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Application of hydrolytic kinetic resolution (HKR) in the synthesis of bioactive compounds

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In memory of my mentor Professor Arya K. Mukerjee

Contents

Keywords: Hydrolytic kinetic resolution; Terminal epoxides; Bis-epoxides; *meso*-Epoxides; Natural products; Synthesis; Biological activity.

Abbreviations: Ac, acetyl; AD, asymmetric dihydroxylation; AE, asymmetric epoxidation; Bn, benzyl; NBS, *N*-bromosuccinimide; Boc, *t*-butoxycarbonyl; *t*-Bu, *tert*-butyl; *m*-CPBA, *m*-chloroperbenzoic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DHP, dihydropyran; DIBAL-H, diisobutylaluminum hydride; DIAD, diisopropylazodicarboxylate; DIPEA, diisopropylethylamine; DMAP, dimethylaminopyridine; DMF, dimethylformamide; 2,2-DMP, 2,2-dimethoxypropane; DMPU, *N*,*N*′-dimethylpropyleneurea; DMSO, dimethyl sulfoxide; Et, ethyl; HMPA, hexamethylphosphoramide; IBX, 2-iodoxybenzoic acid; Im, imidazole; LAH, lithiumaluminumhydride; LTB4, leukotriene-B4; LiHMDS, lithium hexamethyldisiloxane; Me, methyl; MEM, methoxyethoxymethyl; MOM, methoxymethyl; PBu_3, tributylphosphine; Ph, phenyl; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulfonate; RCM, ring-closing metathesis; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBME, *tert*-butyl methyl ether; TES, triethylsilyl; TEMPO, 2,2,6,6,-tetramethyl-1-piperidinyloxy; Tf, triflate; THP, tetrahydropyran; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylenediamine; TMS, trimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Ts, *p*-toluenesulfonyl; TsIm, tosylimidazole.

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1. Introduction

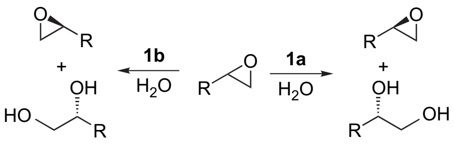
The search for new and efficient methods for the synthesis of optically pure compounds has been an active area of research in organic synthesis. Amongst various syntheses, the enantioselective syntheses of complex natural products containing multiple stereocenters are often the most challenging. The asymmetric catalysis provides a practical, cost effective and efficient synthesis of such molecules. Furthermore, the enantioselective synthesis of natural products by a catalytic process assumes significance since isolation from natural sources can only be accomplished in minute quantities. The use of catalytic methods not only provides an easy access to an enantiomerically pure product but also permits maximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogs required for biological activity. While tremendous advances have been made in asymmetric synthesis, substrate driven or catalytically induced resolution of racemates is still the most important industrial approach to the synthesis of enantiomerically pure compounds. In a kinetic resolution process, one of the enantiomers of the racemic mixture is transformed to the desired product while the other is recovered unchanged.

Epoxides are versatile building blocks that have been extensively used in the synthesis of complex organic compounds. Their utility as valuable intermediates has further expanded with the advent of asymmetric catalytic methods for their synthesis.[1] The terminal epoxides are a most important subclass of these compounds, but no general and practical methods were available for their synthesis in enantiomerically pure form. Hydrolytic kinetic resolution (HKR) developed by Jacobsen has emerged in recent times as a powerful tool to synthesize both terminal epoxides and their corresponding diols in highly enantiomerically pure form.[2] The process uses water as the only reagent, no added solvent, and low loading of recyclable chiral cobalt-based salen complexes to afford the terminal epoxides and 1,2-diol in high yield and high enantiomeric excess. With the advent of the HKR method, synthetic organic chemists have gradually adopted this as the method of choice for the preparation of a variety of terminal epoxides in enantio-enriched form. During the last couple of years, the main emphasis has been on the application of this novel reaction and therefore the main aim of this review is to cover its growing applications in target-oriented synthesis. The compounds covered are classified into 10 categories, which are based on the synthesis of enantiopure epoxides as chiral building blocks prepared through the HKR method. These epoxides were carried through various organic transformations to the target molecules. In this article, an attempt has been made to present the subject in an integrated form and in its proper perspective.

1.1. Jacobsen's HKR procedure

In the HKR method a racemic epoxide is treated with approx. half an equivalent of water either neat or with only approx. 10 mol % of a solvent in the presence of Jacobsen's (salen)Co(III)–OAc (**1a** or **1b**) catalyst (Fig. 1) to produce highly enantio-enriched epoxide and 1,2-diol in almost equal amounts (Scheme 1). The epoxide and diol products differ greatly in their physical characteristics allowing easy separation to give two highly useful enantiomerically pure products.

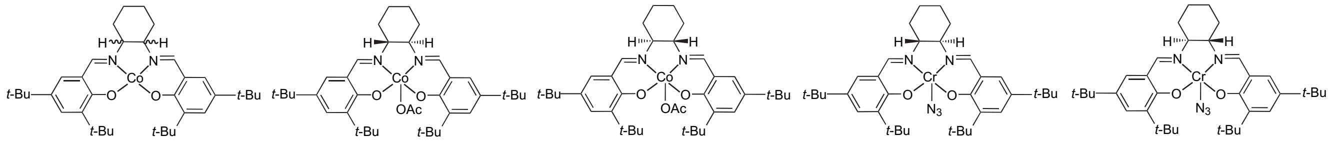
Thus, the salient features of the HKR method include the following: the high accessibility of racemic terminal epoxides; applicability to a wide range of racemic terminal epoxides, most of which are quite inexpensive; access to highly enantio-enriched products in close to theoretical yields; a practical and scaleable protocol; the low loading (0.2–2 mol %) and recyclability of commercially available catalysts at low cost; the use of water as the nucleophile for epoxide ring opening; and the ease of product separation from unreacted epoxide due to large boiling point and polarity differences. Many chiral building blocks based on HKR technology have been developed. Some of these include propylene oxide, methyl glycidate, epichlorohydrin, and 3-chloro-1,2-propanediol.[3]



Scheme 1. Hydrolytic kinetic resolution (HKR) reaction.

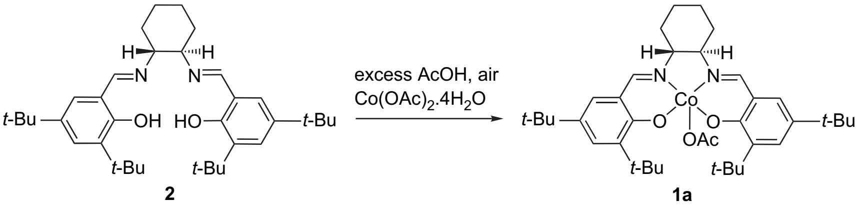
1.2. Jacobsen's catalyst

Both the enantiomers of (salen)Co(II) complex **1** (Fig. 1) are available commercially[4] or they can be prepared from the commercially available ligands using Co(OAc)$_2$.[3] The Co(II) complex **1** is catalytically inactive. The active state of the Jacobsen's catalyst requires the +3 oxidation state of cobalt, not the +2 state of the pre-catalyst. Thus, the Co(II) complex must be subjected to one-electron oxidation to produce a (salen)Co(III)–X complex (X=anionic ligand) prior to the HKR. The conversion of inactive Co(II) salen into active Co(III) salen is simply achieved in situ on a small scale; a solution of the Co(II) salen pre-catalyst is directly exposed to air in the presence of acetic acid. Thus, 2 mol of Co(II) pre-catalyst, 2 mol of acetic acid and a half mole of oxygen are converted into 2 mol of Co(III) catalyst and 1 mol of water. A much more desirable approach would be to generate and isolate Co(III) salen allowing its direct use in HKR reactions.[5] Thus, the parent salen system **2** on treatment with Co(II)acetate tetrahydrate in excess acetic acid with an air sparge gives the Co(III) salen **1a** as a crystalline solid (Scheme 2). It is also possible to recycle the catalyst after the reoxidation. The solid residue obtained after the product separation in the HKR reaction is found to have the characteristic red-brick color of the reduced (salen)Co(II) complex. Reoxidation with air and AcOH leads to the catalyst with undiminished levels of reactivity and selectivity.[2] The 2,2-disubstituted epoxides are unreactive under HKR conditions with catalyst **1**, however, the kinetic resolution in the presence of (salen)Cr catalysts **1c** and **1d** with HN$_3$ proved to be successful.[5d,e] Chromium(salen) complexes (**1c** and **1d**) are indeed a highly effective catalysts for the enantioselective ring opening of epoxides with Me$_3$SiN$_3$. This reaction is notable not only for its high enantioselectivity and the



(*R*) / (*S*)SalenCo (II) complex **(1)**
(*R*,*R*)-SalenCo (III) OAc complex **(1a)**
(*S*,*S*)-SalenCo (III) OAc complex **(1b)**
(*R*,*R*)-SalenCrN$_3$ complex **(1c)**
(*S*,*S*)-SalenCrN$_3$ complex **(1d)**

Figure 1. Jacobsen catalysts.



Scheme 2.

synthetic utility of its products but also for its remarkable efficiency as a catalytic process.

1.3. Oligomeric Jacobsen's Co(salen) catalyst

The HKR reaction is second order in catalyst. This motivated the Jacobsen group to identify a means for fixing or linking two or more Co(salen) units in close proximity to decrease the catalyst requirements by making the reaction pseudo first-order with respect to Co(salen) units. This led to the breakthrough in this area with the discovery of so-called oligomeric Co(salen) catalyst system[6] **1e** (Fig. 2). This system is much easier to synthesize than previous ones due to a locally symmetric Co(salen) unit. The oligomeric Co(salen) displays a dramatic reactivity increase on a per Co(salen) unit basis, and a 50-fold decrease in oligomeric catalyst as compared to the normal Co(salen) system using a typical epoxide. With the oligomeric catalyst, the product purity was consistently higher than that observed with the parent Co(III)-salen.

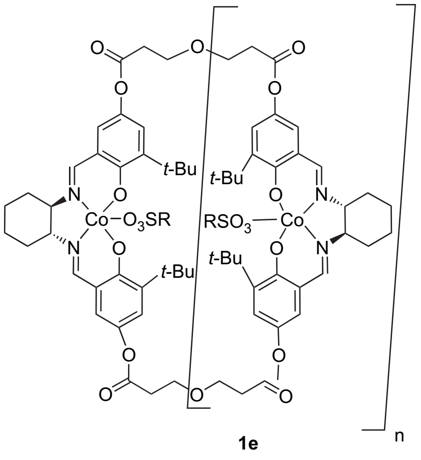
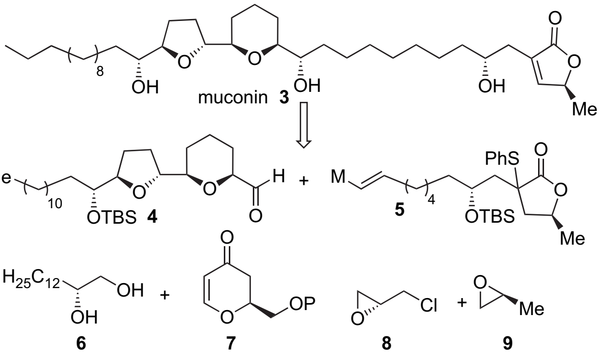


Figure 2. Oligomeric Jacobsen's Co(salen) catalyst (**1e**).

2. Halogenated epoxides or epihalohydrins

2.1. Muconin

Muconin **3** is a novel tetrahydropyran-bearing acetogenin isolated from *Rollinia mucosa* that has exhibited potent and selective in vitro cytotoxicities against pancreatic and breast tumor cell lines.[7] Jacobsen and co-workers developed a convergent approach to the synthesis of **3** by assembly of readily accessible chiral building blocks.[8] Retrosynthesis of the target molecule **3** resulted in four fragments (Scheme 3). These fragments were conveniently prepared in high enantiomeric purity by HKR of the commercially available racemic terminal oxides such as tetradecene oxide, epichlorohydrin, and propylene oxide. In order to prepare the key fragment **4**, (*R*)-tetradecane-1,2-diol **6** was synthesized in 90% yield and >99% ee from HKR of (±)-tetradecene oxide using 0.5 mol % of catalyst **1b** in TBME and 0.5 equiv of H_2O. This was converted into the required acid **12** by selective protection of the secondary hydroxyl group, oxidation, and vinyl Grignard reaction. The coupling of the acid **12** with pyranol **7**, prepared through the hetero-Diels–Alder reaction,[9] resulted in **15**, which was eventually transformed into the key fragment **4** in several steps. To synthesize the key fragment **5**, (*R*)-epichlorohydrin **8** was readily prepared in >99% ee and 82% of theoretical yield by HKR of racemic epoxide using 0.5 mol % of catalyst **1b** and 0.55 equiv of water. This compound was converted into the TBS-protected iodohydrin **18** by copper(I)-catalyzed epoxide ring opening using a Grignard reaction. Lactone **19** was readily prepared in quantitative yield from phenylthioacetic acid and (*S*)-propylene oxide, the latter obtained through HKR in 98% ee and 95% yield. Alkylation of the enolate derived from **19** with iodohydrin **18** afforded **20** in 81% yield. The key fragment coupling was accomplished by hydroboration of **20** and transmetalation followed by addition of aldehyde **4** to the resulting vinylzinc derivative. The addition product was, however, obtained as a mixture of diastereomers. Finally, the desired C(12)-(*S*)-stereochemistry was installed by means of a Swern oxidation/$Zn(BH_4)_2$ reduction sequence. Subsequent synthetic manipulation led to the synthesis of **3** (Scheme 4).

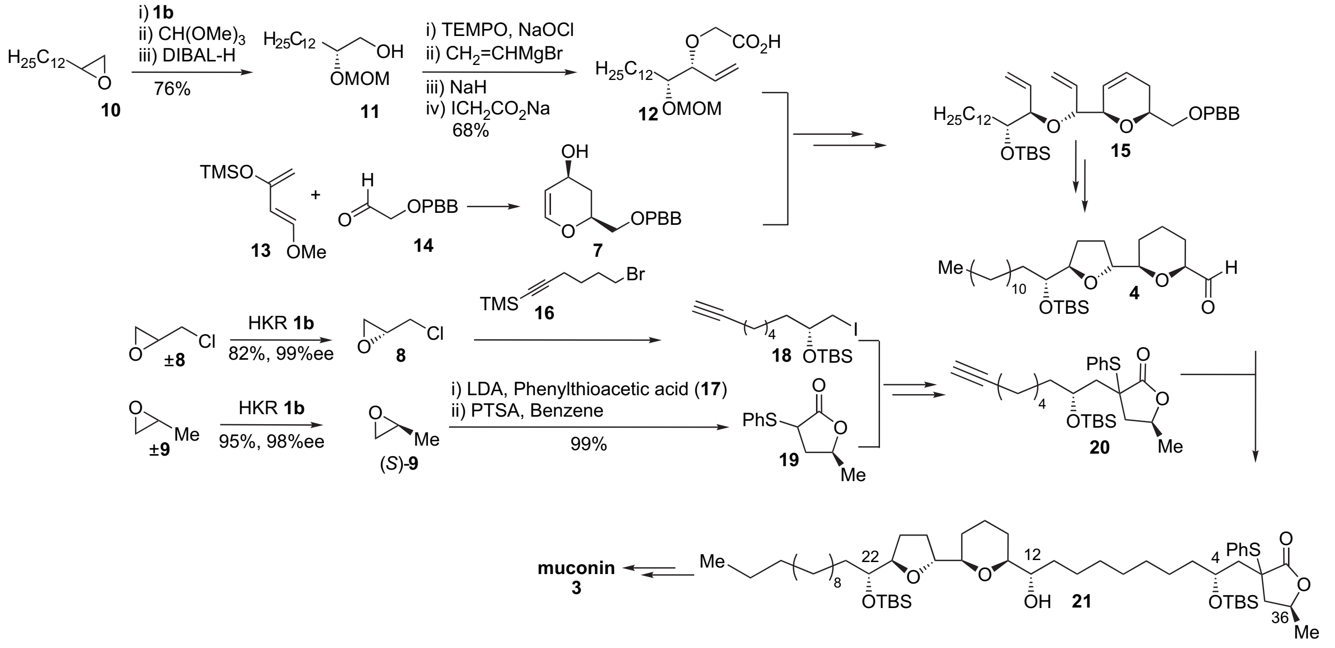


Scheme 3. Retrosynthetic analysis for muconin.

3. Glycidol ethers

3.1. 12(*R*)-HETE, 12(*S*)-HETE, $^2H_2$-12(*R*)-HETE, and LTB_4

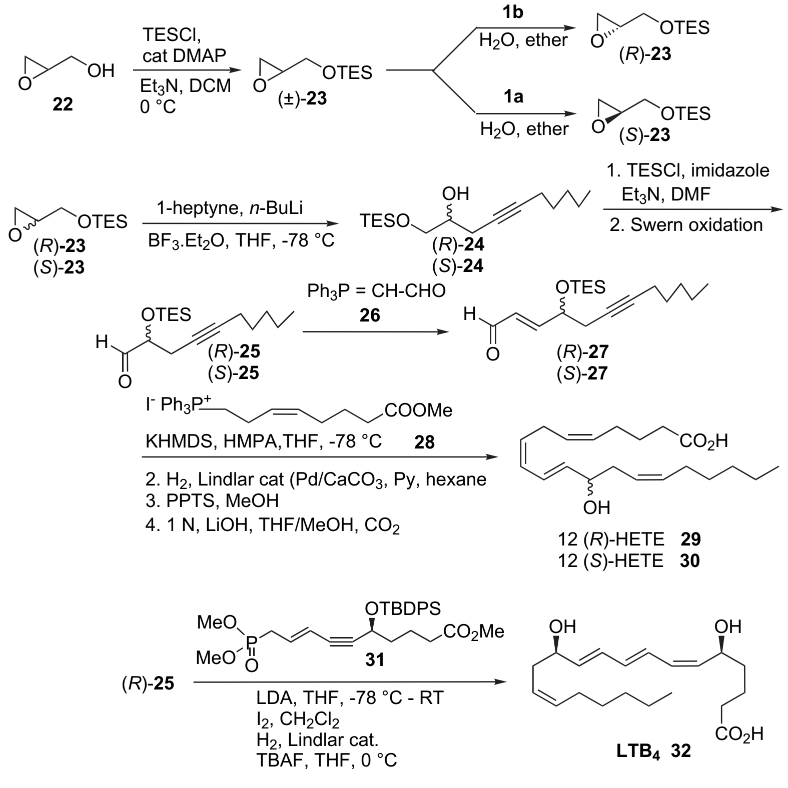
12(*R*)-HETE **29** is found in high concentrations in psoriasis lesions and is formed by the cytochrome P-450 pathway.[10]



Scheme 4.

Its enantiomer, 12(*S*)-HETE **30**, the major 12-lipoxygenase metabolite in platelets,[11a] has been found to play a central role in various stages of metastatic processes in tumors and is therefore a potential target for an anticancer treatment. 12(*S*)-HETE inhibits tumor cell adhesion to endothelial cells.[11b] LTB$_4$ **32**, a metabolite of arachidonic acid, is a potent chemotactic agent for human eosinophils and neutrophils and a modulator of inflammatory responses.[12] It also has high antiviral activity comparable with antiviral drugs such as acyclovir or ganciclovir[13] toward DNA viruses as well as retroviruses including HIV-1 and HIV-2.

The total syntheses of these molecules from racemic glycidol were reported by Spur and co-workers.[14] As shown in Scheme 5, the key steps employed were the hydrolytic kinetic resolution of racemic TES-glycidol, and the selective

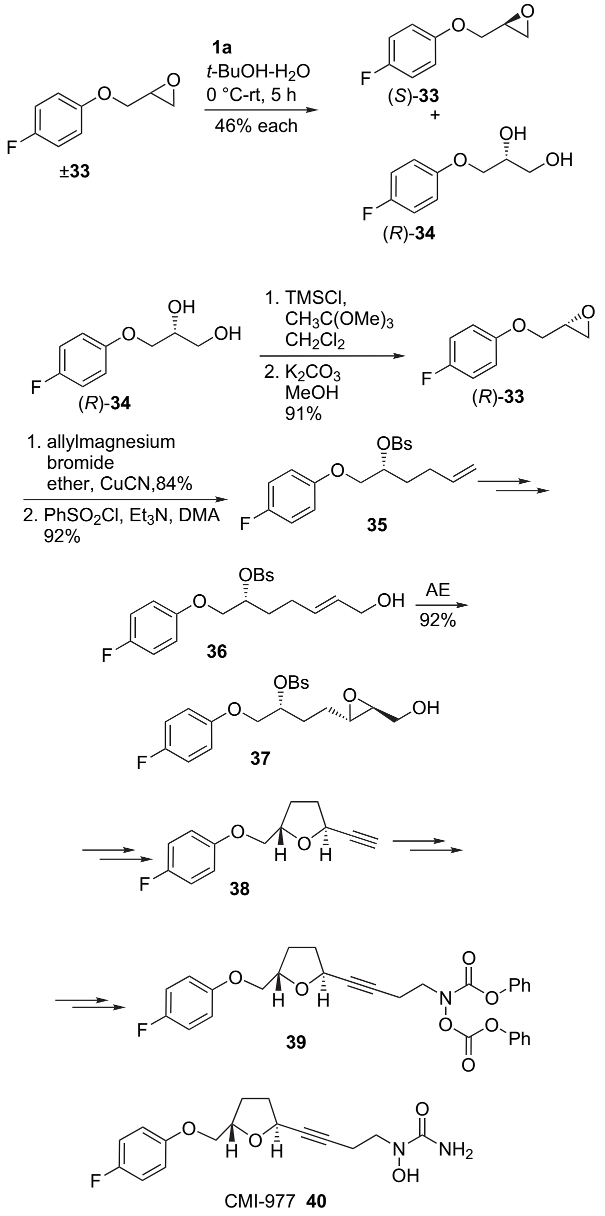


Scheme 5.

oxidation of primary silyl ethers in the presence of secondary ones under Swern conditions. Subsequent Wittig reaction and selective reduction of the triple bond to a *cis*- or *trans*-double bond resulted in the desired target compounds.

3.2. CMI-977 (LDP-977)

CMI-977, (2*S*,5*S*)-*trans*-5-[(4-fluorophenoxy)methyl]-2-(4-*N*-hydroxyureidyl-1-butynyl)tetrahydrofuran, renamed later as LDP-977 **40**, is a promising candidate for chronic asthma,[15] being developed by Cytomed Inc., USA. The synthesis reported by Gurjar and co-workers[16] began with HKR of a glycidyl ether (±)-**33** (prepared by ring opening of (±)-epichlorohydrin with *p*-fluorophenol in the presence of a base), which provided the enantiopure epoxide (*S*)-**33** and the (*R*)-diol (*R*)-**34** in 46% yield each. The epoxide (*R*)-**33** obtained from the diol (*R*)-**34** was subjected to allyl Grignard reaction to afford **35**. Subsequent ozonolysis, two-carbon homologation by Wittig, reduction to allylic alcohol followed by Sharpless epoxidation furnished the epoxy alcohol **37**. Its conversion into α-chloro oxirane, a tandem double elimination and concomitant intramolecular nucleophilic substitution yielded the THF/acetylene derivative **38**, which was converted into the target molecule CMI-977 **40** over several steps (Scheme 6).

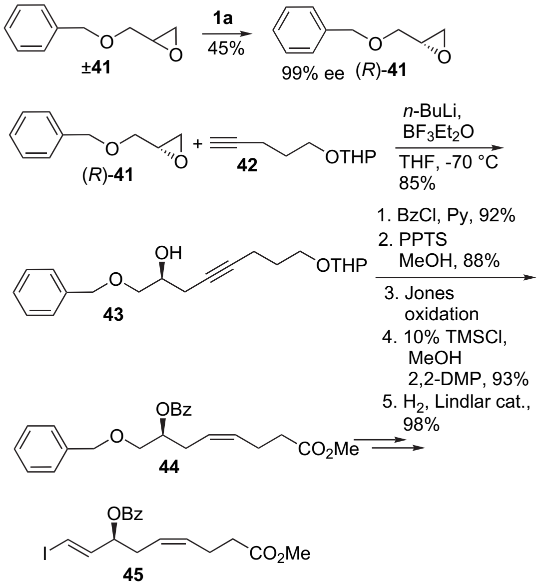


Scheme 6.

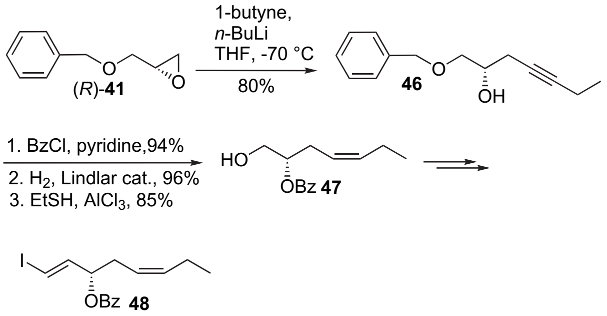
3.3. 7(*S*),17(*S*)-Resolvin D5

Resolvins, a new class of lipid mediators, are known to have anti-inflammatory activities in the pico- or nanomolar range.[17] The first total synthesis of 7(*S*),17(*S*)-resolvin D5, a lipid mediator derived from docosahexaenoic acid, was accomplished by Spur and Rodriguez.[18] A convergent approach was employed to assemble the molecule, which mainly involved the Takai olefination to construct the *trans* double bond, Lindlar reduction for the *cis* double bond, palladium-catalyzed Sonogashira coupling for the construction of the ene–yne moiety, and the simultaneous deprotection and ester cleavage with lipase from *Candida rugosa*.

As outlined in Scheme 7, the enantiopure benzyl glycidyl ether (*R*)-**41** was prepared by HKR in >99% ee following a literature method.[3] The C1–C9 fragment **45** was obtained from (*R*)-**41** and commercially available 2-(4-pentynyloxy)-tetrahydro-2*H*-pyran **42**[19] (Scheme 7). The ring opening of epoxide (*R*)-**41** with lithium acetylide of **42** under Yamaguchi conditions afforded **43**, which was carried through several transformations including Takai olefination to yield the required fragment **45**. Following a similar sequence of reactions, the C15–C22 fragment **48** was synthesized from the chiral glycidyl ether (*R*)-**41** as outlined in Scheme 8. The coupling of **48** with 2 equiv of 1-trimethylsilyl-1,4-pentadiyne **49**[20] gave exclusively the *trans*-ene-diyne **51** after cleavage of the terminal TMS group. The target compound, resolvin **53**, was finally obtained by the Pd-catalyzed second coupling of **45** with **51** followed by selective hydrogenation, deprotection, and saponification (Scheme 9).



