afford the *syn*-alcohol as the sole product in 92% isolated yield. Protection of the OH group led to **709** which upon treatment with DIBAL reduction provided allyl alcohol **710**, which set the platform for introducing two more stereogenic centers via Sharpless asymmetric epoxidation condition. Thus allyl alcohol **710** upon treatment with L-(+)-DIPT yielded epoxy alcohol **711**. Three more steps were needed to reach the stereoselective synthesis of the C8–C19 fragment of cruentarens A and B **706** (Scheme 161).[350]

Aspergillides **712**, the first examples of 14-membered macrolactones embedded with a 2,3,6-trisubstituted tetrahydropyran (THP) moiety, were isolated from the marine fungus *Aspergillus ostianus* strain 01F313 by Kusumi et al. in 2008.[351]

For the synthesis of Aspergillide, the known epoxide **713**, derived from L-ascorbic acid, underwent 12 steps to furnish allylic alcohol **714**. Accordingly, **714** was subjected to Sharpless asymmetric epoxidation with (+)-DIPT. The epoxidation reaction resulted in the 5-*exo* cyclized furan derivative **715** (80%) as the only distinguishable product, instead of giving **716**. It was assumed that due to chelation of the titanium, the thermodynamically more stable and more favored 5-*exo* cyclization resulted in the cleavage of the benzyl ether after the formation of the epoxide, wherein the epoxide opening protocol was governed by Baldwin rules. The $Ti(O\textit{i}\text{-}Pr)_4$ was believed to be acting as an internal acid in activating the epoxide for cyclization.[352]

Due to this unexpected result, δ-hydroxy allylic alcohol **717** was used rather than allylic alcohol **714**. Accordingly, **713** (Scheme 162) upon selective cleavage of the PMB ether with DDQ gave allylic alcohol **717** in 88% yield. The tandem Sharpless asymmetric epoxidation/6-*exo* cyclization of **717** gave the desired tetrahydropyran **718**, which after further reaction steps afforded the target compounds (Scheme 162).[352]

Borrelidin **719**, a structurally unique 18-membered macrolide antibiotic possessing anti-Borrelia activity was first isolated from *Streptomyces rochei* in 1949 by Berger et al.[353] As Yadav et al. revealed, the synthesis began with precursor **720**, which was prepared earlier and utilized to make several natural products.[354] Compound **720** underwent twelve reactions consisting of hydroformylation, olefination, and reduction to yield compound **721**. Compound **721** was converted into xanthate ester, and further reduced to provide compound **722**, which was subjected to debenzylation followed by oxidation and further extension of two carbon units by a C2 Wittig reaction to yield compound **723**. The ester was reduced to an alcohol and subjected to Sharpless asymmetric epoxidation to obtain compound **724**. After 14 more steps the synthesis of C1–C11 fragment of borrelidin **725** was completed. All of the stereogenic centers were obtained through a desymmetrization strategy, Sharpless asymmetric epoxidation, regioselective opening of chiral epoxide and stereoselective alkylation using Evans' chiral auxiliary (Scheme 163).[355]

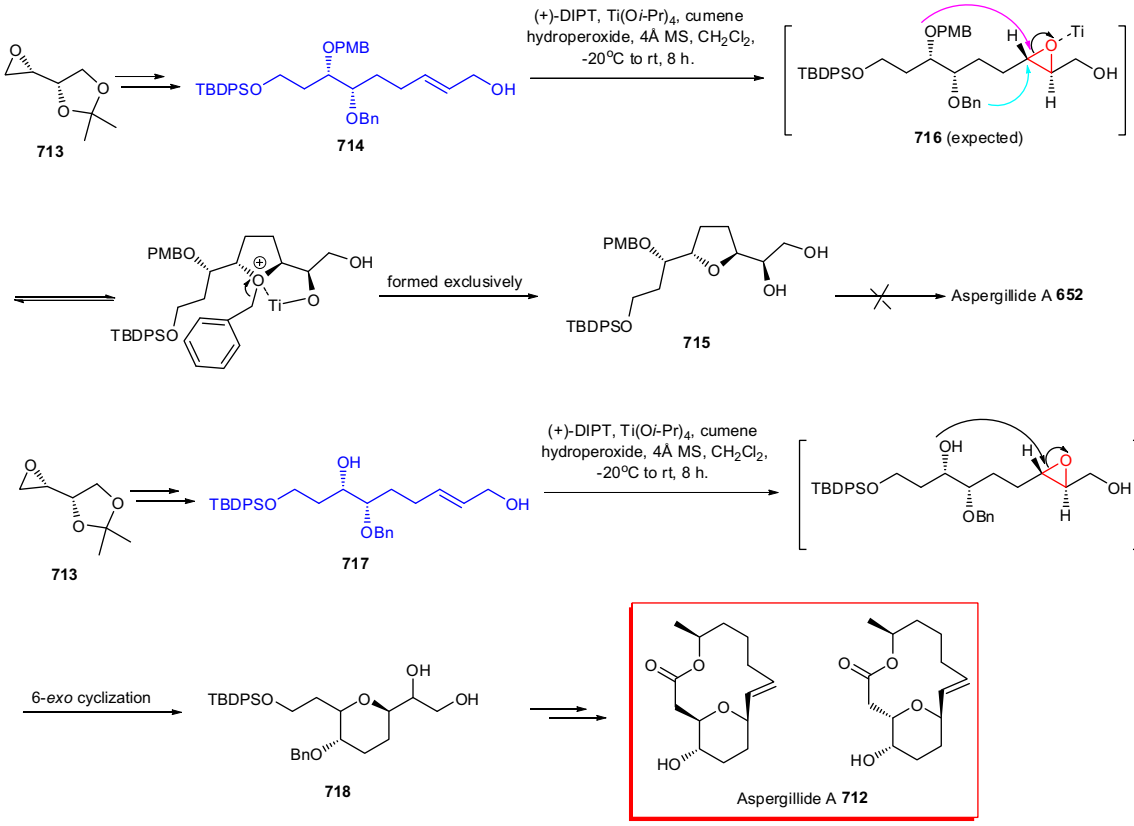
The marine macrolide laulimalide **726** (Fig. 6) was isolated in 1988 by two different groups from various marine sources.[356]

In recent years the search for simplified biologically active and more stable analogues of **726** has been pursued with high intensity to identify an optimal clinical candidate. Gollner et al. reported a strategy for replacing the C5–C9 *trans*-dihydropyran moiety by less complex motifs.

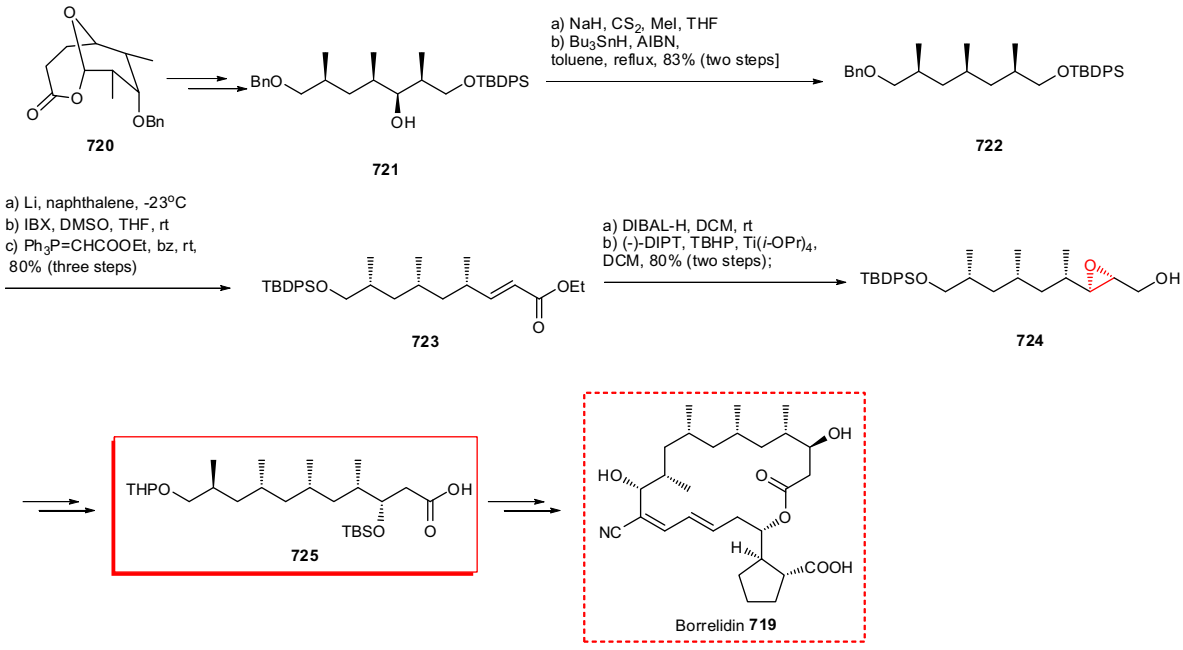
The synthesis started from allylic bromide **727**, which was obtained from the commercially available diol in four steps via a Kulinkovich reaction and subsequent cyclopropyl allyl rearrangement. 12 more steps were required for the synthesis of compound **728**. Finally Lindlar reduction to the labile *Z*-enoate was followed by selective Sharpless asymmetric epoxidation (>20:1 dr) employing the established protocol to deliver the desired analogue **729** (Scheme 164).[357]

Venturicidines A, B, and its aglycone venturicidine X **730**, 20-membered macrolide antibiotics, were isolated from several streptomyces.[358] They were obtained from the synthesis of C15–C27 fragment of venturicidine X **731** using a desymmetrization protocol, substrate-controlled Grignard reaction, Barton–McCombie reaction, Sharpless asymmetric epoxidation, and TBSOTf-mediated rearrangement to produce the aldol product through a non-aldol route as the key step following 23 longest linear sequences with 6.4% overall yield.

The synthesis began with Zn–Cu couple-mediated [4+3] cycloaddition reaction between 2,4-dibromopentan-3-one **732** and furan to form 2,4-dimethyl-8-oxabicyclo-[3.2.1]-oct-6-ene-3-ones, which underwent 18 steps to give compound **733**. IBX oxidation of **733** in DMSO and THF furnished the aldehyde, which upon Wittig homologation afforded α,β-unsaturated ester **734** favoring the desired *E*-isomer. DIBAL-H reduction of the ester afforded the corresponding allylic alcohol. Sharpless asymmetric epoxidation proceeded efficiently to produce epoxide **735** which after ring



Scheme 162.



Scheme 163.

opening led to two stereogenic centers of the target molecule. A further 6 more steps were needed to achieve the C15–C27 fragment of venturicidine X **731** (Scheme 165).[359]

Another approach for the synthesis of the C15–C27 segment of venturicidin X **736** was reported by Suzuki et al. in 2011. In this strategy Allyl alcohol **737** was used as a starting material which after 8 steps gave alcohol **738**. Alcohol **738** was converted into *trans*-allyl alcohol **739** in three steps (84%): (i) Swern oxidation; (ii) Horner–Emmons reaction; (iii) reduction with DIBAH. The Katsuki–Sharpless asymmetric epoxidation of **739** with D-DET

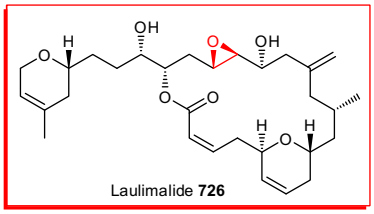


Figure 6.

proceeded smoothly to give *trans*-epoxide **740** in 85% yields. Several more steps were carried out to afford the C15–C27 segment of venturicidin X **736** (Scheme 166).[360]

The C.8(*S*)-methoxyC11 desmethyl analogue of Laulimalide **741** was synthesized by Gallagher et al. using tri-*O*-acetyl-D-glucal **742** as the starting material. The *Z*-enoate **743** was obtained from tri-*O*-acetyl-D-glucal **742** via twenty nine steps. In continuation, Sharpless asymmetric epoxidation of compound **743** produced the desired analogue **741** in 50% yield (Scheme 167).[361]

Another approach to Laulimalide **726** has been reported by Mulzer et al. starting from aldehyde **744**, which produced allylic alcohol **745** in nineteen steps. The final step of the procedure was the Sharpless asymmetric epoxidation of allylic alcohol **745** to obtain laulimalide **726** in 70% yield (Scheme 168).[336]

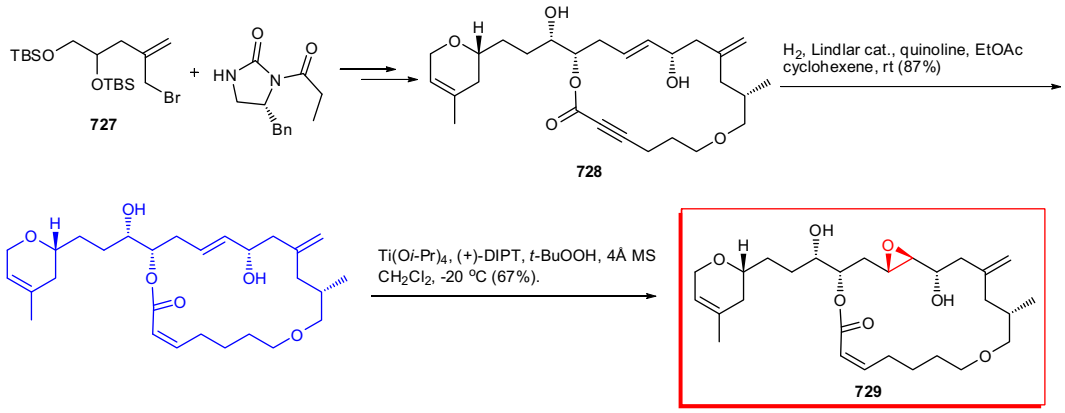
There was another approach to laulimalide **726** reported by Mulzer et al. which is similar in the final step. An α,β-unsaturated lactone **746** was used as the starting material in this approach (Scheme 169).[362]

A stereocontrolled synthesis of the C15–C27 fragment of laulimalide **747** has been reported starting from (*R*)-oxiran-2-yl-methanol **748** which after several steps gave allylic alcohol **749**. Sharpless asymmetric epoxidation of **749** using (+)-DET as the key step afforded epoxide **747** in 55% yield and a diastereomeric ratio of 94:6 (Scheme 170).[363]

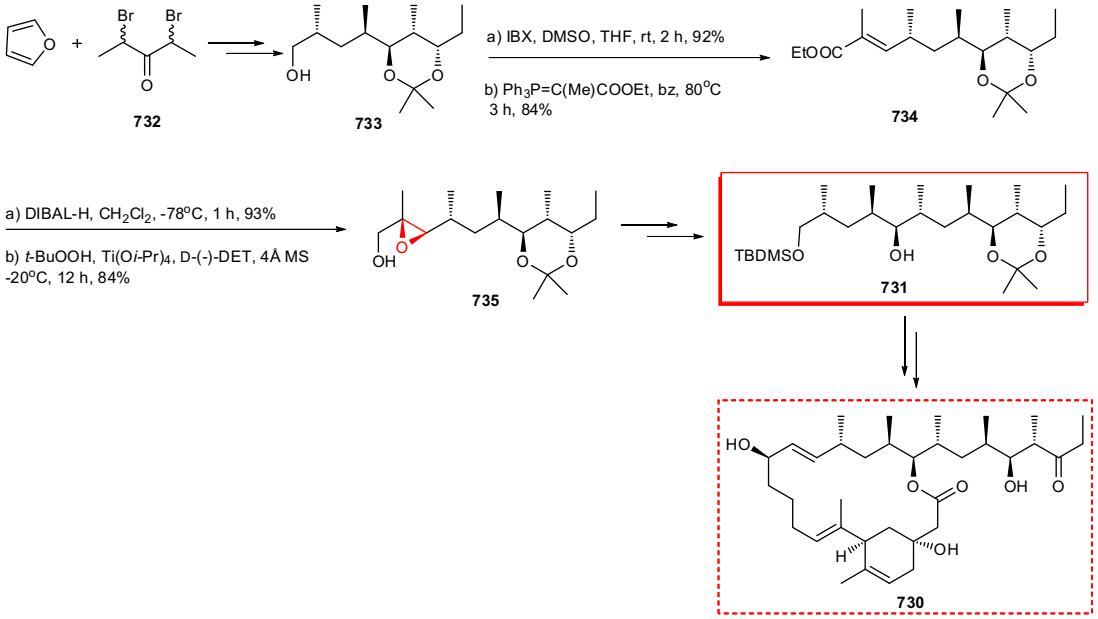
The unusual, novel 16-membered diolides, clavosolides A–D **750** were isolated from extracts of the marine sponge *Myriastra clavosa* collected in the Philippines.[364]

