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Enantioselective Synthesis of Natural Epoxyquinoids

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Abstract: Natural products play an important role as a source not only of potential therapeutic drugs but also of starting materials for semisynthetic new medicines. The epoxyquinoid family, composed by cyclohexane epoxides and related structures, exhibit these characteristics without doubt.

Since 2004, significant efforts have been devoted to the stereocontrolled synthesis of these molecules with different and interesting strategies. More than 50 works on this field have been published during this period of time. In addition, many of these polyoxygenated cyclohexenoids exhibit diverse and impressive bioactive shapes. This review aims to analyze the recent advances in the enantioselective processes that have been performed for the total syntheses of these target molecules. It includes a wide range of methodologies for the introduction of chirality either enzymatic or chemical ones. This summarizes microbial preparation of starting materials, lipase kinetic resolutions, use of compounds from the chiral pool, use of chiral auxiliaries and asymmetric catalysis. In a special section, syntheses of scyphostatin are also included.

Keywords: Chemocatalyst, enantioselective, enzymatic methods, epoxyquinoids, scyphostatin, synthesis.

INTRODUCTION

Epoxycyclohexenones are widely distributed in nature. Biologists and pharmacologists are very interested in them due to their many and varied biological properties. Also the highly functionalized and challenging structures prompted the synthetic chemistry community to redouble efforts in their total synthesis. After emerging reviews in the 80s [1] and 90s [2] dedicated to cyclohexene epoxides and related compounds, Marco-Contelles and co-workers wrote an extensive and comprehensive apropos review [3]. They covered a wide range of naturally occurring cyclohexane epoxides, including sources, biological activities and syntheses. Since that review was published, significant efforts have been devoted to the stereocontrolled synthesis of these types of molecules with different and interesting strategies. This review aims to describe the advances in the enantioselective processes that have been performed since 2004 for the total syntheses of epoxycyclohexene derivatives. We have classified the target molecules into: 1) epoxycyclohexenones (Fig. **1**); 2) epoxycyclohexene-diols and diones (Fig. **2**) and 3) related dimeric epoxyquinoid structures (Fig. **3**). We briefly describe natural sources and biological activities of these compounds. We have organized the advances in the field of synthesis in two broad sections according to the methodologies for the introduction of chirality in the strategy: 1) enzymatic mediated desymmetrizations and 2) chemically stereocontrolled methodologies. Efficient syntheses starting with enantiomerically pure available synthons are also reviewed. Finally, scyphostatin chiral preparations will be separately presented. Epoxycyclohexenes derived from naphtholenoid precursors are not included in this review. This topic was reviewed extensively by Krohn [4], Miyashita [5] and Cai [6].

SOURCES AND BIOLOGICAL ACTIVITIES

Concerning epoxycyclohexenones described in Figure **1**: (+)-epoformin (**1**) was first isolated from the culture broth of *Penicillium claviforme* [7] and exhibited antibiotic and cytotoxic activity. (+)-Epiepoformin (**2**) inhibited the germination of lettuce seeds [8]. This phytotoxin was separated from the culture of an unidentified fungus on diseased crepe myrtle (*Lagerstroemia indica*) leaves. From the culture filtrate of *Phyllosticta sp*. S1019 [9] and *Phorma sp*. [10] a secondary metabolite called (+)-epoxydon (**3**) was isolated, which was described as phyto and cytotoxic agent. A quantum-mechanical calculation of the optical rotatory power of **1**, **2** and **3** was recently reported [11]. (+)-Epiepoxydon (**4**) was isolated from the same source as epiepoformin (**2**) [8]. (+)-Bromoxone (**5**) together with its acetate (**6**) were isolated from marine acorn worms (*Phyllum hemichordata*) [12]. The haloepoxycyclohexenone acetate **6** possess antitumor activity in P388 cells (IC_{50} 10mg/ml). Recently Gong and co-workers [13] identified natural bromoxone as a potent caspase-1-pathway inhibitor among other properties and described a possible mechanism of action. In 1986 Jarvis and Yatawara [14] reported a new antibiotic (+)-isoepiepoformin (**7**) from cultures of the fungus *Myrothecium roridum* CL-514 (ATCC20605). (+)-ECH (**8**) was first isolated from the culture broth of an unidentified fungus strain [15]. This epoxycyclohexenone inhibited Fas-mediated apoptosis by blocking activation of pro-caspase-8 in the death inducing signaling complex [16]. Few months later synthetic (+)-RKTS-33 (**9**) and (+)-RKTS-34 (**10**) were reported as novel non-peptide inhibitors towards death receptor-mediated apoptosis by Kakeya and co-workers [17]. Structure-activity relationships of several semisynthetic C-6 side chain derivatives were also described by the authors. In 2004, they described that ECH (**8**) and RKTS-33 (**9**) were specific inhibitors of the FasL-dependent killing pathway in CTL-mediated cytotoxicity [18,19]. (-)-Harveynone (**11**), a secondary metabolite with phytotoxic activity was isolated from the tea gray blight fungus *Pestalotiopsis theae* [20]. (-)-Tricholomenyn A (**12**) showed antimitotic activitiy and was isolated from the fruiting bodies of the mushroom *Tricholoma acerbum* [21], together with a number of analogs called tricholomenyns B to E. It has been suggested that the biosynthesis of tricholomenyns C-E and maybe also B proceeds via a not yet isolated intermediate. Recently, the synthesis of a putative biogenetic precursor (**13**) was achieved by Banwell´s group [22]. An epoxycyclohexenone that contains a fatty acid side chain was isolated from the related endophytic fungal species [23, 24] *Pestalotiopsis* and

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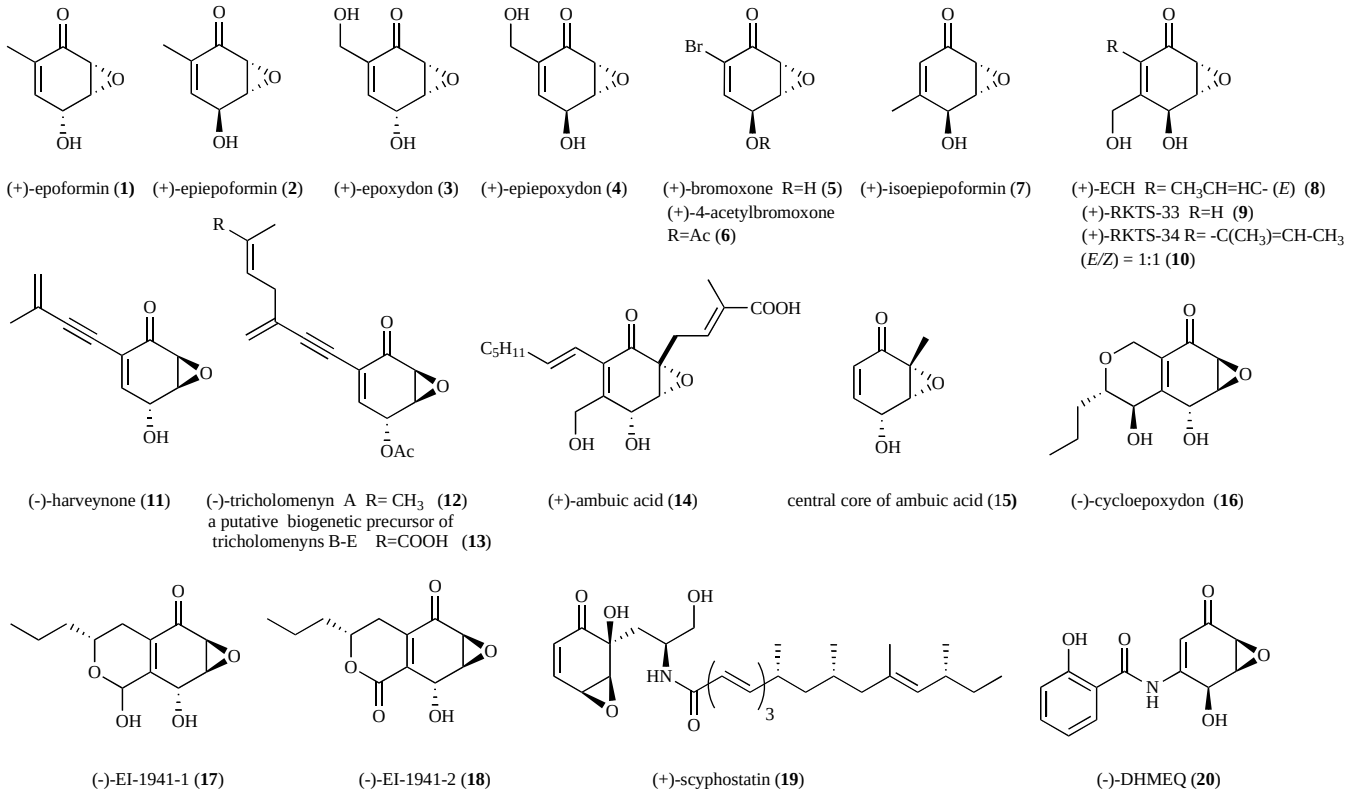


Fig. (1). Epoxycyclohexenones containing halogen, C-C and C-N side chains.

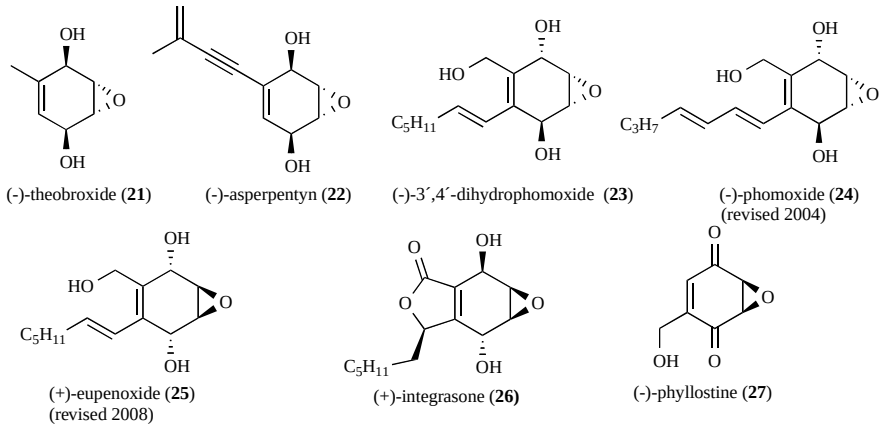


Fig. (2). Natural epoxycyclohexene-diols and diones.

Monochaetia [25] living in the thalli of lichens. It was called ambuic acid (**14**) and displayed antifungal activity against human pathogenic fungi. Recently, ambuic acid derivatives were described in the same fungus (*Pestalotiopsis sp.*) by Ding *et al.* [26]. Ambuic acid and one of its metabolites displayed anti-microbial activity against the gram-positive bacterium *Staphylococcus aureus* according to these authors. Nakayama´s group demonstrated that ambuic acid inhibits the biosynthesis of cyclic peptide quormones of *Staphylococcus aureus* and *Listenia innocua*. This mode of action suggests the potencial application of ambuic acid as a lead compound targeting the quorum-sensing system of gram positive bacteria [27]. A model structure of ambuic acid having an epoxyquinoid structure (**15**) was published by our group in 2008 [28].