Scheme 7.



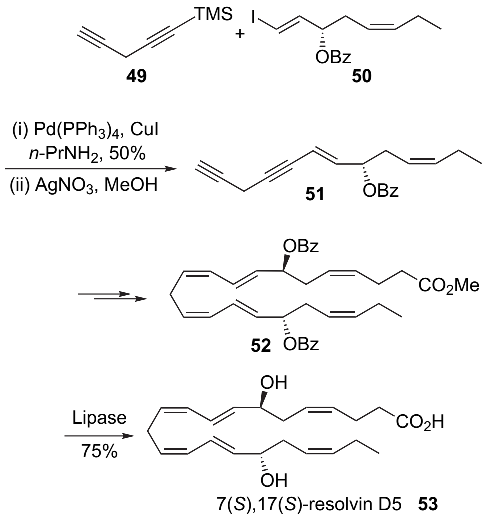
Scheme 8.

3.4. (*S*)-Atenolol

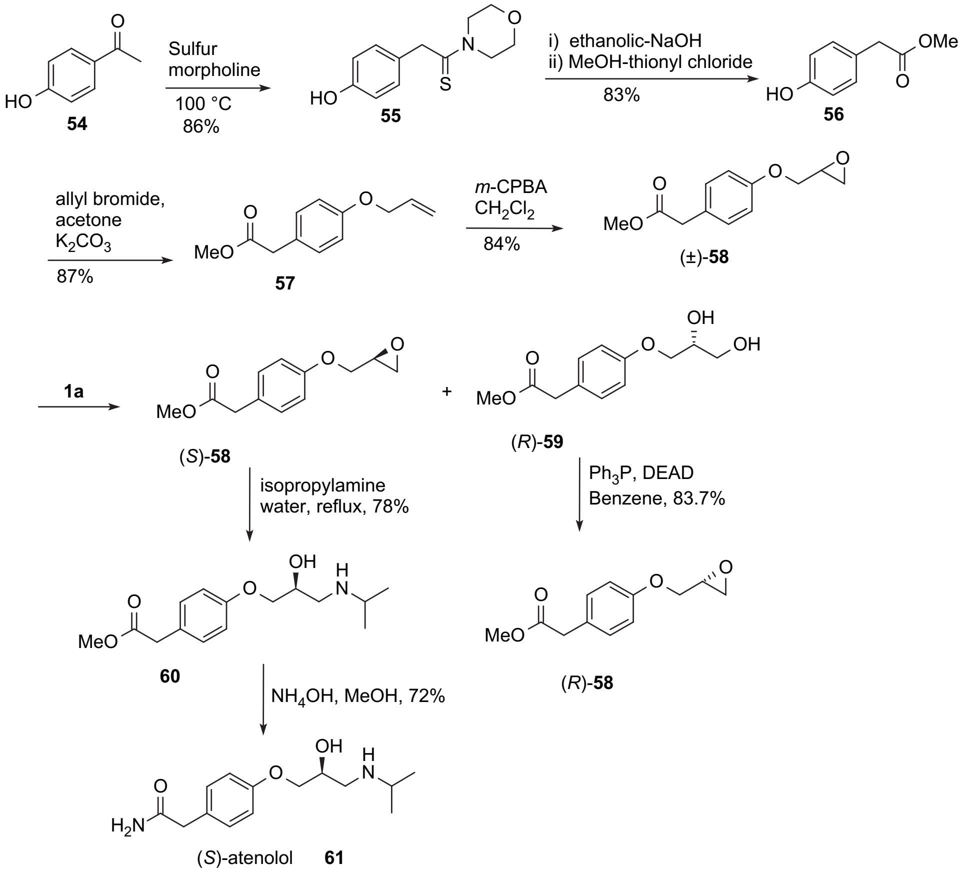
(*S*)-Atenolol **61** is a β-blocker, and is used in the treatment of hypertension and ocular delivery for glaucoma.[21] Its asymmetric synthesis was reported by Bose and Narsaiah in 2005.[22] The terminal epoxide **58** was prepared from 4-hydroxyl acetophenone **54** using a sequence of reactions as shown in Scheme 10 and (±)-**58** was subjected to HKR using catalyst **1a** to give the (*S*)-epoxide (*S*)-**58** in 46% yield and 94% ee. The (*S*)-epoxide was converted into (*S*)-atenolol **61** using standard transformations.

3.5. (*S*)- and (*R*)-Naftopidil

Naftopidil (**67** and **68**) is a vasodilator from the piperazine derivative series.[23] It is a novel α_1-adrenoreceptor antagonist (α_1-blocker), renal urologic drug. Bose and co-workers[24] have successfully carried out the HKR of racemic α-naphthyl glycidyl ether (prepared from α-naphthol and epichlorohydrin) using the catalyst **1a**, which provided the enantiomerically pure (*S*)-naphthyl glycidyl ether (*S*)-**62** and (*R*)-1-naphthyl glycerol **63**. Piperazine derivative **66** was obtained from the coupling of *O*-anisidine and bis(2-chloroethyl)amine hydrochloride **65**, which was prepared from diethanolamine **64**. The enantiomerically pure (*S*)- and (*R*)-naftopidil was synthesized by opening of the

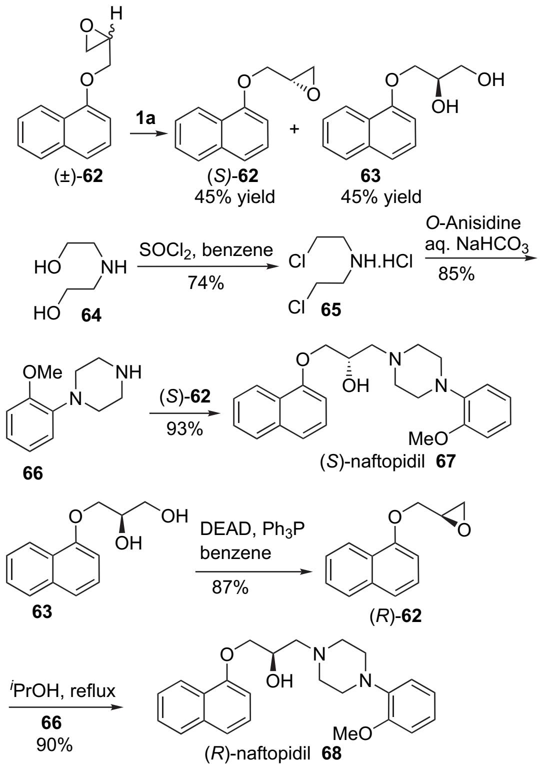


Scheme 9.



Scheme 10.

corresponding pure terminal epoxide with 1-(2-methoxyphenyl)piperazine (Scheme 11).



Scheme 11.

3.6. (*S*)-Betaxolol

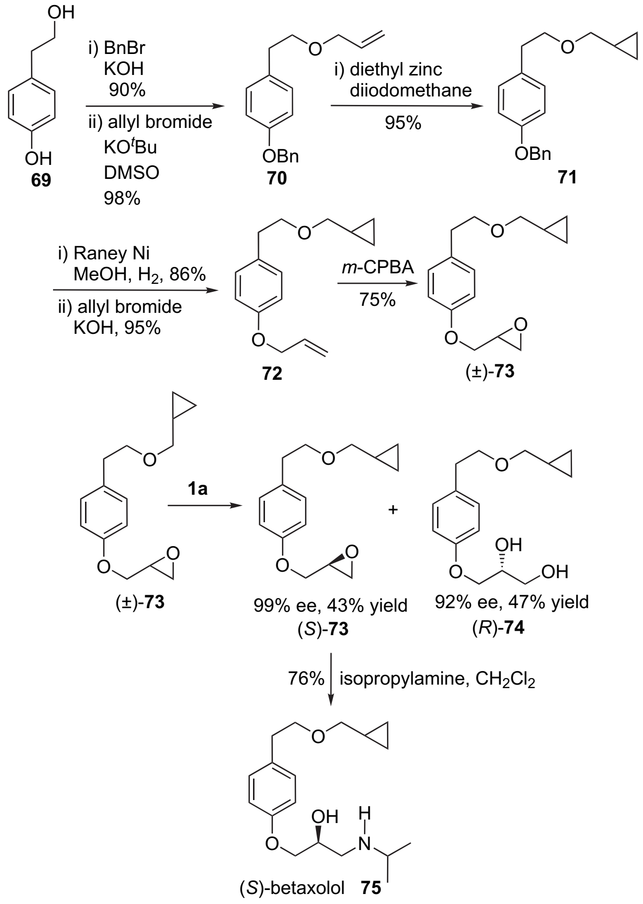
(*S*)-Betaxolol **75** is a β-adrenergic antagonist[25] used in the treatment of cardiovascular disorders such as hypertension, cardiac arrhythmia, angina pectoris, and open-angle glaucoma.[26] Its synthesis was accomplished by Gurjar and co-workers[27a] starting from the commercially available 2-(4-hydroxyphenyl)ethanol **69**. This was converted into the glycidol derivative **73** in several steps, which was subjected to HKR to afford the (*S*)-epoxide (*S*)-**73** in 99% ee and 43% yield and the (*R*)-diol (*R*)-**74** in 92% ee and 47% yield. The epoxide ring opening with isopropylamine led to the target compound, (*S*)-betaxolol **75**, in 76% yield (Scheme 12).

Similarly, other glycidol ethers prepared through HKR have been employed in the synthesis of a various biologically important compounds such as fluoroalanines[27b] and phorboxazoles.[27c]

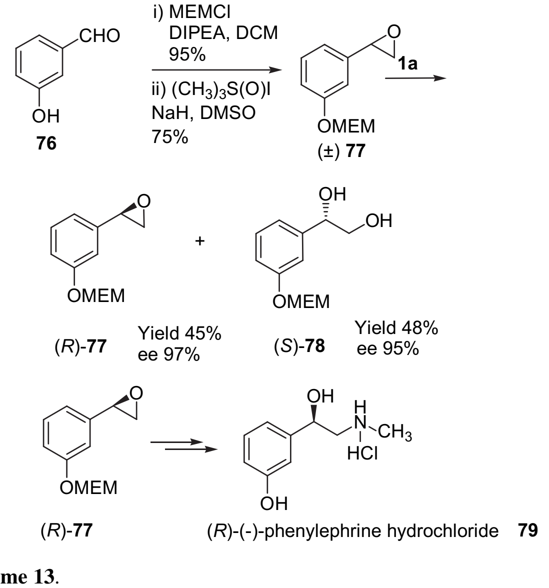
4. Aliphatic/aromatic epoxides

4.1. (*R*)-(−)-Phenylephrine hydrochloride

(*R*)-(−)-Phenylephrine hydrochloride **79** is a clinically potent adrenergic agent and β-receptor sympathomimetic drug, exclusively marketed in the optically active form.[28] Gurjar and co-workers[29] devised a route for its asymmetric synthesis based on hydrolytic kinetic resolution of the styrene oxide derivative (±)-**77**. As shown in Scheme 13, the synthesis began with *m*-hydroxybenzaldehyde **76**, which was converted into the required epoxide after hydroxyl protection and subsequent treatment with trimethylsulfoxonium iodide in the presence of NaH/DMSO. The epoxide (±)-**77** was subjected to HKR using (*R*,*R*)-salen Co(III) acetate complex **1a** to give the (*R*)-styrene oxide, (*R*)-**77**, in 45% yield and 97% ee and (*S*)-diol (*S*)-**78** in 48% yield and 95% ee. Subsequent treatment with methylamine/HCl resulted in (*R*)-(−)-phenylephrine hydrochloride **79** in 97% ee.



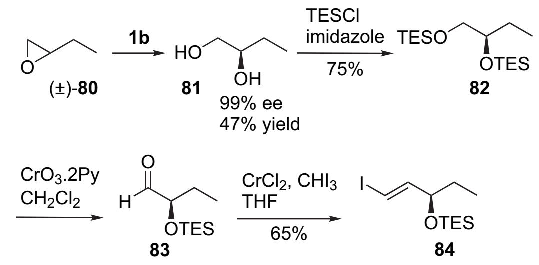
Scheme 12.



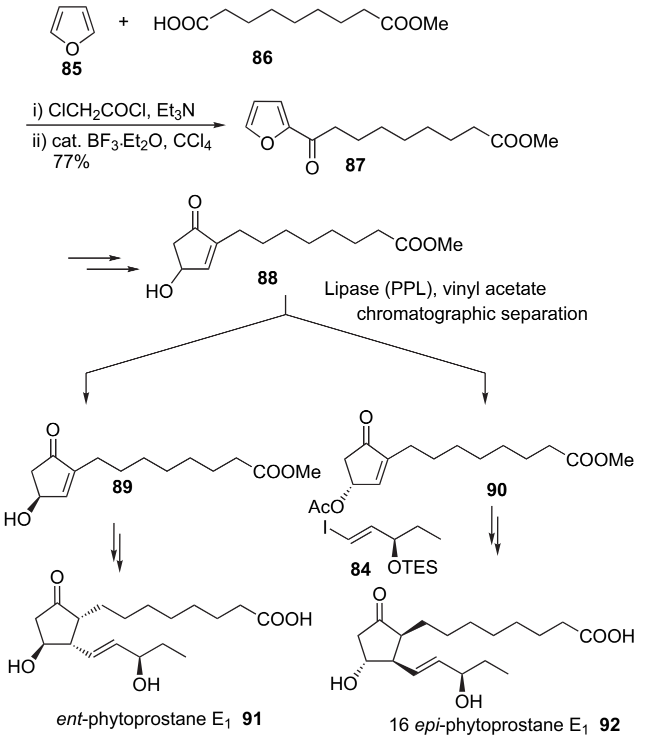
Scheme 13.

4.2. E type 1 phytoprostanes

The first total synthesis of two E type phytoprostanes **91** and **92** was reported by Spur and Rodriguez.[30] Phytoprostanes are known to cause tissue irritation and contribute to allergic reactions in human beings. The synthesis involved two-component coupling of a chiral hydroxycyclopentenone derivative with a *trans*-vinyl iodide and subsequent synthetic manipulations. As illustrated in Scheme 14, the synthesis of the optically active pure iodovinyl side chain started from the kinetic resolution of racemic 1,2-epoxybutane **80** using the *S*,*S*-salen-Co catalyst **1b** to give the diol **81** in 99% ee and 47% yield. Hydroxyl protection, selective oxidation to aldehyde followed by a Takai reaction yielded the required side chain **84**. The racemic hydroxycyclopentenone **88** was obtained from the reaction of furan **85** and mixed anhydride of azelaic monomethyl ester **86** in water under reflux using a catalytic amount of chloral. The *rac*-hydroxycyclopentenone **88** was easily converted into the chiral intermediates in >97% ee by lipase. The synthesis of target compounds **91** and **92** was achieved by two-component coupling following a series of synthetic transformations (Scheme 15).



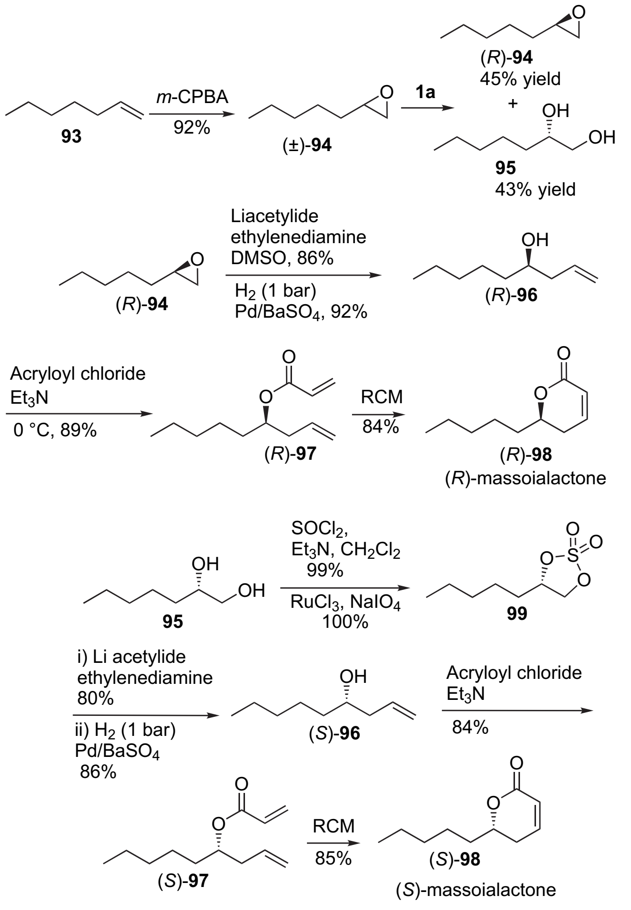
Scheme 14.



Scheme 15.

4.3. Massoialactone

A practical and efficient enantioselective synthesis of both (*R*)- and (*S*)-massoialactone **98** was achieved by Kumar and co-workers.[31] The key steps in the synthesis included the HKR of a racemic epoxyheptane and ring-closing metathesis of homoallylic alcohol-derived acrylate esters using Grubb's catalyst. Thus, as depicted in Scheme 16, the synthesis of the target molecule **98** started from 1-heptene **93**, which was epoxidized with *m*-CPBA and then subjected to HKR using **1a** (0.5 mol %) and water (0.55 equiv) to give the *R*-epoxide, (*R*)-**94**, in 45% yield and >99% ee and (*S*)-diol **95** in 43% yield with 99.5% ee. Opening of the *R*-epoxide, (*R*)-**94**, with lithium acetylide and hydrogenation followed by ring-closing metathesis resulted in (*R*)-massoialactone **98**. The (*S*)-diol **95** was converted into the cyclic sulfate **99**. It was opened with lithium acetylide and converted into the homoallylic alcohol. The synthesis of (*S*)-massoialactone was achieved using a similar sequence of reactions as shown above.

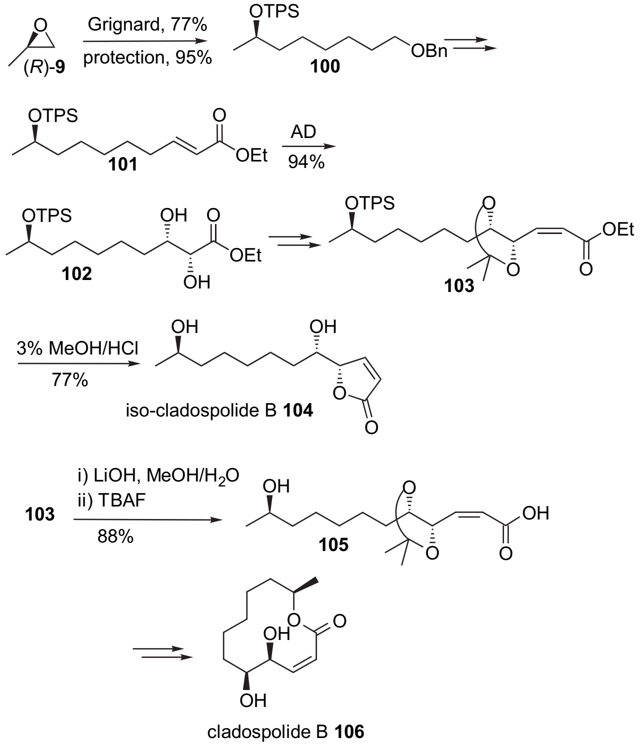


Scheme 16.

4.4. *iso*-Cladospolide B and cladospolide B

The novel hexaketide compounds, *iso*-cladospolide and cladospolide, were isolated from the fungal isolate, I96S215.[32] They have plant growth retardant activity toward rice seedlings.[33] Kumar and Pandey accomplished the total synthesis of *iso*-cladospolide B and cladospolide B from commercially available propylene oxide employing Jacobsen's

HKR, a Sharpless asymmetric dihydroxylation, and Yamaguchi macrolactonization as the key steps.[34a] The chain lengthening of (*R*)-propylene oxide, prepared through HKR, by Grignard, Sharpless asymmetric dihydroxylation, and iterative Wittig reaction followed by acid-induced Yamaguchi lactonization resulted in *iso*-cladospolide B **104** and cladospolide B **106** (Scheme 17). The stereochemistry of the carbon bearing a methyl substituent was derived from HKR while the other two centers were established by Sharpless asymmetric dihydroxylation.



Scheme 17.

Similarly, both (*R*)- and (*S*)-propylene oxide prepared through HKR have been employed in the synthesis of a variety of other biologically important compounds such as neocarazostatin,[34b] nonactin,[34c] elecanacin,[34d] (+)-peloruside A[34e] and carquinostatin A.[34f]

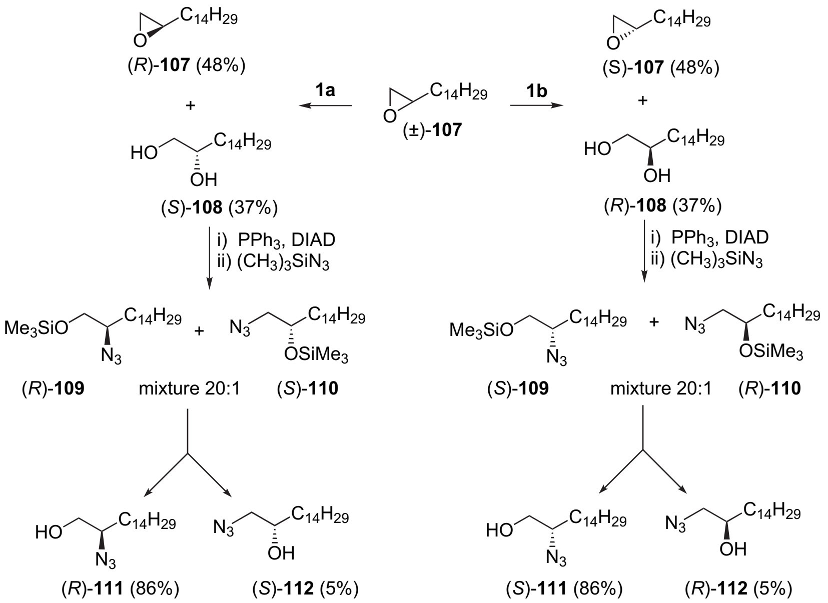
4.5. Neoglycolipid analogs of glycosyl ceramides

Glycosphingolipids or glycosyl ceramides are constituents of animal cell membranes consisting of various oligosaccharides bound to ceramides by a glycosidic bond. They serve as identifying markers and regulate cellular recognition, growth, and development.[35] Boullanger and co-workers[36] synthesized four different types of glycosyl ceramide analogs having D-galactose or 2-acetamido-2-deoxy-D-glucose starting from an epoxide and employing hydrolytic kinetic resolution (HKR) as a key step.

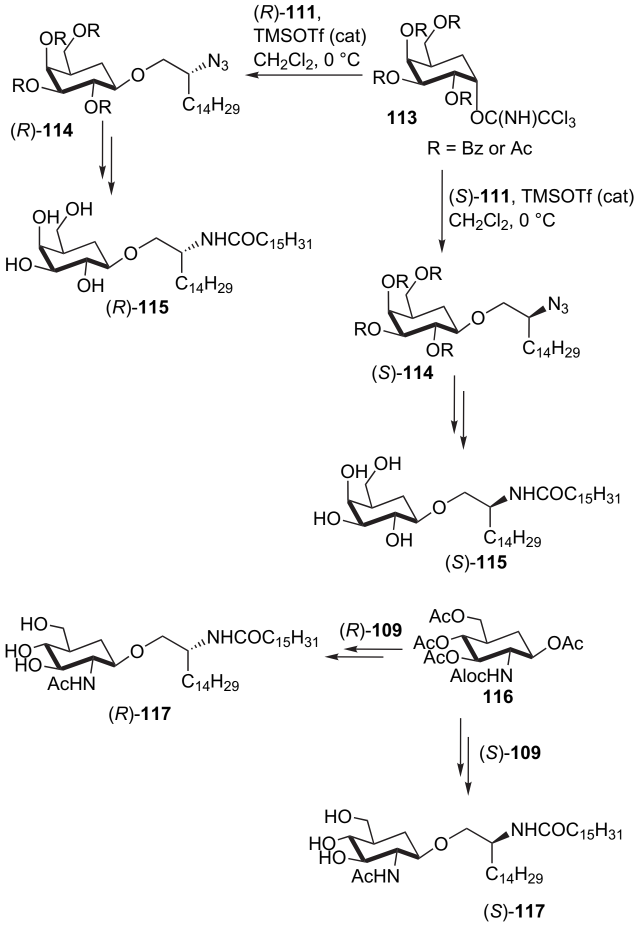
As depicted in Scheme 18, (±)-1,2-epoxyhexadecane, (±)-**107**, was subjected to hydrolytic kinetic resolution with water (0.55 equiv) in THF in the presence of (*R*,*R*) catalyst **1a** to afford the *R*-epoxide, (*R*)-**107**, and *S*-diol, (*S*)-**108**, in 48 and 37% yields, respectively, with >95% ee. Similarly, by using **1b** catalyst *S*-epoxide, (*S*)-**107**, and *R*-diol, (*R*)-**108**, were obtained in the same yields. Treatment of (*S*)-**108** with PPh_3/DIAD and $TMSN_3$ gave an inseparable mixture of regioisomers (20:1), (*R*)-**109** and (*S*)-**110**, in good yield. After desilylation, the two isomers were separated by column chromatography. Next, (*R*)-**112** and (*S*)-**111** were prepared from (*R*)-**108** using a similar sequence of reactions. Finally, galactosylation and glycosylation led to the ceramides (*R*)-**115**, (*S*)-**115**, (*R*)-**117**, and (*S*)-**117** in good yields (Scheme 19).

4.6. Bicyclic γ-lactones

Kitching and co-workers developed a new synthesis of some bicyclic γ-lactones from parasitic wasps (Hymenoptera:



Scheme 18.