The symmetric structure of the 16-membered core diolide ring in these molecules, with highly substituted tetrahydropyran units, disubstituted cyclopropyl rings, and permethylated D-xylose moieties, makes them challenging synthetic targets.[365]

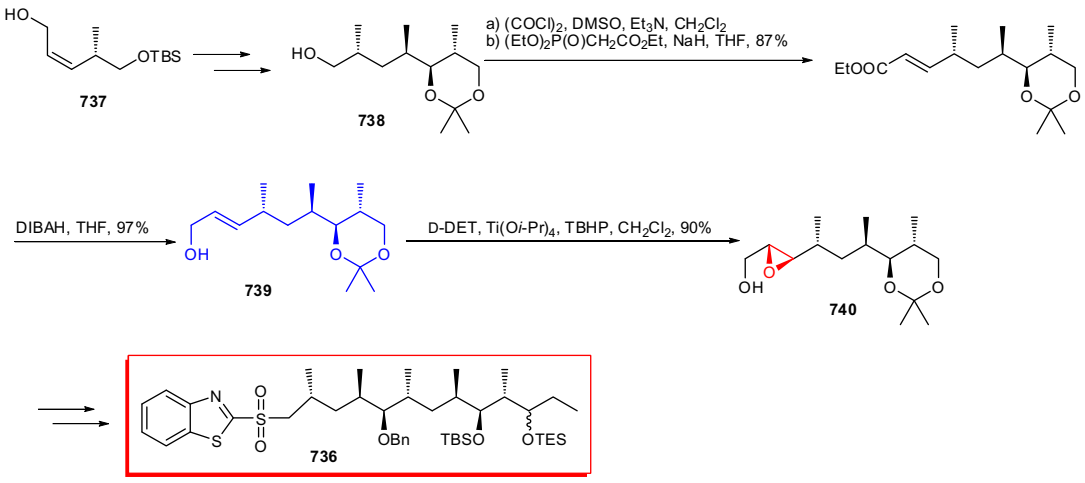
The synthesis started with the appropriately protected intermediate **751**. A three-step process involving, oxidation,



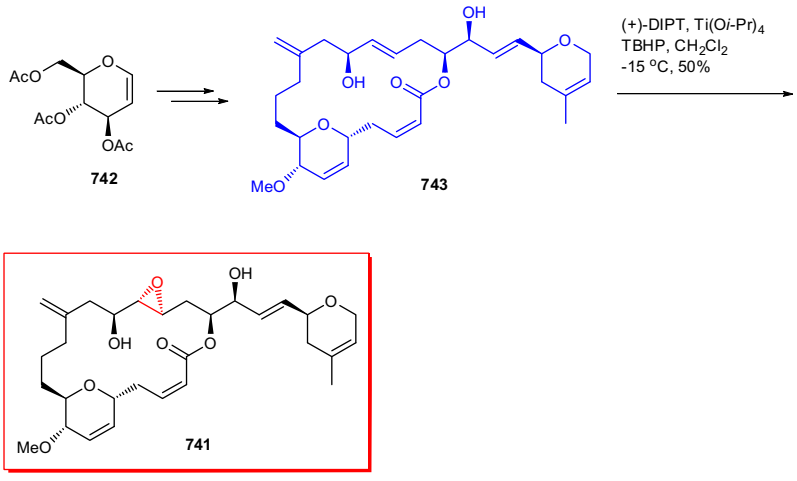
Scheme 164.



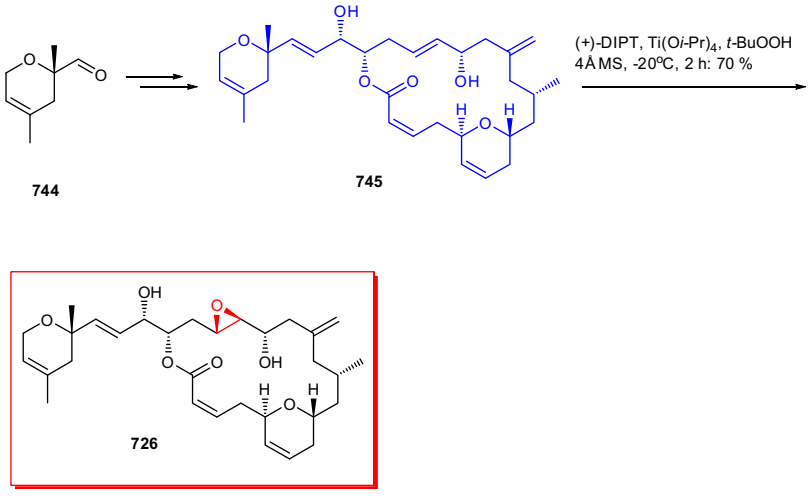
Scheme 165.



Scheme 166.



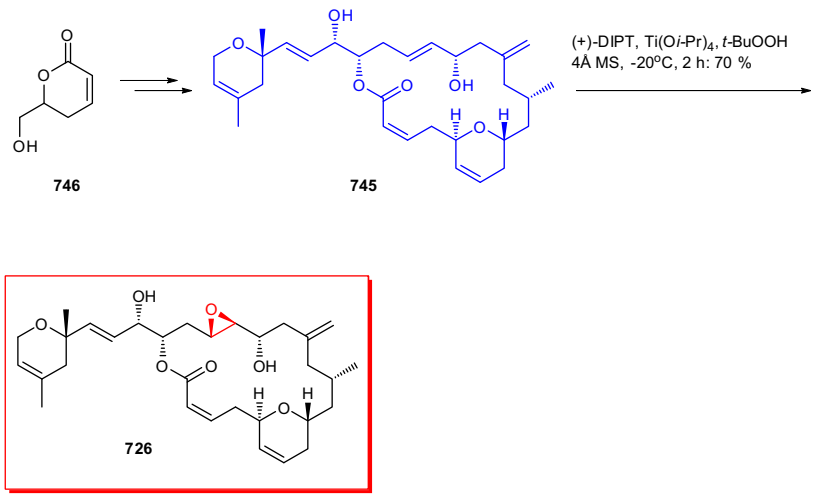
Scheme 167.



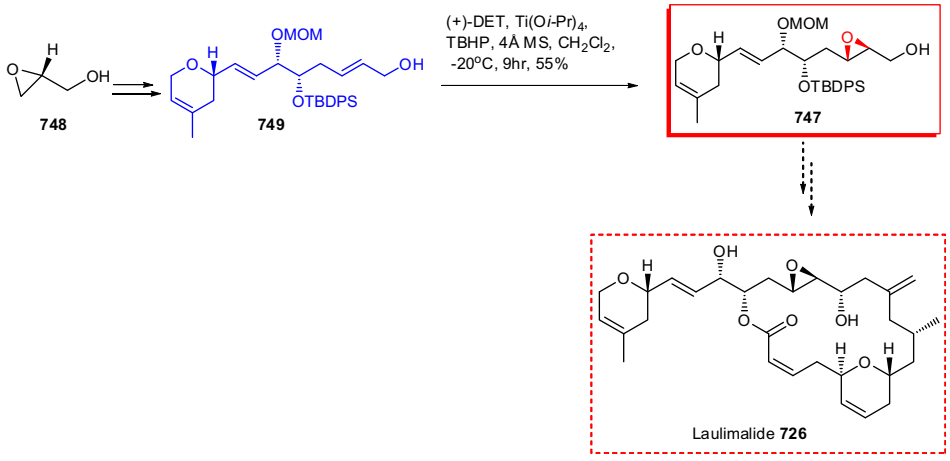
Scheme 168.

olefination, and reduction converted **751** into the corresponding allylic alcohol **752** in high overall yields. Sharpless asymmetric epoxidation of **752** using (−)-DIPT afforded epoxy alcohol **753** (de >96%), which was then converted into the desired molecule **750** through several other steps (Scheme 171).[365]

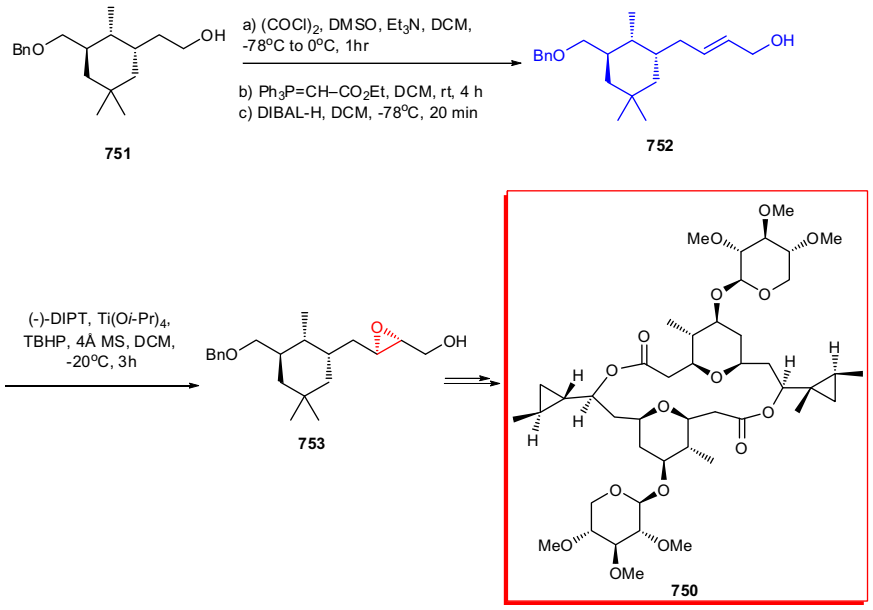
A highly stereoselective and efficient approach for the synthesis of the C_2–C_{12} segment of Borrelidin **754** has been developed starting from *meso*-2,4-dimethyl-1,5-pentandiol **755** which was converted into the bis-allylic alcohol **756**. Bis-epoxide **757** was achieved by Sharpless asymmetric epoxidation of bis-allylic



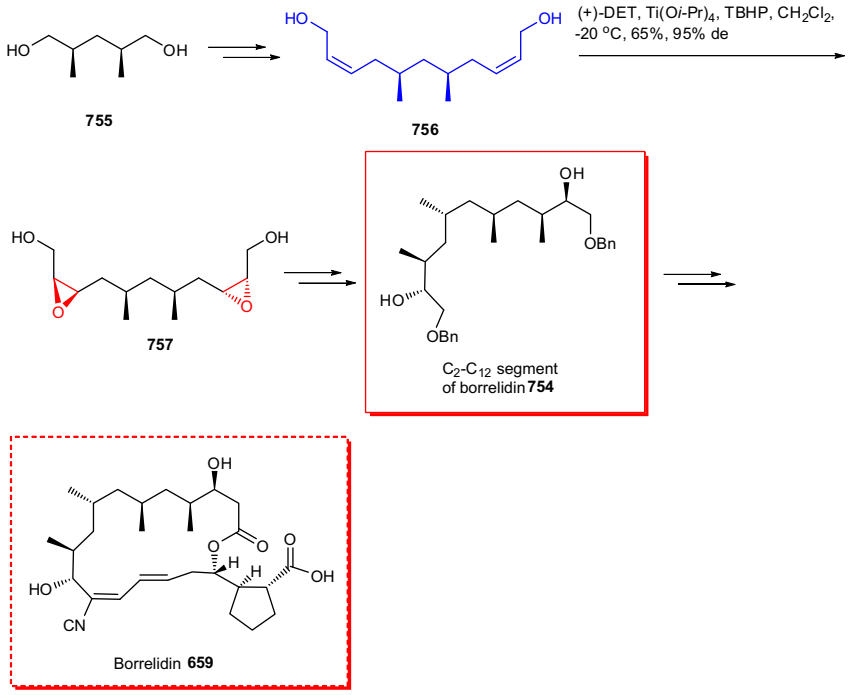
Scheme 169.



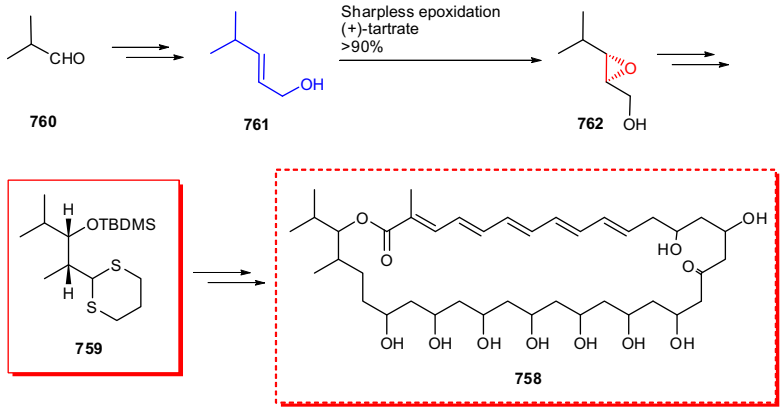
Scheme 170.



Scheme 171.



Scheme 172.



Scheme 173.

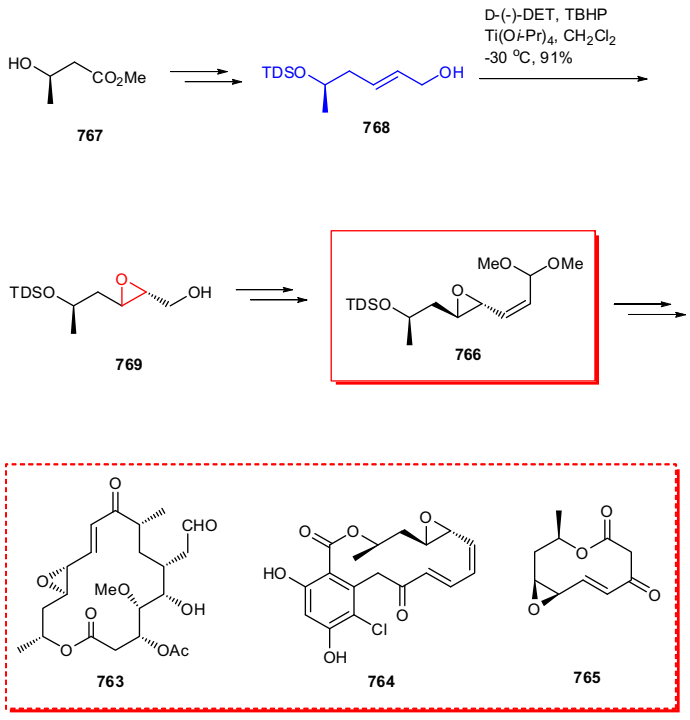
alcohol **756** using (+)-diethyl tartrate. Two other steps transformed bis-epoxide **757** into compound **754** (Scheme 172).[366]

The polyene macrolides, by virtue of their potent antifungal properties, constitute an important class of clinically valuable natural products.[367] As part of the total synthesis of 36-membered macrolide Roflamycoin **758**, Lipshutz et al. reported the synthesis of key sections of it including compound **759**. First, isobutyraldehyde **760** was transformed into allylic alcohol **761** which was then converted into epoxy alcohol **762** upon Sharpless asymmetric epoxidation in 90% yield. Finally, four other reaction steps gave the desired compound **759** as a key section for the total synthesis of Roflamycoin **758** (Scheme 173).[368]