(-)-Cycloepoxydon (**16**) was isolated from the deuteromycete strain 45-93 [29] and exhibited activation of NF-κB [30]. This natural product also showed an inducible ubiquitous transcription factor that regulates the expression of various cellular genes involved in immune and inflammation responses and apoptosis. In 2003, Koizumi and co-wokers [31] reported the isolation of (-)-EI-1941-I (**17**) and (-)-EI-1941-II (**18**) from the fermentation broth of *Farrowia sp*. According to these authors [32], **17** and **18** inhibited selectively human recombinant interleukin-1β(1L-1β) converting enzyme (ICE) activity with IC_{50} values of 0.086 and 0.006 μM, respectively. ICE inhibitors have been suggested as potencial anti-inflammatory drug candidates [33].

(+)-Scyphostatin (**19**) was first isolated from a mycelia extract of *Dasyscyphus mollissimus* Sank 13892 [34]. Up to date, **19** exhibits the most potent (IC_{50} 1.0 μM) inhibitory activity against the neutral enzyme sphingomyelinase (N-SMase) [35-38]. Synthetically produced (-)-DHMEQ (**20**) was found as a potent and specific inhibitor of NF-κB [39] and it showed potent anti-inflammatory and anticancer activities in animals [40-44].

Epoxycyclohexene-diols and diones (Fig. **2**) have also been found in nature: (-)-theobroxide (**21**) was first isolated from the

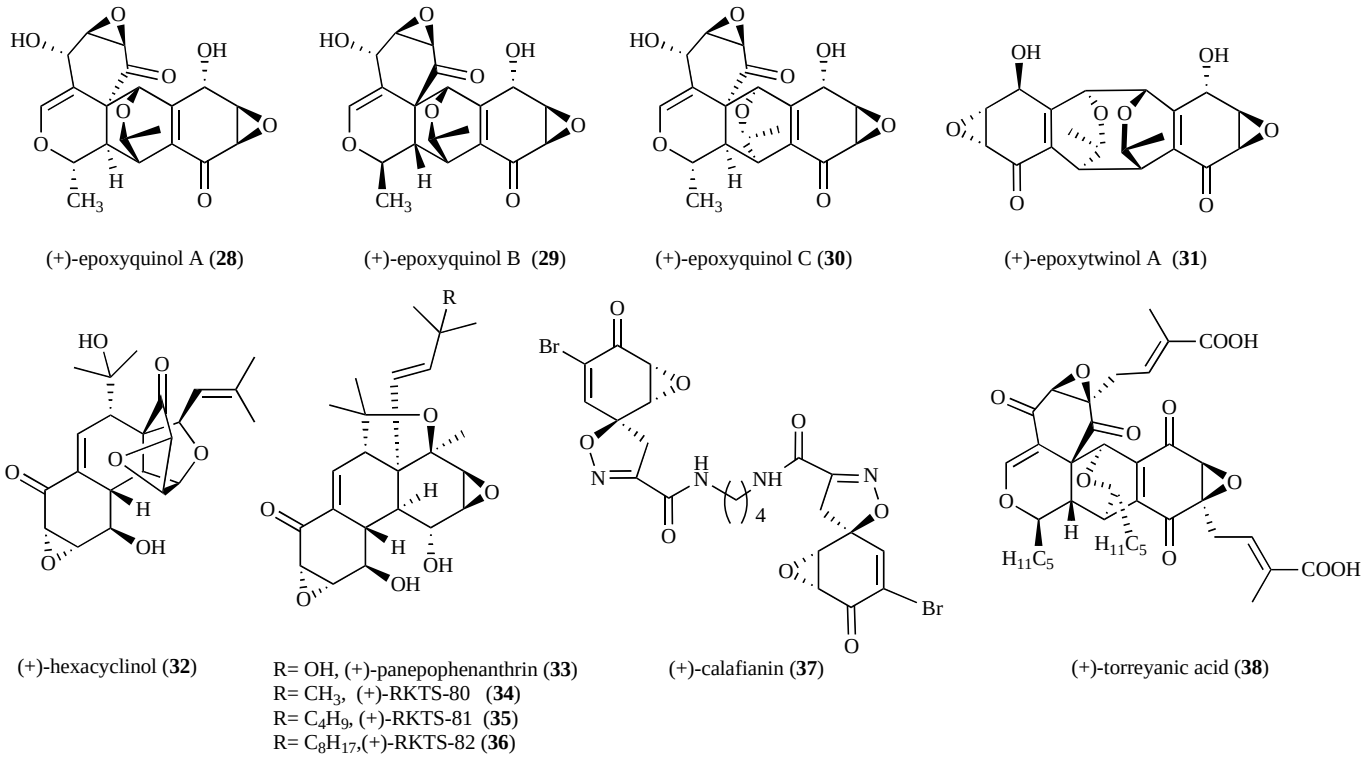


Fig. (3). Dimeric epoxyquinoids.

culture filtrate of the fungus *Lasiodiplodia theobromae* and showed exceptional activity as a potato microtuber inducing *in vitro* [45-50]. It also inhibits stem elongation in spinach and morning glory [51].

Natural (-)-asperpentyn (**22**) was reported by Achenbach [52] in 1988 from the antimicrobial extracts of *Aspergillus duricaulis*. According to this author, asperpentyn showed no activity against *Botrytis cinepea* and *Bacillus subtillis*. To our knowledge, biological activities of asperpentyn and its synthetic enantiomer have not yet been described. In 2003, Liu *et al*. [53] reported the isolation of a natural product miss-assigned as "eupenoxide" from the fermentation of a marine-derived fungus of the genus *Phoma sp*.. Mehta reassigned this structure as 3´, 4´-dihydrophomoxide (**23**) based on identical spectroscopic data compared with its enantiomer, previously synthesized [54, 55]. (-)-Phomoxide, which also had to be revised, was originally isolated from the same natural source [53]. In 2004, Mehta [54] proposed the revised structure **24** by comparison of the spectroscopic data reported for the natural sample with the ones of the synthetically prepared stereostructure. An endophytic fungus of the genus *Eupenicillium* is the source of an antifungal agent called (+)-eupenoxide (**25**) [56]. The chemical structure of eupenoxide has been under revision for several years and was finally clarified by Mehta and co-workers [55]. This compound was also found in the endophytic fungi *Phoma* sp.[57] and *Aspergillus japonicus* [58]. (+)-Integrasone (**26**) was first isolated from an unidentified sterile mycellium (MF63896) [59]. Natural integrasone inhibited HIV-1 integrase which is one of the critical enzymes involved in viral replication. (-)-Phyllostine (**27**) was found in *Phyllosticta sp*. [9]. It exhibited antibiotic and phytotoxic activity [60].

Finally, amazingly complex structures have been reported for dimeric epoxyquinoids of natural origin, as shown in figure **3**. (+)-Epoxyquinol A (**28**) was isolated from an uncharacterized fungus from a soil sample, exhibiting potent angiogenesis inhibition properties [15]. Cancer, reumatoid arthritis and other chronic inflammatory diseases are characterized by extensive angiogenesis [61]. Osada´s group isolated (+)-epoxyquinol B (**29**) [62] from the same fungus, with even more potent angiogenesis inhibition properties than epoxyquinol A. They also reported that **29** inhibits NF-κB signaling by crosslinking TAK1[63]. Pentaketides epoxyquinols A, B and C (**30**) are postulated to be biosynthetically generated from epoxyquinol monomer **8** by a cascade reaction sequence of oxidation, 6π-electrocyclization and Diels-Alder dimerization [64]. Later in 2005, epoxytwinol A (**31**) was isolated from the same fungus [65]. This complex dimeric structure having a 17,19-dioxapentacyclo [8.6.2.$2^{2,9}$.$0^{3,8}$.$0^{11,16}$]icosa-3(8),11(16)-diene, inhibited endothelial cell migration stimulated by vascular endothelial growth factor (ED_{100} = 2.6 μM).

The culture of the fungal strain of *Panus rudis* was the source of bioactive metabolite called (+)-hexacyclinol (**32**) [66]. Antiproliferative effect of hexacyclinol on L-929 cells and its cytotoxic effect on HeLa cells were demonstrated. Hexacyclinol also displayed moderate inhibitory activity against *Plasmodium falciparum* (IC_{50} 2.49 μg/ml). It can be suggested that hexacyclinol may serve as a lead for the development of new antimalary agents. However, its complex chemical structure has been under controversy for years. In 2006, Rychnovsky proposed a revised structure of hexacyclinol based on prediction of NMR chemical shifts by modern computational methods [67]. Porco and co-workers confirmed in 2006 the hexacyclinol structure [68] and they brought light to the "hexacyclinol dispute" [69].

(+)-Panepophenanthrin (**33**) was first isolated from the mushroom strain *Panus rudis* IFO 8994 [70]. This is the first natural product discovered that inhibits ubiquitin activating enzyme (E1). This inhibition affects the ubiquitin-proteasome pathway (PPP) and ubiquitin functions that are involved in serious diseases [71]. Considering this unique biological activity and the complex structure of such dimeric epoxyquinoids, Shoji´s group reported three synthetically panepophenanthrin derivatives RKTS 80-82 (**34**-**36**) and investigated their structure-activity relationships [72]. In 2000, Christophersen and co-workers [73] isolated from the methylene chloride extract of the marine sponge *Aplysina gerardogreeni* a dimeric compound named calafianin [74]. Five years later Ogamino and

Nishiyama proposed a revised structure of (+)-calafianin (**37**) which spectroscopic data concur with the reported data of the natural sample. Surprisingly, spiroisoxazoline moiety that is usually involved in antimicrobial, cytotoxic and anti-inflammatory activities showed no significant biological activity. A secondary metabolite from *Pestalotiopsis microspora* with selective cytotoxicity against human cancer cell lines was isolated by Lee and co-workers in 1996 [75]. The structural determination of torreyanic acid was established as the dimeric quinone **38** that could be biogenerated from ambuic acid (**14**) as the monomer unit. Torreyanic acid demonstrated to be five to ten times more potent in cell lines that are sensitive to the protein kinase C (PKC) agonists and it was found to cause programmed cell death (apoptosis).

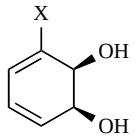
ENANTIOSELECTIVE SYNTHESIS OF EPOXYQUINOIDS

Enzymatic Methods

Enzymes have been used for the introduction of chirality of epoxyquinoids and related molecules, in two different ways: the use of chiral building blocks of microbial origin and the use of lipases for kinetic resolution of enantiomeric mixtures.

Use of Microbial Chiral Building Blocks

The first starting materials of this type we are going to consider are the enantiomerically pure diols that exhibit the structure shown in figure 4. These valuable synthons are available by means of whole cell oxidation of the corresponding monosubstituted benzene [76,77]. They have been widely used for the synthesis of a great variety of natural polyoxygenated products [78-81]. Concerning the synthesis of natural epoxyquinoids, Banwell´s and our own group have taken advantage of this chemoenzymatic methodology.



X = CH_3, Cl, Br, I

Fig. (4). Diols of microbial origin.