Scheme 19.

Braconidae).[37] The authors have employed a palladium(II)-catalyzed hydroxycyclization–carbonylation–lactonization sequence with appropriate pent-4-ene-1,3-diols providing efficient access to the bicyclic γ-lactones. The ene-diols **121a**,**b** were visualized as immediate precursors for the Pd-catalyzed cyclization. The ene-diols **121a**,**b**, in turn, were prepared starting from racemic 1,2-epoxyhexane **118a**/1,2-epoxyoctane **118b**, which were subjected to HKR using **1b** catalyst to afford the (*S*)-epoxide **118a**/**118b** in 33% yield and (*R*)-1,2-hexanediol **119a**/octanediol **119b** in 40% yield (Scheme 20). The treatment of *S*-epoxide with vinylmagnesium bromide delivered the homoallylic alcohols, which, as their THP ethers, were ozonized and again reacted with vinylmagnesium bromide. Deprotection afforded the ene-diols **121a**,**b**, which were successfully converted into the desired lactones **122** and **123** by Pd-catalyzed reactions (Scheme 21).

4.7. C13–C22 fragment of amphidinolide T2

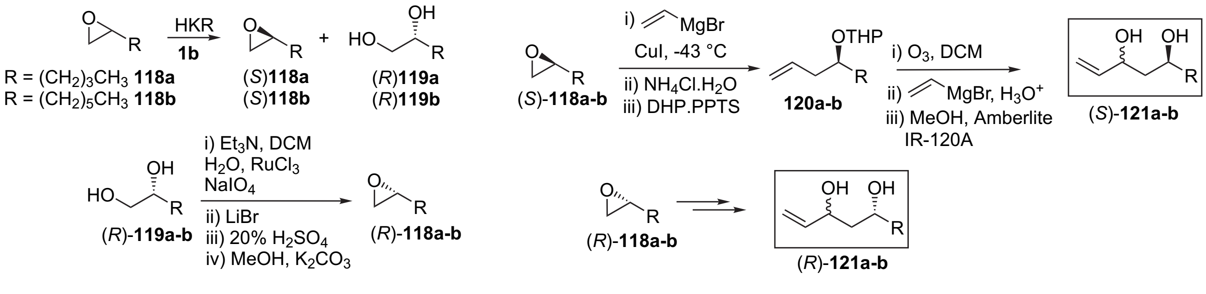
Amphidinolide is a recently discovered molecule with potent biological activity and, therefore, it has attracted a lot of attention from organic chemists worldwide.[38] As a result, several total or partial syntheses of this molecule have appeared in the literature. Jamison and co-workers accomplished the synthesis of the C13–C22 fragment of amphidinolide T2 **131** via nickel-catalyzed reductive coupling of an alkyne and a terminal epoxide.[39] The authors explored several routes to the synthesis of enantiomerically enriched epoxide **128a**, but the use of HKR was most satisfactory to separate the mixture of diastereomeric epoxides.

The HKR of a stereorandom mixture of 1,5-hexadiene diepoxides (**125**/*meso*-**125**/*ent*-**125**=1:2:1)[40] provided the epoxide **125** with >99% ee in only two steps from 1,5-hexadiene **124**. However, the subsequent reduction of **125** with both Red-Al and DIBAL-H resulted in a low yield of **126a** due to rapid cyclization via attack of the hydroxyl group on the epoxide giving undesired tetrahydrofuran **126b** (Scheme 22). Further, the addition of allylmagnesium chloride to *S*-propylene oxide followed by TBS protection and epoxidation with *m*-CPBA (1:1 dr) provided the desired mixture of epoxides in 38% yield over three steps. The two diastereomers were chemically separated by subjecting them again to HKR to afford **128a** in >98% diastereoselectivity, albeit in low yield. The nickel-catalyzed coupling of alkyne **129**[41] and epoxide gave the desired alcohol in >95:5 dr and 39% yield, representing rapid access to a significant fragment of amphidinolide T2 **131**.

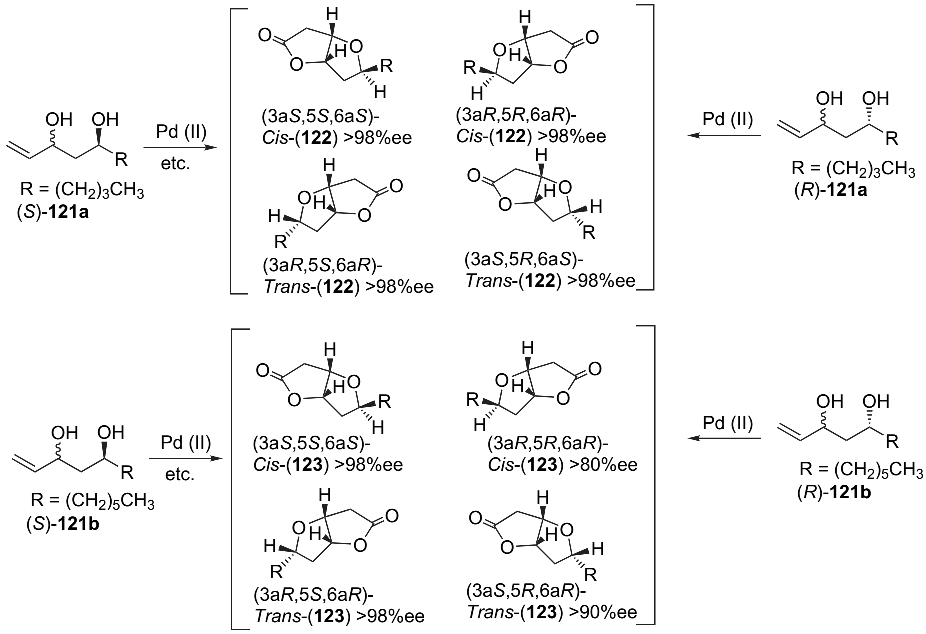
4.8. Dihydrobenzofurans

Enantiomerically enriched dihydrobenzofuran derivatives are an important class of biologically active compounds,[42] e.g., arthrographol shows antifungal properties,[43] while megapodiol[44] and conocarpan[45] exhibit antileukemic and anticancer activity, respectively.

The enantioselective synthesis of 1-benzyloxy-2-oxiranylmethylbenzenes, precursors for dihydrobenzofurans, was reported by Bhoga using the HKR method.[46] As shown in

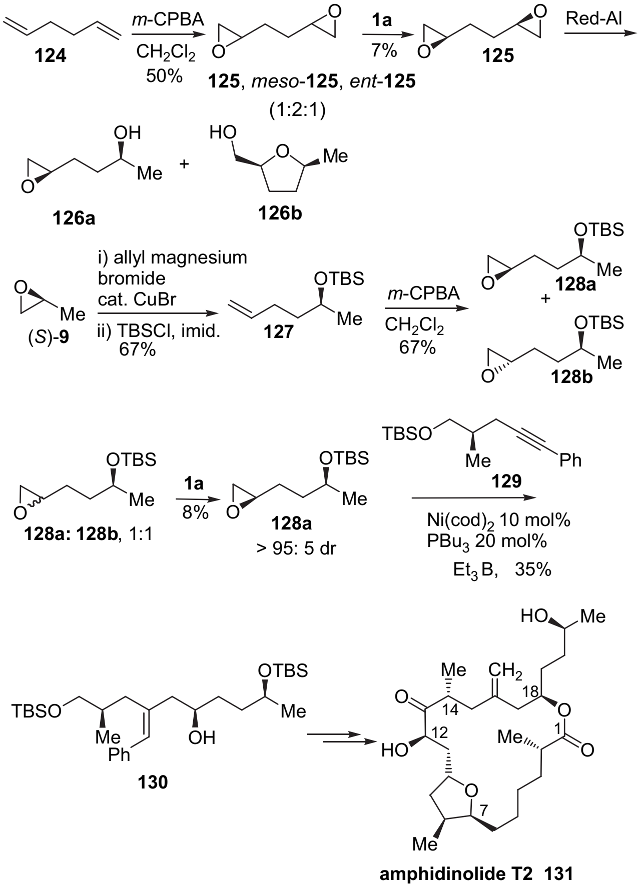


Scheme 20.

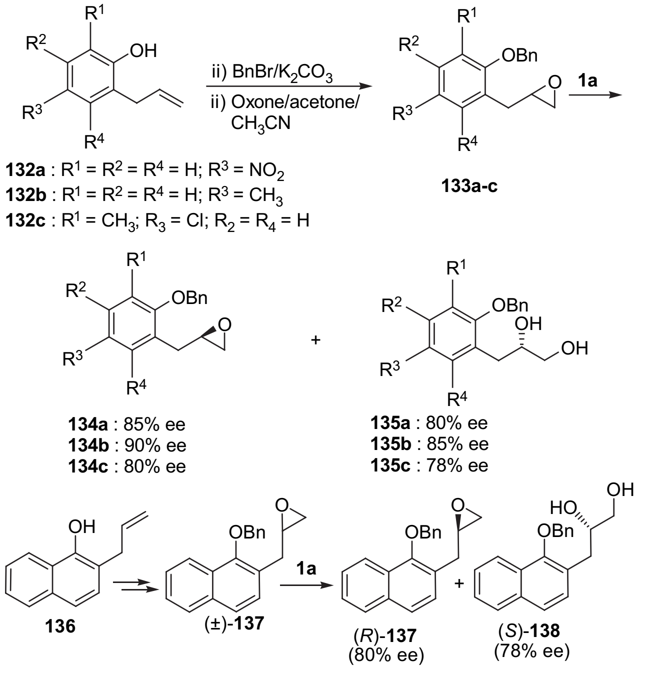


Scheme 21.

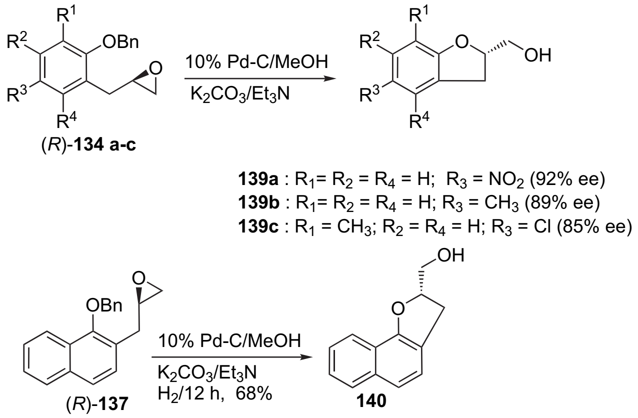
Scheme 23, the HKR substrate was prepared from *o*-allylphenols **132a–c** by their conversion into the corresponding *o*-allylbenzyl ethers followed by epoxidation with dimethyldioxirane to give the racemic 1-benzyloxy-2-oxiranylmethylbenzenes, **133a–c**. The HKR using the chiral salen cobalt complex **1a** gave the optically active pure (*R*)-epoxides **134a–c** and the (*S*)-1,2-diols **135a–c** in 80–90% and 78–85% ee, respectively. Using a similar sequence of reactions, the *o*-allylnaphthol **136** was converted into the racemic epoxide (±)-**137**, which, on HKR under identical conditions, gave the (*R*)-epoxide (*R*)-**137** and (*S*)-1,2-diol (*S*)-**138** in 80 and 78% ee, respectively. Subsequent intramolecular epoxide opening followed by in situ cyclization resulted in the target molecules **139** and **140** (Scheme 24).



Scheme 22.



Scheme 23.



Scheme 24.

4.9. Spongiacysteine

Spongiacysteine **141** (Fig. 3), a novel cysteine derivative, was isolated from marine sponge *Spongia* sp.[47] It shows antimicrobial activity against rice blast fungus *Pyricularia oryzae* (IC_{90}=100 ppm). Kigoshi and co-workers elucidated the gross structure and absolute stereostructure by spectroscopic analysis and total synthesis starting from the chiral pool starting material, *N*-methylcysteine, and using HKR and diastereoselective epoxidation as the key steps.[48] As depicted in Scheme 25, 1,2-epoxypentane (±)-**144** was subjected to hydrolytic kinetic resolution with H_2O catalyzed by **1a** to provide the optically active epoxide (+)-**144**, which, on ring opening with lithium acetylide followed by methylation and partial hydrogenation, furnished the homoallylic alcohol **145** in 83% yield. The epoxide **146** derived from **145** by diastereoselective epoxidation was coupled with cysteine derivative **143** leading to the target molecule **141** along with regioisomer **147**.

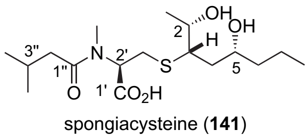
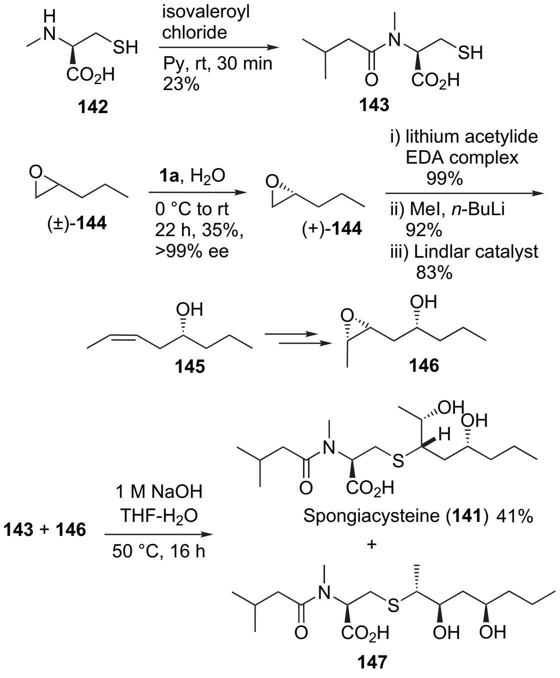


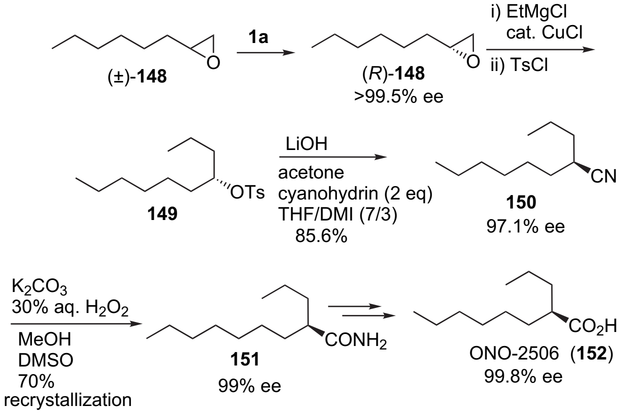
Figure 3.



Scheme 25.

4.10. Astrocyte activation suppressor, ONO-2506

ONO-2506 (**152**) delays the expansion of cerebral infarction by modulating the activation of astrocytes through inhibition of *S*-100β synthesis. It has been developed as a novel therapeutic agent for stroke, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease.[49] Hasegawa and co-workers[50] developed a new process for the synthesis of ONO-2506 using the hydrolytic kinetic resolution method. Racemic 1,2-epoxyoctane (±)-**148** was subjected to HKR using **1a** catalyst to give the (*R*)-epoxide (*R*)-**148** with >99% ee. Opening of the *R*-epoxide with ethylmagnesium bromide, tosylation by directly quenching with tosyl chloride, and cyanation with acetone cyanohydrin followed by hydrolysis resulted in ONO-2506 (**152**) (Scheme 26).



Scheme 26.

4.11. (*S*)-2-Tridecanyl acetate: sex pheromone of Douglas-fir cone gall midge, *Contarinia oregonensis*

Gries and co-workers[51a] identified compound **154** (Fig. 4) as the sex pheromone of the female Douglas-fir cone

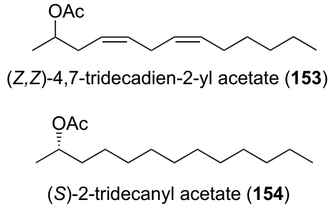
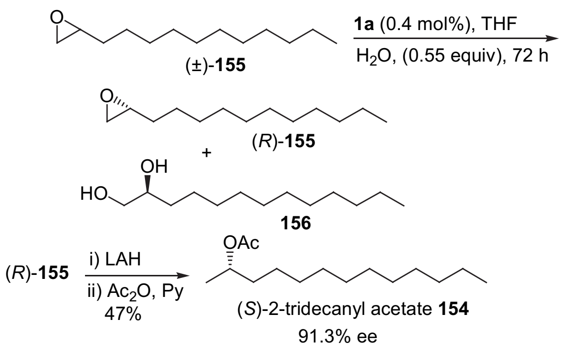


Figure 4.

gall midge, *C. oregonensis*. They synthesized (*S*)-2-tridecanyl acetate **154** employing hydrolytic kinetic resolution as the key step. As depicted in Scheme 27, 1,2-epoxytridecane (±)-**155** was subjected to HKR using H_2O (0.55 equiv) and catalyst **1a** for three days at room temperature to give the *R*-epoxide (*R*)-**155**, which was separated from the *S*-diol **156** by flash chromatography. Ring opening of epoxide (*R*)-**155** with LAH followed by acetylation gave the target molecule, (*S*)-2-tridecanyl acetate **154**, in 47% overall yield and with 91.3% ee. The hydrolytic kinetic resolution of epoxide (±)-**155** with **1b** catalyst in a similar manner gave the (*R*)-2-tridecanyl acetate in 47% yield with 91.3% ee.

Similarly, other aliphatic epoxides prepared through HKR have been employed in the synthesis of a variety of biologically important compounds such as pamamycin-607,[51b] Annonaceous acetogenins,[51c] and trisubstituted tetrahydrofurans.[51d]

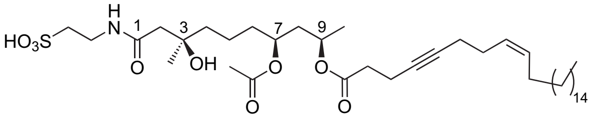


Scheme 27.

5. Dialkyl-substituted epoxides

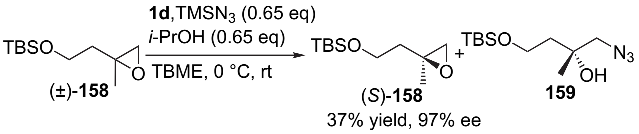
5.1. Taurospongin A

Taurospongin A **157** (Fig. 5) is a structurally interesting fatty acid derivative isolated recently from the Okinawan marine sponge *Hippospongia* sp. It is found to exhibit remarkable dual activity as a potent inhibitor of both DNA polymerase β and HIV reverse transcriptase.[52] Jacobsen and Lebel have accomplished the total synthesis of taurospongin.[53] The retrosynthetic analysis reveals that the chiral component (*S*)-**158**, one of the key intermediates in the synthesis, can be derived from the 2,2-disubstituted epoxide (±)-**158**. While the Co-salen catalyst has been successfully used for the resolution of a wide variety of monosubstituted terminal epoxides, 2,2-disubstituted epoxides, e.g., (±)-**158**, failed to react under HKR conditions. In contrast, kinetic resolution with salen Cr catalyst **1d** and $TMSN_3$ proved to be successful, providing the desired enantio-enriched epoxide (*S*)-**158** in 37% yield and 97% ee (Scheme 28). The epoxide was carried through a series of transformations to eventually complete the synthesis of the target molecule, taurospongin A **157** (Scheme 29).

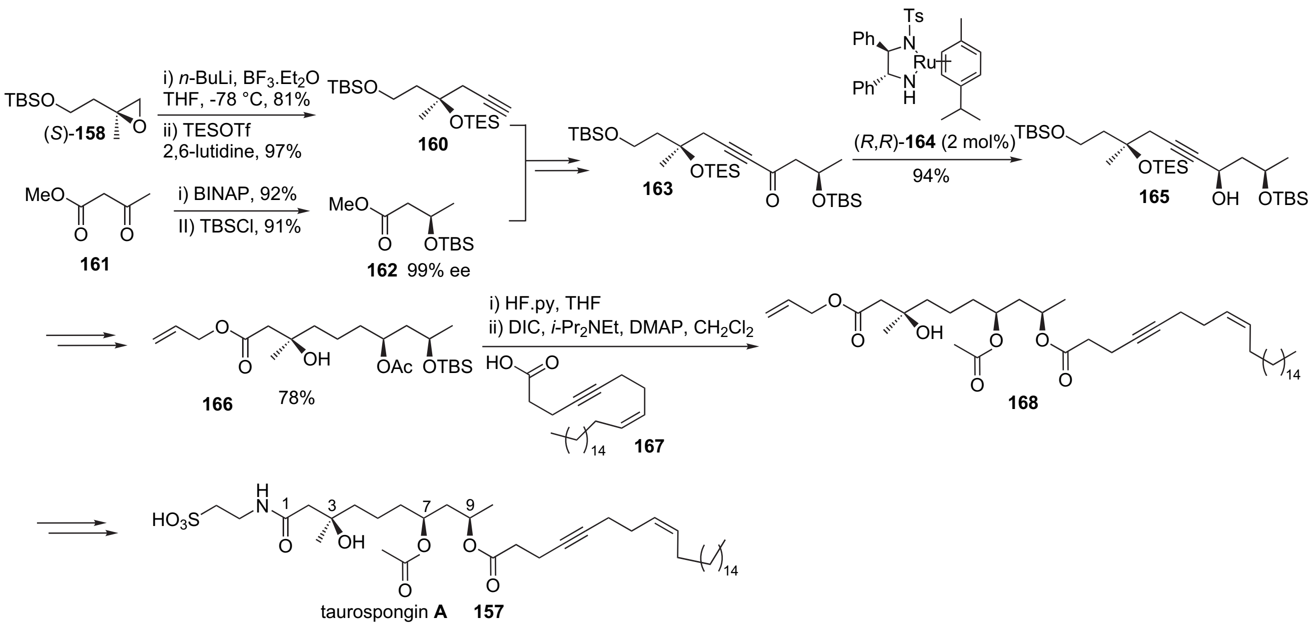


157

Figure 5. Taurospongin A.



Scheme 28.

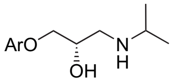


Scheme 29.

6. Amine-substituted epoxides

6.1. β-Adrenergic blocking agents

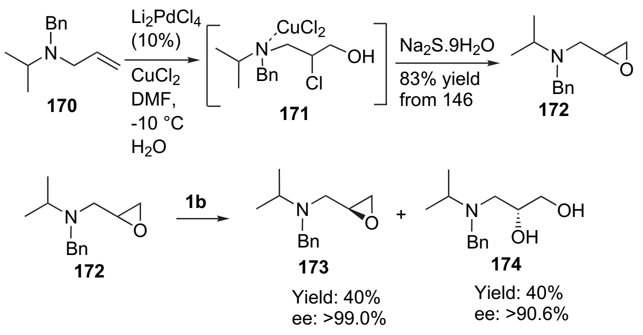
β-Adrenergic blocking agents of the 3-(aryloxy)-2-hydroxy-*N*-isopropylamine type **169** (Fig. 6) are a group of drugs, the biological activity of which resides almost exclusively in the (*S*)-enantiomer. Hou and co-workers have developed a concise, divergent, five-step synthesis of three β-adrenergic blocking agents in high enantiomeric excess using (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine as the key intermediate.[54] As illustrated in Scheme 30, *N*-benzyl-*N*-isopropylallylamine (prepared from the reaction of *N*-benzyl-*N*-isopropylamine and allyl bromide) was treated with water in the presence of $Li_2PdCl_4/CuCl_2$ at −10 °C in DMF, followed by decomplexation of $CuCl_2$ from the chlorohydroxylation product with an excess of $Na_2S\cdot 9H_2O$, to give the amine-substituted epoxide **172** in high yield. This was subjected to HKR using 0.55 equiv water catalyzed by 0.01 equiv of **1b** to provide (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine **173** in 40% yield and >99% ee and diol **174** in 51% yield and 90.6% ee. Further, the authors have observed that, if the benzylcarbonate protecting group (Cbz) replaced the benzyl group, the HKR was not satisfactory and only 45% yield of the epoxypropylamine could be obtained with 47% ee. This means that the amino group may play a role in this reaction. The epoxypropylamine **173** was then reacted with phenol in refluxing NEt_3 followed by debenzylation with 10% Pd/C to give the target molecules **169a–c** in essentially quantitative yield (Scheme 31).



169

	ArOH	β-blocker
169a :	α-Naphthol	propranolol
169b :	Guaiacol (2-methoxyphenol)	moprolol
169c :	*m*-Cresol (3-methylphenol)	toliprolol

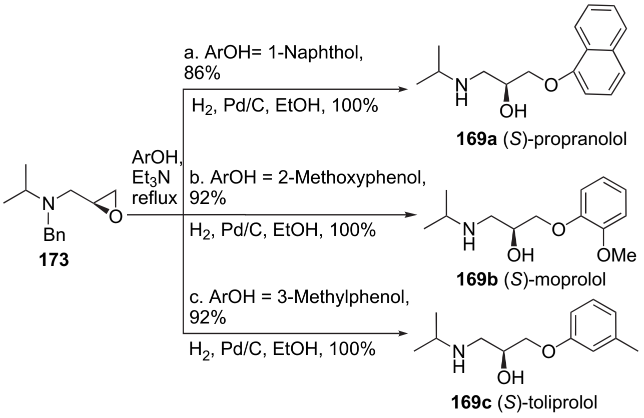
Figure 6.



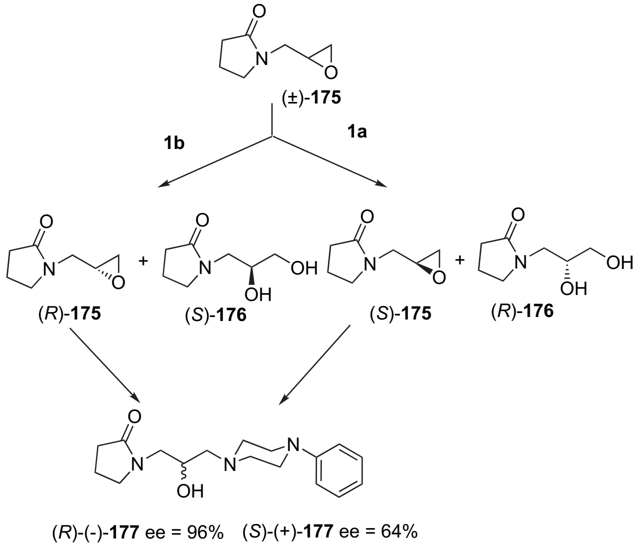
Scheme 30.