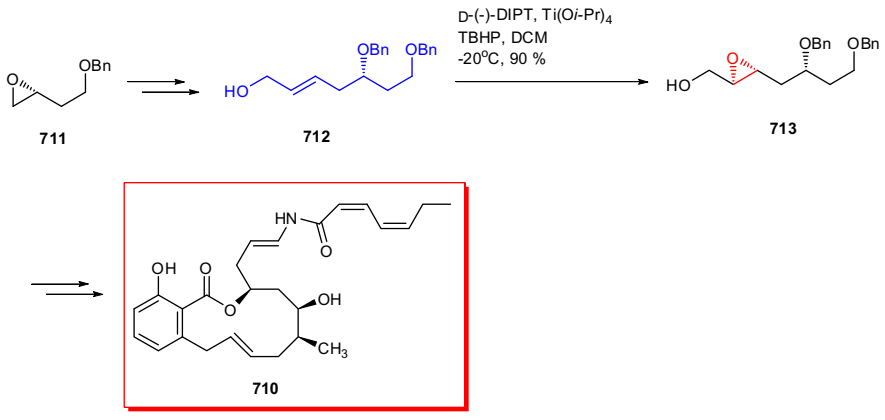
Numerous macrocyclic natural products such as the aglycon of carbomycin A **763**, radicicol **764** and decarestrictine F **765** embody a β-hydroxyvinyl epoxide unit. Therefore, the development of an efficient synthetic route to such a building block would be highly desirable. The synthesis of a protected β-hydroxyepoxide macrolide building block **766** from commercially available (*R*)-3-hydroxybutyric acid methyl ester **767** in 68% overall yield has been described. Thus, (*R*)-3-hydroxybutyric acid methyl ester **767** was converted into the allylic alcohol **768** which upon Sharpless asymmetric epoxidation gave epoxy alcohol **769** in 91% yield. Finally, the silyl-protected vinyl epoxide **766** was obtained through other two steps (Scheme 174).[369]

Salicylihalamide **770** is a macrolide isolated from *Haliclona* genus (South-Western Australian coast), which exhibited cytotoxicity against a 60-cell line human tumor assay with GI_{50} of 15 nM.[370] Starting from epoxide **771**, salicylihalamide **770** was prepared through allylic alcohol **772**, which upon Sharpless asymmetric epoxidation gave epoxy alcohol **773** in 90% yields. At the end, the epoxy alcohol **773** was converted into salicylihalamide **770** through more than twelve steps (Scheme 175).[371]

Aigialomycin D **774** is a resorcyclic macrolide, which was isolated from the mangrove fungus, *Aigialus parvus* BCC 5311.[372] Xinfu et al. used propargyl alcohol **130** as a starting material which upon two steps gave allylic alcohol **775**. The strategy was



Scheme 174.



Scheme 175.

continued by Sharpless asymmetric epoxidation of **775** to gain epoxy alcohol **776** in 89% yields. Fifteen other steps completed the synthesis of aigialomycin D **774** (Scheme 176).[373]

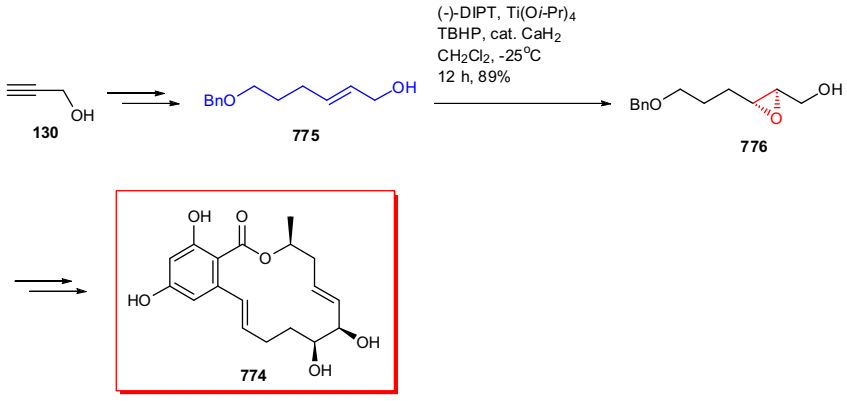
Aspicilin **777** is a polyhydroxylated, eighteen membered macrolide isolated from the lichen of the Lecanoraceae family.[374] (3*R*,4*R*)-1,5-Hexadiene-3,4-diol **778** has been used as starting material in a strategy developed by Hou et al. for the total synthesis of aspicilin **777**. The synthesis began with the mono-protection of **778** with a methoxymethyl (MOM) group. The resulting allylic alcohol **779** underwent Sharpless asymmetric epoxidation to give the epoxide **780** in 69% yield which then was used to produce aspicilin **777** in ten steps (Scheme 177).[375]

Pattenden et al. have synthesized the iodostannyl ester **781** as a key precursor for the synthesis of amphidinolide B **782**. The synthesis began with methyl hydrogen (*R*)-3-methylglutarate **783**, which was converted into allylic alcohol **724** through six steps. Then, Sharpless asymmetric epoxidation of compound **784** resulted in epoxy alcohol **785** in 62% yield. Finally, the iodostannyl ester **782** was obtained from compound **785** through seven steps (Scheme 178).[376]

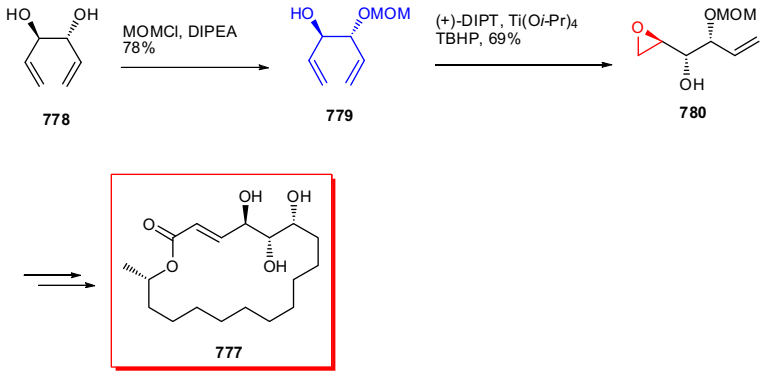
Amphidinolides G **786** and H **787** are important components of cancer chemotherapy.[377] A stereoselective synthesis of the C1–C18 segment of amphidinolides G and H **788** started from methyl hydrogen (*R*)-3-methylglutarate **789** which was converted into the allylic alcohol **790**. Upon Sharpless asymmetric epoxidation conditions, the latter was converted into epoxide **791**. Starting from the latter, six further steps gave **788** (Scheme 179).[378]

Rapamycin **792** is an immunosuppressive agent. The C_{10}–C_{17} carbon portion of rapamycin **793** as synthesized by Leg et al. Allylic alcohol **794** was used as a starting material, which upon Sharpless asymmetric epoxidation gave epoxy alcohol **795** in 75% yield. Compound **793** was prepared from epoxy alcohol **795** through fifteen steps (Scheme 180).[379]

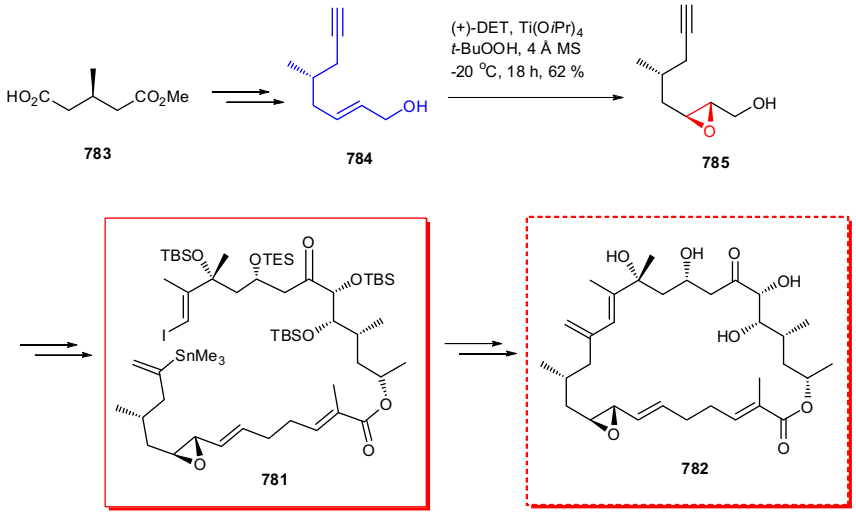
The structurally complex spongipyran macrolides, altohyrtins **796**, exhibit extraordinarily potent cytotoxicity against human



Scheme 176.



Scheme 177.

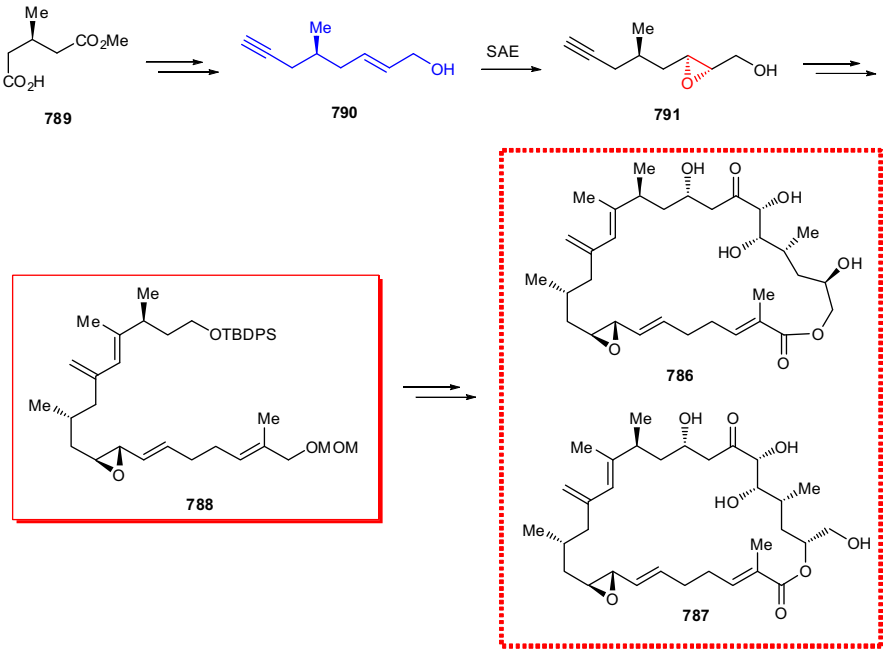


Scheme 178.

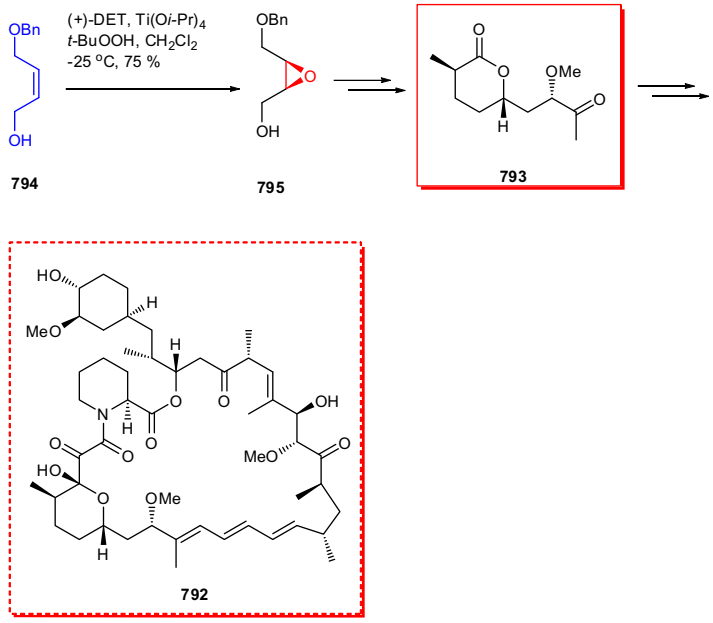
cancer cell lines.[380] A protected F-pyran fragment **797** has been synthesized using α,β-unsaturated aldehyde **798**. Asymmetric epoxidation of allylic alcohol **799** into epoxy alcohol **800** by means of Sharpless methodology was a key step in this strategy. A further thirteen steps led to the formation of the desired compound **797** (Scheme 181).[387]

(−)-Spongidepsin **801** was isolated from the sponge *Spongia* sp. collected from the waters of the Vanuata Islands, Australia.[382] First, commercially available (+)-methyl-L-β-hydroxyisobutyrate (Roche ester) **802** was converted into allylic alcohol **803**, which upon Sharpless asymmetric epoxidation gave epoxy alcohol **804** in 88% yield. Epoxy alcohol **804** was transformed into (−)-spongidepsin **801** through more than twelve steps (Scheme 182).[383]

Macrosphelides were isolated as inhibitors of the adhesion of HL-60 cells to a monolayer of LPS-activated human-umbilical-vein endothelial cells. Macrosphelides I **805** and G **806** were isolated from a strain of *Periconia byssoides* separated from the gastrointestinal tract of the sea hare *Aplysia kurodai*.[384] The initial steps of the synthesis of these two compounds were similar. (*S*)-Lactic acid **807** resulted in allylic alcohol **808** which underwent



Scheme 179.

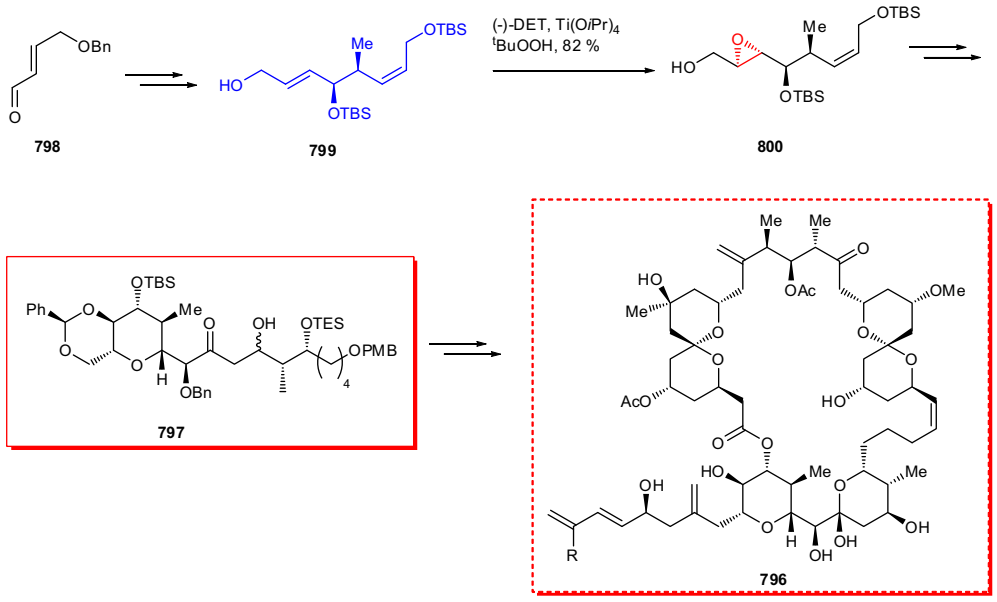


Scheme 180.