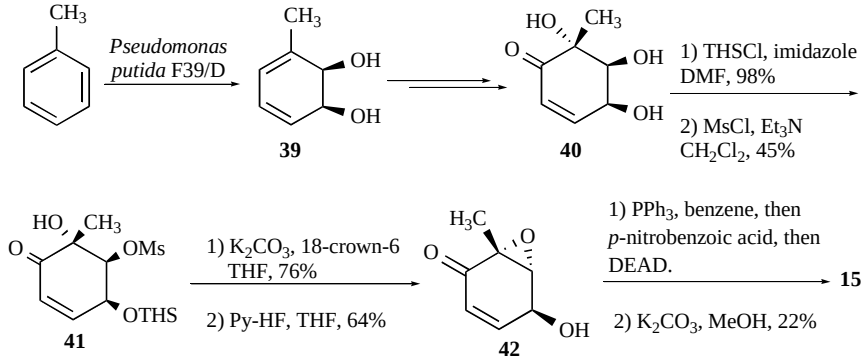
In 2008, we have reported the synthesis of a model compound of the central core of ambuic acid [28], starting from toluene as the aromatic substrate to be biotransformed into the corresponding *cis*-diol by *Pseudomonas putida* F39/D [76]. This constituted the first application of this methodology to the synthesis of a chiral epoxyenone (scheme **1**).

Enone **40** has been previously prepared from toluene-derived chiral diol **39** [82]. Protection of the less hindered alcohol with a bulky silylating agent and thus conversion of the other secondary alcohol into a good leaving group, permitted us to obtain **41** that in basic medium led to epoxyenone **42**. Mitsunobu inversion afforded **15** that constitutes a model molecule for the central core of ambuic acid.

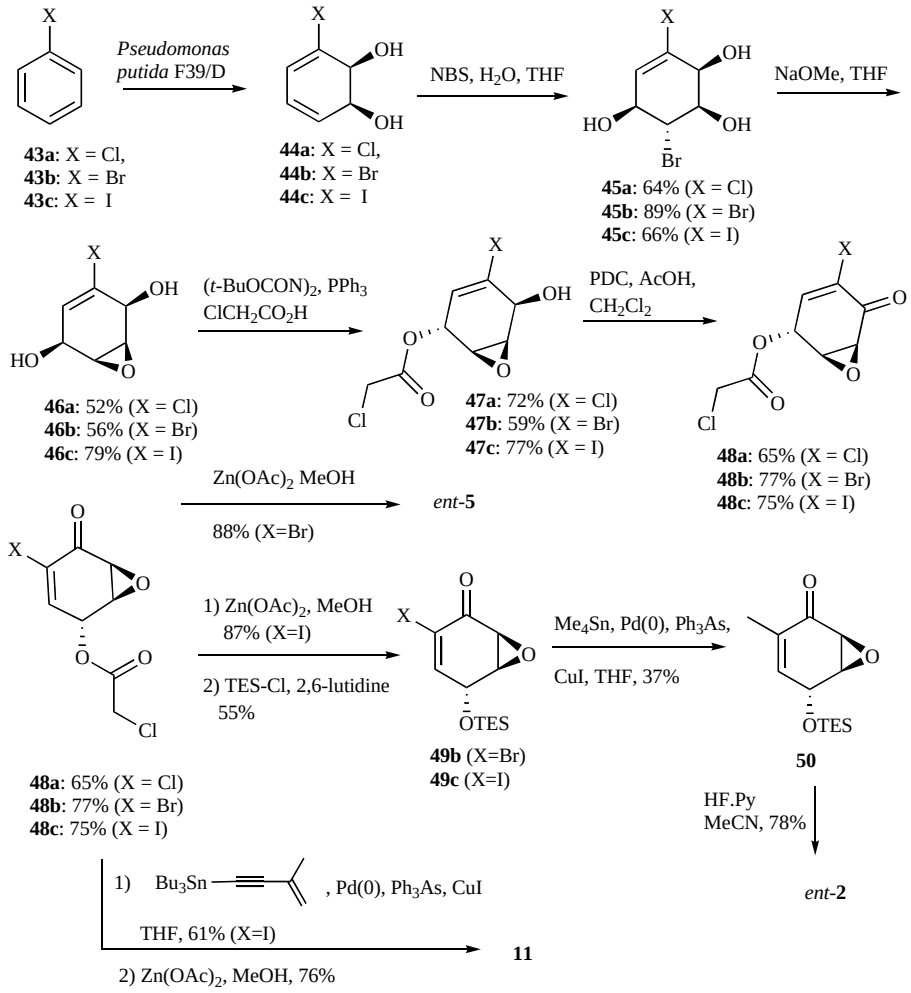
In 2009, Banwell and co-workers started to use these metabolites for the synthesis of natural epoxyquinols. In an extensive work [83], they reported the chemoenzymatic preparation of *ent*-bromoxone (*ent*-**5**), *ent*-epiepoformin (*ent*-**2**), (-)-harveynone (**11**), (+)-panepophenanthrin (**33**) and (+)-hexacyclinol (**32**). The key intermediates in this case were compounds **48a-c** that can be easily obtained from chiral halo-*cis*-cyclohexadiendiols **44a-c**, as it is shown in scheme **2**. Any of the three halo-diols, when treated with NBS yielded the corresponding bromohydrins **45a-c**. These products, under basic conditions underwent epoxide ring closing by nucleophilic attack of the C3-hydroxyl group (**46a-c**). Mitsunobu inversion proceeded regioselectively on carbon 4 yielding **47a-c**. Further oxidation led to key intermediates **48a-c**. *ent*-Bromoxone (*ent*-**5**) and *ent*-epiepoformin (*ent*-**2**) were obtained efficiently from these epoxyenones. In the case of *ent*-bromoxone just deprotection of **48b** afforded the desired product. In the case of *ent*-epiepoformin, after switching protective groups on the iodo compound **48c** to afford **49c**, Stille cross-coupling reaction permitted to introduce the methyl group. After silyl ether removal, *ent*-epiepoformin was obtained. In the case of (-)-harveynone (**11**), no change of protective group was necessary. Compound **48c** reacted under Stille conditions, and after removal of chloroacetate, the natural product was prepared. Taking advantage of this protocol, the dimeric compound (+)-panepophenanthrin (**33**) was also synthesized (scheme **3**). In this case, Stille coupling was performed on iodoalcohol **47c**, with **51a** as the cross-coupling partner, and then it was oxidized to **52a**. Deprotection yielded compound **53a**. This compound has been proposed to be a biosynthetic precursor of the dimer. In fact, it was spontaneously transformed into panepophenanthrin (**33**) just standing neat at room temperature.

Appling exactly the same sequence, but using the methoxylated tin compound **51b**, pre-hexacyclinol (**54**) was obtained. Under acid-catalyzed conditions it was converted into (+)-hexacyclinol (**32**).

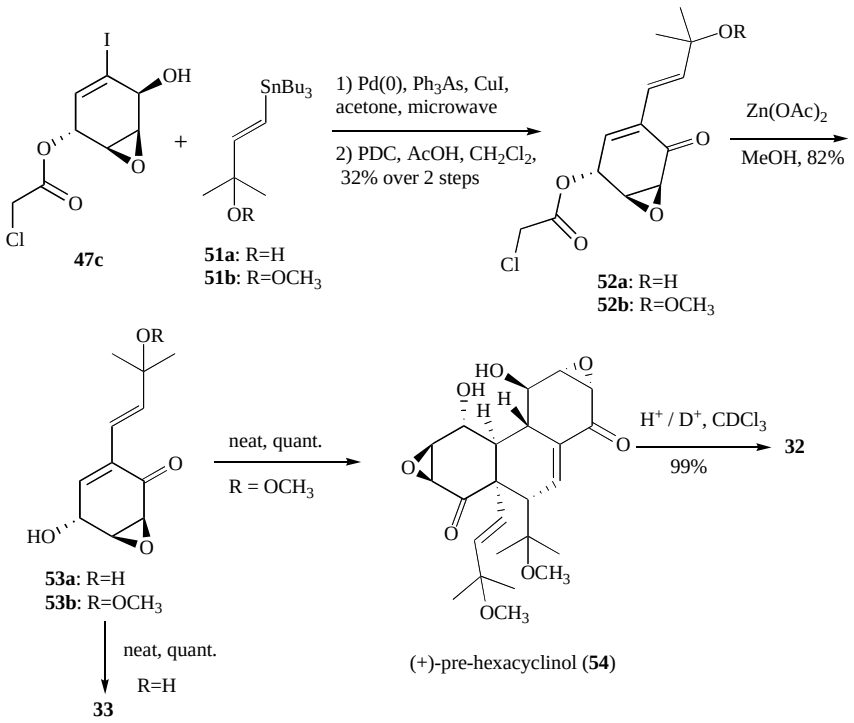
In an extension of this work, Banwell's group published a very concise synthesis of *ent*-bromoxone acetate (*ent*-**6**) and (-)-tricholomenyn A (**12**) (scheme **4**) [84]. In this case, Mitsunobu inversion was performed over compounds **46b** and **46c** with acetic acid instead of chloroacetic acid. Acetates **55a-b** were obtained. So, the enantiomer of bromoxone acetate (*ent*-**6**) was directly prepared, using the same strategy of the previous work. When the same protocol was applied to the iodocompound **46c**, having the appropriate tin compound in hands, they prepared (-)-tricholomenyn A (**12**) through a Stille cross coupling reaction performed on epoxyenone **56**.



Scheme 1.



Scheme 2.



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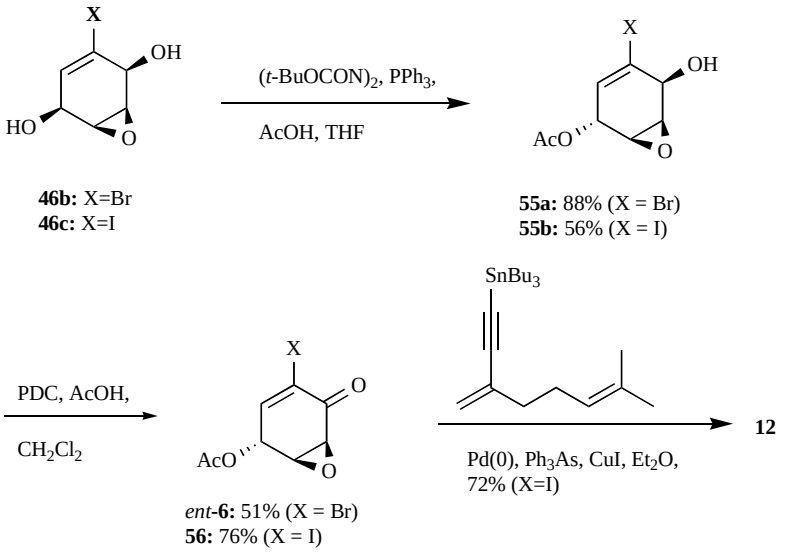
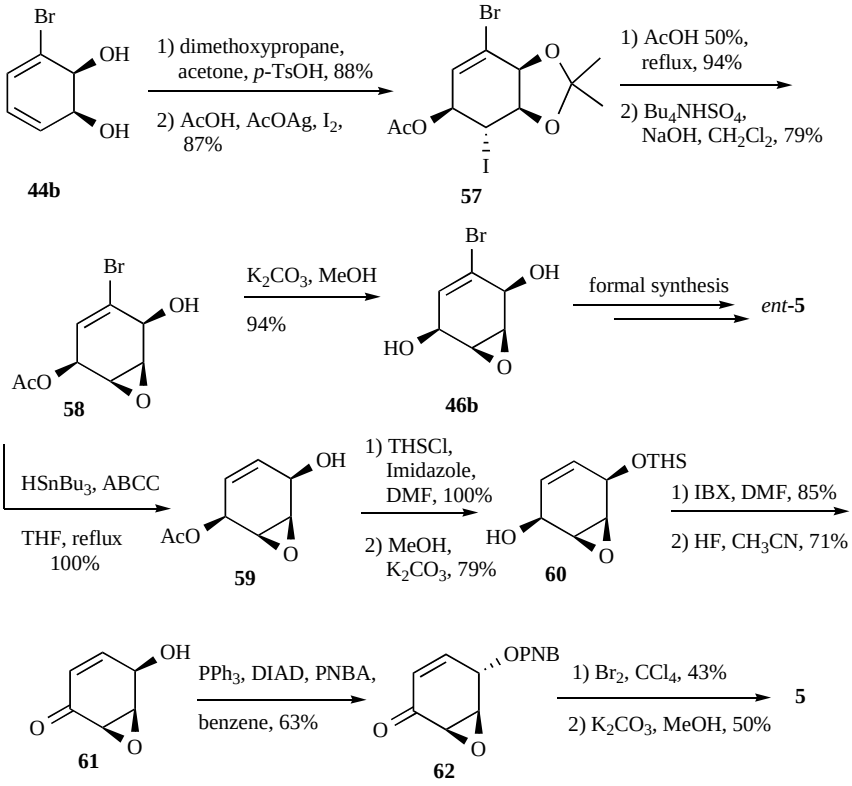


Scheme 4.