6.2. 1-[2-Hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one

Compound **177** belongs to a class of antiarrhythmic drugs and also showed hypotensive effects and α_1 and α_2 adrenergic blocking activities.[55] Malawska and co-workers developed an asymmetric synthesis of 1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)-propyl]-pyrrolidin-2-one **177** using AD or hydrolytic kinetic resolution methods.[56] The enantiomers of compound **177**, which were obtained by HKR, showed a higher ee than those which were synthesized by AD and epoxidation. As depicted in Scheme 32, racemic **175** was subjected to HKR in the presence of **1a/1b** and water to give the *R*/*S*-epoxide, which, on treatment with phenylpiperazine, furnished the desired product (*R*)-(−)-**177** in 96% ee and (*S*)-(−)-**177** in 64% ee.



Scheme 31.

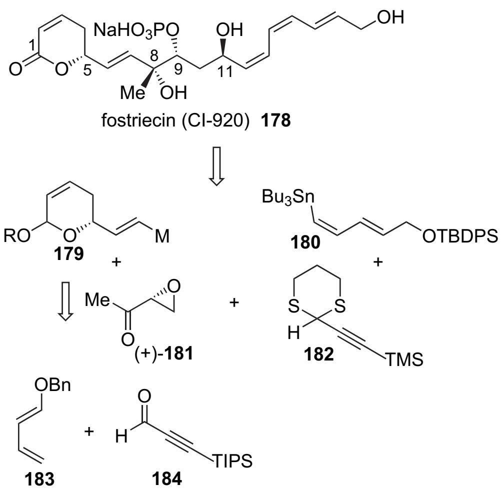


Scheme 32.

7. Epoxides bearing a carbonyl functionality

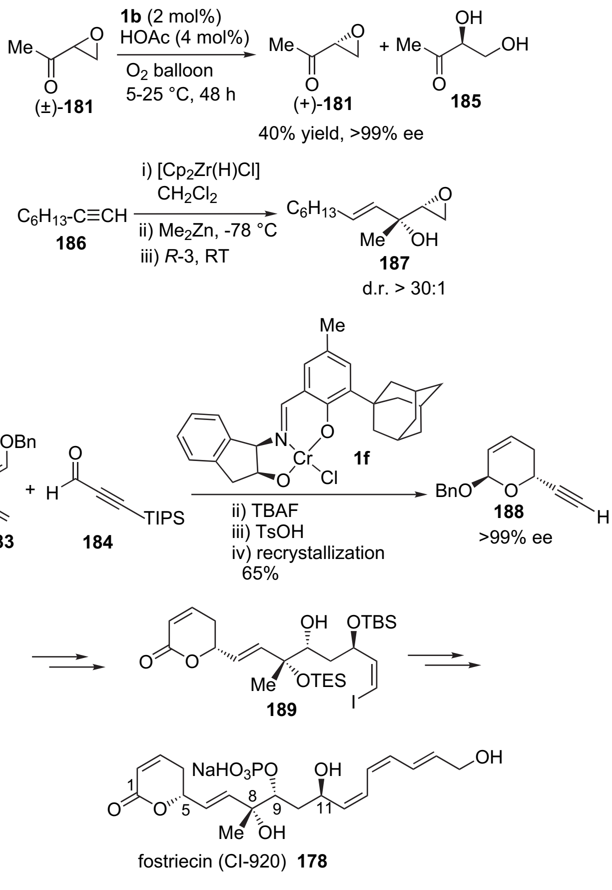
7.1. Fostriecin

Fostriecin (CI-920) **178** is a structurally interesting antitumor agent that was isolated in 1983 by scientists at Warner Lambert–Parke Davis.[57] It displayed in vitro activity against a broad range of cancerous cell lines as well as in vivo antitumor activity.[58] A new synthesis of this molecule reported by Jacobsen and Chavez[59] involves the assembly of four fragments (**179**–**182**) of similar complexity (Scheme 33). Epoxyketone **181** played a central role, serving as the source of the C9 stereocenter. The racemic **181** was prepared easily



Scheme 33. Retrosynthetic analysis for fostriecin (CI-920).

from the inexpensive methyl vinyl ketone.[60] However, the preparation of enantio-enriched **181** proved to be challenging by HKR. Under standard conditions, precipitation of the catalyst as the reduced [salen Co(II)] complex was observed with low substrate conversions. However, when the reaction was carried out under an atmosphere of oxygen instead of nitrogen or air, reduction of the catalyst was avoided and the HKR proceeded to completion, affording (+)-**181** in >99% ee and 40% yield (Scheme 34). To install the stereochemistry of the C-8 *tert*-hydroxyl group, the coupling reaction of **183** and **184** using the Wipf procedure resulted in the required product **188**, which was carried through a series of transformations to furnish, eventually, the target molecule, fostriecin **178**.



Scheme 34.

7.2. C1–C19 fragment of ulapualide A

Ulapualide A **190** (Fig. 7), first isolated from the red egg masses of the nudibranch *Hexabranchus sanguineus*, belongs to a unique family of tris-oxazole-containing metabolites.[61] It exhibits inhibitory activity against L1210 leukemia cell proliferation and also displays ichthyotoxic and antifungal properties. Asymmetric synthesis of a C1–C19 fragment of ulapualide A was reported by Panek and Celatka[62a] in which a C3 hydroxyl-bearing stereocenter was established by Jacobsen's hydrolytic kinetic resolution of a terminal epoxide. As shown in Scheme 35, the synthesis of the C1–C6 subunit **193** began by HKR of the readily available racemic epoxide (±)-**191** with **1a** to provide the (*R*)-epoxide (*R*)-**191** in 94% yield and 99% ee. The epoxide ring opening with vinylmagnesium bromide, protection of the hydroxyl group as the TBS ether followed by oxidative cleavage of the terminal olefin, and Takai iodo-olefination provided the C1–C6 fragment **193** as a 5:1 mixture of isomers. The C7–C19 subunit **197** was constructed starting from α-benzyloxyacetaldehyde through a series of transformations. The coupling of the two fragments was accomplished through a Kishi–Nozaki reaction to afford the desired C1–C19 fragments **199** of the target molecule **190**.

Mycalolide A was also synthesized by using the same epoxide **191**.[62b]

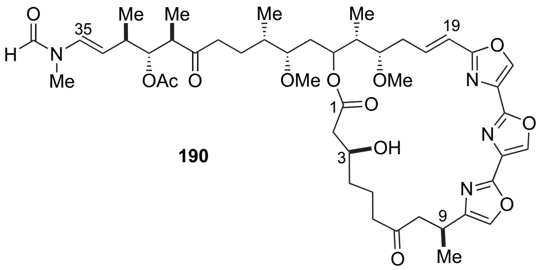
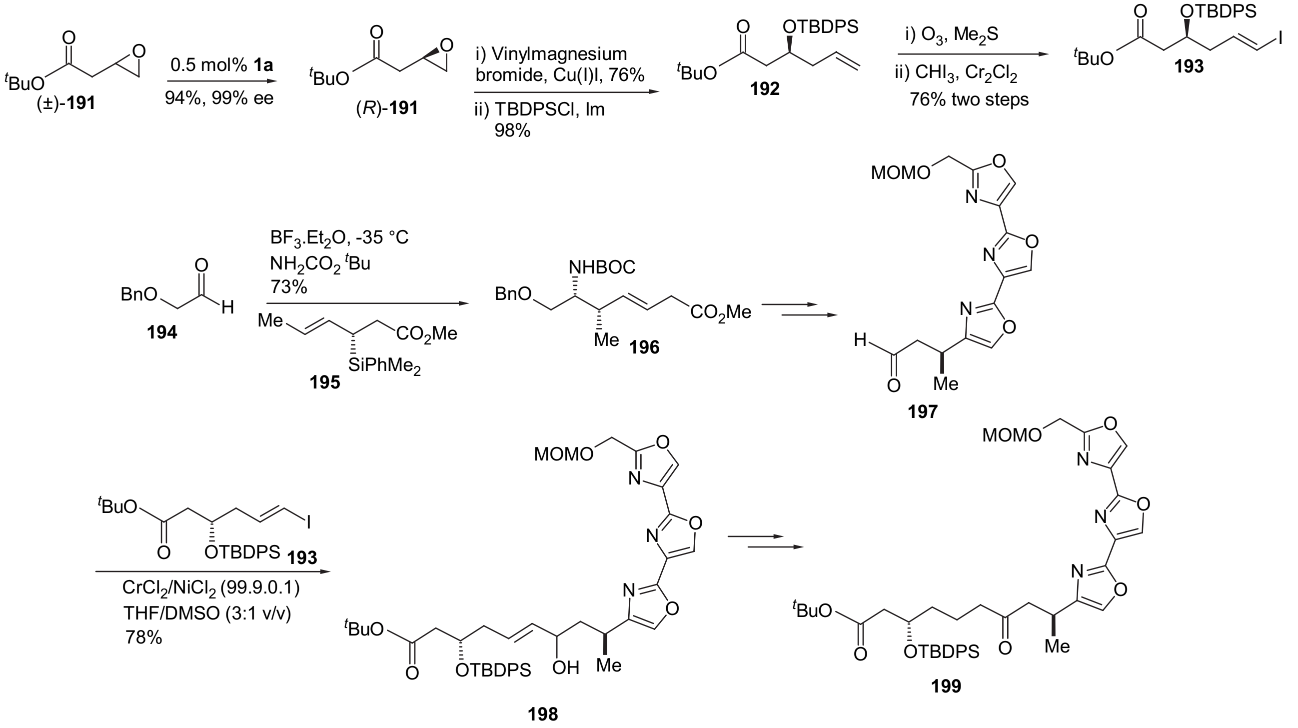


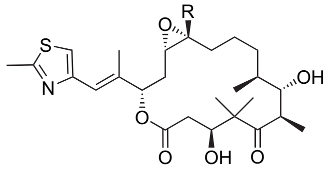
Figure 7. Ulapualide A.

7.3. Epothilone A

Epothilones A and B **200** and **201** (Fig. 8), a new class of macrolides, which were isolated by Hofle and co-workers,[63] have attracted much attention among synthetic organic chemists, due to their high antitumor activity. Liu and co-workers accomplished the total synthesis of epothilone A based on simple asymmetric catalytic reactions and through a stereospecific α-epoxidation of 3-*O*-PMB epothilone C in a total of 25 steps and 4.4% overall yield.[64] The synthesis was accomplished by the coupling of four fragments and the chiral centers were introduced by asymmetric catalytic reactions. The synthesis of one of the fragments is based on Jacobsen's HKR and methoxycarbonylation of the chiral



Scheme 35.

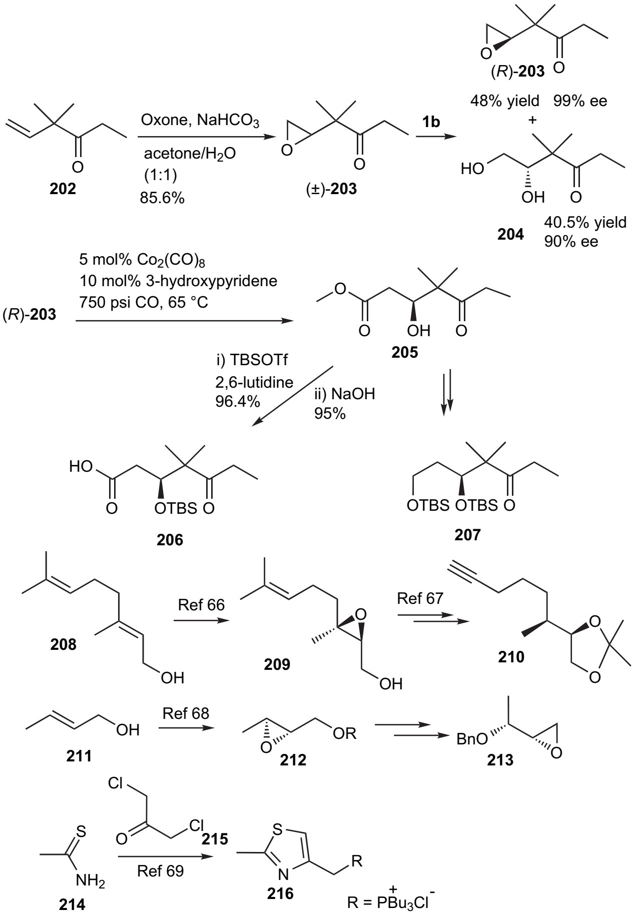


R = H epothilone A : **200**

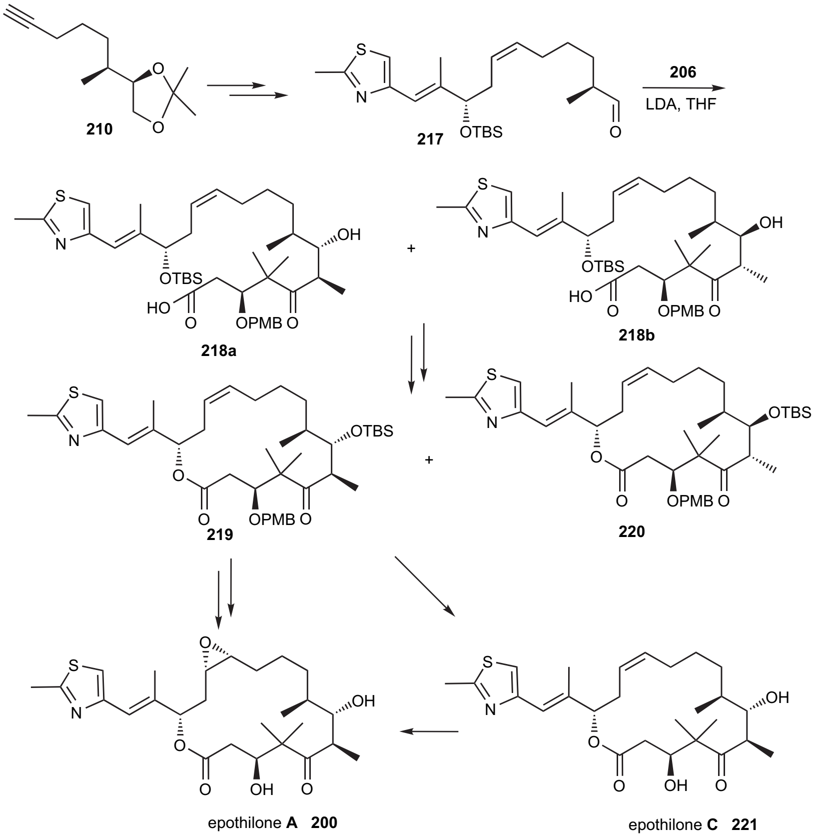
R = Me epothilone B : **201**

Figure 8.

terminal epoxide. As shown in Scheme 36, the vinyl ketone **202**[65] was epoxidized with oxone to give the racemic epoxide (±)-**203**, which was subjected to HKR conditions to afford the desired chiral epoxyketone (*R*)-**203** in >99% ee and 48% yield and the chiral diol **204** in 90% ee and 40.5% yield, which was easily converted into the required epoxyketone (*R*)-**203** with an additional three steps. Regioselective carbomethoxylation of the chiral terminal epoxyketone in the presence of $Co_2(CO)_8$ as catalyst and 3-hydroxypyridine as co-catalyst afforded the β-hydroxyl ester **205**. Hydroxyl protection as the silyl ether and subsequent saponification provided the desired keto acid **206** as one of the fragment required for the synthesis of the target molecule. The synthesis of the acetylide segment **210** was accomplished starting from geraniol according to a modified previously reported synthesis.[66,67] Similarly, another epoxide **213** was obtained in 98% ee employing a Sharpless epoxidation strategy from crotyl alcohol.[68] The modified Wittig reagent **216** was easily synthesized from 1,3-dichloroacetone using a literature procedure.[69] Coupling of these fragments following a series of transformations led to the target molecule, epothilone A **200** (Scheme 37).



Scheme 36.



Scheme 37.

7.4. *N*-Substituted 4-hydroxypyrrolidin-2-one

Optically active 4-substituted pyrrolidin-2-ones can be found in various biologically active compounds, e.g., CS-834, **222a**, an oral carbapenem antibiotic,[70] rolipram **222b**, an antidepressant agent,[71] and oxiracetame **222c**, a nootropic drug for the Alzheimer's disease[72] (Fig. 9). Ahn and co-workers[73] developed the asymmetric synthesis of active 4-substituted pyrrolidin-2-ones using hydrolytic kinetic resolution as the key step. As depicted in Scheme 38, crotyl chloride **223** was esterified followed by oxidation with *m*-CPBA to afford the HKR substrate (±)-**225**. This was subjected to HKR using 0.5 equiv of water catalyzed by **1a** to provide the *R*-epoxide (*R*)-**225** in 84% yield and 99% ee. The epoxide (*R*)-**225** was then reacted with glycinamide hydrochloride **228** followed by cyclization to give the target molecule (*R*)-**222c** in 45–50% yield. Similarly, (*R*)-**227** was synthesized by the reaction of epoxide (*R*)-**225** and benzylamine in 47% yield.

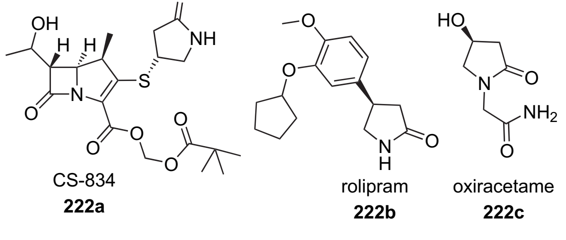
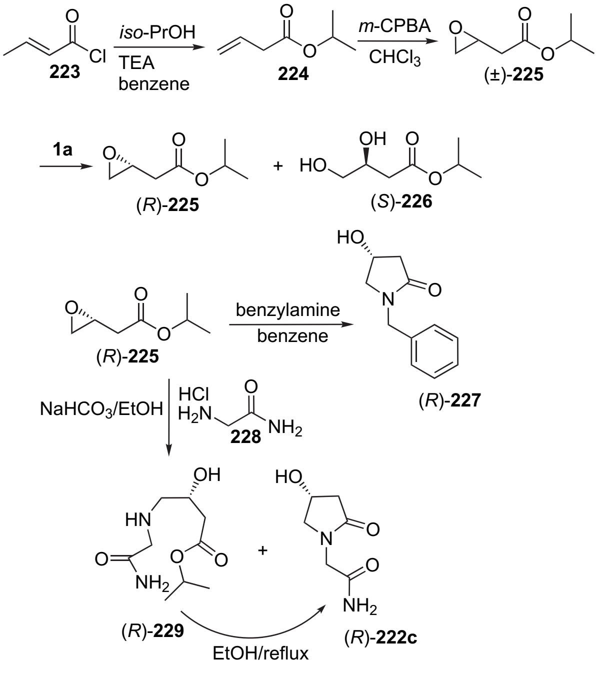
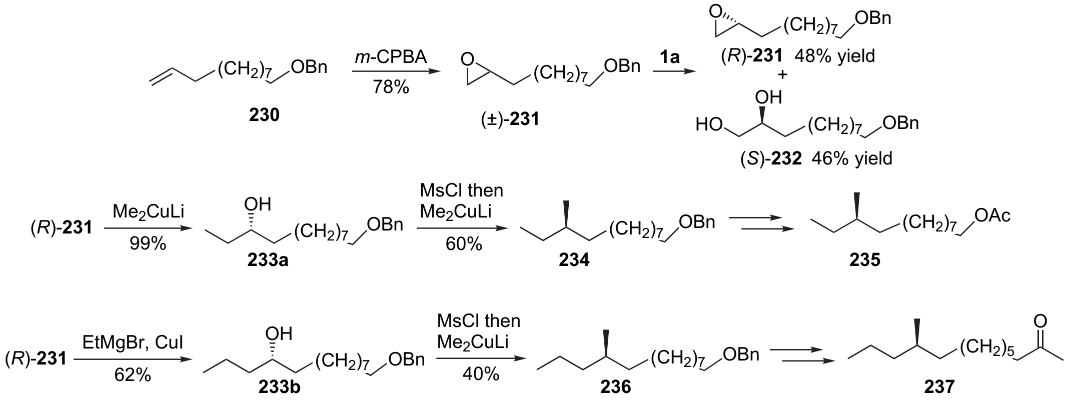


Figure 9.



Scheme 38.



Scheme 39.

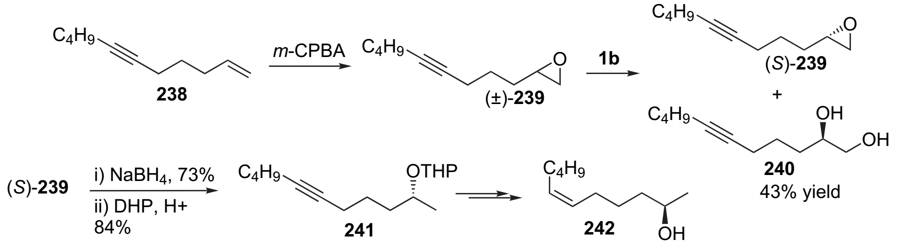
8. Mono- and bis-epoxide

8.1. Insect pheromones

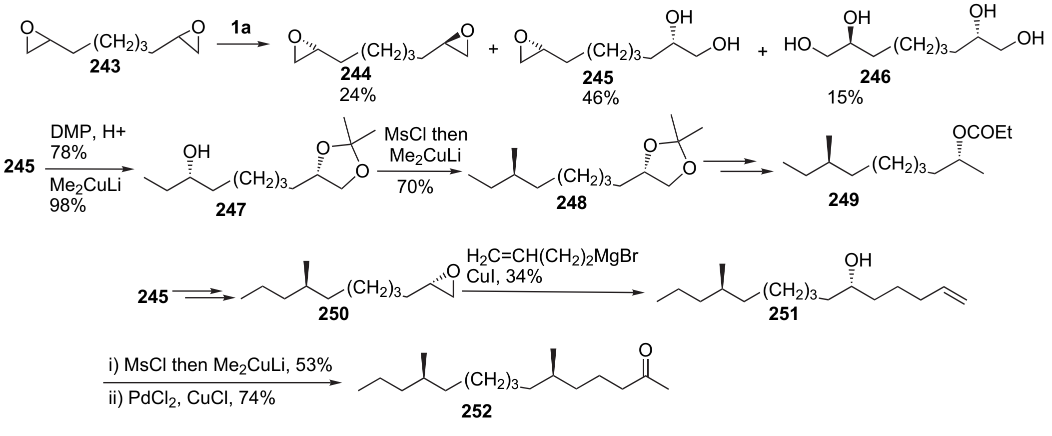
Kitching and Chow have studied the HKR of functionalized mono- and bis-epoxide.[74] The synthetic utility of products such as epoxides, diols, epoxydiols, and tetrols obtained in high enantiomeric excess was further demonstrated by their efficient transformations to important insect pheromones. As illustrated in Scheme 39, the benzyl ether of undecen-10-ol **230** was epoxidized to furnish the HKR substrate (±)-**231**. This, on reaction with 0.5 mol % of **1a** and 0.55 mol equiv water for 20–24 h, gave the *R*-epoxide (*R*)-**231** and the *S*-diol (*S*)-**232**. Further synthetic manipulation afforded the (*R*)-acetate **235**. The acetate **235** is a pheromone from the smaller tea tortrix moth (*Adoxophyes* sp.), with the (*R*)-enantiomer slightly more bioactive than the (*S*)-enantiomer. Similarly, the methyl ketone **237** was obtained by processing the epoxide (*R*)-**231** through a series of transformations, as shown in Scheme 39.

An important component from ant-lions (*Euroleon nostras* and *Grocus bore*) is (*R*)-(−)-(*Z*)-undec-6-en-2-ol (nostrenol) **242**. Its synthesis began with the chemoselective epoxidation of enyne **238**. HKR of epoxide (±)-**239** furnished the (*S*)-epoxide (*S*)-**239** with 95% ee. Ti-mediated stereospecific *Z*-reduction of the protected alcohol led to the (*R*)-(−)-pheromone **242** (Scheme 40).

The same authors have further explored the HKR of bis-epoxides, as depicted in Scheme 41. The racemic bis-epoxide **243** was exposed to **1a** and 0.8 equiv H_2O to provide (2*R*,8*R*)-bis-epoxide **244** (24%), epoxydiol **245** (46%), and tetrol **246** (15%). The epoxydiol **245** was carried through a series of transformations to afford (1*R*,7*R*)-1,7-dimethylnonyl propanoate **249**, the female-produced sex pheromone



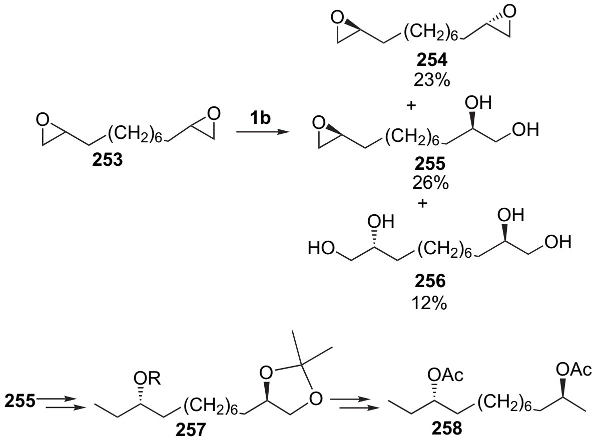
Scheme 40.



Scheme 41.

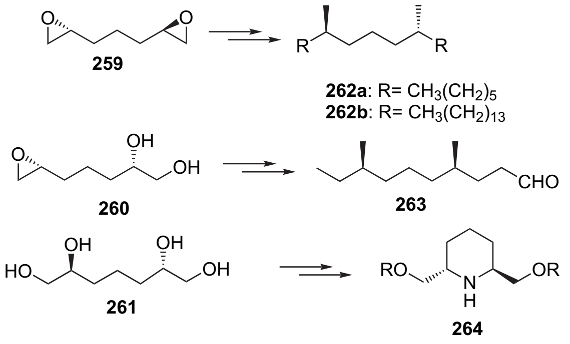
of the Western corn rootworm (*Diabrotica virgifera*). The same epoxydiol **245** provided the bioactive (6*R*,12*R*)-6,12-dimethylpentadecan-2-one **252**, the female-produced pheromone of the banded cucumber beetle (*Diabrotica balteata*) by the procedure summarized above.