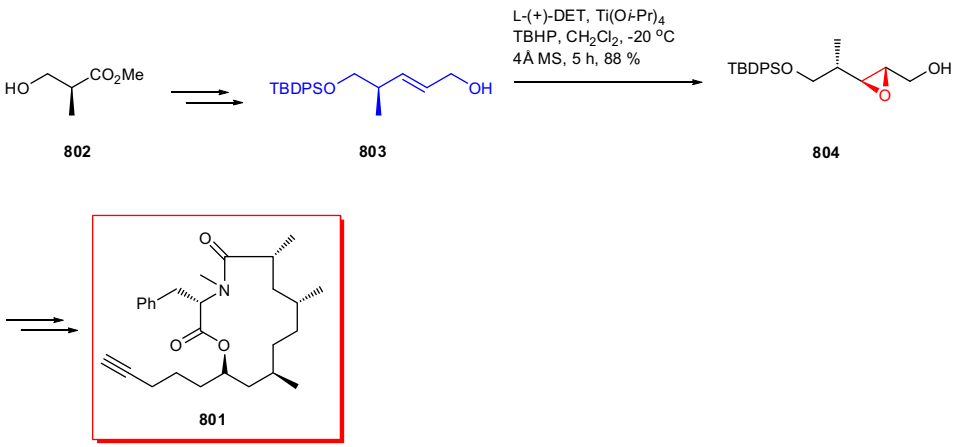
Sharpless asymmetric epoxidation to produce epoxy alcohol **809**. Epoxy alcohol **809** was treated in different procedures each with nine and six steps to give macrosphelides I **805** and G **806**, respectively (Scheme 183).[81]

Acremodiol **810** and acremonol **811**, two 14-membered bismacrolides, were isolated by Berge et al. from a soil sample of the Bermuda Islands, *Acremonium*-like anamorphic fungus.[385] These two macrolides have shown activity against a series of Gram positive bacteria and fungi. Chiral propylene oxide **812** as used as a starting material in the total synthesis of acremodiol **810** and acremonol **811** which was transformed into allylic alcohol **813** in five steps. Sharpless asymmetric epoxidation of allylic alcohol **813** using (+)- and (−)-DIPT furnished epoxy alcohols **814a** and **814b**, respectively. Treatment of epoxy alcohols **814a** and **814b** in eleven and thirteen reaction steps led to acremodiol **810** and acremonol **811** (Scheme 184).[386]

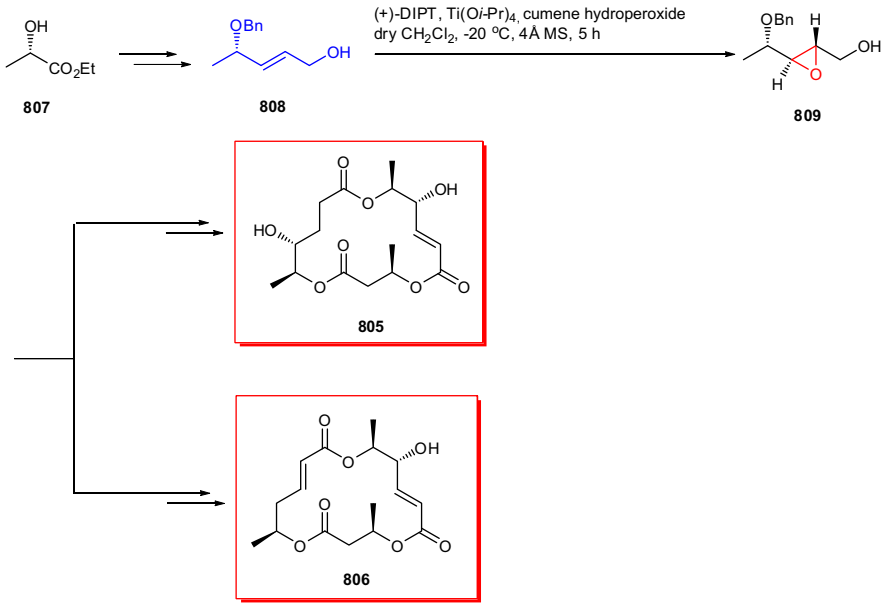
Oleandomycin **815**, a 14-membered macrolide antibiotic, was isolated from actinomycete *Streptomyces antibioticus* by Sobin et al. in 1955.[387] Oleandomycin **815** unravels its biological activity by binding to the 50-S ribosomal subunit and interfering with the transpeptidation or translocation reaction.[388] The synthesis of the C_1–C_7 subunit of oleandolide **816** was reported by Kalesse et al. Ketene acetal **817** was used as a starting material to give allylic alcohol **818** after being treated in three reaction steps. The allylic alcohol **818** was then subjected to Sharpless asymmetric epoxidation to produce epoxy alcohol **819** in 90% yield. The desired compound **815** was prepared from epoxy alcohol **819** through three steps (Scheme 185).[389]



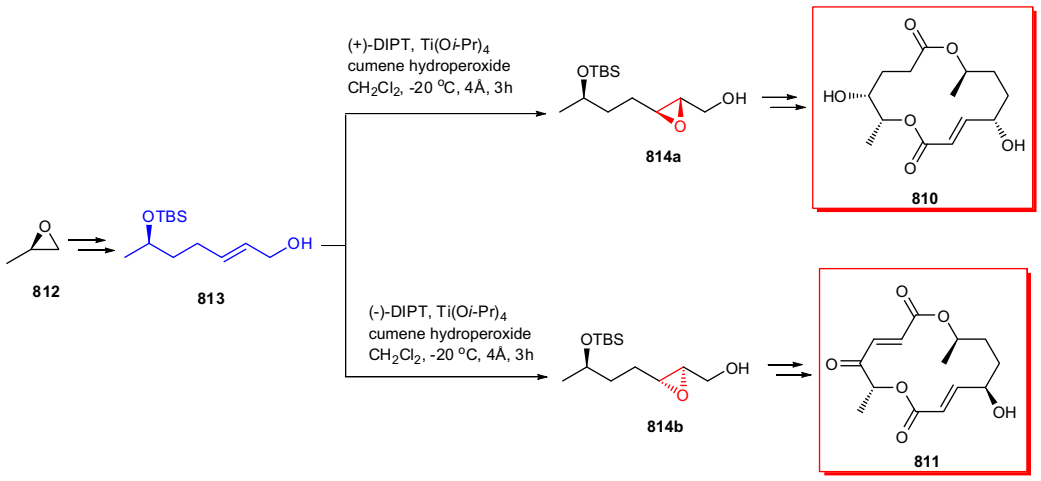
Scheme 181.



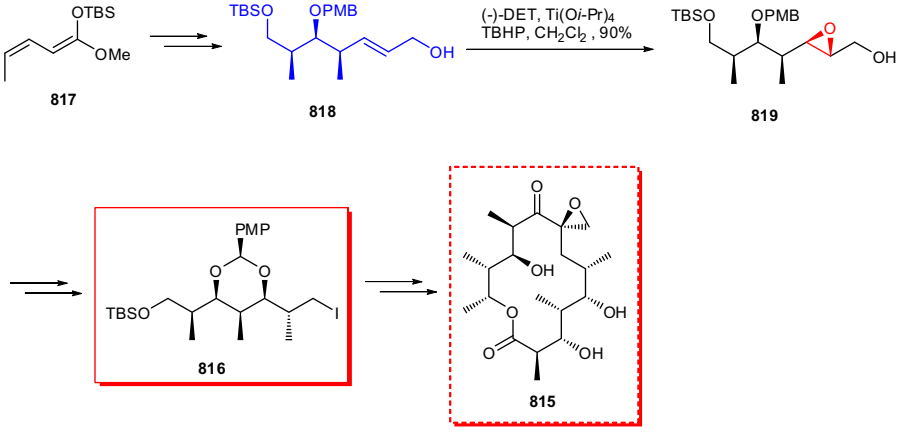
Scheme 182.



Scheme 183.



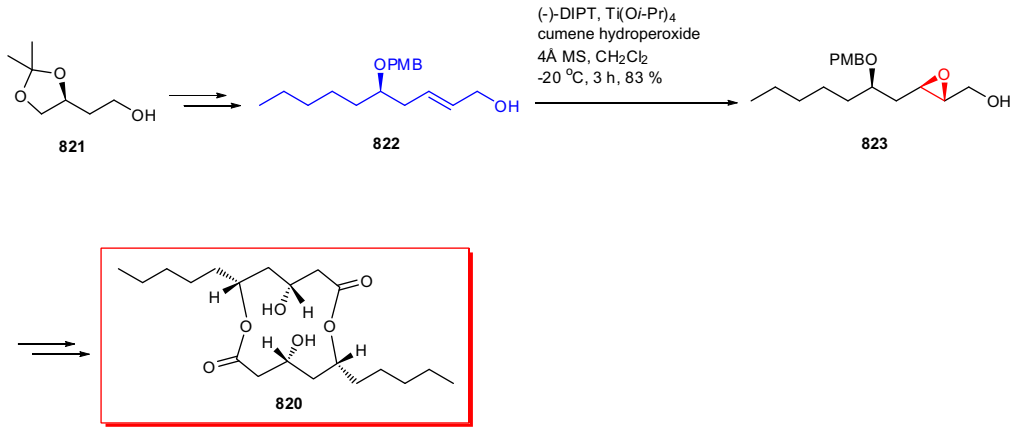
Scheme 184.



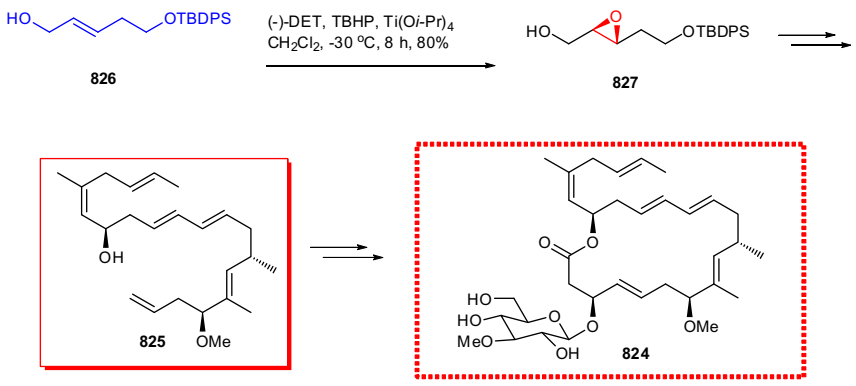
Scheme 185.

Verbalactone **820**, a macrocyclic dimer lactone, was isolated from the roots of *Verbascum undulatum* and exhibited interesting antibacterial activity.[390] In order to synthesize verbalactone **820**, Sharma et al. used alcohol **821** as starting material and converted it into allylic alcohol **822** through ten steps. Sharpless asymmetric epoxidation of compound **822** gave epoxy alcohol **823** in 83% yield. A further eleven steps transformed the epoxy alcohol **823** into the desired verbalactone **820** (Scheme 186).[391]

Suenaga et al. have explored a new 18-membered macrolide natural product from cyanobacterium *Lyngbya* species.[392] The synthesis of C5–C23 fragment **825** of biselyngbyaside was reported using the corresponding allyl alcohol **826** as the starting material which underwent Sharpless asymmetric epoxidation reaction in the presence of (−)-diethyl tartrate to give the corresponding epoxy alcohol **827** in high yields. Eleven more steps were required



Scheme 186.



Scheme 187.

for the formation of compound **825**, the C5–C23 fragment of biselyngbyaside **824** (Scheme 187).[393]

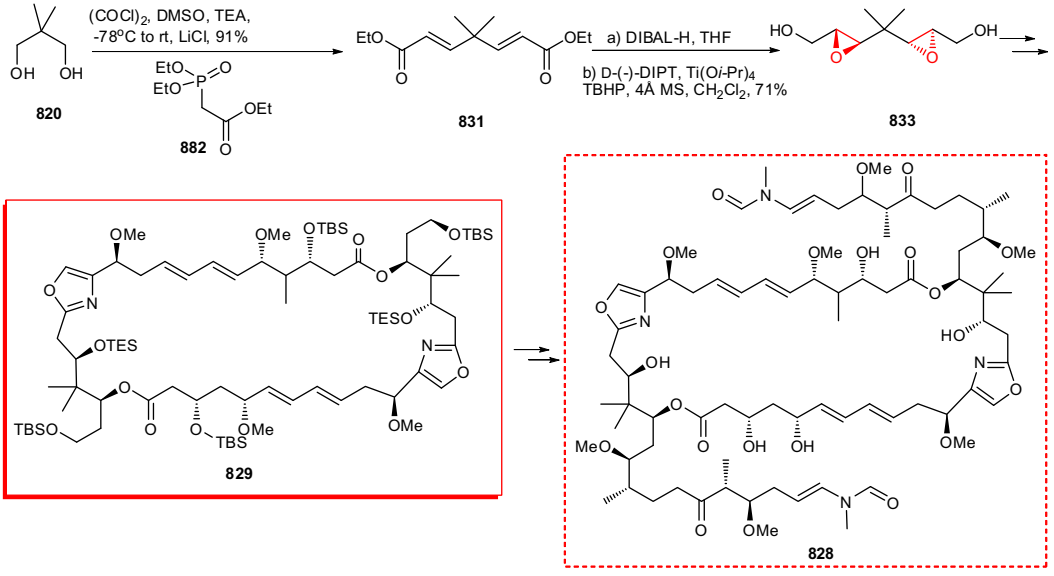
Rhizopodin **828** has recently been isolated from marine natural products and characterized. It shows extraordinary biological activities, such as potent cytostatic activity against a non-polar range of tumor cell.[394] The synthesis of **829** related to fully functionalized macrocyclic core of rhizopodin was described by Song et al.[395]

The synthesis involves elongation of diol **830** in two directions into the respective α,β-unsaturated diester **831**. Initially Swern oxidation of diol **830** gave the expected dialdehyde, which was submitted to Horner–Wadsworth–Emmons olefination with phosphonate **832** to afford **831** in high chemical yields in a two step reaction. Upon reduction using DIBAL-H, the latter was converted into the corresponding allylic alcohol, which is an appropriate precursor to undergo Sharpless asymmetric epoxidation with D-(−)-DIPT to provide the diepoxy alcohol **833** in very good yields (Scheme 188). The latter requires several more conversions to afford the macrocyclic core of dimer of rhizopodin **829**.[395]

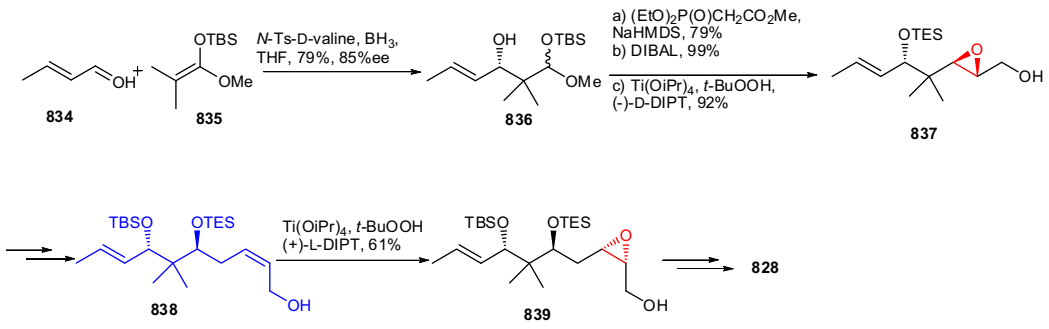
In 2013, Manuel Kretschmer et al. reported an alternative approach to Rhizopodin **828**. They designed a stepwise strategy involving 29 steps, which relied on an Evans aldol reaction for the synthesis of the C20/C21-*syn*-relationship, and an asymmetric Sharpless asymmetric epoxidation to assemble the stereogenic center at the C18 position.

A stepwise protocol was designed based on an Evans aldol reaction for the synthesis of the C20/C21-*syn*-relationship, and a sequential reaction involving Sharpless asymmetric epoxidation to introduce the stereogenic center at the C18 position. To begin with, an asymmetric Mukaiyama aldol reaction previously presented by Kiyooka et al.[396] between crotonaldehyde **834**, **835**, and silylacetal **836** gave in high ee of 85% regarding the C16 stereogenic center.[397] Upon treatment with a base in the presence of methyl diethylphosphonoacetate, a 1,5-*O*-silyl migration occurred to provide an aldehyde intermediate, which was transformed into the respective unsaturated ester in very good yields.[398] Upon reduction using DIBAL the ester was converted into the allylic alcohol, a desirable precursor for Sharpless asymmetric epoxidation to afford the corresponding[399] epoxide **837** in high yields and more importantly in a diastereomeric ratio of 8:1 in which the favorite isomer was the desired one which was then used in the 6 next steps to provide allylic alcohol **838**. The latter underwent another Sharpless asymmetric epoxidation to give the epoxide **839** eventually gives rhizopodin **828**. This total synthesis which uses Sharpless asymmetric epoxidation strategy two times consist 29 steps with overall yield of 0.25%. (Scheme 189).[400]

The isolation of three different macrocyclic lactones, callipeltosides A–C, from the same aglycon back bone joined with unlike sugar subunits, from the shallow-water lithistid sponge *Callipelta* sp., was reported by Minal et al. in 1996. The sample



Scheme 188.