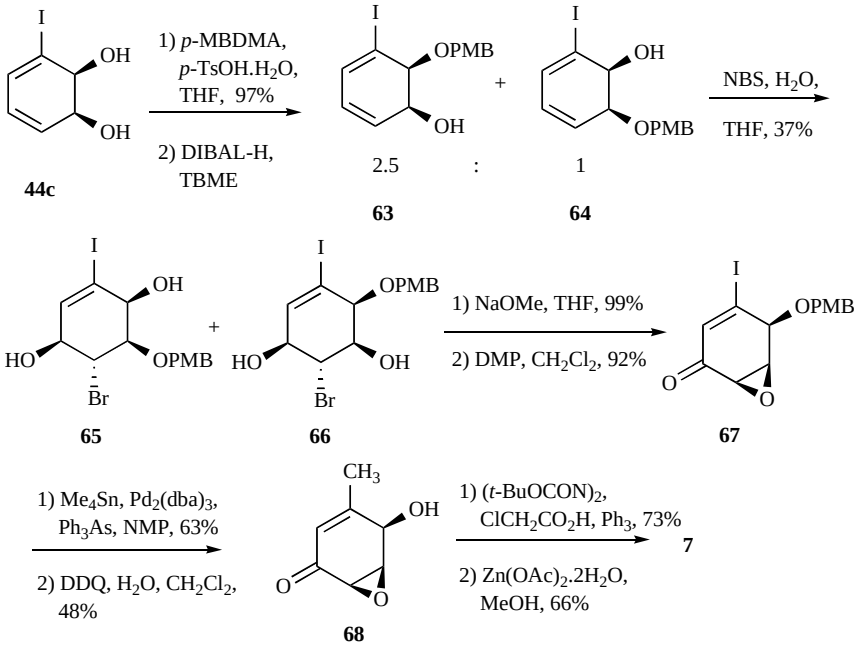
Scheme 5.

While Banwell and co-workers were performing the syntheses shown above, our group was also using a closely related strategy. The outcome of this work was the total enantiodivergent synthesis of (+) and (-)-bromoxone [85]. Our chiral starting material was the same as Banwell´s: the diol derived from bromobenzene (**44b**). In this case, we build a key intermediate from which both bromoxone enantiomers could be obtained. The strategy is shown in scheme **5**.

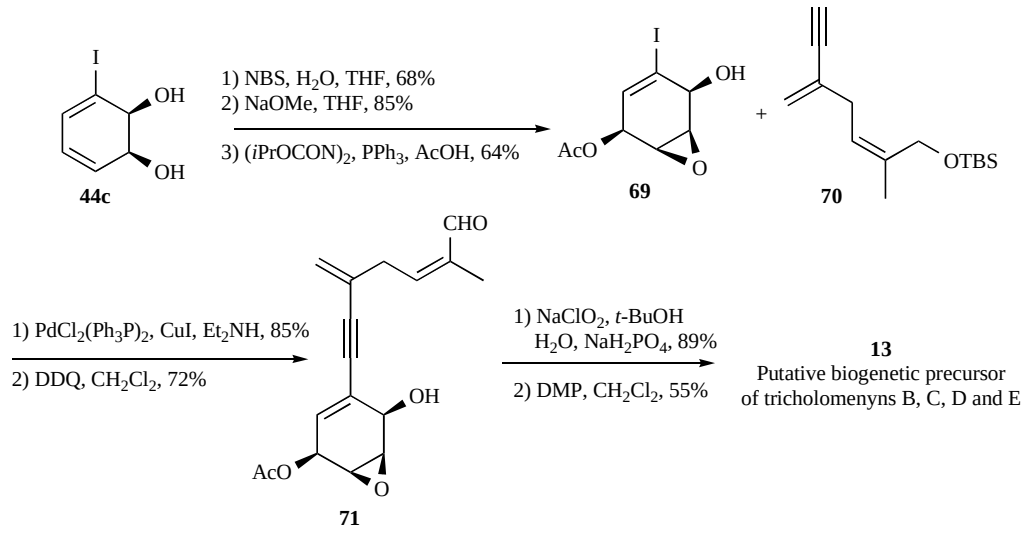
Bromodiol **44b** was protected as acetonide and subsequently iodohydroxylated to give iodo acetate **57**. Removal of the acetonide protective group and treatment with base permitted the cyclization of the oxirane ring present in the key intermediate **58**. Methanolysis of the acetate yielded epoxydiol **46b**, from which Banwell obtained *ent*-bromoxone (*ent*-**5**) (see scheme **2**), thus constituting a formal synthesis of this non-natural epoxyenone.

For the synthesis of the natural product, we needed to debrominate intermediate **58**. Manipulation of protective groups on **59** led to **60**, and oxidation with IBX provided epoxyenone **61** in very good yield. Although it was not easy to achieve α-bromination, it was possible when it was assayed over the *p*-nitrobenzoate derived from the Mitsunobu inversion (**62**). Methanolysis of the benzoate yielded (+)-bromoxone (**5**).

Going on working on this methodology, Banwell and co-workers accomplished the preparation of (+)-isoepiepoformin (**7**) starting from the iodobenzene derived diol **44c** [86]. This time, the



Scheme 6.



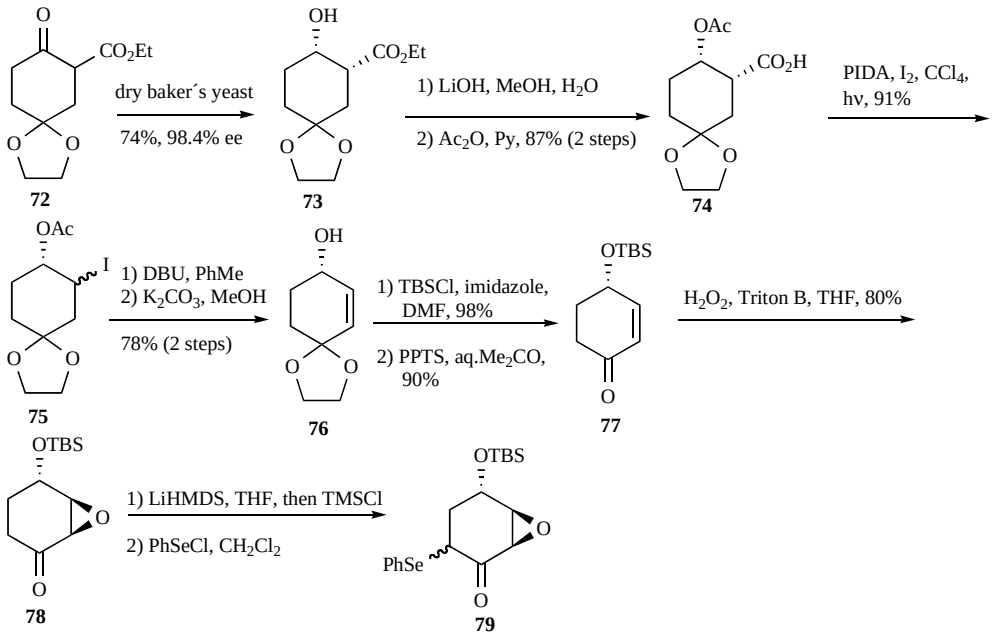
Scheme 7.

authors protected the diol **44c** as a *p*-methoxybenzyl acetal that was reduced with DIBAL-H, to produce a mixture of the corresponding monoprotected diols **63** and **64**. As it is shown in scheme **6**, the mixture when treated with NBS yielded a mixture of bromohydrins (**65** and **66**), but only regioisomer **66** could be isolated and purified. Epoxide **67** was efficiently prepared, and then, Stille reaction followed by deprotection of the hydroxyl group to form **68** permitted the preparation of the epimer of the natural product. Mitsunobu protocol for inversion of configuration led to (+)-isoepiepoformin (**7**).

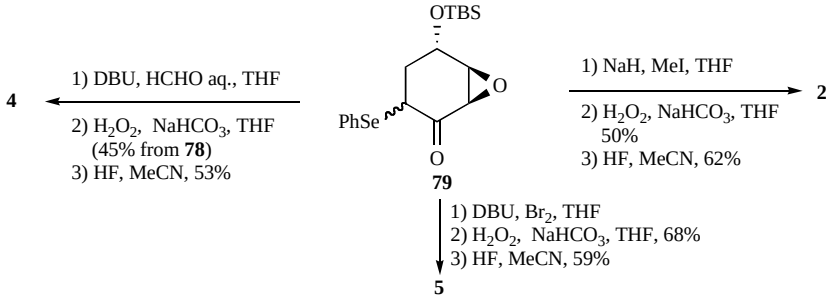
The last work of Banwell´s group concerning these kind of molecules was the preparation of a putative biogenetic precursor of tricholomenyns B, C, D and E [87], once again starting from chiral iododiol **44c** (scheme **7**). This diol was subsequently treated with NBS, then with base for epoxide formation, and finally under Mitsunobu conditions to yield acetate **69.** After a significant synthetic effort to construct the appropriate side chain (**70**), it was coupled with compound **69** by means of a Sonogashira reaction.

Once the side chain was inserted, the aldehyde **71** was obtained by treatment with DDQ. Further oxidative steps (Pinnick and Dess-Martin oxidation) yielded **13**, the putative precursor of tricholomenyns B, C, D and E. Nevertheless, the attempts to convert **13** into any of the corresponding tricholomenyns failed, showing that maybe this is not a precursor or perhaps the conversion into the natural products is an enzymatic process not easy to mimic chemically.