HKR of the bis-epoxide of dodeca-1,11-diene **253** afforded the epoxydiol **255**, which has been converted into the (2*S*,11*S*)-2,11-diacetoxytridecane **258**, a sex pheromone component of the female pea midge, *Contarinia pisi*, a serious pest of commercial peas (Scheme 42).



Scheme 42.

Scheme 43 illustrates the application of bis-epoxide **259** and epoxydiol **260** prepared by the HKR of bis-epoxide hepta-1,6-diene with 1.4 mol % **1a** and 1.0 mol equiv H_2O. Routes to (4*R*,8*R*)-4,8-dimethyldecanal (tribolure) **263**, an important pheromone component of several *Tribolure* sp. including the red flour and confused flour beetles, and the C_2-symmetric dimethylalkanes **262a**,**b**, pheromone components of female spring hemlock looper (*Lambdina athasaria*) and female stable flies (*Stomoxys calcitrans*), respectively, have been developed. Tetrol **261** was converted into C_2-symmetric piperidines **264**.



Scheme 43.

9. Multifunctionalized epoxides

9.1. Corossolin

Annonaceous acetogenins (AAs) are a relatively new class of natural products, which have been isolated from the tropical and subtropical plants of the Annonaceae family.

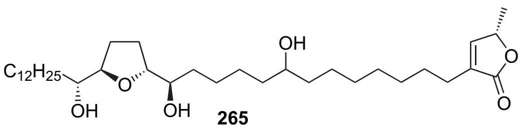
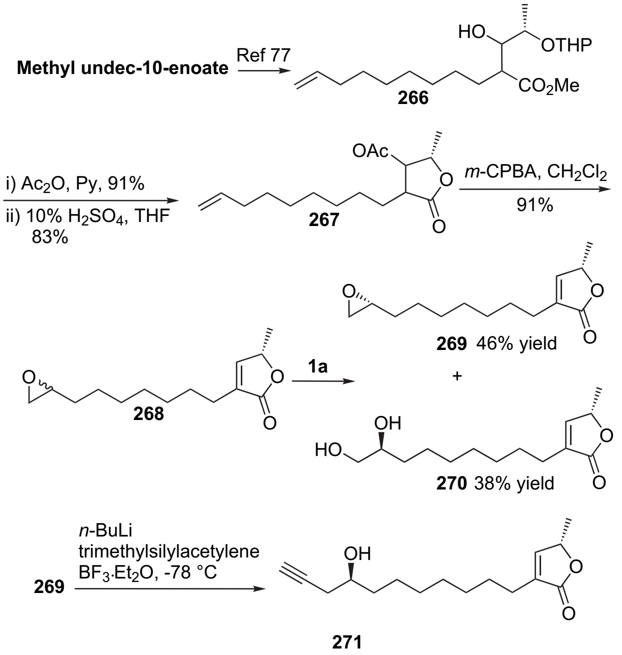


Figure 10.

They are characterized by the presence of one or more tetrahydrofuran rings together with a terminal α,β-unsaturated γ-lactone on a 35- or 37-carbon chains. A majority of these compounds exhibit high cytotoxicity and immunomodulating activities, which make them potential parasiticidal, insecticidal, and powerful tumoricidal agents.[75] Wu and co-workers devised a new synthetic strategy of a key intermediate for corossolin **265** (Fig. 10) using hydrolytic kinetic resolution of epoxides.[76]

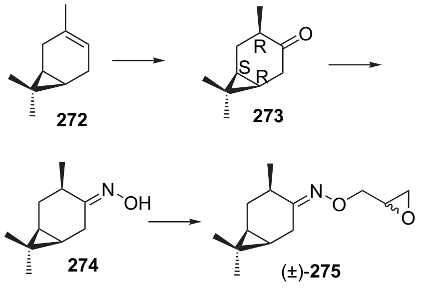
The substrate for HKR, the racemic epoxide **268**, was prepared from alcohol **266**,[77] as shown in Scheme 44. The epoxide **268** was subjected to HKR using **1a** (0.5 mol %) and water (0.55 equiv) to yield epoxide **269** (46%) and diol **270** (38%). Treatment of the epoxide **269** with lithium trimethylsilylacetylide gave the diastereomerically pure (99%) **271**, a key intermediate for corossolin.



Scheme 44.

9.2. Aminohydroxyiminocarenes

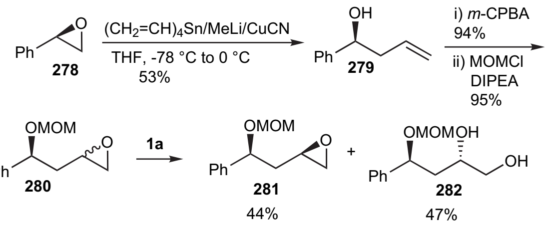
Lochyński and co-workers developed a stereoselective HKR process for diastereomeric mixtures of epoxyiminocarene intermediates, which was applied as the first step in the synthesis of novel chiral aminohydroxyiminocarene derivatives KP-23 with local anesthetic activity.[78] As shown in Scheme 45, (−)-*cis*-carene-4-one oxime **274** is readily available from (+)-3-carene **272** by a three-step pathway: stereoselective borohydration–oxidation followed by Brown–Garg oxidation, and reduction of ketone **273** with hydroxylamine hydrochloride. The reaction of racemic epichlorohydrin with **274** gave a diastereomeric mixture (*R*,*S*)-**275**, which was subjected to HKR on reaction with water catalyzed by a (salen)Co(III)complex. A mixture of the 1,2-diol (*S*)-**276** (97% ee) and unreacted epoxide (*R*)-**275** (99% ee) was obtained after 7 h using catalyst **1a** in 76% yield. Diol (*S*)-**276** was converted into the epoxy isomer (*S*)-**275** in 71% yield under Mitsunobu conditions. Similarly, HKR of (±)-**275** by the use of catalyst **1b** required a longer reaction time (20 h), affording the desired epoxide in moderate yield (56%). Both (*R*)- and (*S*)-epoxy compounds were reacted with an excess of isopropylamine followed by treatment with anhydrous ethereal HCl to give the crystalline, water-soluble hydrochlorides, KP-23*R*·HCl (*R*)-**277** and KP-23*S*·HCl (*S*)-**277** (Scheme 46).



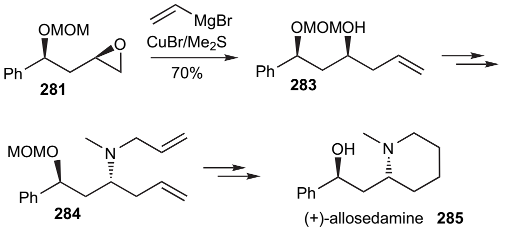
Scheme 45.

9.3. (+)-Allosedamine

A concise synthesis of (+)-allosedamine was developed by Chang and Kang[79] using HKR and ring-closing metathesis as the key steps. The authors have employed HKR to install both the stereocenters. As shown in Scheme 47, the synthesis began with (+)-styrene epoxide **278**,[3] which can be obtained on a gram scale via a hydrolytic kinetic resolution of racemic styrene epoxide. Opening of the epoxide was achieved by using cuprate reagents derived from tetravinyltin to give the homoallylic alcohol **279**. Subsequent epoxidation with peracid or peroxide under various conditions gave the diastereomeric mixture of products. After protection of the free hydroxyl group of the epoxide, the MOM ethers **280** were subjected to HKR with catalyst **1a** (1 mol %), acetic acid (4 mol %), and water (0.55 equiv) in THF at room temperature to give the enantiomerically pure epoxide **281** in >98% ee and 44% yield. The diol **282** was isolated in 47% yield as a single diastereomer. Epoxide opening of the oxirane **281** with a vinyl Grignard reagent, introduction of the required amino group at the homoallylic position through mesylate, and, finally, ring closure by RCM led to the synthesis of the target molecule **285** (Scheme 48).



Scheme 47.

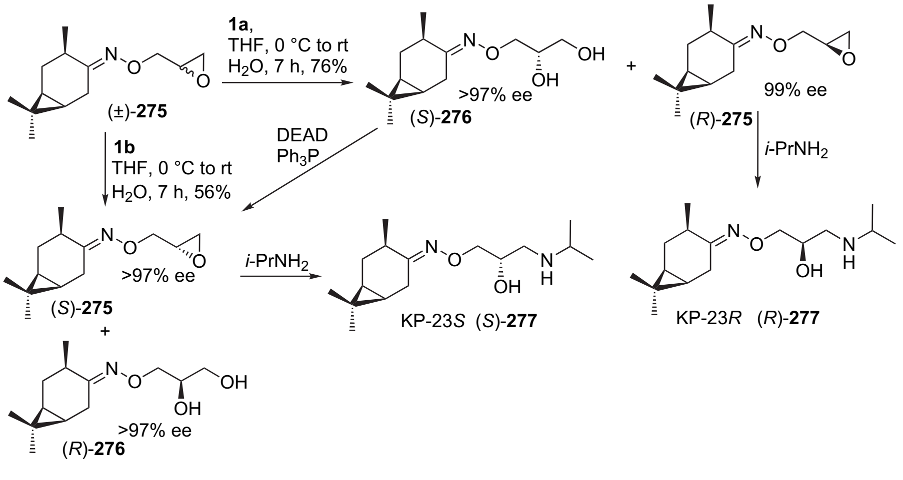


Scheme 48.

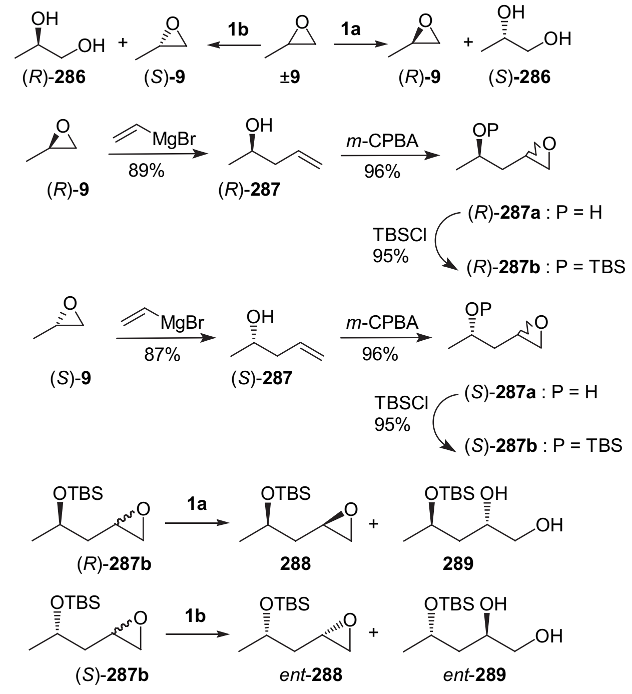
9.4. Tarchonanthuslactone and cryptocarya diacetate

Optically active *syn*- and *anti*-1,3-polyols/5,6-pyrones are ubiquitous structural motifs in various biologically active compounds.[80] Tarchonanthuslactone **294** and cryptocarya diacetate **300** are such examples. Short and practical enantioselective syntheses of these molecules were achieved by Kumar and co-workers in high diastereomeric excess using Jacobsen's hydrolytic kinetic resolution, diastereoselective iodine-induced electrophilic cyclization, and ring-closing metathesis as the key steps.[81]

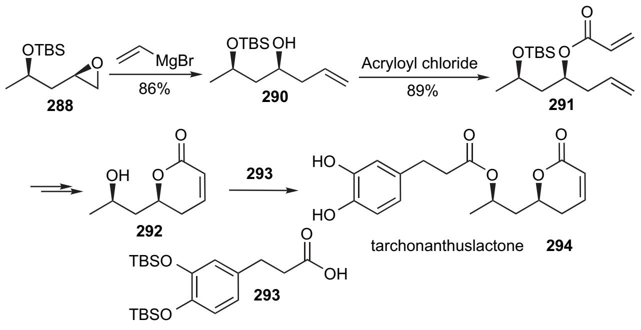
The commercially available racemic propylene oxide (±**9**) was subjected to HKR to afford the enantiomerically pure



Scheme 46.

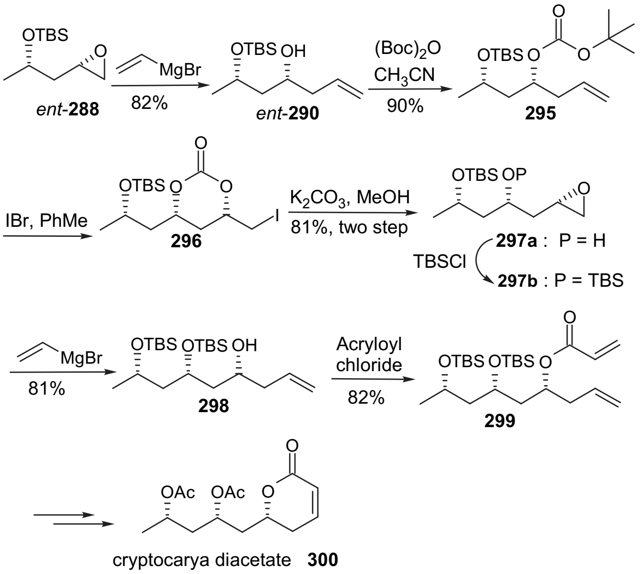


Scheme 49.



Scheme 50.

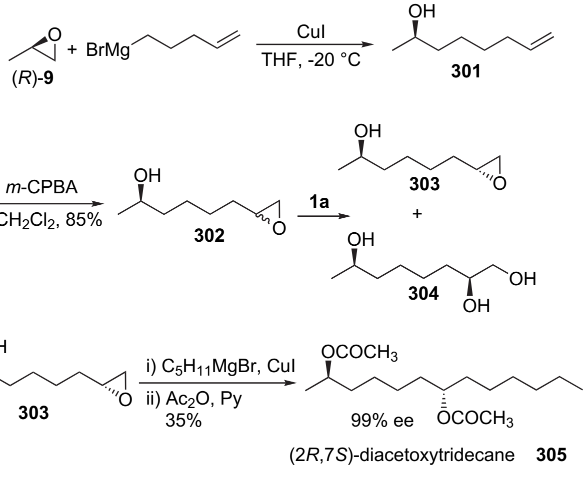
(*R*)-**9** and (*S*)-**9** propylene oxides, which were reacted with a vinyl Grignard to give the homoallylic alcohols **287**. Subsequent iterative epoxidation of the homoallylic alcohol followed by HKR gave the diastereomerically pure epoxide **288** (Scheme 49). Ring opening of the epoxide **288** with a vinyl Grignard generated the second stereocenter (Scheme 50). In the case of cryptocarya diacetate, the third stereocenter was generated via iodine-induced diastereoselective electrophilic cyclization to give the *syn*-configuration. The *syn*- and *anti*-configuration of the hydroxyl functionality can be manipulated by the use of a **1a** or **1b** Jacobsen's catalyst in the resolution step. The conversion of the hydroxyl group into acrylate and subsequent ring-closing metathesis gave the target molecules, tarchonanthuslactone **294** (Scheme 50) and cryptocarya diacetate **300** (Scheme 51).



Scheme 51.

9.5. (2*R*,7*S*)-Diacetoxytridecane: sex pheromone of the aphidophagous gall midge, *Aphidoletes aphidimyza*

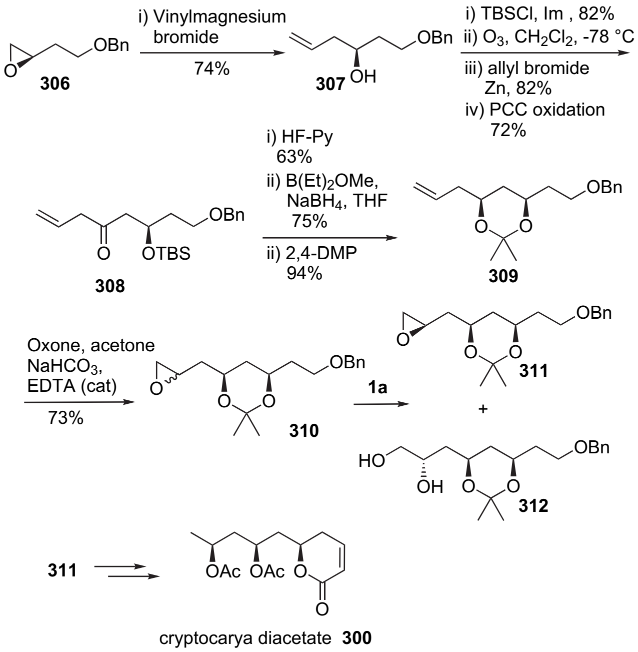
Gries and co-workers[82] identified and synthesized the sex pheromone, (2*R*,7*S*)-diacetoxytridecane **305**, from females of the aphidophagous midge, *A. aphidimyza*, which was evidenced by females releasing a sex pheromone to attract mates. As shown in Scheme 52, the ring opening of (*R*)-propylene oxide with 4-penten-1-ylmagnesium bromide followed by epoxidation of the resulting secondary alcohols with *m*-CPBA afforded the HKR substrate **302** in good yield. The epoxides **302** were subjected to hydrolytic kinetic resolution with H_2O using a **1a** catalyst to yield the four isomers of 1,2-epoxy-7-hydroxyoctane **303** in good yield and with good diastereoselectivity. Opening of these epoxides with amylmagnesium bromide and subsequent acetylation furnished all four isomers of the sex pheromone **305**.



Scheme 52.

9.6. Cryptocarya diacetate

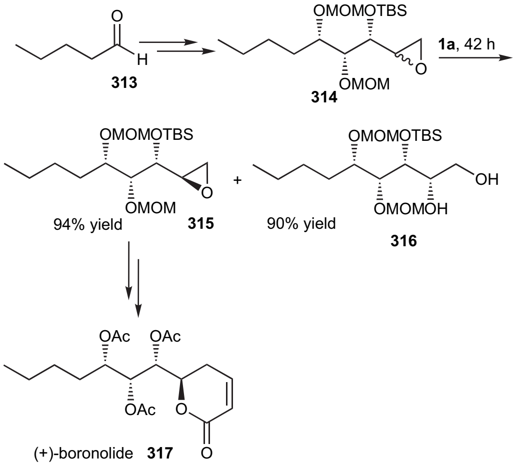
Krishna and Reddy employed a combination of HKR and stereoselective reduction of ketones as the key steps for the construction of a 1,3-polyol moiety, which was subsequently transformed into (+)-cryptocarya diacetate.[83] As shown in Scheme 53, the epoxide **306** was obtained through HKR of the racemic epoxide, which was treated with a vinyl Grignard to give the homoallylic alcohol **307**. Hydroxyl protection as its TBS ether, reductive ozonolysis of olefin to an aldehyde followed by allylation with allyl bromide/Zn gave the homoallylic alcohol in 82% yield. Subsequent PCC oxidation followed by desilylation afforded the β-hydroxyl ketone **308**, which, on selective reduction with $NaBH_4$ in the presence of a chelating agent, $B(Et)_2OMe$, resulted in exclusive formation of the *syn*-1,3-diol (>98% de). Hydroxy-group protection as acetonide and epoxidation yielded the epoxide **310**, which, on HKR with 0.55 equiv of water using **1a** catalyst, provided the enantiomerically pure epoxide **311** (de 94%) and diol **312** in 43% yield each. The epoxide was smoothly converted into the target molecule **300** in several steps through synthetic manipulation.



Scheme 53.

9.7. (+)-Boronolide

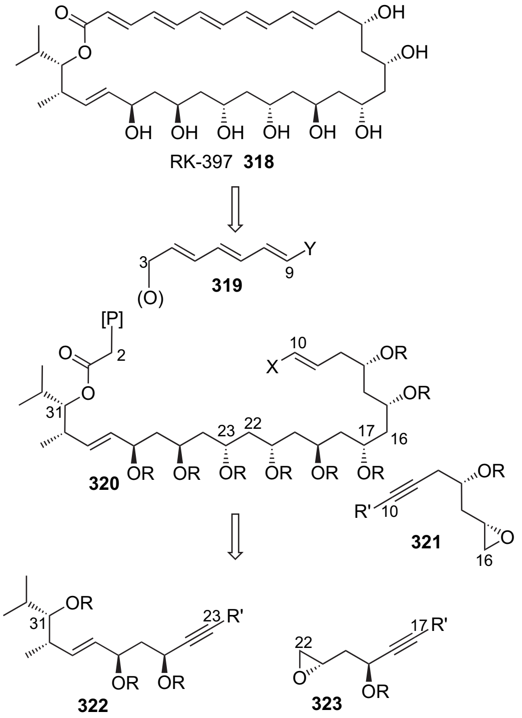
α-Pyrones possessing polyhydroxy or polyacetoxy side chains are an important class of heterocycles because of their usefulness as biologically active compounds. Examples of such compounds include (+)-boronolide **317**. This compound has antimalarial properties and is isolated from the species, *Tetradenia fruticosa*[84] and *Tetradenia barberae*,[85] which have been used as a local folk medicine in Madagascar and South Africa.[86] Kumar and Naidu[87] developed an innovative route for the total synthesis of (+)-boronolide starting from valeraldehyde. The key steps include a Sharpless asymmetric hydroxylation, a chelation-controlled vinyl Grignard followed by asymmetric epoxidation, HKR, and a ring-closing metathesis. Scheme 54 highlights its synthesis involving the resolution of multifunctionalized epoxides by HKR to obtain the enantiomerically pure epoxides. Thus, the HKR substrate **314** prepared in a multistep sequence from valeraldehyde **313** was subjected to HKR with **1a** (0.5 mol %) and water (0.4 equiv) to yield the epoxide (2*R*,3*R*,3*R*,5*S*)-**315** in 94% yield (as calculated from 80% epoxide) and diol (2*S*,3*R*,3*R*, 5*S*)-**316** in 90% yield (as calculated from 20% other epoxide). The epoxide **315** was further converted into the target molecule by vinyl Grignard and ring-closing metathesis.



Scheme 54.

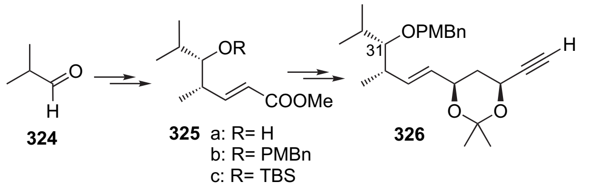
9.8. Polyene-polyol macrolide RK-397

McDonald and Burova reported the total synthesis of the natural product RK-397, an antifungal compound, which is based on a new synthetic strategy for assembling polyacetate structures, by efficient cross coupling of nucleophilic terminal alkyne modules with electrophilic epoxides bearing another alkyne at the opposite terminus.[88] The retrosynthetic strategy (Scheme 55) reveals that the target molecule can be constructed from four principal modules: a polyene precursor for carbons 3–9, and three alkyne-terminated modules for carbons 10–16, 17–22, and 23–31. The authors have employed HKR methods to synthesize modules C17–C22 and C10–C16.

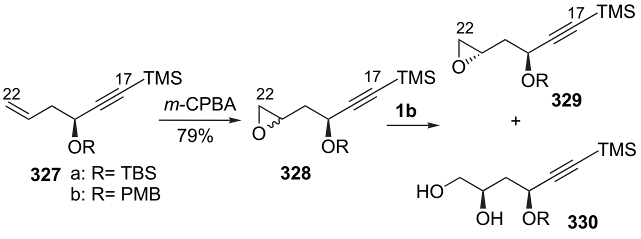


Scheme 55. Retrosynthetic analysis for polyene-polyol macrolide RK-397.

The C23–C31 module was prepared from isobutyraldehyde in several steps as shown in Scheme 56. As depicted in

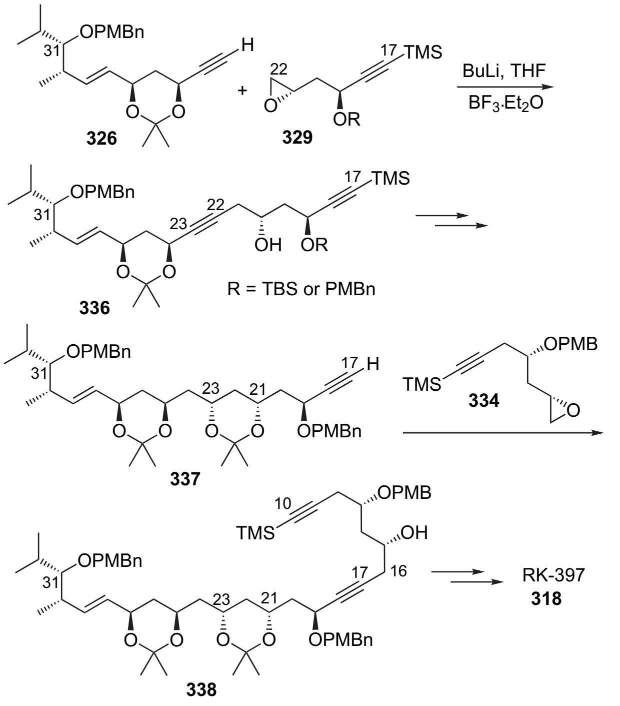


Scheme 56. Synthesis of C23–C31 module.



Scheme 57. Synthesis of C17–C22 module.