Scheme 189.

had been collected from the east coast of New Caledonia.[401] Initial biological screening of (−)-callipeltoside A **840** showed it could inhibit in vitro proliferation of P388 cells. Further study disclosed that this activity is cell-cycle-dependent, jamming cell proliferation in the G1 phase. As a result callipeltoside A **840** was recognized as an interesting mechanism based and a good candidate for total synthesis. A highly stereoselective synthesis of the C1–C14 macrolactone core of the cytotoxic macrolide (−)-callipeltoside was reported by Yadav et al. Initially an aldol condensation between chiral *N*-acylthiazolidinethiones **841** and *trans*-cinnamaldehyde **842** mediated by $MgBr_2{\cdot}OEt_2$[402] was performed to provide the expected *anti*-aldol adduct **843**. A sequential reaction involving reduction, Wittig and methylation was successfully performed to obtain ester **840**. Reduction of ester **844** with DIBALH in THF as a known reductive agent afforded allyl alcohol **845** (98%), which underwent Katsuki–Sharpless asymmetric epoxidation[399] reaction conditions to obtain α-epoxy alcohol **846** in excellent yields. An easy epoxide ring opening followed by 3 more reactions gave aldehyde **847** as the C5–C10 dipropionate chain. Subsequently, freshly synthesized but unpurified aldehyde **847** was initially transformed into α,β-*trans*-unsaturated ester **848** via a Wittig reaction to obtain the requisite (*E*)-trisubstituted alkene while complete geometry of the double bond was controlled. Reduction of ester **847** using DIBAL-H in THF provided trisubstituted allylic alcohol **848** in almost quantitative yields. The latter was subjected to Swern oxidation followed by Wittig olefination, to give (2*E*,4*E*)-dienyl ester **849** in excellent yields. The latter upon reduction with DIBAL-H gave the corresponding (2*E*,4*E*)-dienyl allylic alcohol **850**, which was easily isolated by silica gel column chromatography as a single isomer. The latter then underwent Sharpless asymmetric epoxidation reaction to give β-epoxy alcohol **851** in high yields. From this point, 11 more steps were required to obtain the C1–C14 core of (−)-Callipeltoside A **852** (Scheme 190).[403]

The polyol, polyene macrolides are formed by bacterial pathogens of the genus *Streptomyces* (Fig. 7).[404]

In 2013, the synthesis of building block **856** for the unnatural enantiomers of useful, polyol, polyene was reported. The total pathway started from monoepoxide *anti*-**797**. The latter was in turn provided from divinylcarbinol **858** via Sharpless asymmetric epoxidation strategy. The desired monoepoxide *anti*-**857** practically is obtained as an inseparable mixture with its diastereomer *syn*-**857** in a ratio of approximately 75:25 (Scheme 191).[405]

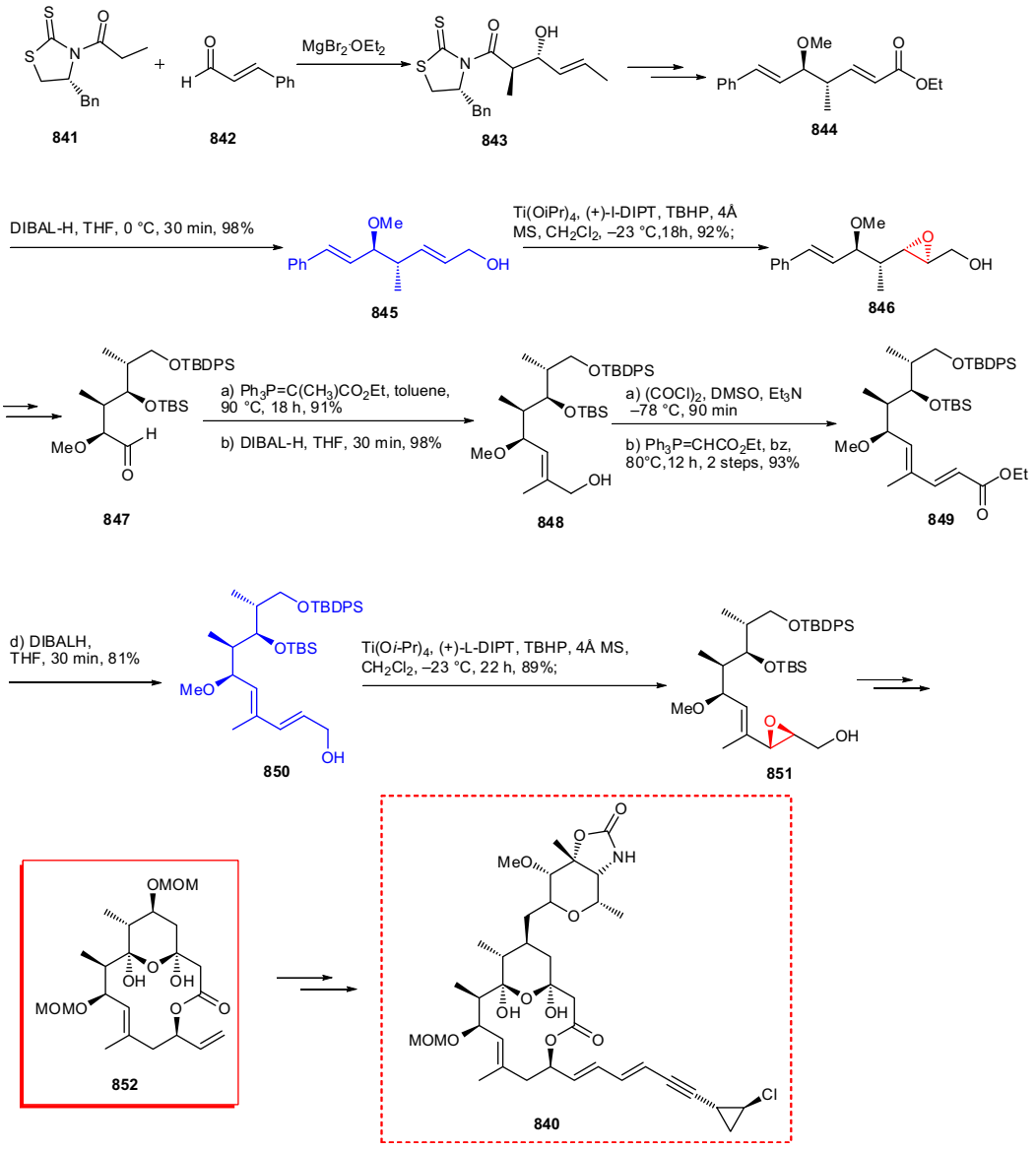
Nachbauer and Brückner reported a synthesis of the universal C*n*–C*n*+6 building block **859** being used for the synthesis of macrolide antibiotics **853** to **855** starting from propargyl ether **860**, using the same strategy. The pathway involves 15 steps in the longest linear sequence. The average yield calculated was 71% per step and the overall yield was 2.0%. Notably the enantioselectivity was achieved via Sharpless asymmetric epoxidation strategy to divinylcarbinol *cis*,*cis*-**861** (Scheme 192).[406]

Moore et al. reported the isolation of a brominated macrolide, lyngbyaloside B **862**, from a Palauan collective marine cyanobacterium *Lyngbya* sp. Yadav et al. reported a highly stereoselective total synthesis of the C1–C16 macrolactone core fragment of the cytotoxic macrolide lyngbyaloside B **863**. This total synthesis started with an aldol condensation of the chlorotitanium enolate of *N*-propionyl thiazolidine-thione **841** and aldehyde **864** mediated by (−)-sparteine as a base to afford non-Evans *syn*-aldol adduct **865** in good chemical yields with 98:2 dr.[407] Sequential protection of the latter followed by reductive cleavage of the chiral auxiliary afforded the aldehyde,[408] which subsequently underwent Wittig olefination to afford α,β-unsaturated ethyl ester **866**. The latter upon reduction using DIBAL-H in THF gave the corresponding allylic alcohol **867** in almost quantitative chemical yields as an appropriate precursor which was submitted to Sharpless asymmetric epoxidation, known as Katsuki–Sharpless asymmetric epoxidation reaction conditions to afford the corresponding epoxy alcohol **868** (a/β _ 25:1) in excellent yields. After several more steps, the total synthesis of C1–C16 macrolactone core of lyngbyaloside B **863** was successfully accomplished (Scheme 193).[399,409]

In 2006, Fenical et al. reported the isolation of marinomycins A **869**.[410] The total synthesis of **869** started with the four-step preparation of enantiopure acetonide **870**, which was synthesized from s-symmetrical dialkenyl carbinol **871** from a sequential reactions involving a Katsuki–Sharpless asymmetric epoxidation as a key step,[411] Mitsunobu inversion, followed by Red-Al reduction of an epoxy alcohol with simultaneous loss of a benzyloxy group, and acetonide formation (Scheme 194). Several more steps were required to achieve the marinomycins A **869** from **870** (Scheme 194).[412]

Macrodiolides (macrocyclic dilactones) are well-recognized in Nature as both homo and heterodimers and involve a wide range of scaffolds, ring sizes, and a wide variety of functional groups. The total synthesis of the (5*R*,8*S*,13*R*,16*S*)-isomer of pyrenophorol **873** was accomplished starting from (*R*)-propylene oxide. The key issues of this total synthesis involve sequential: (a) Jacobsen's hydrolytic kinetic resolution; and (b) intermolecular Mitsunobu cyclization. Its analogues have also attracted interest from synthetic organic chemists.

The known epoxide upon reaction with allyl magnesium chloride in ether and subsequent silylation of the product gave **874** in fair yields. Ozonolysis of **874** followed by Wittig olefination of the resulting aldehyde provided **875** in good yields, which upon reduction using DIBAL-H afforded allylic alcohol **876**. The latter was subjected to Sharpless asymmetric epoxidation protocol to form **877** in good yields (Scheme 195). To achieve the synthesis



Scheme 190.

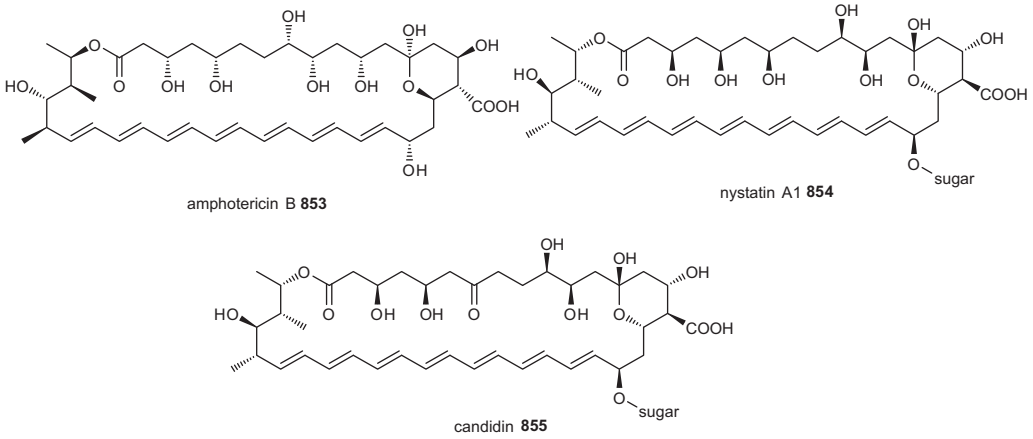
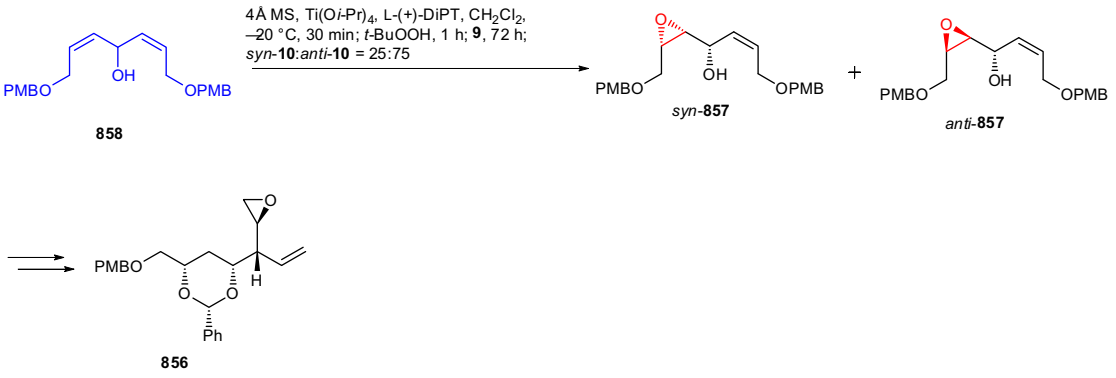
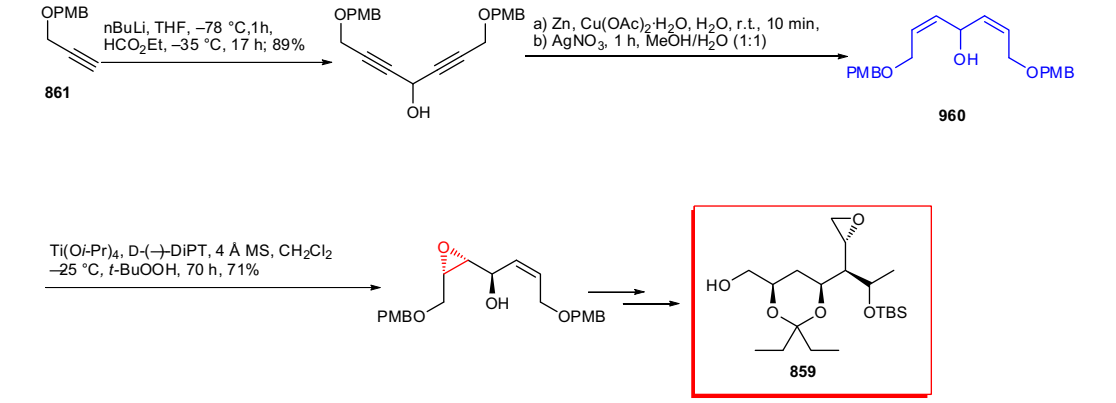


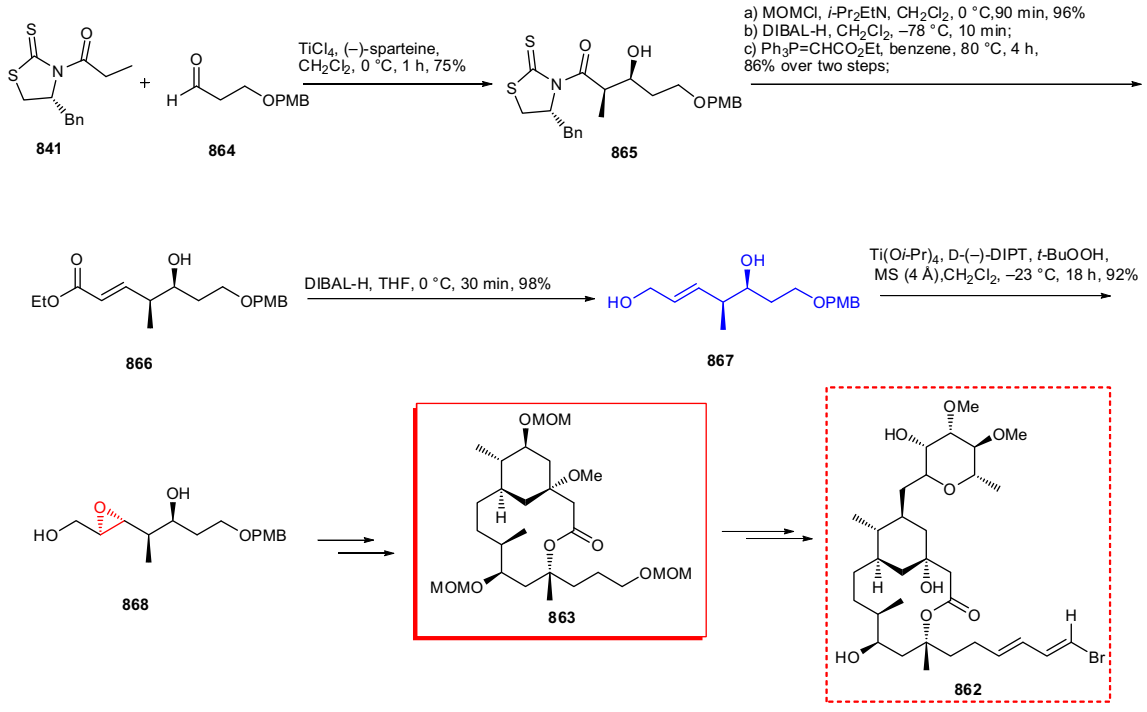
Figure 7.