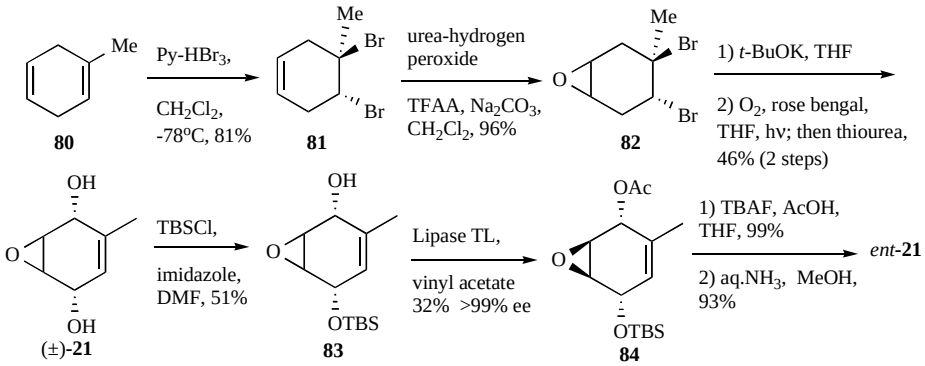
Besides of the use of the chiral diols derived from aromatics, Tachihara and Kitahara reported the preparation of (+)-bromoxone (**5**), (+)-epiepoformin (**2**) and (+)-epiepoxydon (**4**) [88], from a chiral building block enzymatically obtained. The starting material was obtained by an enantioselective reduction with baker´s yeast of the corresponding β-ketoester **72**, as shown in scheme **8**, where the preparation of the key intermediate **79**, an organoselenium compound, is illustrated. Chiral **73** was subjected to hydrolysis and further acetylation yielding **74**. Iodine substitution generated **75**, which upon elimination conditions yielded **76**. Silyl ether formation



Scheme 8.



Scheme 9.



Scheme 10.

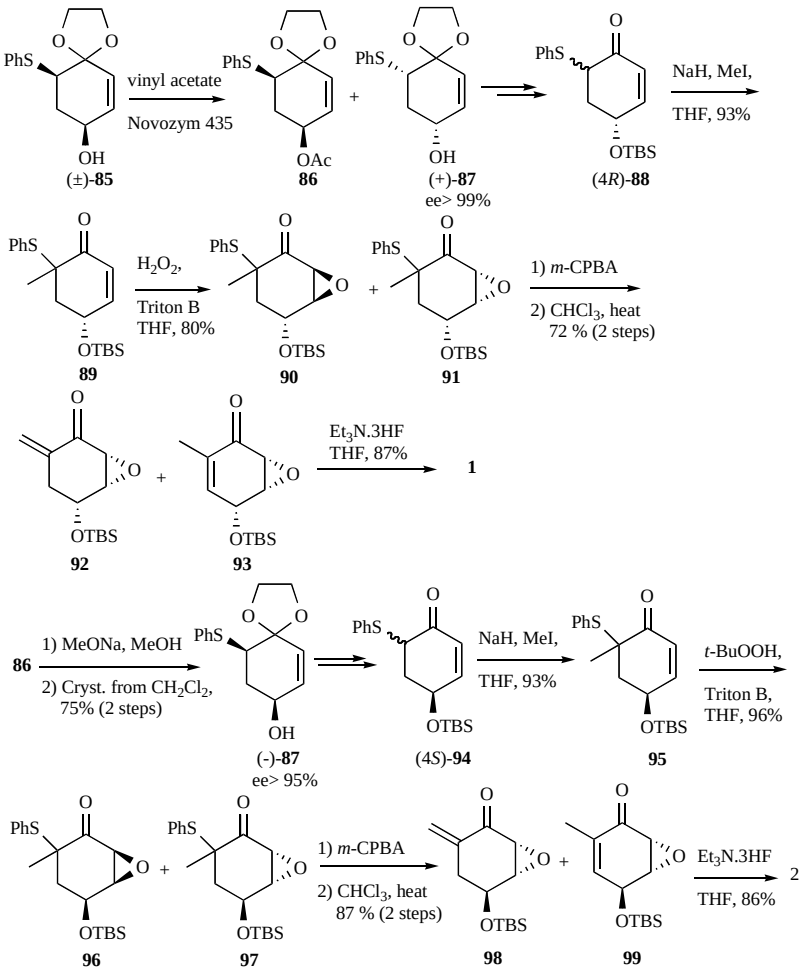
followed by ketal deprotection gave **77**, which upon epoxidation yielded **78**.

α-Selenylation afforded key selenide **79** that was easily converted into the three target natural products, as shown in scheme **9**. (+)-Epiepoxydon (**4**) was prepared by α-selenylcarbanion formation and reaction with formaldehyde, followed by elimination of phenylselenide and deprotection. (+)-Bromoxone (**5**) was prepared by a similar protocol involving an α-bromination, and the strategy to form (+)-epiepoformin (**2**) was achieved through an α-methylation.

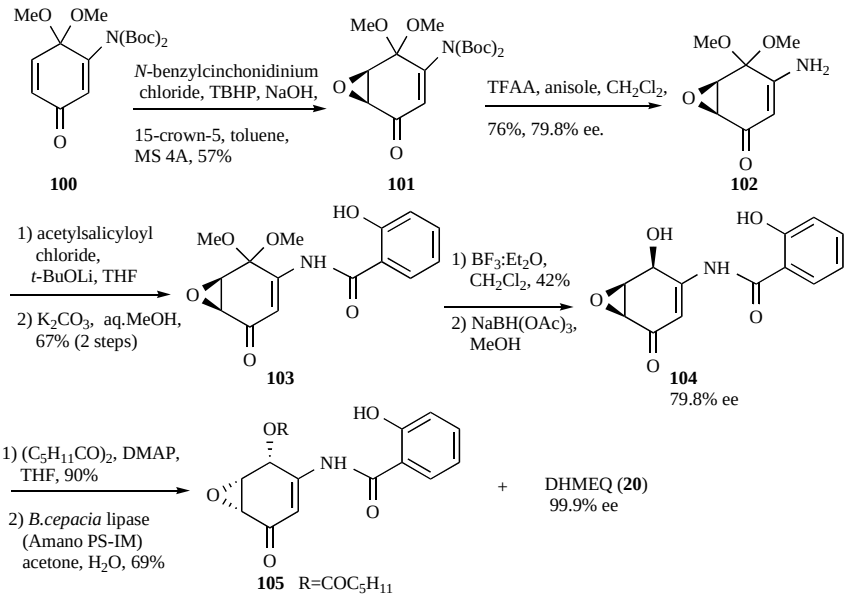
Use of Lipase-Mediated Kinetic Resolutions

Lipases have been widely used in this synthetic field to resolve racemic mixtures. In 2005, the preparation of (+)-theobroxide (*ent*-**21**), a reduced epoxyquinoid molecule, was reported making use of an acetylation with lipase to obtain the enantiomer of the natural product [89]. It consisted in a very concise synthesis starting from dihydrotoluene (**80**), as shown in scheme **10**.

After *trans*-bromination of **80** to form **81**, the epoxide **82** was obtained as a 1.2:1 mixture of diastereomers. Double elimination of bromide, followed by photosensitized oxidation and reduction of the non-isolated endoperoxide yielded the racemic **21**. It was selectively silylated on the less hindered alcohol to give **83** and then the racemic mixture was resolved by means of a lipase, thus obtaining chiral acetate **84**. Removal of the protective groups permitted to achieve the total synthesis of (+)-theobroxide (*ent*-**21**).



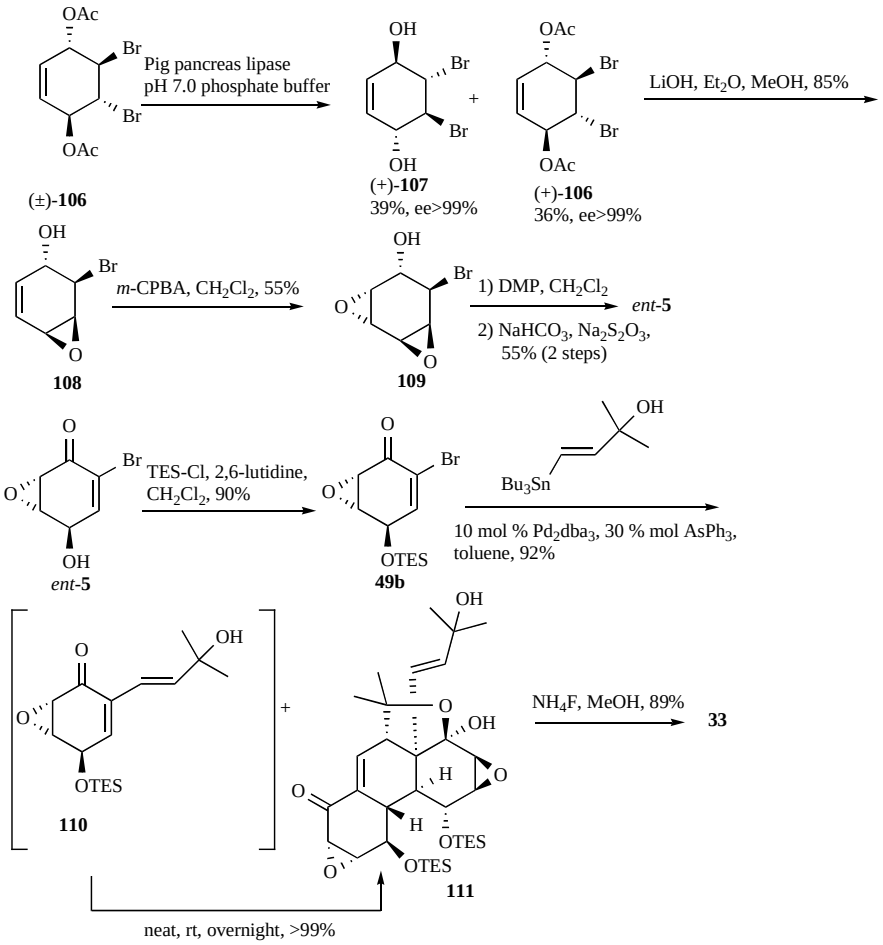
Scheme 11.



Scheme 12.

(+)-Epiepoformin (**2**) and (+)-epoformin (**1**) have been synthesized [90] using chiral hydroxyenones obtained by lipase resolution in a previous work of the authors [91]. As it is shown in scheme **11**, racemic sulfur-functionalized hydroxycyclohexenone **85**, protected as a dioxolane, was resolved with Novozym 435 to yield (+)-**87** with an ee higher than 99%. After protection-deprotection steps, the 4*R* (**88**) and 4*S* (**94**) silylated compounds became the starting materials for (+)-epoformin and (+)-epiepoformin, respectively.

α-Methylation of **88** rendered a mixture of diastereomers (**89**), which subjected to epoxidation conditions yielded the corresponding diastereomeric oxiranes **90** and **91**. The oxidation/pyrolysis process of **91** gave a mixture of endo-and exocyclic olefins (**92** and



Scheme 13.

93) that when treated for removal of the silyl group, were transformed into the corresponding natural product **1**. In a parallel route, compound **86** was deacetylated and crystallized to give (-)-**87**. This product was subjected to a similar protocol, obtaining subsequently ketone **94**, methylated **95**, a mixture of epoxides **96** and **97** and olefins **98** and **99**, to afford **2**.

Lipases have also been used in the synthesis of (-)-DHMEQ (**20**) reported by Hamada *et al.* [92] In this case, the enzymatic resolution was used to improve the ee obtained when preparing the starting material (**102**) by an asymmetric epoxidation of an aminoquinine monoketal (**100**) already described [93] (scheme **12**). In the hands of the authors, the methodology was not reproducible, and the best ee obtained was 79.8%.

Compound **100** was transformed into epoxide **101** and deprotected to furnish **102**. Amide formation led to **103**. Deprotection and reduction generated **104**. This compound was treated with hexanoic anhydride to give a dihexanoate, which upon enzymatic resolution with Amano lipase generated DHMEQ (**20**) and hexanoate **105**. The lipase completely hydrolyzed the enantiomer (2*S*, 3*S*, 4*S*), bearing the absolute configuration of the synthetic target, thus constituting a straightforward route to DHMEQ.