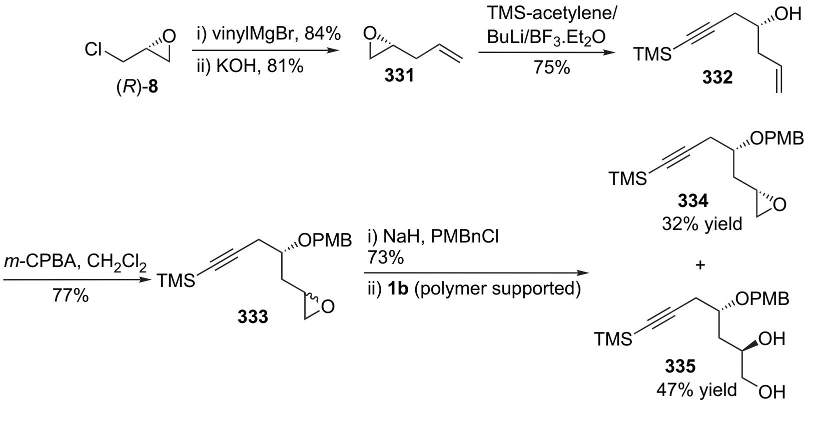
Scheme 57, the C17–C22 module was prepared starting from the (*S*)-enynol **327**. Epoxidation of either the silyl or *p*-methoxybenzyl ether **327** gave **328** as a ca. 1:1 mixture of diastereomers, and a single diastereomer was prepared by the HKR procedure. Similarly, the seven-carbon C10–C16 module was constructed from (*R*)-epichlorohydrin and copper bromide-promoted addition of vinylmagnesium bromide to give **331**, which was converted into the enynol **332**. The epoxidation with or without hydroxyl protection resulted in a mixture of diastereomers in different proportions. The compound **333**, as a mixture of diastereomers, when subjected to HKR gave the enantiomerically pure epoxide **334** as a single diastereomer, which was easily separated from the more polar diol **335** (Scheme 58). The alkynyl alcohol obtained from alkyne–epoxide couplings was converted into the 1,3-diols by a sequence of hydroxyl-directed hydrosilylation, C–Si bond oxidation, and stereoselective ketone reduction, and these were finally converted into the target compound in several steps (Scheme 59).



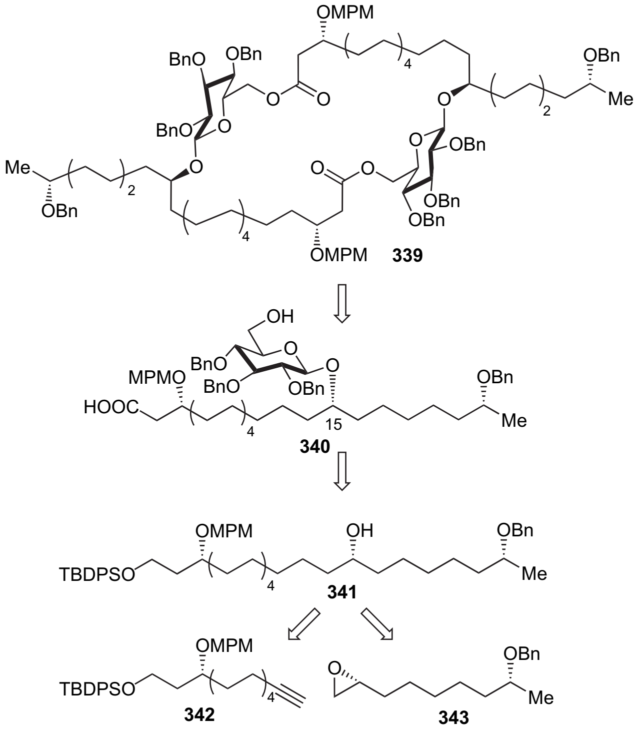
Scheme 59. Coupling of various modules and completion of RK-397 synthesis.

9.9. Macroviracin A

Macroviracin A, a 42-membered macrodiolide core consisting of a C_{22} fatty acid dimer possessing D-glucose residues, was isolated from the mycelium extracts of *Streptomyces* sp. BA-2836.[89] This type of natural product exhibits powerful antiviral activity against herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV). Takahashi and co-workers[90] synthesized the C_2-symmetric macrodiolide core **339** of macroviracin A in a single step by the intramolecular macrodimerization of the C_{22}-hydroxy carboxylic acid **340** (Scheme 60). The acid **340** was synthesized through a series of reactions such as coupling of acetylene with epoxide and stereoselective glycosidation. The right-half epoxide **343** can be synthesized through hydrolytic kinetic resolution. As shown in Scheme 61, olefin **346** was synthesized from methyl ester **344** by reduction and tosylation followed by chain extension with 1-pentenylmagnesium bromide. The epoxide **347** derived from *m*-CPBA oxidation of **346** was subjected to hydrolytic kinetic resolution with 0.9% **1a** catalyst in the presence of water (0.65 equiv) at room temperature to give the epoxide **343** in 44% yield

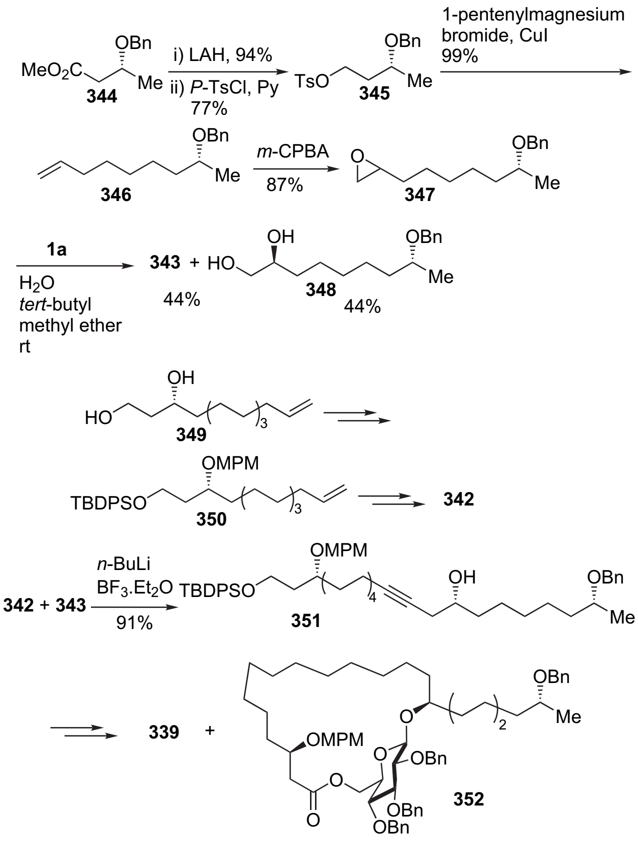


Scheme 58. Synthesis of C10–C16 module.



Scheme 60. Retrosynthetic analysis for macrodiolide core unit of macroviracin A.

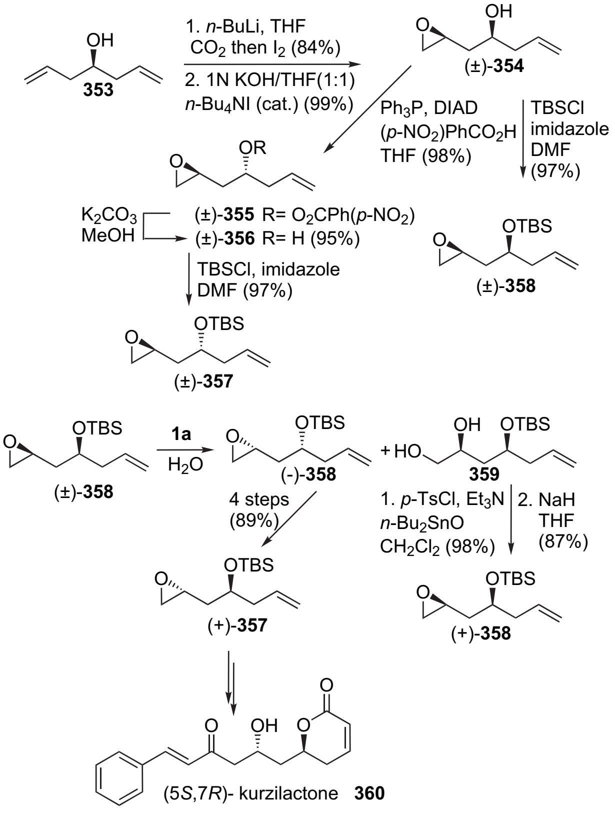
and diol **348** in 44% yield with >99% optical purity. The left-half segment **342**, which was synthesized in several steps, was coupled with epoxide under Yamaguchi conditions to afford the coupling product **351** in 91% yield, which was converted into the target molecule **339** in several steps.



Scheme 61.

9.10. (5*S*,7*R*)-Kurzilactone

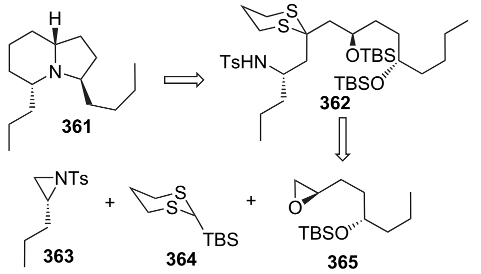
Tae and Kim synthesized enantiomerically pure *syn*- and *anti*-2-silyloxy-1-oxiranyl-4-pentenes by using the HKR method, which was used in the total synthesis of (5*S*,7*R*)-kurzilactone **360** having strong cytotoxicity against KB cells.[91] The authors have developed a route to synthesize both *syn*- and *anti*-1,3-diol in the desired fashion using the HKR method. As shown in Scheme 62, the *syn*-epoxide (±)-**354** was prepared from 1,6-heptadien-4-ol using a literature procedure.[92] The *anti*-epoxide (±)-**356** was generated by a Mitsunobu inversion reaction of (±)-**354**. The racemic TBS-protected epoxides (±)-**358** and (±)-**357** were then prepared for the HKR studies. Treatment of *syn*-epoxides (±)-**358** with **1a** (0.3–0.5 mol %) and H_2O (0.8 equiv) at room temperature led to the formation of epoxide (−)-**358** in 42–48% yield and in 98–99% ee. The diol **359** was formed in 48–49% yield and 93–94% ee. In contrast, HKR of *anti*-epoxide (±)-**357** under the same conditions yielded the epoxide (69–88% ee). A subsequent ring-opening reaction of epoxide with the acyl anion equivalent and RCM led to the synthesis of (5*S*,7*R*)-kurzilactone **360**.



Scheme 62.

9.11. (−)-Indolizidine 223AB

(−)-Indolizidine 223AB (**361**) is an alkaloid isolated from the skin of the neotropical dart-poison frogs belonging to the genus *Dendrobates*.[93] Smith and Kim[94] have accomplished

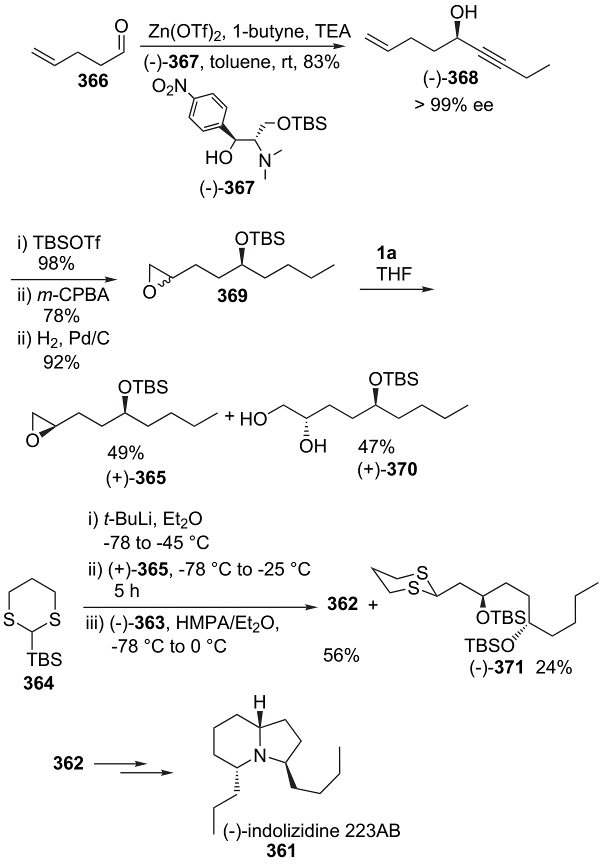


Scheme 63. Retrosynthetic analysis for (−)-indolizidine 223AB.

the total synthesis of (−)-indolizidine 223AB (**361**) exploiting a three-component linchpin coupling of silyldithiane **364** with epoxide **365** and a known aziridine **363**,[95] followed by a one-pot sequential cyclization in an overall yield of 10% in the longest linear sequence (Scheme 63). The epoxide **365** was constructed by exploiting Carreira alkyne methodology[96] followed by HKR. As shown in Scheme 64, 4-pentenal **366** was treated with 1-butyne via a Carreira protocol using Jiang ligand (−)-**367**[97] followed by hydroxyl protection as its TBS ether. Subsequent treatment with *m*-CPBA and hydrogenation furnished **369** as a 1:1 diastereomeric mixture. HKR of **369** using **1a** catalyst furnished the desired epoxide **365** along with diol **370** in high diastereomeric excess. The undesired diol **370** was converted into the desired epoxide **365** by conventional methods. A three-component linchpin coupling of silyldithiane **364** with epoxide **365** as the first electrophile and aziridine **363** as the second electrophile furnished **362**, which, on cyclization in a one-pot sequential manner followed by reductive removal of the dithiane, gave the target molecule **361**.

9.12. Optically active 1,4-anhydropentitols and 2,5-anhydrohexitols

Kakuchi and co-workers[98] synthesized chiral anhydroalditol alcohols in extremely high enantiomeric excess using hydrolytic kinetic resolution. They studied diastereoselective cyclizations of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-glucitol (**372**) and the regio- and stereoselective cyclizations of C_2-symmetric dianhydrosugars such as 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (**373**) and 1,2:5,6-dianhydro-3,4-di-*O*-methyl-L-arabinitol (**375**) using catalysts **1a** and **1b** (Fig. 11). These reactions arise from the enantioselective hydrolysis of one of the epoxides, followed by cyclization of the resulting diol into the other epoxide. The dianhydrosugar **372** possesses two epoxy groups, the reactivities of which are non-equivalent. In the cyclization of **372** using water (1.1 equiv) in the presence of **1a** (0.5 mol %) at room temperature, the color of the reaction mixture changed from dark to light brown as the reaction proceeded (the reaction results are summarized in Table 1). The reaction using **1a** was complete in 3 h, while **1b** needed about 51 h. The cyclization of **373** with **1a** proceeded rapidly at room temperature and produced **380**, **381**, and **382** in 57.2, 27.9 and 5.9% yields, respectively, while with **1b** no product was obtained (the reaction results are summarized in Table 2). The cyclization of **374** with **1a** proceeded with no products, while with **1b** only the five-membered ring compound **380** was



Scheme 64.

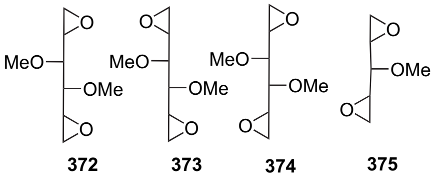


Figure 11. Structures of *meso*-diepoxides.

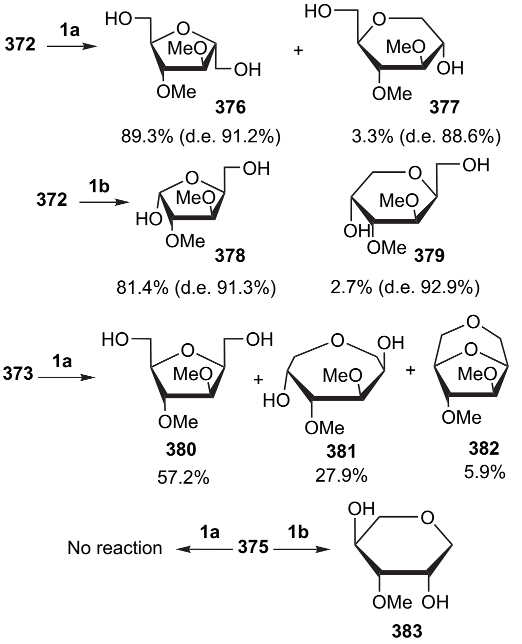
Table 1. Cyclization of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-glucitol (**372**) using chiral (salen)Co(III)–OAc and other conditions

Catalyst	Time (h)	*T* (°C)	Yield (%)			
			376	**378**	**377**	**379**
1a	3	rt	89.3	4.1	3.3	0.2
1b	51	rt	3.7	81.4	0.1	2.7
HCl	24	rt	37.0	35.2	10.3	9.8
KOH	24	60	47.3	35.9	8.5	6.6
None (H_2O)	7	100	46.5	17.9	21.5	8.3

Table 2. Cyclization of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (**373**) and 1,2:5,6-dianhydro-3,4-di-*O*-methyl-L-iditol (**374**) using (salen)-Co(III)–OAc

Substrate	Catalyst	Time (h)	Yield (%)		
			380	**381**	**382**
373	**1a**	3	57.2	27.9	5.9
	1a	3	30.4	35.0	6.8
	1b	6	0	0	0
374	**1a**	6	0	0	0
	1b	48	49.1	0	0

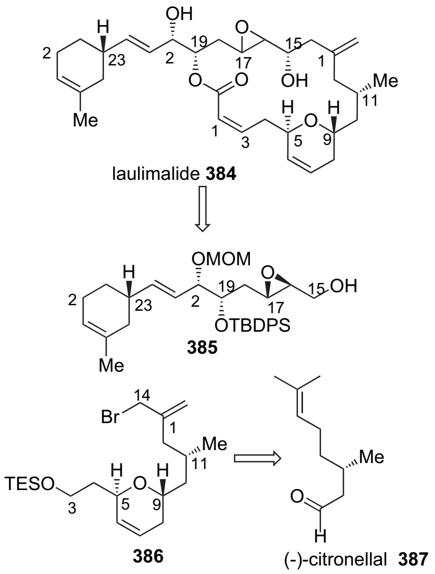
formed. The cyclization of **375** with **1b** proceeded smoothly to afford **383** in 85% yield, while no reaction was observed with **1a** (Scheme 65).



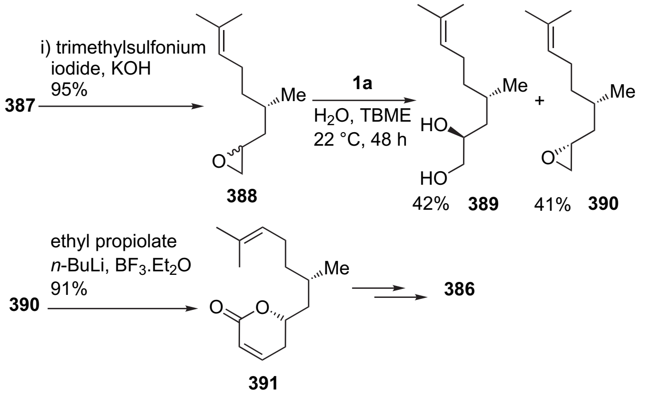
Scheme 65.

9.13. C3–C14 fragment of antitumor agent, laulimalide

Laulimalide **384**, isolated from various marine sponges,[99] shows microtubule stabilization in eukaryotic cells and is distinguished by an unusually high antitumor activity against multidrug resistant cells lines.[100] Mulzer and co-workers[101] synthesized the C3–C14 fragment of laulimalide from naturally occurring (−)-citronellal using hydrolytic kinetic resolution (HKR) (Scheme 66). As shown in Scheme 67, aldehyde **387** was converted into a racemic epoxide **388** via Corey's sulfonium ylide addition, and this was subjected to HKR using H_2O (0.5 equiv) catalyzed by **1a** in TBME for 48 h to give the epoxide **389** and diol **390** in 41 and 42% yields, respectively, and in good diastereoselectivity. The ring opening of epoxide **389** with ethyl propiolate followed by partial hydrogenation and in situ cyclization furnished the lactone **391** in quantitative yield. Lactone **391** was further converted into the desired C3–C14 fragment **386** in several steps.



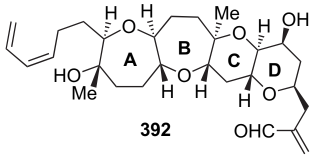
Scheme 66. Retrosynthetic analysis for C3–C14 fragment of antitumor agent, laulimalide.



Scheme 67.

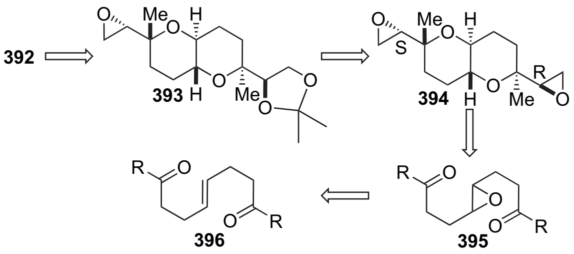
9.14. Hemibrevetoxin B: synthesis of a key intermediate

Polycyclic ether marine natural products, such as ciguatoxins (e.g., CTX1B), brevetoxins, and yessotoxin originated from the 'red tides' of marine unicellular algae as potent neurotoxins that bind to a common site of, and activate, voltage-sensitive sodium channels.[102] Nelson and co-workers[103] synthesized an intermediate **393** for hemibrevetoxin B **392** (Fig. 12) by desymmetrization of a centrosymmetric diepoxide **394**, which can be synthesized by cyclization of an epoxy carbonyl compound **395**, which, in turn, could be synthesized from the corresponding alkene **396** (Scheme 68).



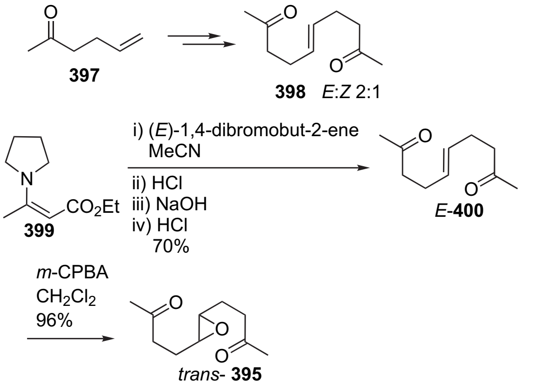
392

Figure 12.

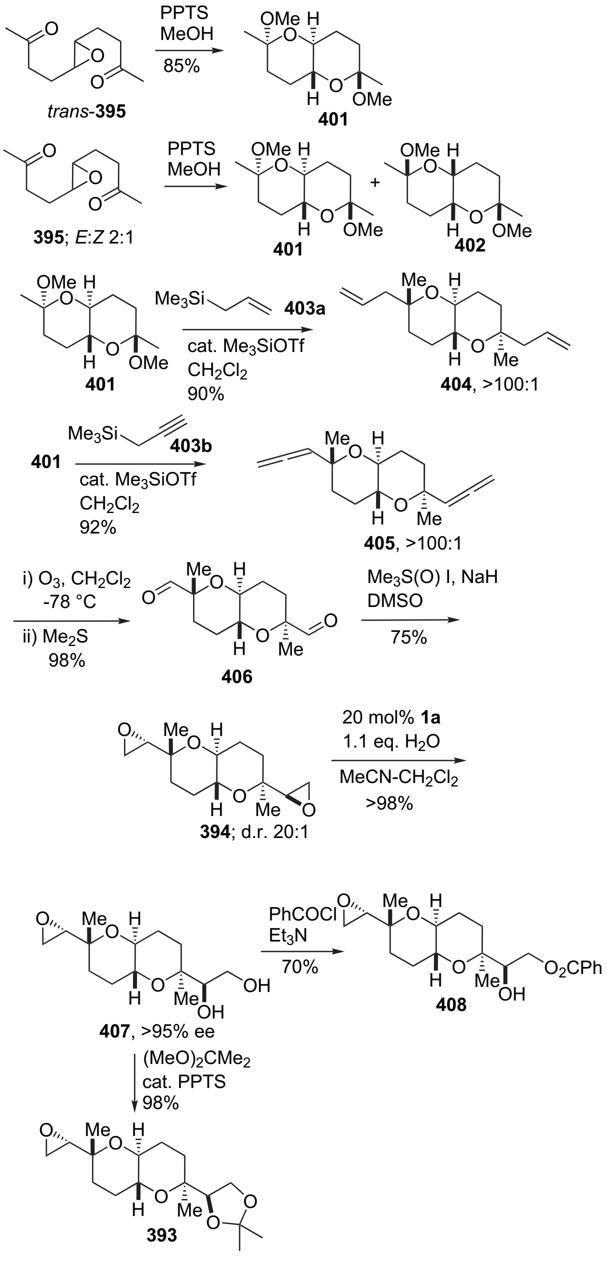


Scheme 68. Retrosynthetic analysis for a key intermediate of hemibrevetoxin B.

As shown in Scheme 69, the *trans*-epoxide **395** was synthesized from the γ,δ-unsaturated enone **397** in several steps, and this was cyclized with PPTS in methanol to give the



Scheme 69.



Scheme 70.

thermodynamically more stable centrosymmetric diacetal **401**. Centrosymmetric diacetal **401** was subjected to two-directional nucleophilic substitution using a range of nucleophiles such as allylic silane, or propargylsilane to give the centrosymmetric diTHPs **404** and **405**, respectively, with >100:1 diastereoselectivities. Ozonolysis of diallene **405** followed by treatment with dimethylsulfonium ylide gave the diepoxide **394** as a 20:1 mixture of centrosymmetric and unsymmetrical diastereomers. Finally, a wide range of solvents were used for desymmetrization of bis-epoxide **394** by hydrolytic kinetic resolution. The best results were obtained when HKR was carried out in the presence of water (1.1 equiv) and 1:1 acetonitrile/dichloromethane catalyzed by **1a** (20 mol %) to furnish the diol **407** in 98% yield and 95% ee, which was converted into the key intermediate **393** in essentially quantitative yield (Scheme 70).

9.15. (4*R*)-Hydroxy analogs of Annonaceous acetogenins

Yao and co-workers[104a] devised a new synthesis for the (4*R*)-hydroxylated analogs of an Annonaceous acetogenin-mimicking compound on the basis of the naturally occurring Annonaceous acetogenin, bullatacin **409d** (Fig. 13). Preliminary screening of this mimicking compound showed an enhancement effect against HCT-8 and HT-29, compared with those of **409c**. The target compound **409e** was synthesized based on a two-directional C-alkylation of 1,7-octadiyne **417** with epoxides **413** and **416** as key steps. As shown in Scheme 71, the intermediate **413** was synthesized by HKR of the racemic epoxide **412**.