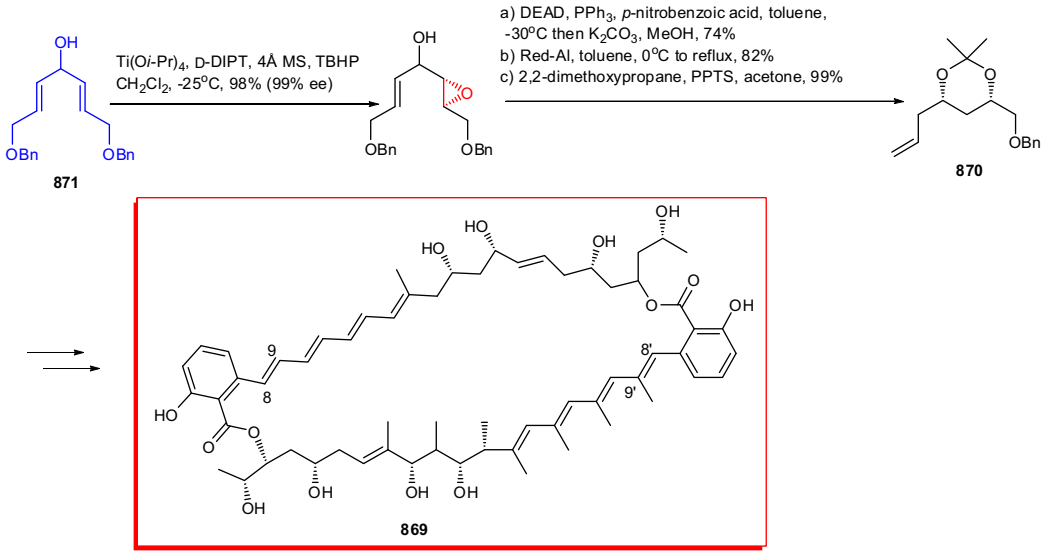
Scheme 191.



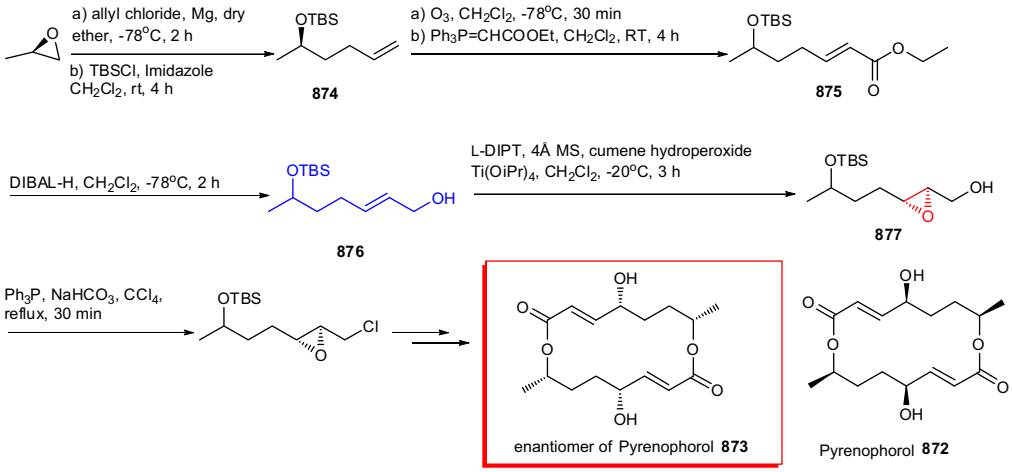
Scheme 192.



Scheme 193.



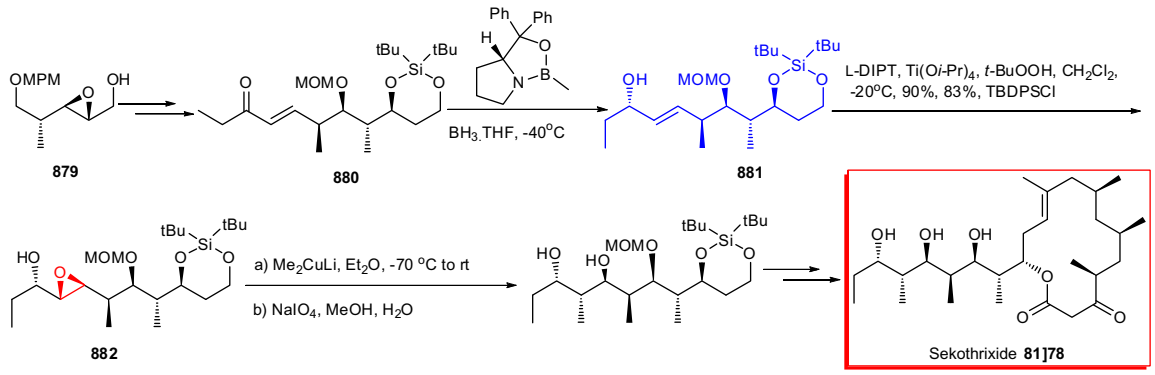
Scheme 194.



Scheme 195.

of the isomer of pyrenophorol, 6 more steps were required (Scheme 195).[413]

Multidrug resistance is a severe setback in cancer chemotherapy.[414] Seto et al. reported that sekothrixide **878**, a natural product isolated from *Saccharothrixide* sp. CF24, shows good cytocidal activity.[415] Their approach involved several types of epoxy ring opening and modification of the projected structure of sekothrixide. They started from epoxy alcohol **879**, and after more fifteen steps obtained **880**. By using a stoichiometric amount of chiral oxazaborolidine **880** upon CBS reduction, the desired alcohol **881** was obtained as the main component with an epimeric ratio of 15:1. Allylic alcohol **881** underwent Sharpless asymmetric epoxidation using L-DIPT at −30 °C, which was adequately matched with the (*S*)-configuration at the C19 position, to create β-epoxide **882** as the sole isomer in 83% yield. From this point 32 more steps was attempted to accomplish the target sekothrixide (Scheme 196).[416]



Scheme 196.

2.10. Miscellaneous

(−)-Balanol **883** is a metabolite isolated from the fungi *Verticillium balanoides*[353] and *Fusarium merismoides*,[417] and has a unique structure that represents an important new lead structure in the quest for selective inhibitors of protein kinase C (PKC). It is also a selective inhibitor of PKC isozymes which have a wide range of therapeutic potential.[418]

This target could be formed stereospecifically via kinetic resolution of allylic alcohol **884** via Sharpless asymmetric epoxidation conditions using (−)-DIPT. After nine more steps involving different functional group transformations, the chiral hexahydroazepine domain of the target compound **885** was obtained which subsequently was converted into the natural product **883** in several more steps (Scheme 197).[355]

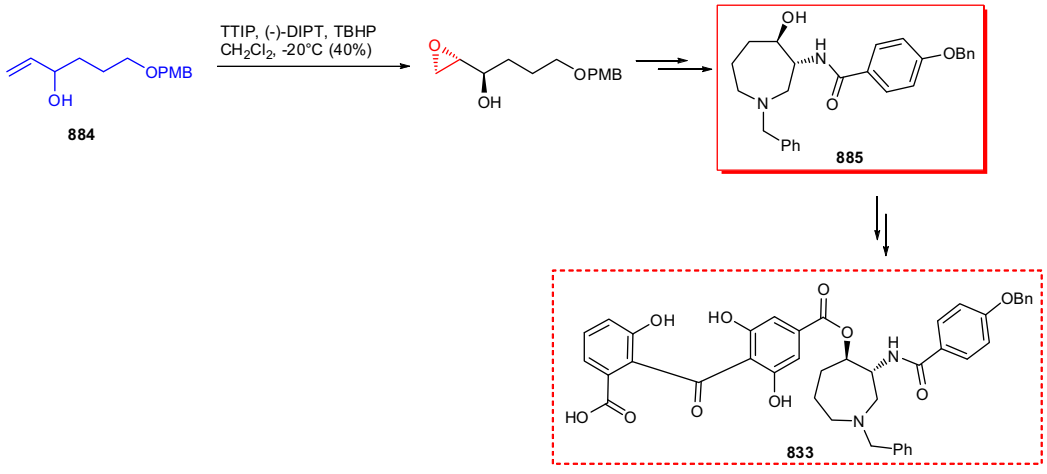
Recent research activities by Ojika et al. focused on the identification and characterization of small molecules showing NGF-like properties resulted in the isolation of novel diyne polyols called petrosiols, including petrosiol D **886**, extracted from a library of marine organism (Okinawan marine sponge) using PC12 cells.[419] Petrosiol D **886** shows a dose-dependent inhibitory effect on PDF-induced DNA synthesis.[419,420] The total synthesis of petrosiol D **886** was presented using (+)-diethyl L-tartrate as a starting material, which was transformed into the corresponding allyl alcohol **887** via a several step reaction. The latter was subjected to Sharpless asymmetric epoxidation reaction to the corresponding epoxy alcohol **888** in 80% yield in the absence of tartrate as the ally alcohol **887** was used as a chiral substrate, thus no chiral media was required. The chiral epoxy alcohol **888** was then submitted to four reaction steps to give petrosiol D **886** (Scheme 198).[421]

Sesquiterpenolides are metabolites generally generated by the Compositae (Asteraceae) family of plants.[422]

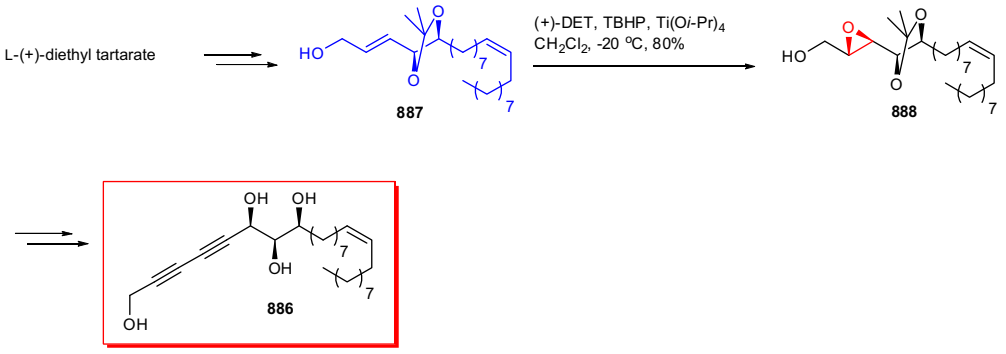
Melampolide **889** is a member of the Sesquiterpenolides family. A practical route for the synthesis of the latter started from **890**, which was initially deprotected using TBAF in dichloromethane to give diol **891** in high yields. Upon Sharpless asymmetric epoxidation, **891** using *tert*-butyl hydroperoxide and $VO(acac)_2$, gave epoxydiol **892** in 75% yield. Notably, the oxidation of the primary hydroxyl group was found to be difficult, resulting in a complex mixture. However, it was the use of TPAP20 and NMO that resulted in melampolide **889** due to of isomerization of the C-1–C-10 double bond (Scheme 199).[423]

Two new natural occurring products, bearing both diacetylene and hydroxyl moieties, oploxyne A **893** and oploxyne B (+)-**894**, were extracted by Yang et al. from the stem of *Oplopanax elatus*. Oploxyne A **893** inhibits the formation of nitric oxide (NO) and prostaglandin E2 (PGE2) in lipopolysaccharide (LPS).[424] The synthesis of oploxyne A **893** and (−)-oploxyne B **894** as accomplished using *cis*-2-butene-1,4-diol **895**, which afforded the mono-benzyl ether **896**. The latter was exposed to Sharpless asymmetric epoxidation conditions to afford the epoxy alcohol **897** in 85% yield (de, 94.5%), which was then transformed into oploxyne A **894** in nineteen steps. The Lewis acid catalyzed ring opening of the epoxide from oploxyne A **893** with methanol catalyzed by copper triflate afforded the (−)-oploxyne B **894** (Scheme 200).[425]

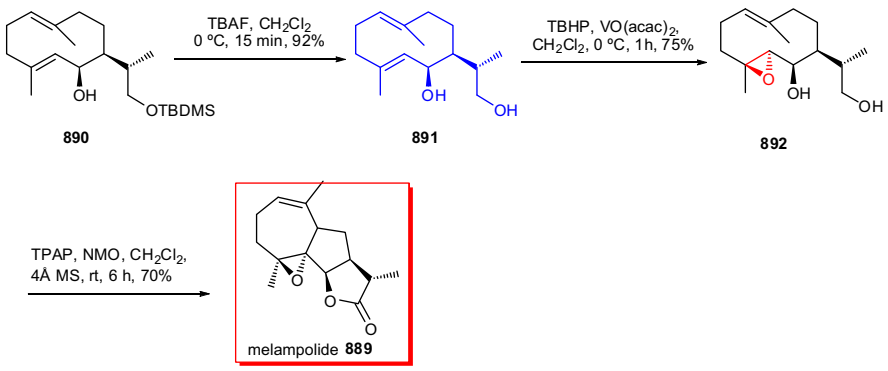
Phenolic sesquiterpenes are found in the bisabolane family and show particular biological activities, which are dictated by their stereochemical structures. These include benzylic alcohols curcutetraol **898** and sydonol **899**, which were both isolated from microbial Nature. Tetrol (+)-**898** was isolated[426] from the marine



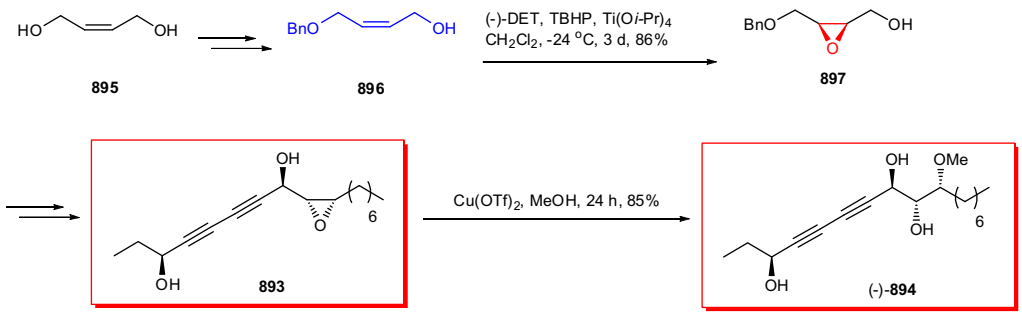
Scheme 197.



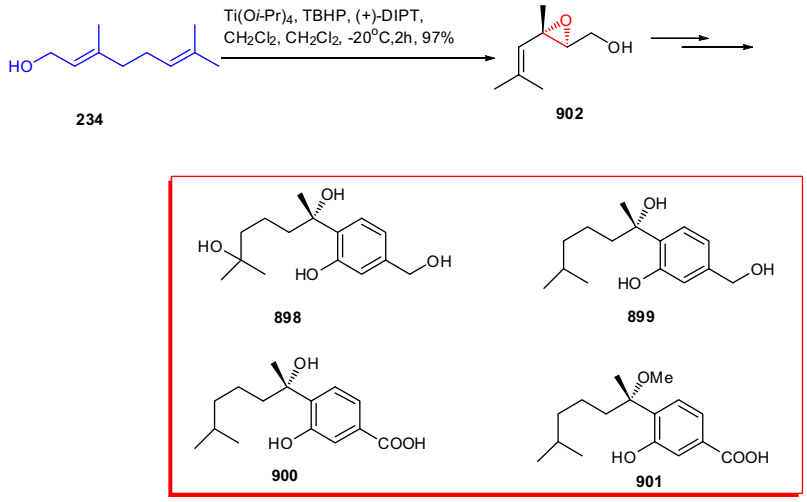
Scheme 198.