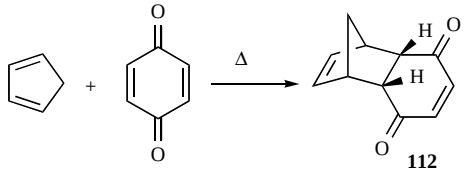
During the revision process of this review, Niitsu *et al.* published a very similar synthetic sequence for DHMEQ [94]. In this case, the authors prepared epoxide **103** in a racemic way, and converted it into a dihexanoate. This diester was resolved again with *B. cepacia* lipase (Amano PS-IM). Further oxidation, deprotection and reduction steps provided (-)-**20** in an enantiomerically pure state.

In 2006, Comméiras *et al.* reported the total synthesis of the dimeric epoxyquinol (+)-panepophenanthrin (**33**) [95]. The authors took advantage of the enzymatic resolution by PPL used in 2000 for the synthesis of (+)-bromoxone [96] by Altenbach´s group. In this case, they chose the other enantiomer of **106** (scheme **13**) for preparing (-)-bromoxone as the precursor for panepophenanthrin.

Enzymatic resolution of racemic **106** generated compounds (+)-**106** and (+)-**107** in optically pure form. Methanolysis of (+)-**106** produced **108** which upon epoxidation yielded **109**. Oxidation followed by epoxide opening and elimination generated *ent*-**5**.

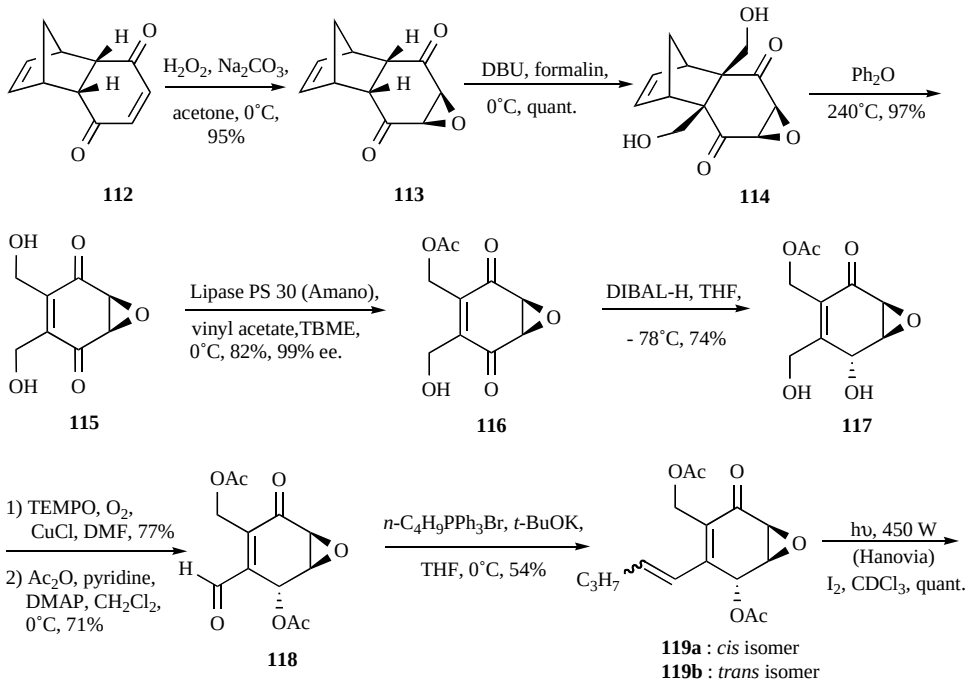
Having prepared (-)-bromoxone, the remaining alcohol was protected to produce **49b** and Stille C-C coupling was performed, to obtain the enantiomerically pure monomer **110**. A biomimetic dimerization proceeded smoothly in an spontaneous way to yield **111**. Deprotection of hydroxyl groups led to the natural dimer **33**.

Mehta and co-workers synthesized a large number of natural products of the epoxyenone family taking advantage of lipase resolutions. Their synthetic strategy starts from the readily available Diels–Alder adduct **112** [97] (scheme **14**) and the key step is the lipase mediated enzymatic desymmetrization of **112** derivatives.

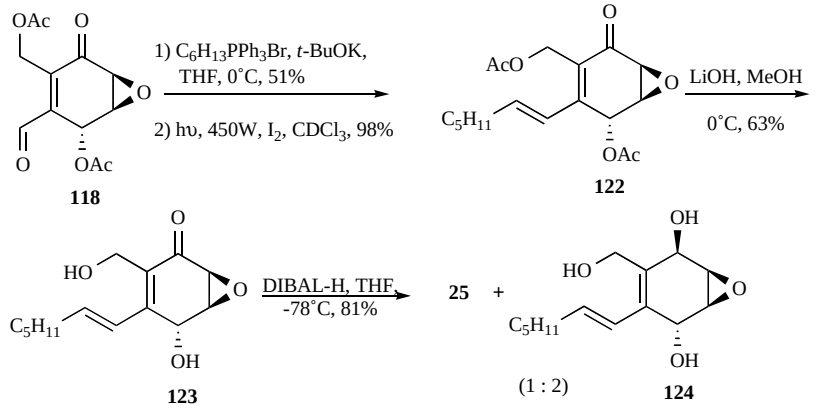


Scheme 14.

In 2004, Mehta and co-workers reported the enantioselective total synthesis of (-)-cycloepoxydon (**16**) [98]. As shown in scheme



Scheme 15.

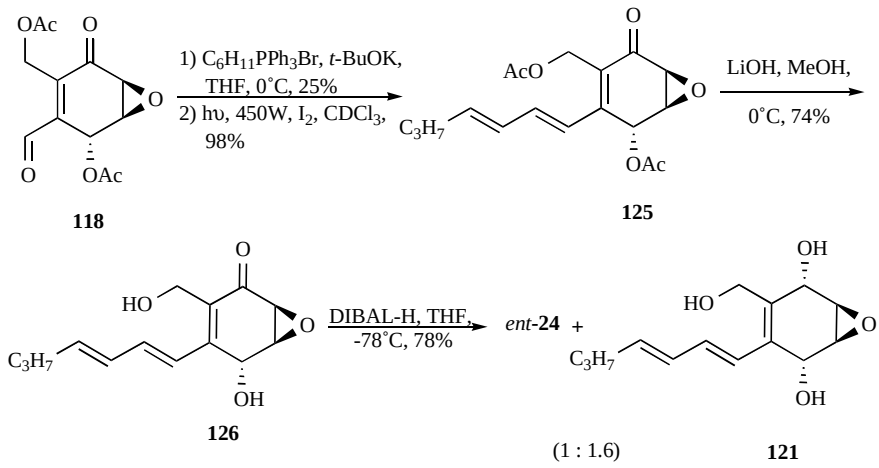


Scheme 16.

15, they synthesized optically active epoxyketone **116** employing lipase-mediated desymmetrization of *meso*-diol **115** which was easily obtained from **112** [99]. Dione **112** was epoxidized to **113**, followed by diformylation to give **114.** Classical retro Diels-Alder reaction of **114** afforded **115** in excellent yield. Both regio- and stereoselective DIBAL-H reduction of **116** furnished **117**. TEMPO-mediated oxidation of the allylic primary hydroxyl and protection of the secondary hydroxyl gave diacetate **118**. The four-carbon side chain was constructed through a Wittig olefination while both isomers, **119a** and **119b** were obtained. Photochemical *cis-trans* isomerization of the disubstituted double bond afforded **119b** quantitatively. Acetate hydrolysis and selective protection of the primary hydroxyl group rendered TBS derivative **120**. Epoxidation of the double bond located at the side chain with *m*-chloroperbenzoic acid occurred stereoselectively. Removal of the protective group furnished (-)-cycloepoxydon (**16)**.

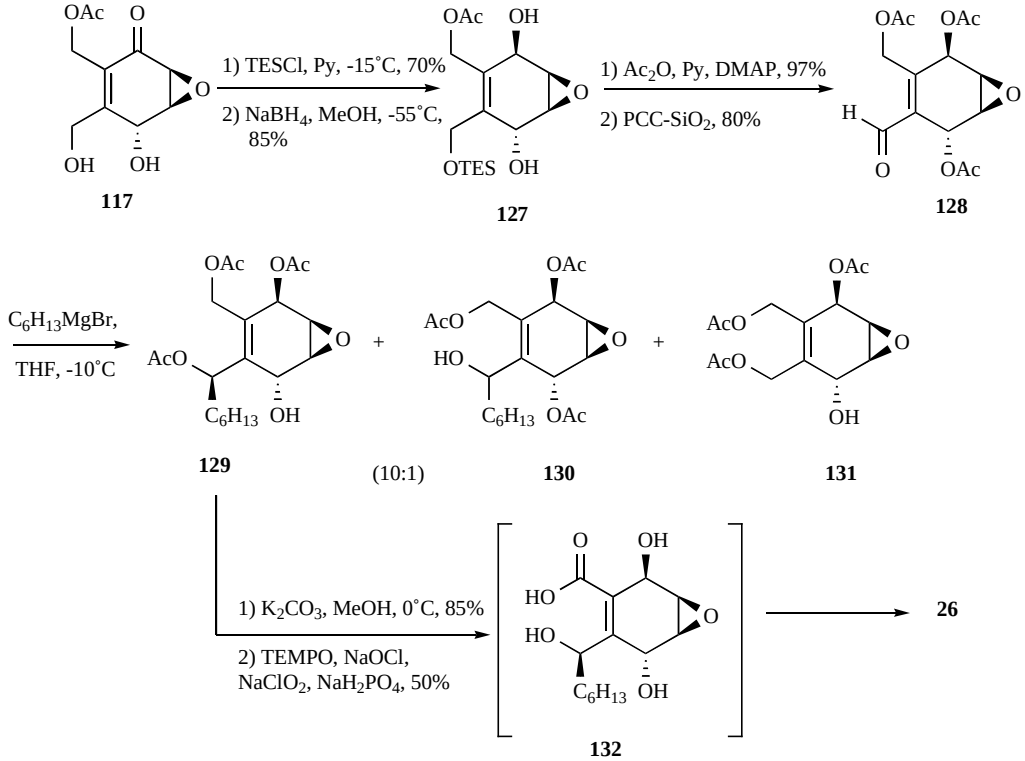
In a previous work, [100] Metha had already prepared chiral epoxide **116** in the same way as shown in scheme **15**. In that case, **116** was used as a key intermediate for the synthesis of (-)-epoxyquinols A and B. This publication was discussed by Shoji in 2007 [64].

For the enantioselective synthesis of (+)-eupenoxide (**25)** and putative "(+)-phomoxide" (**121**), the enantiomerically pure diacetate **118** was chosen as starting material (scheme 16) [54]. The side chain was linked through a Wittig olefination and then a photoisomerization furnished the desired *E*-isomer **122**. Protective group removal gave **123** and further DIBAL-H reduction of the carbonyl group led to a mixture of epimeric alcohols **25 a**nd **124**.



118 **125** **126** **121**

Scheme 17.