The butenolide unit **411** was synthesized from **410** by an aldol reaction with (*S*)-*O*-tetrahydropyranyl lactol followed by acid-catalyzed THP cleavage, in situ lactonization, and β-elimination. The racemic epoxide derived from olefin **411** by *m*-CPBA oxidation was subjected to HKR in the presence of water (0.55 equiv) catalyzed by **1b** to afford **413** in 43% yield with 99% de and diol **414** in 50% yield with 70% de. The other epoxide **416** was synthesized from glyceraldehyde in several steps. The epoxide ring opening with diyne **417** and further manipulations led to the target molecule **409e**.

Similarly, the epoxide **413** was employed in the synthesis of several other acetogenins such as longimicin C[104b] and murisolins.[104c]

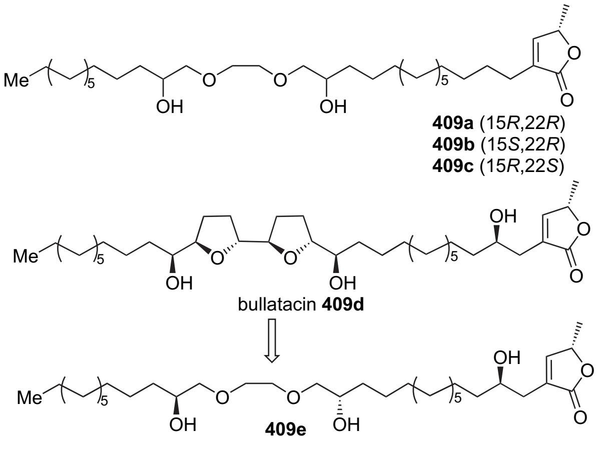
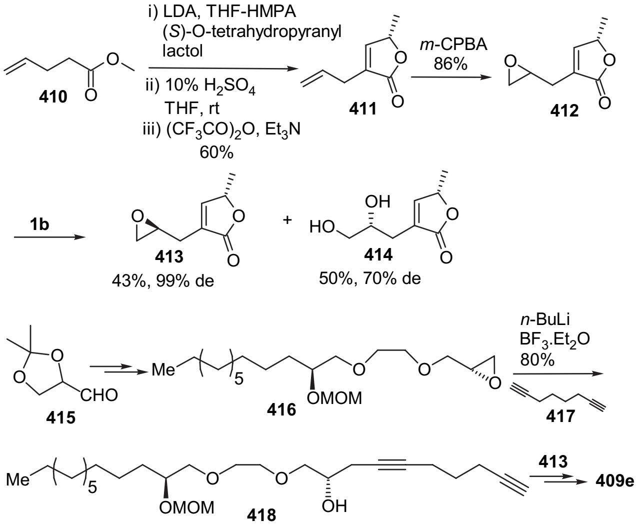


Figure 13.

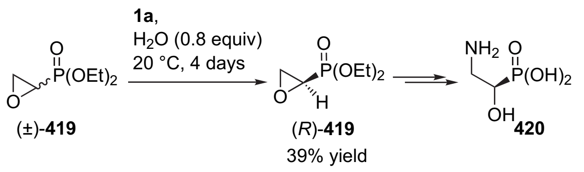


Scheme 71.

10. Miscellaneous epoxides

10.1. (*R*)-2-Amino-1-hydroxyethylphosphonic acid

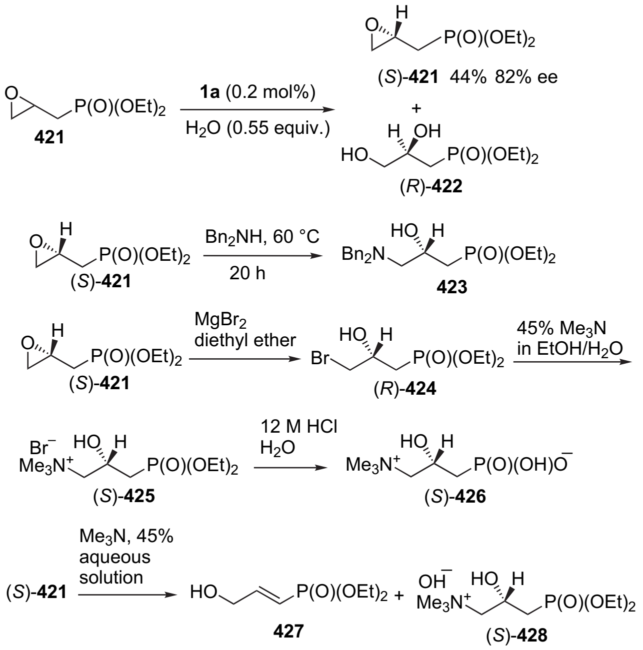
Wyatt and Blakskjaer[105] have shown for the first time that the HKR method can be successfully applied to diethyl oxiranephosphonate **419**, which could provide an easy access to a useful new homochiral building block. Accordingly, the racemic epoxide **419** was subjected to HKR in the presence of the catalyst **1a** (0.05 mmol) and H_2O (4.44 mmol) at 20 °C for four days (Scheme 72). This resulted in the isolation of enantiomerically pure epoxide (*R*)-**419** in 39% yield as a single isomer. The enantiomeric purity of the epoxide was checked by its conversion into a single diastereomer by its reaction with (*R*)/(*S*)-1-phenylethylamine or 1,1′-carbonyldiimidazole. Opening of the resultant (*R*)-epoxide by benzylamine followed by phosphate ester hydrolysis, and hydrogenolysis resulted in the protozoal plasma membrane component, (*R*)-2-amino-1-hydroxyethylphosphonic acid **420**.



Scheme 72.

10.2. Enantiomeric 2,3-epoxypropylphosphonates and (*S*)-phosphocarnitine

Enantiomeric 2,3-epoxypropylphosphonates are useful three-carbon phosphonate chirons for the synthesis of various phosphonate analogs, e.g., phosphocarnitine,[106a] phosphonic acid antibiotics FR-33289 and FR-33699,[106b] and isosteres of glycerophosphoric acid.[106c] Wróblewski and Halajewska-Wosik[107] synthesized enantiomeric (*S*)-phosphocarnitine, based on the hydrolytic kinetic resolution of diethyl 2,3-epoxypropylphosphonate.



Scheme 73.

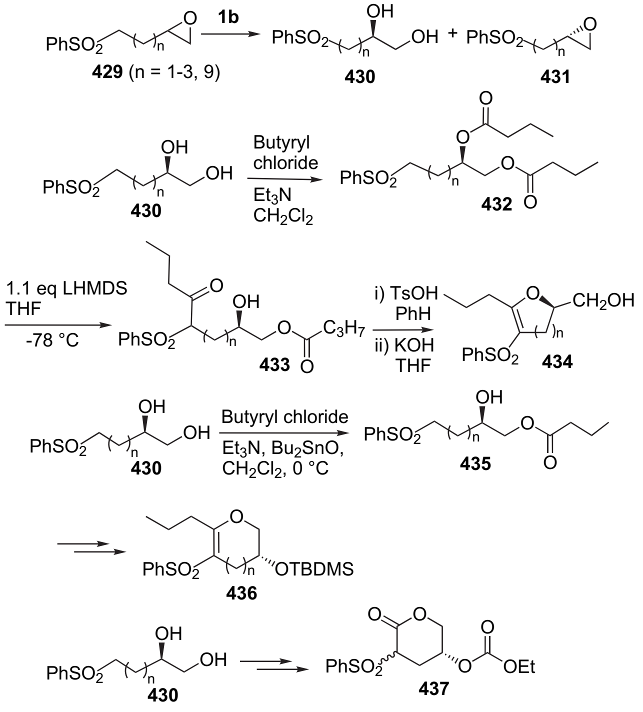
As shown in Scheme 73, hydrolytic kinetic resolution of the racemic epoxide (±)-**421** using **1a** (0.2 mol %) in the presence of water (0.55 equiv) afforded epoxide (*S*)-**421** in 34% yield with 94% ee and diol (*R*)-**422** in 31% yield with 86% ee. Ring opening of the epoxide (*S*)-**421** with $MgBr_2$, followed by bromide substitution with Me_3N and hydrolysis, furnished the target molecule (*S*)-**426**. Attempts to cleave the epoxide (*S*)-**421** with aqueous trimethylamine gave the eliminated product **427** as a major component (60%), together with (*S*)-**428** (20%) and some unidentified products.

10.3. Oxacyclic ring systems

Gopalan and co-workers[108] prepared a number of chiral 1,2-dihydroxysulfones in high enantiomeric excess by the HKR method.[76] The (±)-epoxysulfones prepared from ω-phenylsulfonyl-1-alkenes by the oxidation with *m*-CPBA were stirred at room temperature in the presence of **1b** catalyst (1.0 mol %) and H_2O (0.55 equiv). The product 1,2-diols and the unreacted epoxides were separated by silica gel chromatography. As shown in Scheme 74, the intramolecular cyclization reaction of the acyl and ethoxycarbonyl derivatives of these dihydroxysulfones has been exploited to access a variety of functionalized chiral non-racemic cyclic ethers and lactones such as **434**, **436**, and **437**.

10.4. Monofluorinated analogs of (lyso)phosphatidic acid

(Lyso)phosphatidic acid **441** (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) (Fig. 14) is a naturally occurring phospholipid. It has received increasing attention due to a variety of biological responses that it evokes including platelet aggregation, smooth muscle contraction, changes in cell morphology, and mitogenesis.[109] Prestwich and co-workers have



Scheme 74.

reported the synthesis of the target molecules and related analogs.[110] Scheme 75 illustrates the synthesis and HKR of fluorophosphonate epoxides. The HKR substrate was prepared in four steps in the following manner. The commercially available diethyl dibromofluoromethylphosphonate **442** was converted into iodomonofluoromethylphosphonate **443** by tributylphosphine reduction and iodine quench of the intermediate zinc species. The Pd-catalyzed addition of **443** to allyl alcohol gave the corresponding iodohydrin **444**, which, on treatment with K_2CO_3/MeOH at room temperature, provided the desired racemic oxide **445** in good yield. The reaction of racemic epoxide **445** with 0.45 equiv of H_2O in a minimum volume of THF in the presence of **1a** (1.0 mol %) gave the diol **447a** in 90% ee and 73% isolated yield. Similarly, catalyst **1b** provided the opposite configuration of the diol in 89% ee and 90% yield. These diols were smoothly converted into *sn*-1-*O*-acyl-α-fluoromethylenephosphonate analogs **448a**,**b** by regioselective acylation of the primary hydroxyl group.

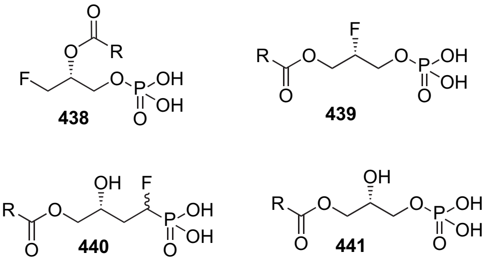
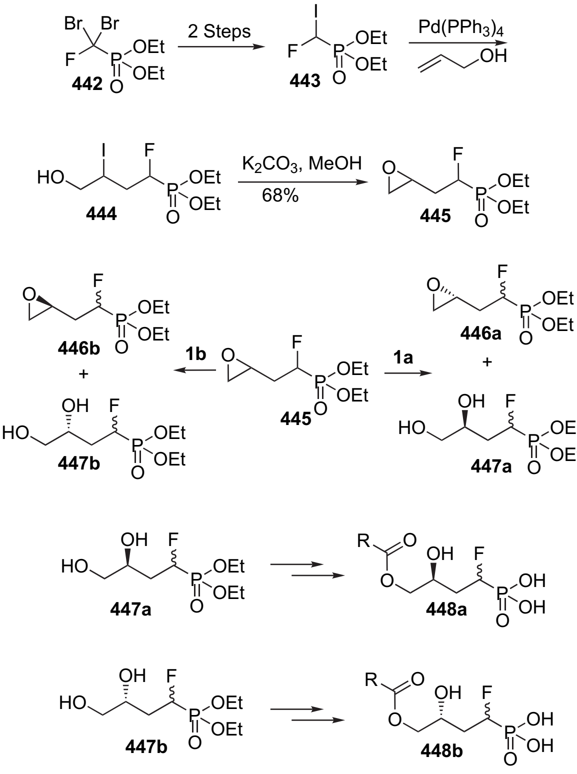


Figure 14.



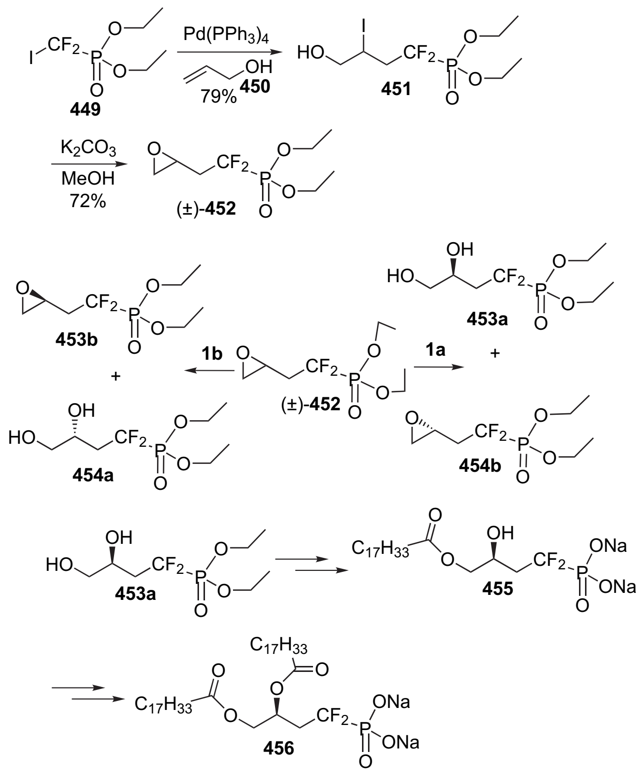
Scheme 75.

10.5. Chiral (α,α-difluoroalkyl)phosphonate analogs of (lyso)phosphatidic acid

The same authors have reported the resolution of 1,1-difluoro-3,4-epoxy-butylphosphonate (prepared in a similar manner as described above) by the HKR method.[111] This example constitutes the first application of HKR in a substrate containing both fluorine and phosphonate functionalities. As shown in Scheme 76, the reaction of racemic epoxide (±)-**452** with 0.45 equiv of H_2O in THF in the presence of **1a** (1.0 mol %) gave the diol **453a** in 99% ee and 69% yield. Similarly, the catalyst **1b** provided the opposite configuration of the diol **453b** in 99% ee and 70% yield. The diol was transformed into the target molecule **456** by regioselective acylation of the primary alcohol.

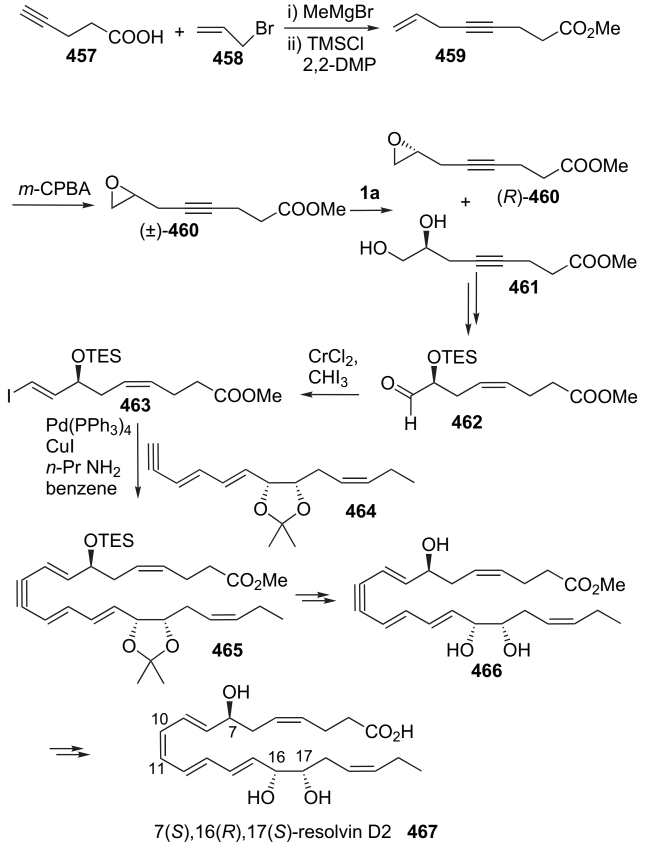
10.6. 7(*S*),16(*R*),17(*S*)-Resolvin D2

7(*S*),16(*R*),17(*S*)-Resolvin D2 is a new class of lipid mediator derived from docosahexaenoic acid that possesses potent anti-inflammatory and immunoregulatory activities. Spur and Rodriguez have accomplished the first total synthesis of this molecule encompassing the hydrolytic kinetic resolution of a terminal epoxide combined with a chiral pool strategy.[112] The chiral center at C-7 was obtained via HKR of a terminal epoxide, whereas the centers at C-16 and C-17 were installed by the chiral pool strategy. As shown in Scheme 77, alkylation of the dimagnesium complex of pentynoic acid **457** with allyl bromide in the presence of a catalytic amount of CuBr/Me_2S followed by in situ esterification gave the ester **459**. Subsequent epoxidation with *m*-CPBA furnished the epoxide (±)-**460**. The epoxide (±)-**460** was subjected to HKR in the presence of 5% of catalyst **1a** to



Scheme 76.

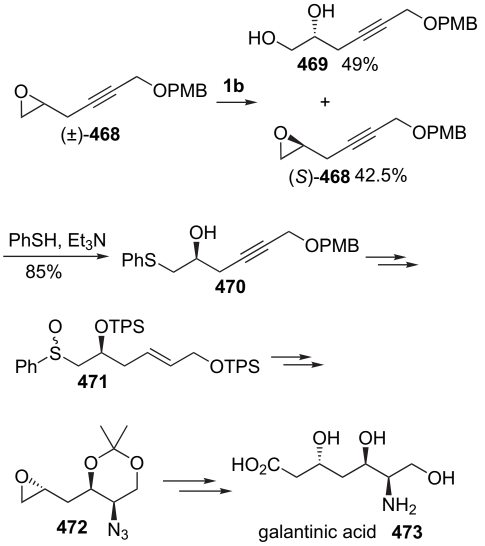
give the diol **461** in >94% ee. The other enantiomer was obtained in >95% ee employing the catalyst **1b**. The chiral diol thus obtained was converted into the C1–C9 fragment **463** through series of organic transformations and finally coupled with the C10–C22 fragment **464** to afford the target molecule, 7(*S*),16(*R*),17(*S*)-resolvin D2 **467**.



Scheme 77.

10.7. (−)-Galantinic acid

(−)-Galantinic acid **473**, a non-proteogenic amino acid, is a constituent of the peptide antibiotic, galantin I, which was isolated from the culture broth of *Bacillus pulvifaciens*.[113] Raghavan and co-workers developed a stereoselective synthesis of (−)-galantinic acid, which includes the hydrolytic kinetic resolution of a racemic epoxide and regio- and stereoselective heterofunctionalizations of an olefin using a pendant sulfinyl group as the nucleophile as the key steps.[114] As illustrated in Scheme 78, the HKR of the racemic epoxide **468**[115] with **1b** afforded the optically pure epoxide (*S*)-**468** in 42.5% yield along with the diol **469** (49%). Triethylamine-promoted opening of epoxide (*S*)-**468** by thiophenol gave the homopropargyl alcohol **470**. Deprotection of the PMB group, reduction of the resulting propargyl alcohol with $LiAlH_4$, and protection of the hydroxyl group as the silyl ether followed by oxidation of sulfide with $NaIO_4$ yielded an equimolar, inseparable mixture of sulfoxides **471**, which were converted into the target molecule, (−)-galantinic acid **473**, over several steps.



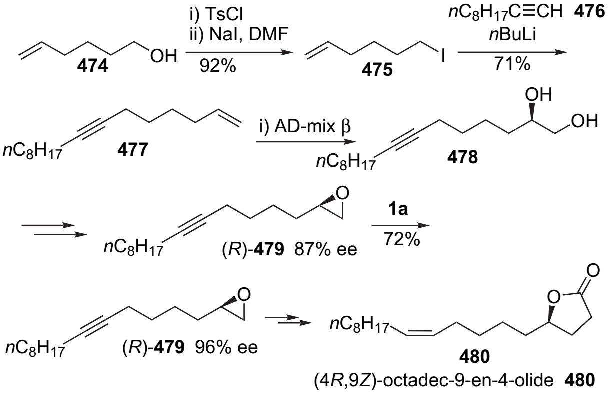
Scheme 78.

10.8. (4*R*,9*Z*)-Octadec-9-en-4-olide, the female sex pheromone of *Janus integer*

(4*R*,9*Z*)-Octadec-9-en-4-olide **480** is a female-specific and antennally active compound from the female currant stem girdler, *J. integer* Norton, a pest of redcurrant in North America.[116] It was then found to be the sex pheromone of that insect. Mori has developed a multi-gram synthesis of this pheromone by employing Sharpless asymmetric dihydroxylation (AD) and Jacobsen's hydrolytic kinetic resolution (HKR).[117]

Scheme 79 illustrates the synthesis and purification by resolution. Commercially available hex-5-en-1-ol **474** was converted into the corresponding iodide **475** via the tosylate.

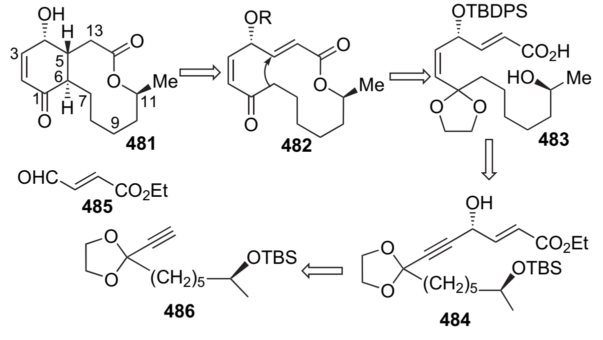
Alkylation of dec-1-yne with *n*-butyllithium followed by Sharpless AD with AD-mix β gave the crystalline (*R*)-diol **478** in about 75% ee and 84% yield. This was converted into the epoxide (*R*)-**479** by the method of Kolb and Sharpless.[118] Compound **479** obtained in 87% ee was subjected to further purification by HKR in the presence of 0.7 mol % of **1a** and 0.4 equiv of water for three days at room temperature to give (*R*)-**479** in 96% ee and 72% yield. Further synthetic manipulations led to the formation of the target molecule **480**.



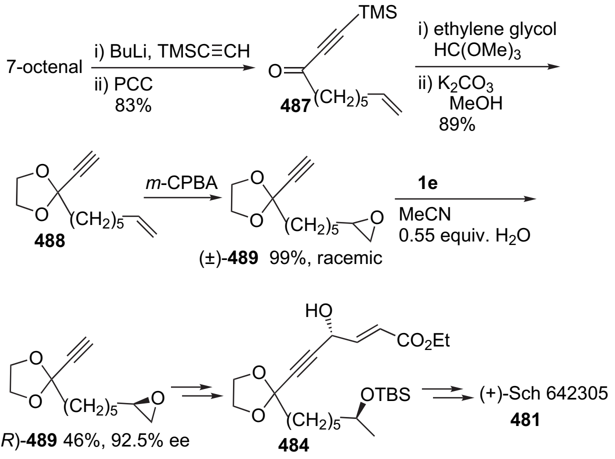
Scheme 79.

10.9. (+)-Sch 642305

(+)-Sch 642305 (**481**) is a bicyclic macrolide, isolated from *Penicillium verrucosum* (culture ILF-16214),[119] which inhibits bacterial DNA primase with an EC_{50} value of 70 μM. It also inhibits HIV-1 Tat, a regulatory protein required for viral replication.[120] Snider and Zhou[121] accomplished the total synthesis of (+)-Sch 642305 using a transannular Michael reaction of **482** with NaH in THF, Yamaguchi macrolactonization, and hydrolytic kinetic resolution of racemic epoxide (±)-**489** as the key steps (Scheme 80). As shown in Scheme 81, 7-octenal was treated with LiC≡CTMS to afford the propargyl alcohol, which, on subsequent PCC oxidation, gave **487**. Dioxolane formation and TMS deprotection gave **488** in 89% yield. The racemic epoxide formed by oxidation of **488** with *m*-CPBA was subjected to HKR with 0.5 equiv of water catalyzed by an oligomeric (salen)Co(III) catalyst in MeCN to give (*R*)-**489** in 46% yield with 92.5% ee. The epoxide was opened with hydride using $NaBH_4$. Further synthetic manipulation led to the formation of the target molecule **481** in 1.6% overall yield.



Scheme 80. Retrosynthetic analysis for (+)-Sch 642305.

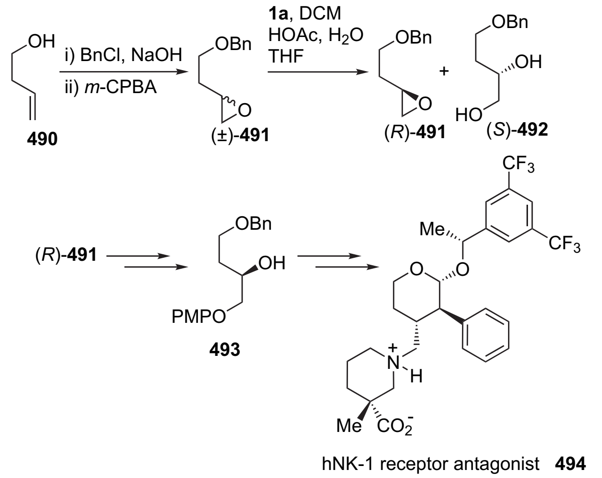


Scheme 81.

10.10. hNK-1 receptor antagonist

The neuropeptide, substance P, has been found to preferentially bind to the human neurokinin-1 (hNK-1) receptor.[122] The hNK-1 receptor is involved in a wide array of biological functions, and it has been suggested that modulating the interaction between substance P and the hNK-1 receptor may affect numerous and diverse disease states.[123] Tetrahydropyran **494** has been identified as one such selective hNK-1 receptor antagonist.[124] Nelson and co-workers have developed a new and concise synthesis of this hNK-1 receptor antagonist, which involved an α-alkoxy sulfonate as a key intermediate.[125] The epoxide (*R*)-**491** required for the synthesis of the key intermediate was prepared by HKR of a terminal epoxide **491**.