Scheme 199.



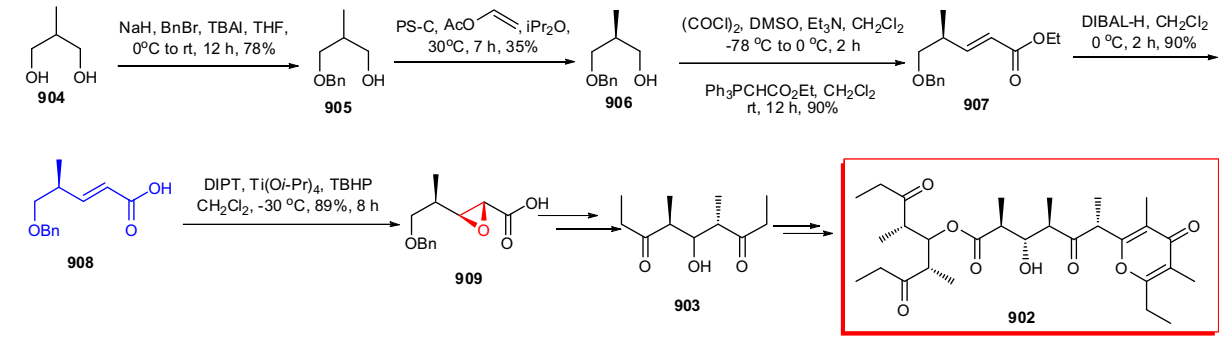
Scheme 200.



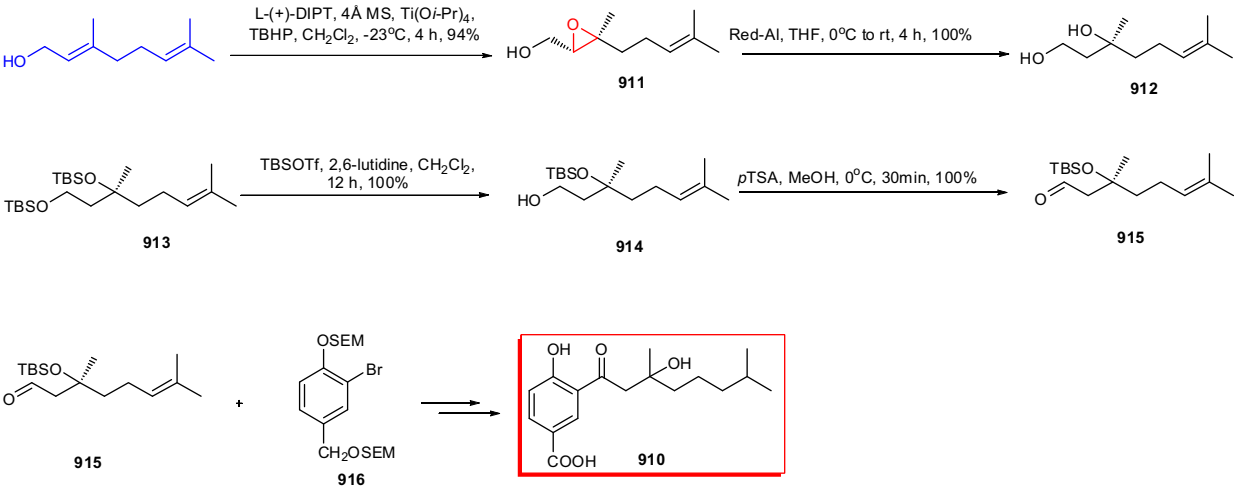
Scheme 201.

bacterium CNH-741 and fungus CNC-979 while triol **899** was extracted from a different strain of *Aspergillus* sp. either as (+)-(*S*)-[427] or (−)-(*R*)-[428] stereoisomers. Compound (+)-**899** showed antifungal activity against *Cochliobolus lunata*[427] (IFO6299) while (−)-**899** disclosed[428] selective antibacterial potency. Acidic **900**[429] and **901**[430] are also extracted from microorganisms but show only moderate biological activities. The asymmetric synthesis of four compounds **898** to **901** has been reported by Serra et al. using common and easily accessible geraniol **234** as the starting material which was transformed into the corresponding epoxy alcohol **901** upon submission to Sharpless asymmetric epoxidation conditions. Fourteen, thirteen, thirteen and twelve steps, respectively led to the formation of (+)-curcutetraol **898**, (+)-sydonol **899**, (+)-sydonic acid **900** and (+)-7-*O*-methylsydonic acid **901** (Scheme 201).[431]

Baconipyrones A–D, **902 A–D** were isolated in 1989 by Faulkner et al. from *Siphonaria baconi* collected from intertidal rock platforms near Melbourne, Australia. The total synthesis of (−)-baconipyrone C is reported by Yadav et al. The synthesis of intermediate **903** commenced with compound **904**, which was protected as its monobenzyl ether to furnish **905** in 78% yield (Scheme 202). Enzymatic resolution of methyl group **905** with PS-C enzyme resulted in compound **906** in 35% yield. Swern oxidation of primary alcohol and reaction with stable ylide (ethoxycarbonylmethylene) triphenyl phosphorane furnished *trans*-α,β-unsaturated ester **907** in 90% (*E*/*Z*, 95:5) yield. The DIBAL-H



Scheme 202.



Scheme 203.

reduction of **907** furnished **902** in high yields. At this step, Sharpless asymmetric epoxidation of **908** using (+)-DIPT gave the chiral epoxy alcohol **909** in 89% yield. Opening of epoxide **909** with Gilman's reagent (Me_2CuLi) followed by 7 other steps led to the synthesis of the C1–C8 fragment **903**.[432]

Piperaceae species have been extensively investigated as a source of new natural products with potential antitumor, antimicrobial, antifungal, and insecticidal activities.[433]

(−)-Crassinervic acid **910**, has been obtained starting from geraniol and *p*-hydroxybenzoic acid.

Initially, the enantiomer with an (*S*)-absolute configuration was prepared. Thus, asymmetric epoxidation of geraniol using L-(+)-diisopropyl tartrate (DIPT) was carried out to give epoxide **911**. The enantiomeric excess was determined to be 93% by comparing its specific rotation with the data reported in the literature. Regioselective ring opening of **911** using Red-Al as a reducing agent led to chiral diol **912** in quantitative yields and without any loss of enantiomeric purity. Protection of both hydroxy groups with TBSOTf, gave deprotected diol **913**. It was then selectively deprotected with *p*-TSA/MeOH to obtain the monoprotected diol **914**. Oxidation of the primary alcohol **914** furnished aldehyde **915**. The combination of aldehyde **915** with aromatic fragment **916** after four steps led to Crassinervic acid **910** in 12% overall yield (Scheme 203).[434]

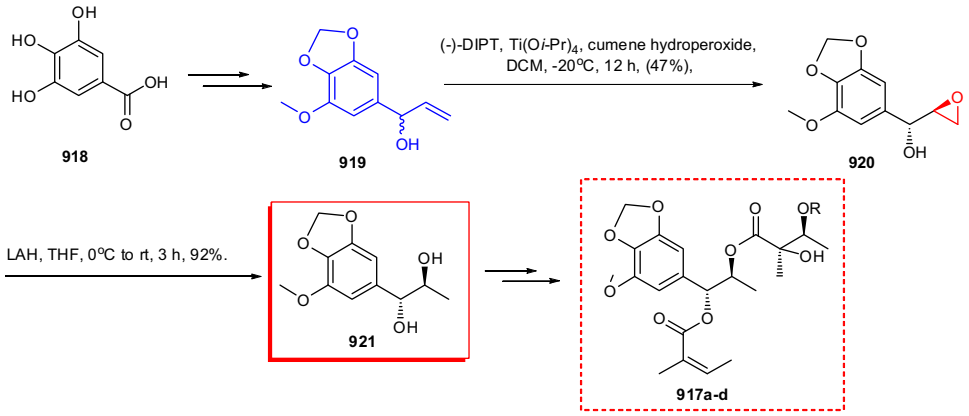
Neohelmanticins A–D **917** are an architecturally novel group of highly oxygenated phenyl propanoid class of compounds isolated from the European medicinal plant *Tapsia garganica* (umbelliferaceae) by Liu et al. in 2006.[435]

The synthesis began with gallic acid **918**, which was converted into secondary alcohol **919**. The Sharpless kinetic resolution of this racemic mixture of secondary alcohol **919** furnished epoxide **920** (47%) with 99% ee. Finally, ring opening of epoxide **920** with LAH in THF afforded the basic phenylpropanoid core **921** (dihydroxyphenyl propane) of the neohelmanticins (Scheme 204).[436]

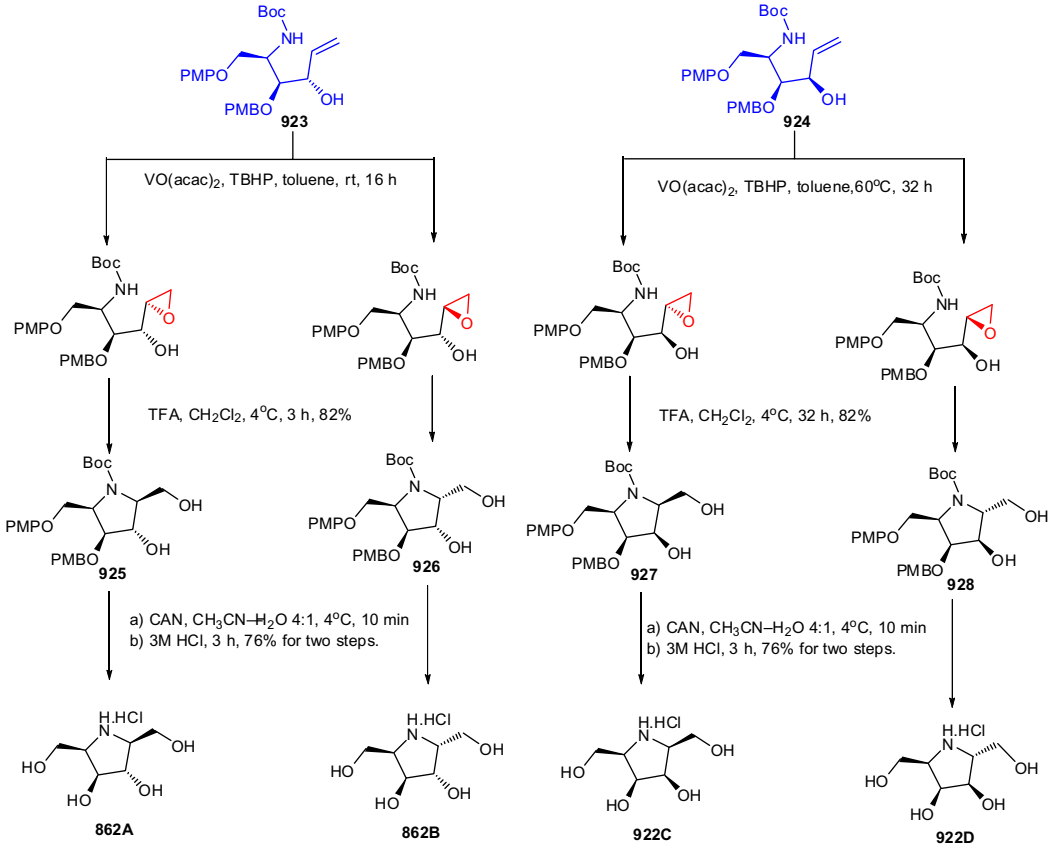
Pyrrolidines have been found in a large number of biologically active natural and artificial compounds.[437]

The epoxidation–intramolecular cyclization cascade of allylic alcohols can provide an extremely convenient tool for the asymmetric synthesis of polyhydroxylated pyrrolidines. Singh et al. reported the synthesis of polyhydroxylated pyrrolidines **922A–D** using this methodology. With the stage set for the allylic epoxidation, **923** and **924** were treated with various epoxidation reagents including peracetic acid, MCPBA, $VO(acac)_2$/ROOH, and Sharpless asymmetric epoxidation reagents, among which the $VO(acac)_2$/*t*-BuOOH (TBHP) system gave the best results.[438] After separation, cyclization of the surviving epoxides in the presence of TFA afforded diastereomeric pyrrolidine **925** to **928**. Deprotection of the PMP group by CAN followed by exhaustive acidic hydrolysis of the resulting triols furnished the polyhydroxylated pyrrolidine **922A–D** as their HCl salts (Scheme 205).[438]

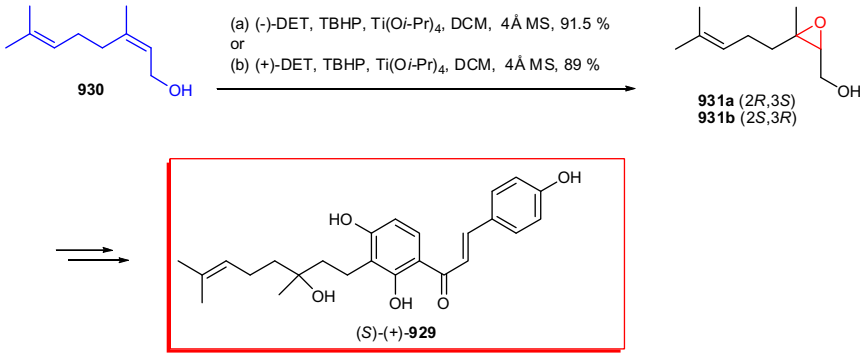
Akihisa et al. reported the isolation of xanthoangelol J **929** from *Angelica keiskei* stem mixed with 11 other compounds.[439] Xanthoangelol J **929** was synthesized using commercially available nerol **930** which was subjected to Sharpless asymmetric epoxidation protocol as key step, via either conditions a or b [using either (+)- or (−)-tartrate] to produce the corresponding epoxy alcohol **931a** or **931b**, respectively. Seven more steps led to the formation of xanthoangelol J **929** from epoxy alcohol **931a** (Scheme 206).[440]



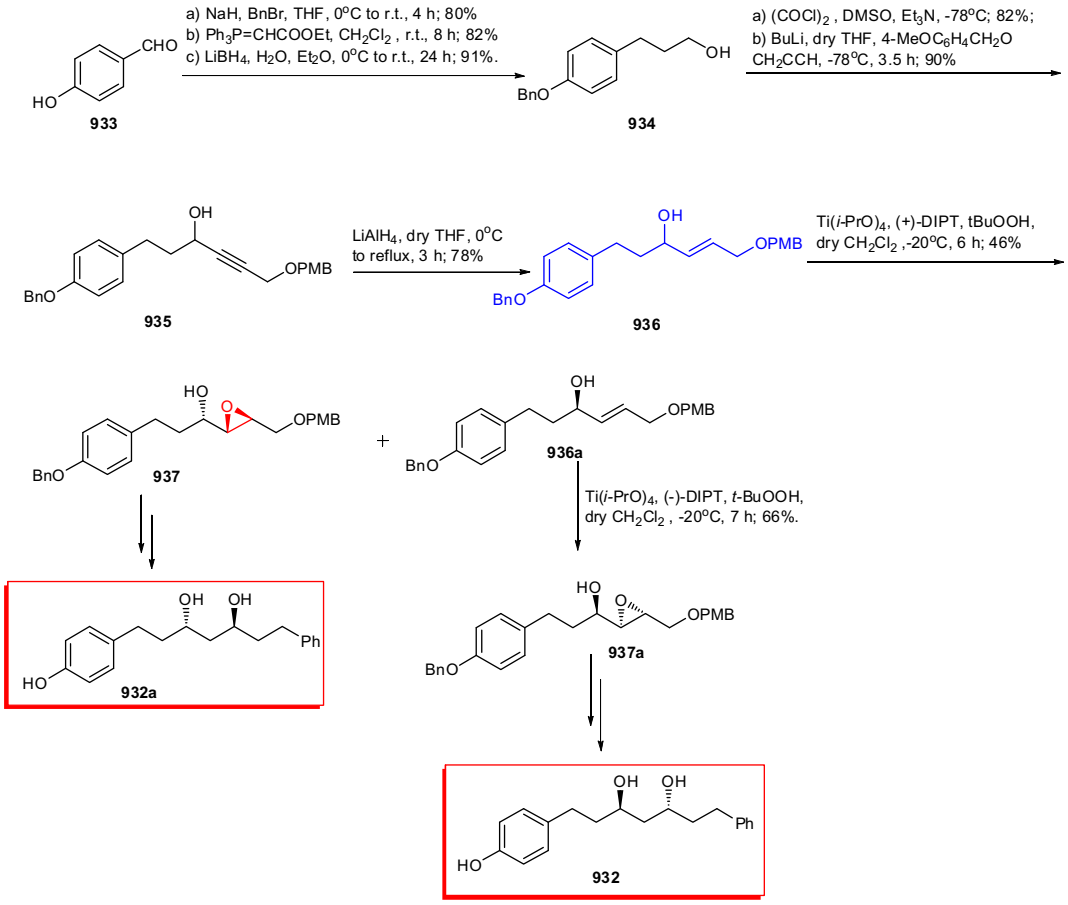
Scheme 204.