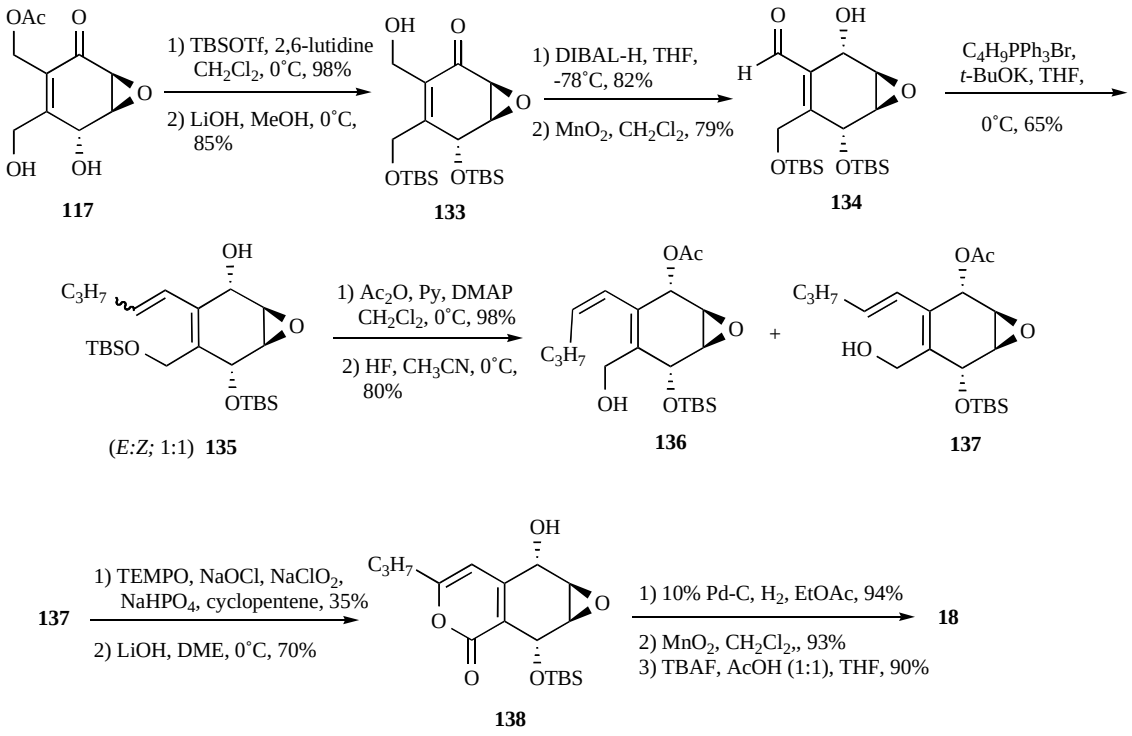
117 **127** **128** **129** **130** **131** **132** **26**

Scheme 18.

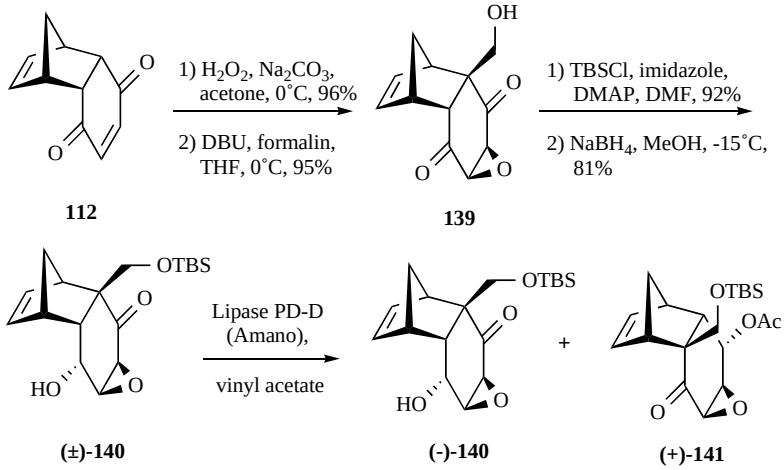
On the other hand, to prepare a structure named as "(+)-phomoxide" (**121**), an analogous strategy using (*E*)-2-hexenyltriphenylphosphonium bromide in the Wittig reaction was employed in order to link the corresponding diene side chain (scheme **17**). Deprotection of diacetate **125** to **126** and DIBAL-H reduction led to a mixture of triols *ent*-**24** and **121** where the major epimer corresponds to the assigned structure for "(+)-phomoxide" (**121)**.

In this paper, the authors suggested the revision of the stereostructures assigned previously by Duke and Rickards [101] in 1984, based on the mismatch of spectral data with the synthesized molecules. A few years later, they published a paper establishing the structure of the natural products eupenoxide and phomoxide [55]. They concluded that (+)-eupenoxide, originally reported by Rickards, has stereostructure **25** while (-)-phomoxide must be revised to **24** (Fig. **2**).

The enantioselective synthesis of the natural product (+)-integrasone (**26**) was accomplished by Mehta in 2005 [102]. As shown in scheme **18**, they used intermediate **117** as starting material, protecting selectively the primary hydroxyl group. Further stereoselective sodium borohydride reduction took place from the opposite face of the epoxide ring furnishing diol **127**. Convenient manipulation led to aldehyde **128** through TES deprotection and oxidation of the primary hydroxyl group. Treatment of aldehyde **128** with hexylmagnesium bromide afforded stereoselectively **129** and **130** (10:1). The triacetate **131** was also obtained through the reduction of aldehyde **128** involving acetate migration. Careful base hydrolysis over the major isomer **129** and selective oxidation of the primary hydroxyl functionality with sodium chlorite catalyzed by TEMPO and bleach was accomplished. This reaction directly furnished integrasone **26** through the concomitant cyclization of the proposed carboxylic acid intermediate **132**.



Scheme 19.



Scheme 20.

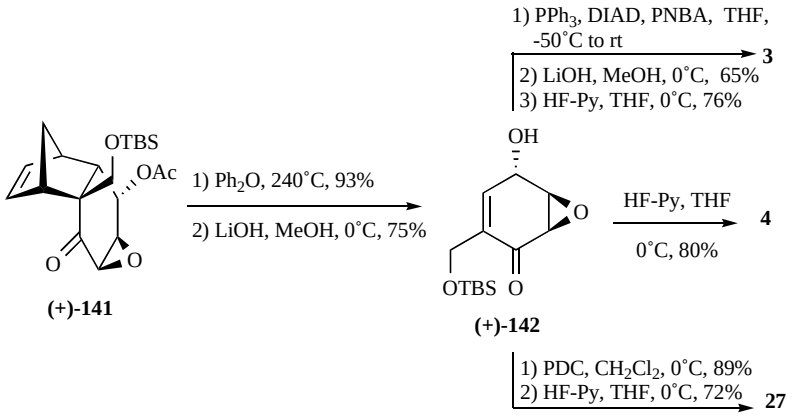
Mehta also described the asymmetric synthesis of the natural product (-)-EI-1941-2 (**18)** starting from intermediate **117** [103]. Protection as di-TBS derivative and acetate hydrolysis led to hydroxyenone **133** which was further reduced and oxidized in the primary hydroxyl group to deliver the α-hydroxyaldehyde **134** (scheme **19**).

Wittig olefination over **134** with the ylide derived from *n*-butyltriphenylphosphonium bromide led to a 1:1 mixture of *E:Z* isomers not amenable to chromatographic separation. Acetylation of **135** and chemoselective deprotection of the primary hydroxyl group afforded the readily separable olefines (*Z*)-**136** and (*E*)-**137**.

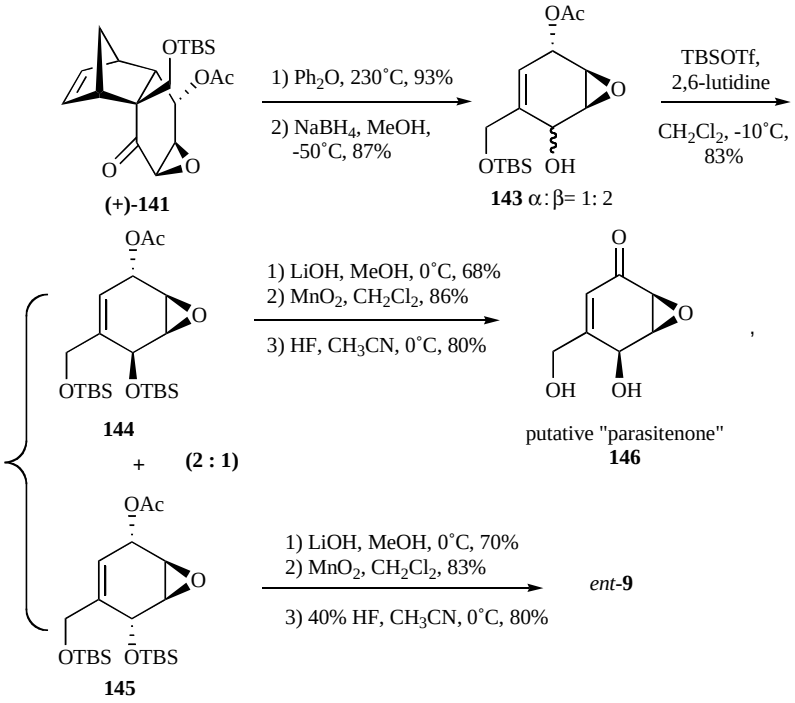
The primary hydroxyl group in *E*-isomer was subjected to oxidation with sodium chlorite in the presence of TEMPO and sodium hypochlorite to deliver lactone **138** after acetate hydrolysis. Although the mecanism of formation of the lactone is not clear, the authors suggested an oxidative 6π-electrocyclization. Partial catalytic hydrogenation over **138** proceeded stereoselectively from the β face. Oxidation and silyl ether cleavage delivered (-)-EI-1941-2 (**18**) in good yield.

Epoxydon (**3**), epiepoxydon (**4**), and phyllostine (**27**) were synthesized by Mehta and co-workers in 2004 [104]. The key reaction was the desymmetrization of **140** through enzymatic resolution using lipase PD-D (Amano) (scheme **20**). Precursor **139** was obtained by epoxidation and hydroxymethylation of **112** in excellent yield. Further protection of the primary hydroxyl group and stereoselective reduction of the carbonyl moiety furnished **140** as a racemic mixture. Enantiomerically pure (-)-**140** and (+)-**141** served as starting materials for the enantioselective preparation of the desired compounds.

As depicted in scheme **21**, retro Diels-Alder reaction and removal of the acetate over (+)-**141** furnished epoxyenone (+)-**142** which after complete deprotection rendered (+)-epiepoxydon (**4**). Inversion of the configuration at C4 on **(+)-142** using Mitsunobu´s protocol and posterior removal of the silyl group furnished (+)-



Scheme 21.



Scheme 22.

epoxydon (**3**). Oxidation of the hydroxyl functionality in (+)-**142** and removal of the protective group led to (-)-phyllostine (**27**).

In 2005 Mehta reported the preparation of *ent*-RKTS-33 (*ent*-**9**) and a putative structure of natural product "parasitenone" [105]. In this letter they used enantiomerically pure (+)-**141** as starting material. Retro Diels-Alder reaction and further reduction, led to a epimeric mixture **143**. Protection of the secondary hydroxyl group afforded a separable mixture of **144** and **145**. As shown in scheme **22**, convenient manipulation of **145** furnished enantiomerically pure *ent*-RKTS-33 (*ent*-**9**). In a similar strategy, manipulation of **144** gave enone-diol **146** corresponding to the structure previously assigned to the natural product "parasitenone". However, the spectral data of this compound and those reported by Son *et al.* [106] were different. Through a critical examination of the spectral data reported for "parasitenone" the authors determined that the natural product isolated from *Aspergillus parasiticus* was already known epoxydon (**3**) instead of a new one called "parasitenone".