As shown in Scheme 82, treatment of the alkene **490** with benzyl chloride followed by epoxidation with *m*-chloroperbenzoic acid afforded the racemic epoxide (±)-**491**, which readily underwent hydrolytic kinetic resolution with 1.5 mol % catalyst **1a** and 50 mol % H_2O. The required epoxide (*R*)-**491** was conveniently separated from the newly formed antipode (*S*)-**492** by distillation. The enantiomeric excess of the epoxide was found to be >99%. The synthesis of the target molecule **494** was achieved by the epoxide ring opening and through several subsequent organic transformations.



Scheme 82.

10.11. L-Carnitine and α-lipoic acid

Bose and co-workers[126] developed a general and practical approach for the synthesis of the biologically important natural products, L-carnitine **496** and α-lipoic acid **497** (Fig. 15), by synthesizing C-4 chiral building blocks through hydrolytic kinetic resolution (HKR). (*R*)-Carnitine **496**,[127] also known as vitamin B_T, plays an important role in β-oxidation of fatty acids, acting as a carrier of fatty acids over the mitochondrial membrane, while α-(*R*)-lipoic acid **497** is an important protein-bound coenzyme and growth factor found in animal tissues, plants, and microorganisms. As shown in Scheme 83, racemic epoxide (±)-**491** was subjected to HKR using H_2O (0.5 equiv) catalyzed by **1a** to afford a mixture of *R*-epoxide (*R*)-**491** in 47% yield (96% ee) and 1,2-diol (*S*)-**492** in 43% yield. Hydrogenolysis of the benzyl ether followed by oxidation and opening of the epoxide with NH_4OH furnished **496**. Regiospecific opening of epoxide (*R*)-**491** with but-3-enylmagnesium bromide furnished **499**, which was converted into α-lipoic acid **497** in several steps (Scheme 84).

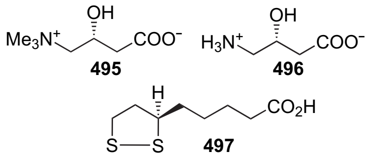
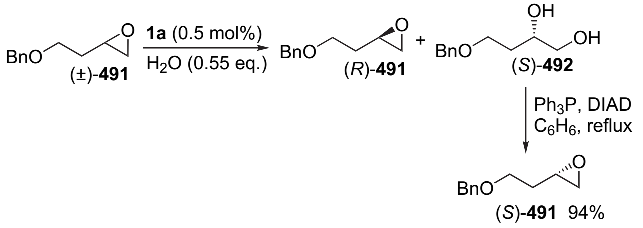
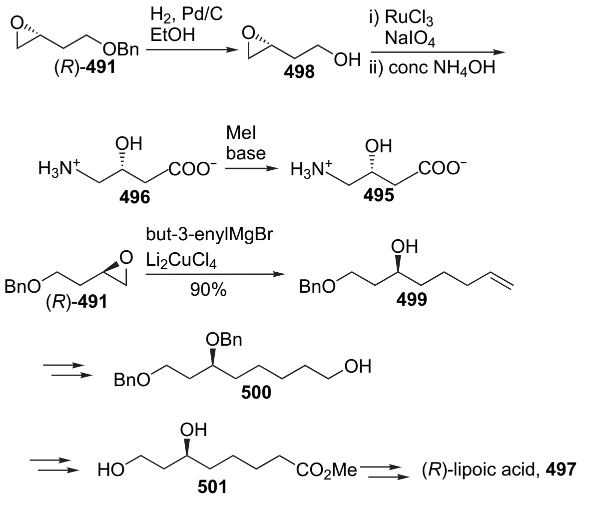


Figure 15.



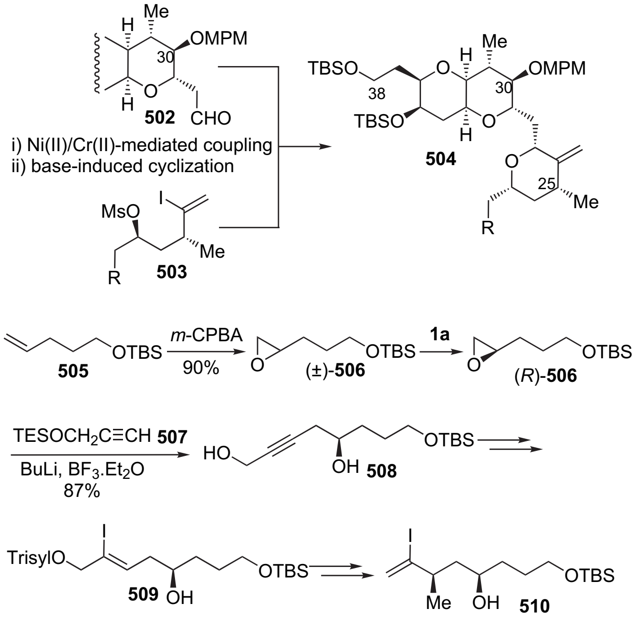
Scheme 83.



Scheme 84.

10.12. C20–C26 building block of halichondrins

Halichondrin B, a polyether macrolide, isolated from a variety of sponge genera,[128] displays an in vitro IC_{50} value of 0.3 nM against L1210 leukemia and remarkable in vivo activities against various chemoresistant human solid tumor xenografts.[129] Kishi and co-workers[130] developed a general methodology for the synthesis of the C20–C26 building block of halichondrin. As shown in Scheme 85, the epoxide (±)-**506** derived from olefin **505** was subjected to hydrolytic kinetic resolution using water catalyzed by **1a** to give the optically active epoxide (*R*)-**506** in good yield. Opening of the epoxide with propargyl triethylsilyl (TES) ether **507** under Yamaguchi conditions followed by hydrostannation and iodine quenching furnished a 55:6:2:1 mixture of all four possible products, with the desired product **509** as the major isomer. Further synthetic manipulation yielded the target intermediate **510**.[131]

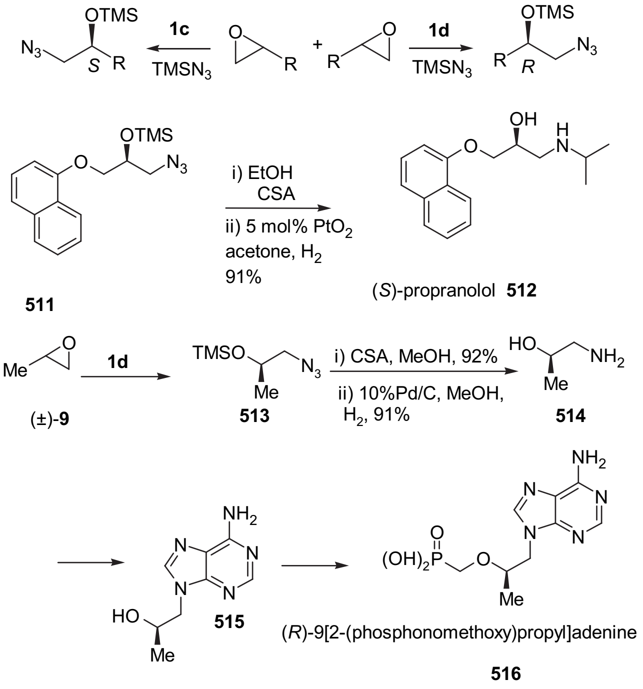


Scheme 85.

10.13. (*S*)-Propranolol and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine (*R*-PMPA)

Jacobsen and co-workers have developed a (salen)Cr-catalyzed **1c** epoxide ring-opening reaction of a racemic epoxide leading to the efficient synthesis of 1-azido-2-trimethylsiloxyalkanes (Scheme 86). The viability of this strategy is illustrated in the practical synthesis of (*S*)-propranolol, a widely used antihypertensive agent, and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine (*R*-PMPA), a compound recently demonstrated to display prophylactic activity against SIV infection.[132]

The treatment of neat racemic propylene oxide with 0.5 equiv of $TMSN_3$ in the presence of (salen)CrN_3 complex **1d** (1 mol %) resulted in the clean conversion to a mixture of epoxide and ring-opened product, 1-azido-2-trimethylsiloxypropane, in 97% ee and in essentially quantitative yield after 18 h at 0 °C. Thus, the kinetic resolution of the racemic epoxide derived from chlorohydrin and 1-naphthol afforded



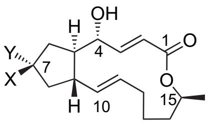
Scheme 86.

the corresponding azido silyl ether **511** in 74% yield and in 93% ee. In a one-pot, two-step procedure, transformation to (*S*)-propranolol **512** was accomplished by desilylation followed by azide reduction and in situ reductive alkylation. The synthesis of (*R*)-PMPA was effected similarly in a highly efficient manner via kinetic resolution of propylene oxide, as shown in Scheme 86. A desilylation–reduction sequence yielded the synthetically important amino alcohol, (*R*)-1-amino-2-propranolol **514**, in excellent yield. Further transformation of this compound to (*R*)-PMPA **516** was accomplished using known methods by conversion of the amine into an adenine base[133] followed by alkylation of the alcohol and standard deprotection of the phosphonate.[134]

10.14. Total synthesis of (+)-brefeldin A

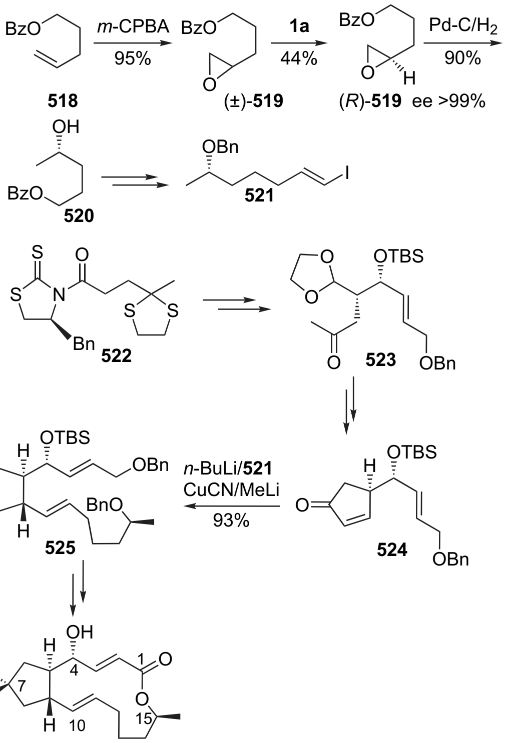
Brefeldin A **517** (Fig. 16) was first isolated from *Penicillium decumbens*,[135] and shows a range of biological activities such as antifungal,[136] antiviral,[137] antitumor,[138] and nematocidal activities.[139]

Wu and co-workers[140] developed a convergent synthesis through Michael addition between cyclopentenone **524** and vinyl iodide **521**. The key intermediate cyclopentenone **524** was synthesized in several steps from **522**, which was readily prepared from the corresponding acid. The vinyl iodide **521** fragment was prepared from the known alkene **518** by hydrolytic kinetic resolution. The epoxide (±)-**519** formed from alkene **518** with *m*-CPBA was subjected to HKR using **1a** in the presence of water at 25 °C to afford the *R*-epoxide (*R*)-**519** in 44% yield with >99% ee. In this reaction, the author observed that, if benzyl was replaced with benzoyl, the enantiomeric excess was lowered to 97% under the same conditions. The *R*-epoxide (*R*)-**519** was hydrogenated to give the hydroxy compound in 90% yield. The benzyl ether formed from the secondary hydroxy group was hydrolyzed followed by tosylation. Replacement with lithium acetylide and further manipulation gave the vinyl iodide **521**. Final coupling of both fragments led to the target molecule over several steps (Scheme 87).



517a : X = H, Y = OH
517b : X = OH, Y = H

Figure 16.

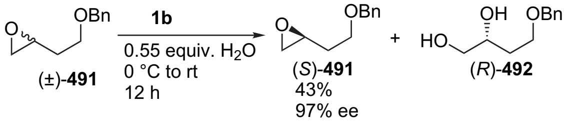


517a: X = H, Y = OH
517b: X = OH, Y = H

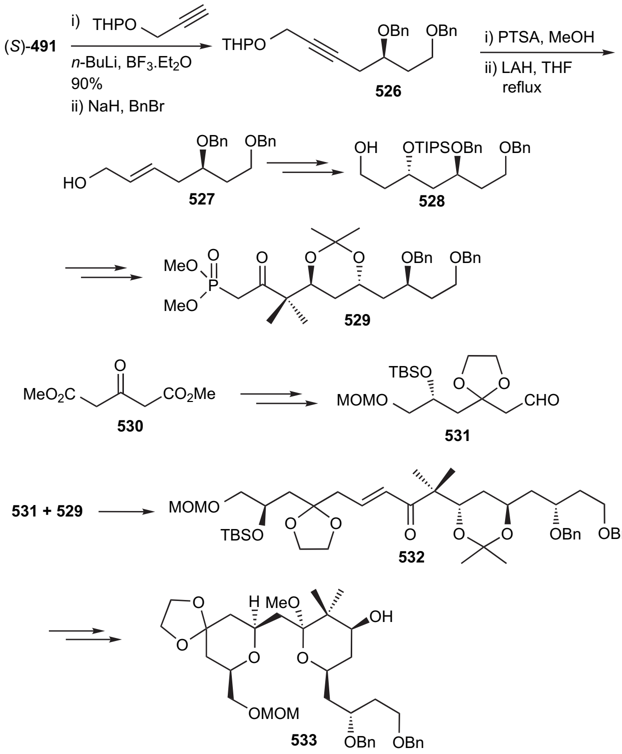
Scheme 87.

10.15. C1–C16 fragment of bryostatins

Bryostatins were isolated from the marine bryozoan *Bugula neritna* Linn. and *Amathia convoluta*. These bryostatins and related biologically active marine macrolides exhibit exceptional antineoplastic activity against lymphocytic leukemia and ovarian carcinoma,[141] and inhibit the tumor promotion of phorbols related to protein kinase C.[142] Yadav and co-workers[143a] synthesized the C1–C16 fragment of bryostatins using hydrolytic kinetic resolution, a Horner–Wadsworth–Emmons coupling reaction, and 1,4-Michael-type cyclization as the key steps. As shown in Scheme 88, the synthesis of the C1–C9 fragment started with hydrolytic kinetic resolution of racemic epoxide (±)-**491** with catalyst **1b** to give the chiral epoxide (*S*)-**491** in 47% yield and 97% ee. The epoxide (*S*)-**491** was opened with THP-protected propargyl alcohol. Further synthetic manipulations afforded the fragment **529**. The C10–C16 fragment **531** was synthesized from dimethyl 1,3-acetonedicarboxylate **530** in several steps and was coupled with **529** by Horner–Wadsworth–Emmons olefination to furnish the α,β-unsaturated ketone **532**, which was converted into the target intermediate **533** (Scheme 89).



Scheme 88.

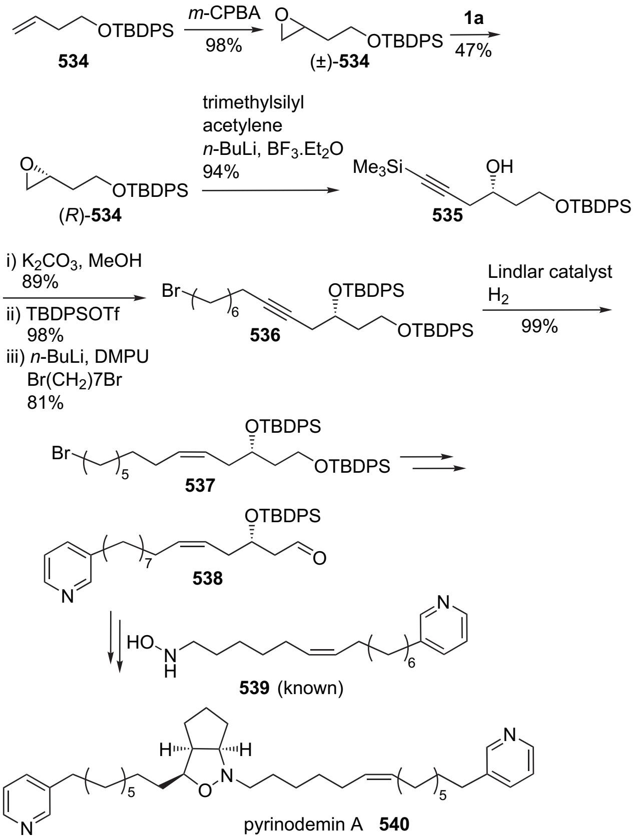


Scheme 89.

A similar application of this epoxide has been reported in the synthesis of (−)-salicylihalamides A and B.[143b]

10.16. Pyrinodemin A

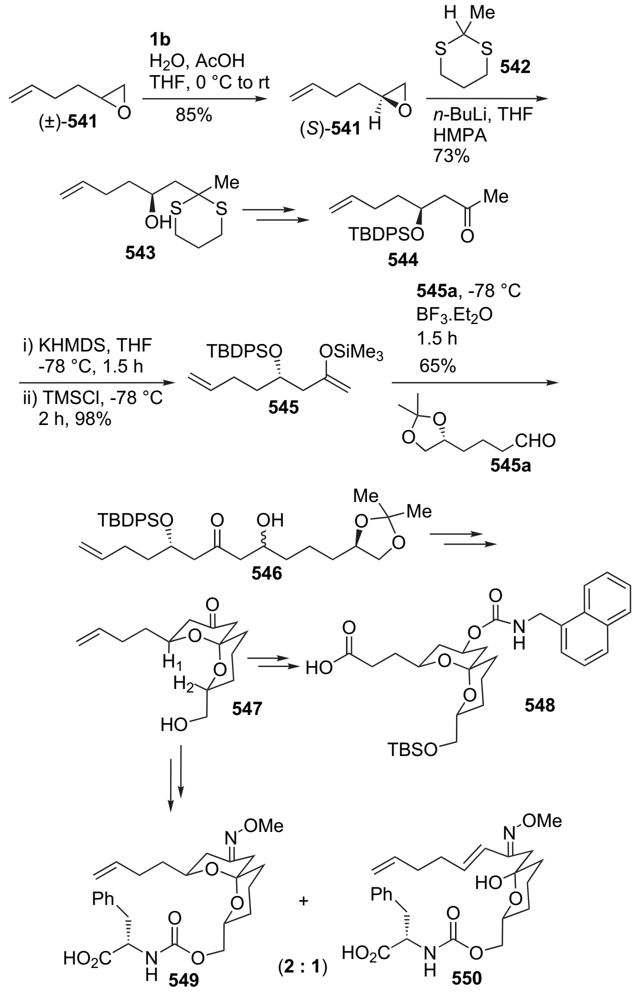
Pyrinodemin A **540** is a bis-3-alkylpyridine, which was isolated from the Okinawan marine sponge *Amphimedon* sp.[144] Because of its interesting cytotoxicity toward murine leukemia L1210 and KB epidermoid carcinoma cells and the uncertainty in its absolute stereochemistry, Lee and co-workers[145] established the absolute configuration by synthesis of pyrinodemin A **540** via a nitrone, which could be derived from an aldehyde. As shown in Scheme 90, the epoxide (*R*)-**534** was obtained through the HKR of the racemic epoxide **534**, which was treated with lithium trimethylsilylacetylide to afford the secondary alcohol **535**. Removal of the trimethylsilyl group, hydroxyl protection as its TBDPS ether followed by alkylation of acetylene with 1,7-dibromoheptane in the presence of *n*-BuLi and DMPU furnished compound **536** in 81% yield. Semi-hydrogenation of the triple bond followed by treatment with lithiated 3-picoline, deprotection of the primary silyl ether, and subsequent IBX oxidation furnished the aldehyde **538** in 88% yield. The aldehyde **538** was further converted into the target molecule **540** in a few steps through synthetic manipulations.



Scheme 90.

10.17. Combinatorial synthesis of natural product-like molecules

Porco and co-workers[146] have reported the use of the dioxaspiro[5,5]undecane (spiroketal) moiety as a rigid-core template for elaboration using parallel synthesis techniques. In this paper, they have used the scaffold to generate a small combinatorial library of natural product-like molecules. The synthesis of functionalized spiroketals **548**, **549**, and **550** could be achieved from spiroketal ketone **547**, which, in turn, was prepared from condensation of chiral ketone **545** and aldehyde **545a** using standard reaction sequences. As shown in Scheme 91, hydroxyl ketone fragment **544** was synthesized by HKR. The epoxide (±)-**541** was subjected to HKR using **1b** and water (0.55 equiv) to yield epoxide (*S*)-**541** in 85% yield. The treatment of epoxide with 2-methyl-1,3-dithiane **542** provided the hydroxyl dithiane **543**, which was converted into silyl-protected hydroxyl ketone **544** in two steps. Enolization of **544** followed by condensation with aldehyde **545a** under Mukaiyama reaction conditions gave **546**, which, on further synthetic manipulations, gave the spiroketal scaffold and highly functionalized molecules.



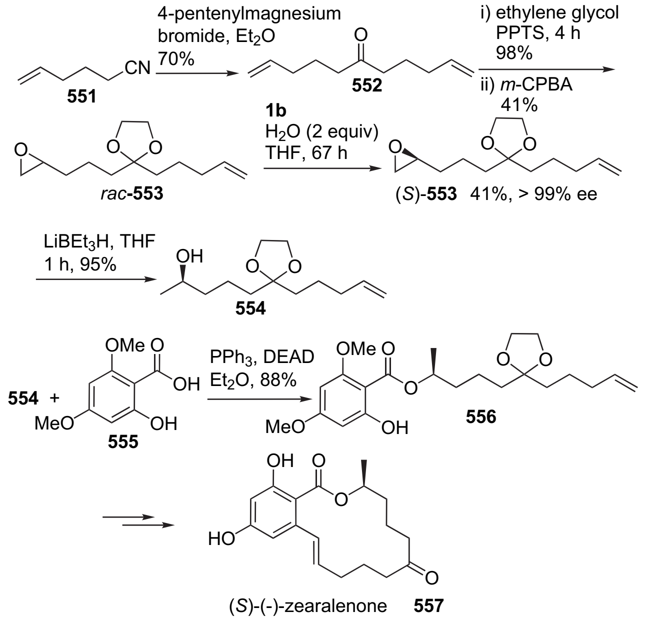
Scheme 91.

10.18. (*S*)-(−)-Zearalenone

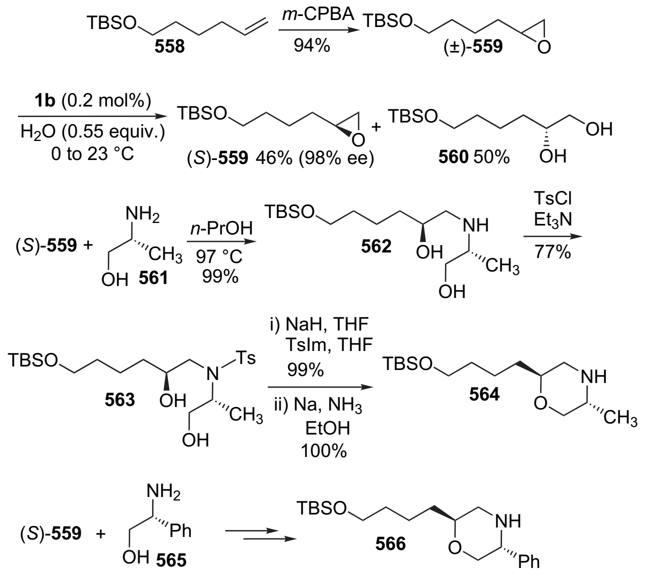
Zearalenone **557**, also known as RRL and F-2 toxin, is a potent estrogenic metabolite, isolated from the mycelia of the fungus *Gibberella zeae*.[147] Fürstner and co-workers[148] accomplished the total synthesis of (*S*)-(−)-zearalenone **557** using a ring-closing metathesis and HKR as the key steps. As shown in Scheme 92, racemic epoxide (±)-**553** (prepared from 1-cyano-4-pentene **551** in two steps) was subjected to HKR using **1b** catalyst and water (2 equiv) to give the required epoxide (*S*)-**553** in optically pure form (ee>99%). Reaction of (*S*)-**553** with $LiBEt_3H$ afforded the alcohol **554**, which, on esterification with salicylic acid derivative **555** under Mitsunobu conditions followed by ring-closing metathesis, gave the target molecule **557**.

10.19. *trans*-2,5-Disubstituted morpholines

In the course of a large-scale preparation of *trans*-2,5-disubstituted morpholine derivatives required for solid-phase synthesis of a library of saframycin analogs,[149] Myers and Lanman[150] established a simple route for their synthesis starting from readily available, enantiomerically pure starting materials. As depicted in the Scheme 93, the racemic epoxide **559** (derived from olefin **558** by *m*-CPBA oxidation) was subjected to hydrolytic kinetic resolution in the presence of water (0.55 equiv) catalyzed by **1b** to form the *S*-epoxide (*S*)-**559** in 46% yield with 98% ee and *R*-diol **560** in 50% yield. (*S*)-Epoxide (*S*)-**559** on ring opening with amino alcohols **561** and **565** followed by *N*-protection, selective hydroxy activation, ring closure, and *N*-deprotection gave the *trans*-2,5-disubstituted morpholines **564** and **566**, respectively, in excellent yields.



Scheme 92.



Scheme 93.

11. Conclusions

As evidenced by the foregoing discussion, one of the most effective and recent methods for obtaining several classes of chiral building blocks is Jacobsen's hydrolytic kinetic resolution (HKR). The method provides general access to many chiral epoxides and 1,2-diols that are otherwise difficult to obtain in high conversions and enantiopurities from inexpensive racemic starting materials. We have shown in this review that the HKR method has broad applications in organic synthesis. In particular, it is quite useful in the synthesis of biologically active products. The synthesis of chiral building blocks by the HKR method is a blossoming field and there is enormous scope for using this method in the synthesis of diverse compounds, which may have applications as biologically active agents. In view of the easy availability of the chiral ligand and the simplicity of the reaction with water being used as the nucleophile, they will continue to play an important role in asymmetric synthesis and judicious application of the knowledge in this area will give the desired result. We anticipate many more applications to emerge in the near future and this review just presents the state of the art knowledge on how a synthetic organic chemist can exploit this novel tool for the total synthesis of complex natural products.

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Biographical sketch

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