Scheme 205.



Scheme 206.



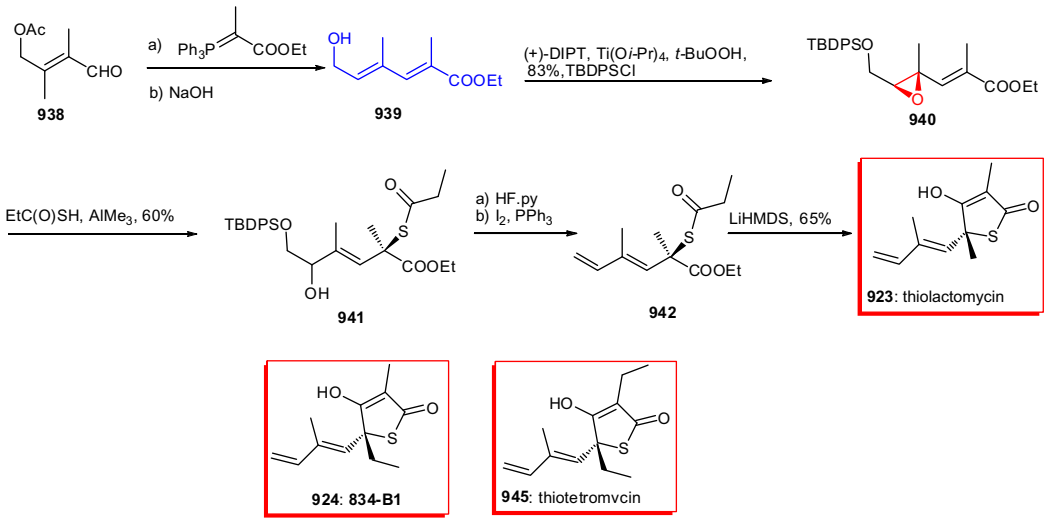
Scheme 207.

Diarylheptanoids are a vital family of natural products due to their various appealing biological potencies.[441] The synthetic pathway of **932** and **932a** involves an initial conversion of **933** into its benzyl ether, which was subsequently subjected to Wittig olefination followed by reduction to afford the known alcohol **934**. Upon Swern oxidation conditions, the latter was converted into the respective aldehyde, which upon treatment with 4-methoxybenzyl (PMB)-protected propargyl alcohol and BuLi gave rise to the corresponding acetylenic compound **935**. Upon the reduction, the latter was converted into the (*E*)-configured allyl-alcohol **936** as the major isomer along with a small quantity of its (*Z*)-isomer. The Sharpless asymmetric epoxidation protocol, performed to **936** using (+)-DIPT led to the generation of the corresponding chiral epoxy alcohol **937** and the allyl alcohol **936a**. Now everything is ready for a key role playing of Sharpless asymmetric epoxidation protocol for, compound **936** and in this case using (−)-DIPT to form the enantiomeric epoxy alcohol **937a**. Four more steps are should be performed to achieve the target diarylheptanoid **932** (Scheme 207).[442]

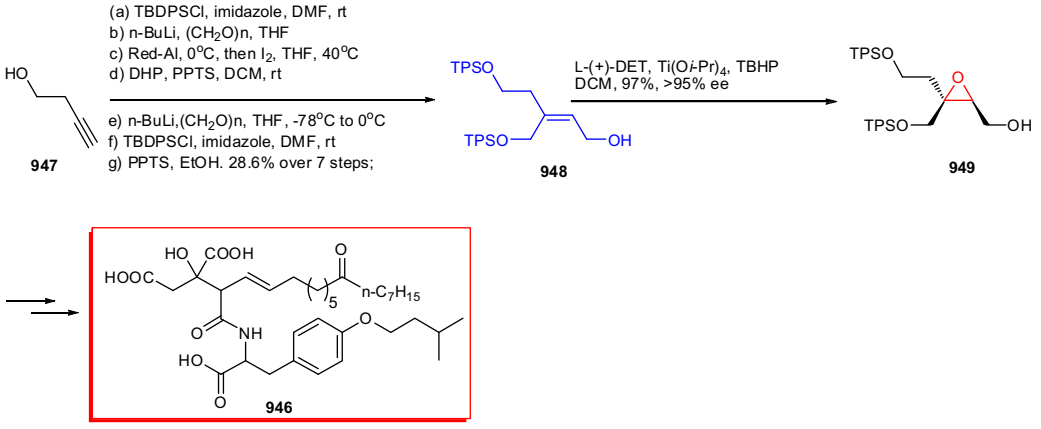
An efficient and relatively short route to thiolactomycin **23** was recently reported by Dormann et al. Their protocol commenced from enal **938**, which is an intermediate in the BASF mass production of vitamin A. The latter upon Wittig reaction and subsequent acetate cleavage afforded allylic alcohol **939**, which underwent Sharpless asymmetric epoxidation along with in situ protection of the primary alcohol to provide epoxide **940** in 83% chemical yield and with 93% ee. This approach was the first catalytic asymmetric strategy to thiolactomycin. The tertiary sulfide was then assembled via S_N2' addition of thiopropionic acid promoted by trimethylaluminum, in a way that directed the addition *syn* to the epoxide to give **941**. After silyl deprotection and vicinal dideoxygenation of the obtained diol, installation of the thiolactomycin side chain in **942**, the known Dieckmann cyclization occurs to give the desired natural product. This protocol gives thiolactomycin **943** in just seven steps and in an approximate 15% overall yield. This approach was also employed for the first total synthesis of the related compounds 834-B1 **944** and thiotetromycin **945** (Scheme 208).[443]

HCV is a global infectious pathogen that causes chronic liver diseases.[444] The total synthesis of the NA255 derivative **946** was accomplished by a Japanese group in 2013. The synthesis was started from **947**, which was converted into allyl alcohol **888** in 7 steps in 28.6% overall chemical yield. Katsuki–Sharpless asymmetric epoxidation furnished epoxide **949** with excellent ee and isolated chemical yield. Several more steps involving the functional group manipulation to achieve **946** as a derivative of NA255 (Scheme 209).[445]

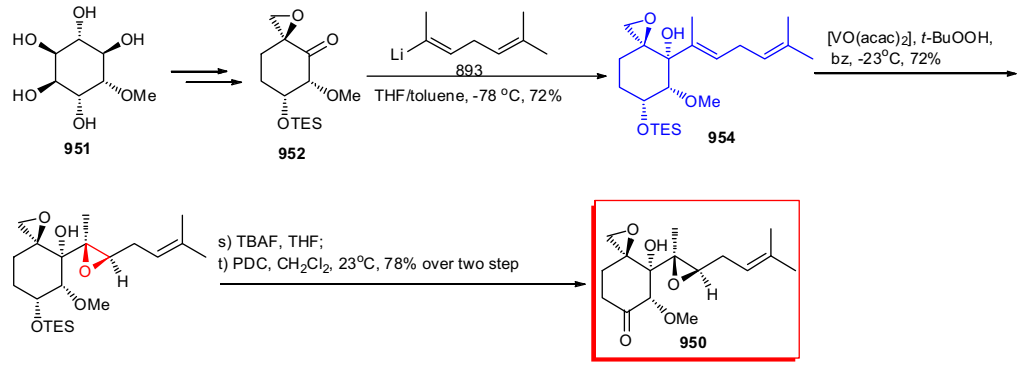
Fumagillin was isolated and characterized in 1949 by Elbe and Hanson[446] from the microbial organism *Aspergillus fumigatus*. The latter was isolated from *Sporothrix* sp. FO-4649 but the total synthesis was reported by Samadi et al. They achieved the asymmetric synthesis of (−)-**950** starting from l-quebrachitol **951**. After several reactions epoxyketone **952** was obtained, which upon treatment with the vinyllithium reagent **953** following an amendment of Corey's procedure afforded **954**. Finally, the latter was subjected to Sharpless asymmetric epoxidation conditions as a key step, with



Scheme 208.



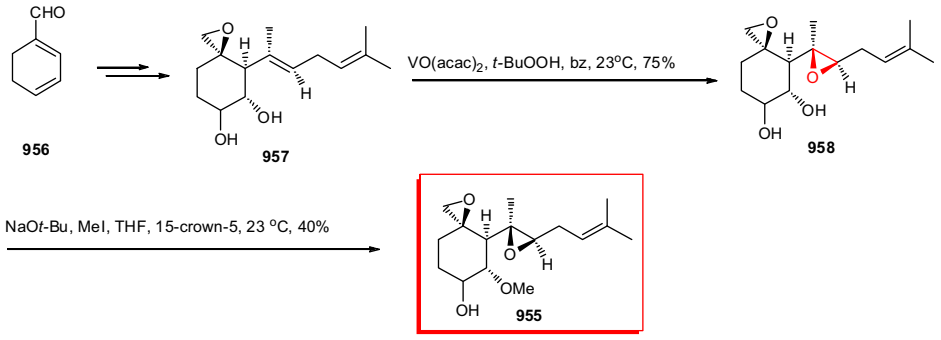
Scheme 209.



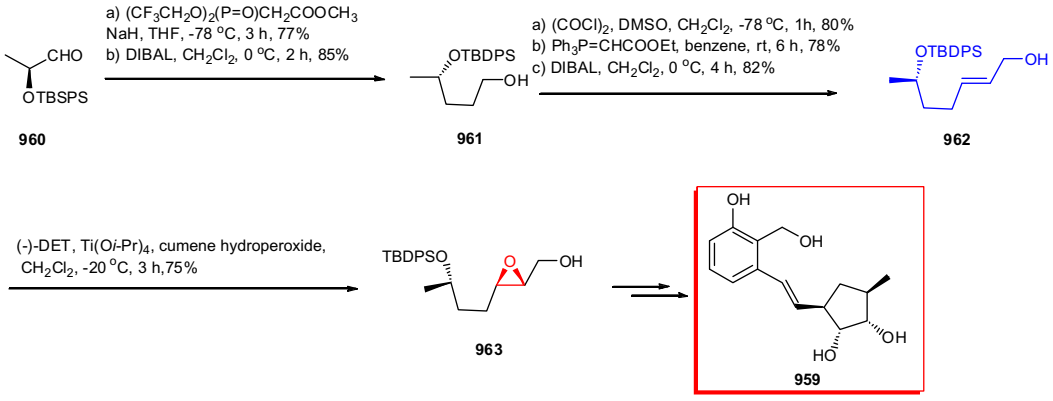
Scheme 210.

subsequent of removal of the TES group, followed by PDC oxidation to provide (−)-**950**. This first total synthesis of (−)-**950** was completed in 20 steps (Scheme 210).[447]

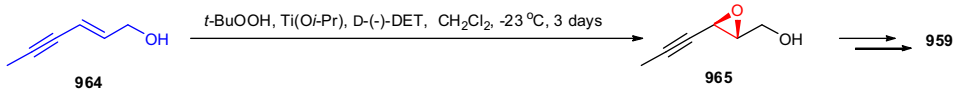
Recently the total synthesis of racemic **955** was performed and reported by Sorensen et al. Readily accessible 1,3-cyclohexadiene-1-carbaldehyde **956** was selected as the starting material. To introduce the second oxirane functionality, vanadium-catalyzed epoxidation was performed in several steps to give the corresponding epoxide **957**. The C5 hydroxyl group acting as a directing unit allowed for the formation of bis-epoxide **958** as a 4.3:1 mixture of diastereomers with the desired product being predominant. At the end, selective methylation of the C5 hydroxy group by using a tiny alteration of Coreys procedure led to a 40% yield of (−)-**955**, and a 40% yield of recoverable starting material. Although



Scheme 211.



Scheme 212.



Scheme 213.

the selectivity in the side-chain epoxidation could profit from this development, Sorensen's strategy designing an 11-step sequential reaction remains as a very short and effective synthesis of racemic **955** (Scheme 211).[448]

(+)-Varitriol **959**, isolated from the marine fungus *Emericella variecolor*, has illustrated much greater activities with regards to toxicity toward various types of cancer cell lines.[449] The key intermediate for the cross metathesis reaction generated from D-ribose provided the product in 27.5% yield; other endeavors are still required for the total synthesis of the furanoside sub-unit. This total synthesis started from ethyl (*S*)-lactate. The protected lactaldehyde **960** underwent olefination using a Still–Gennari protocol to provide the respective α,β-unsaturated ester with *Z*-regioselectivity which upon DIBAL reduction afforded allylic alcohol **961** which in turn was subjected to Swern oxidation to give the corresponding aldehyde, which underwent Wittig reaction with stabilized phosphorane (*trans* selectivity) and then again DIBAL reduction to give alcohol **962**. Thus everything is ready for Sharpless asymmetric epoxidation, converting the allyl alcohol into the corresponding epoxide **963** with excellent enantiomeric purity. The latter after a multi-step strategy resulted in (+)-varitriol **959** (Scheme 212).[449]

Norbert et al. designed and reported the synthesis of (+)-varitriol **959** via reagent-controlled introduction of all stereogenic centers employing a combined rarely used metal catalyst approach.[52] The synthesis of the furanoside motif started from enyne **964** which upon catalyzed Katsuki-Sharpless epoxidation using D-(−)-DET gave epoxide **965** with excellent ee. The latter after 8 steps afforded varitriol (+)-**959** (Scheme 213).[449]

3. Conclusion

In this review, we have shown the Sharpless asymmetric epoxidation, as one of the most important, essential, unique, and sometimes as an only one of its kind applied in the total synthesis of natural products and complex molecular targets. Since the reaction was discovered and reported by Sharpless et al. in 1980, a plethora of attempts, endeavors and activities have been devoted in the modification and variation of the reaction as well as its application in asymmetric synthesis and the synthesis of natural products, particularly in their crucial steps where a certain configuration is required at stereogenic centers.

The stereochemistry of the resulting epoxide on which diastereomer of the chiral tartrate diester is employed in the reaction. Among, the various oxidizing agents, *tert*-butyl hydroperoxide was found to be the agent of choice. The commercial availability of both diastereomeric tartrate diesters, titanium isopropoxide and *tert*-butyl hydroperoxide as well as several substituted allyl

alcohols and other readily synthesized non-commercial ones, as the starting materials, the relative ease of operation and work up procedure, obtaining products with high and controlled diastereoselectivity, undoubtedly, nominate Sharpless asymmetric epoxidation as one of most ideal, important, and useful asymmetric reactions.

In this report all applications of this important asymmetric protocol leading to high stereoselective epoxides as the potential intermediates in a key step of the total synthesis of naturally occurring biologically active compounds have been collected and presented.

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