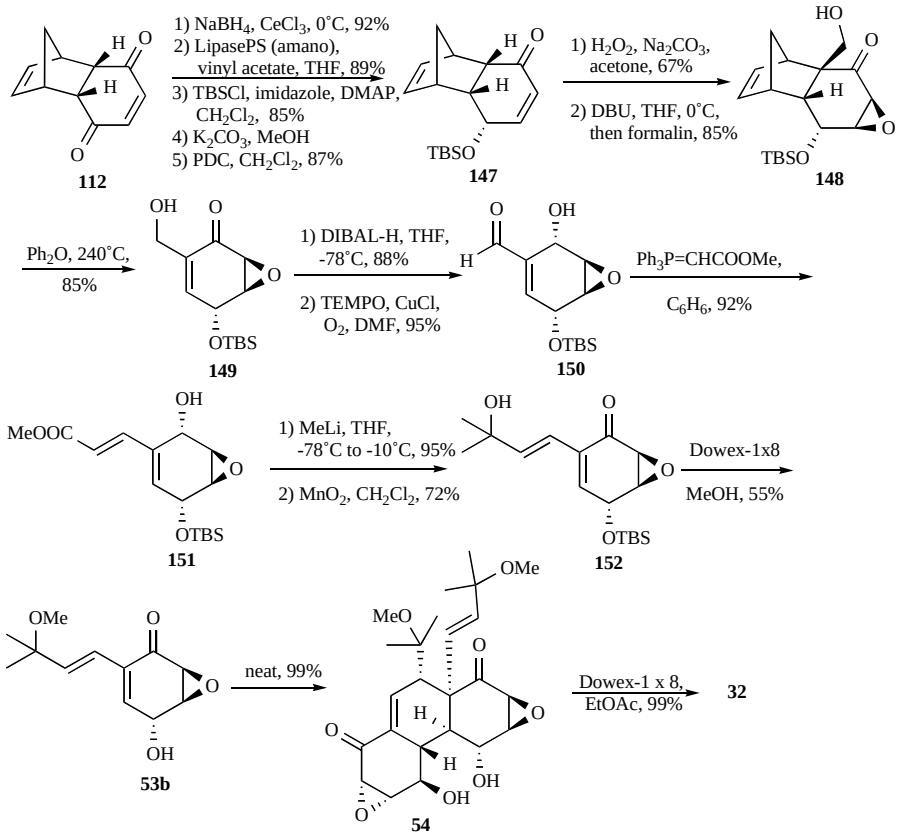
In 2008 Mehta accomplished the enantioselective synthesis of natural (+)-hexacyclinol (**32)** (scheme **23**) [107]. Using adduct **112** as starting material, they obtained enantiomerically pure **147** based on a previously reported protocol [108]. Compound **147** was further converted to epoxide **148** and epoxyenone **149** following reported procedures, which involved epoxidation, hydroxymethylation and retro Diels-Alder reaction [109]. Stereoselective DIBAL-H reduction and further oxidation of the primary hydroxyl group furnished epoxyaldehyde **150**. Wittig olefination rendered (*E*)-α,β-unsaturated ester **151** in high yield. Addition of methyl lithium afforded tertiary alcohol and they obtained dienone **152** after oxidation of allylic *sec*-hydroxyl group. Exposure of **152** to Dowex-1 resin in methanol led to **53b** through a concomitant methylation and desilylation reaction. Through a stereospecific intermolecular Diels-Alder reaction **53b** was converted into the dimer **54**.

A second exposure to Dowex-1 resin triggered the S_N2' displacement/cyclization in **54** to furnish exclusively the natural product (+)-hexacyclinol **32**.

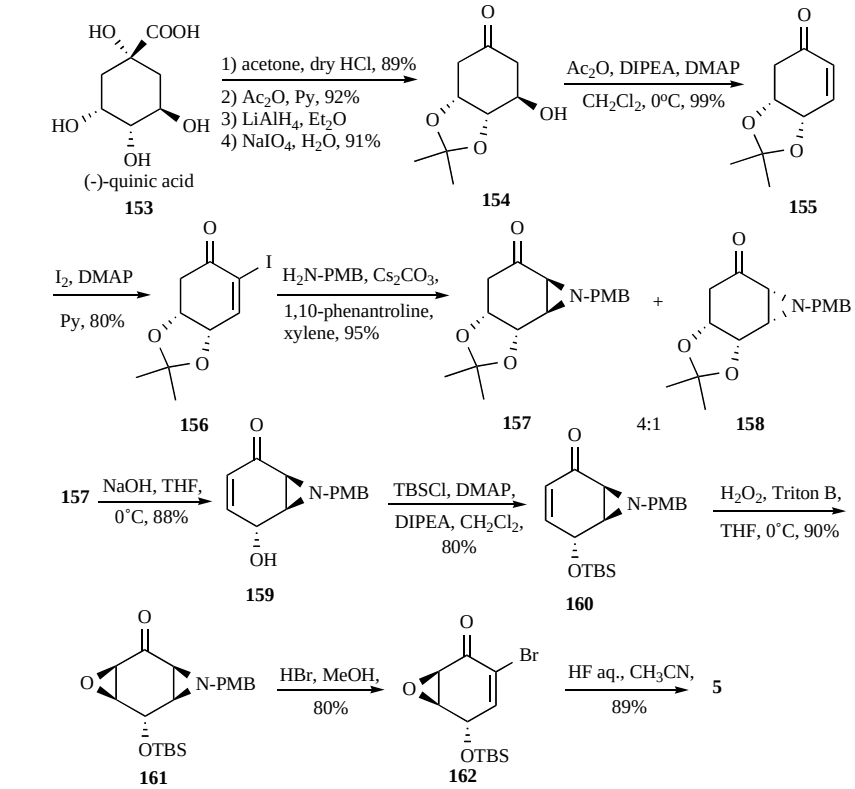
Non-enzymatic Methods

Maycock´s synthesis of (+)-bromoxone

Maycock´s group prepared (+)-bromoxone (**5**) in a short and efficient synthesis, using a natural compound of the chiral pool as the

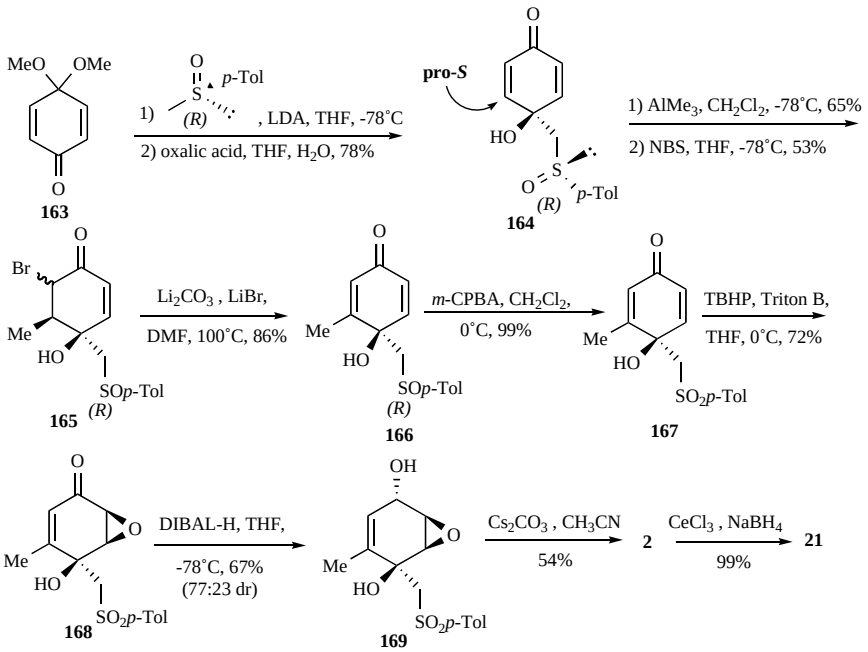


Scheme 23.



Scheme 24.

source of chirality [110]. The methodology involved the use of an aziridine as protective and directing group in the cyclohexenone core (scheme **24**). (-)-Quinic acid (**153**) was transformed to **155** through alcohol **154** as already reported for the synthesis of (+)-eutypoxide by the same authors [111]. α-Iodination of this compound delivered **156**, which was subjected to an aziridination with 4-methoxybenzylamine through a Michael addition cyclization. The presence of an adjacent asymmetric center induced the stereoselec-



Scheme 25.

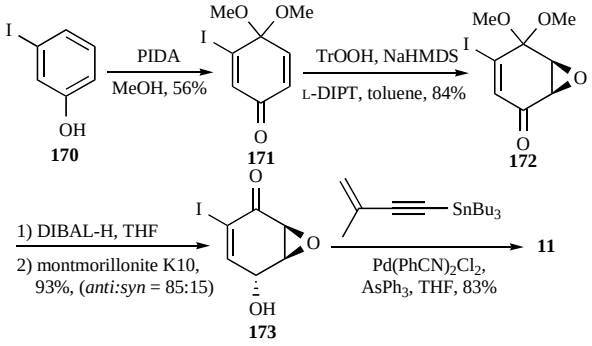
tivity in the formation of **157** in favor to **158** (*anti:syn*, 4:1). Elimination of **157** afforded **159**, which was protected to yield compound **160**. The aziridine group showed a directing ability for the epoxidation of the double bond, delivering **161** exclusively. Hydrobromic acid treatment to eliminate the aziridine moiety afforded **162**, which was deprotected to give (+)-bromoxone (**5**).

Carreño's Methodology

In Carreño's synthesis of (+)-epiepoformin (**2**) and (-)-theobroxide (**21**) [112,113] the key step involved a stereocontrolled conjugated addition of trimethylaluminium to a chiral sulfoxide-*p*-quinol [114] in order to introduce the required asymmetry (scheme **25**). *p*-Benzoquinone dimethylmonoacetal (**163**) reacted with the lithium anion of (*R*)-methyl-*p*-tolylsulfoxide, and then was subjected to hydrolysis of the acetal to afford sulfoxide **164**. Diastereo- and regioselective addition of $AlMe_3$ occurred at the pro-*S* conjugated position, on the same face of the hydroxyl group. Trapping the enolate intermediate with NBS furnished α-bromoketone **165**. HBr elimination with lithium salts afforded **166**, which was oxidized to sulfone **167** with *m*-CPBA. Epoxidation with TBHP led to **168** as a unique diastereomer. Reduction of the carbonyl group with DIBAL-H furnished a 77:23 mixture of diastereomers which were isolated after flash chromatography to afford **169** as the major compound. Elimination of methyl *p*-tolylsulfone allowed the preparation of natural product (+)-epiepoformin (**2**) with 96% ee. Luche´s reduction of this natural compound afforded (-)-theobroxide (**21**) almost quantitatively. An advanced precursor of (+)-harveynone (**11**) was also synthesized through this methodology [112], but the isolation of the natural product was not possible due to enone instability under the basic conditions required to eliminate the β-hydroxysulfone. This constitutes a limitation of the use of the β-hydroxysulfoxide group.

Taylor's Synthesis of (-)-harveynone (11)

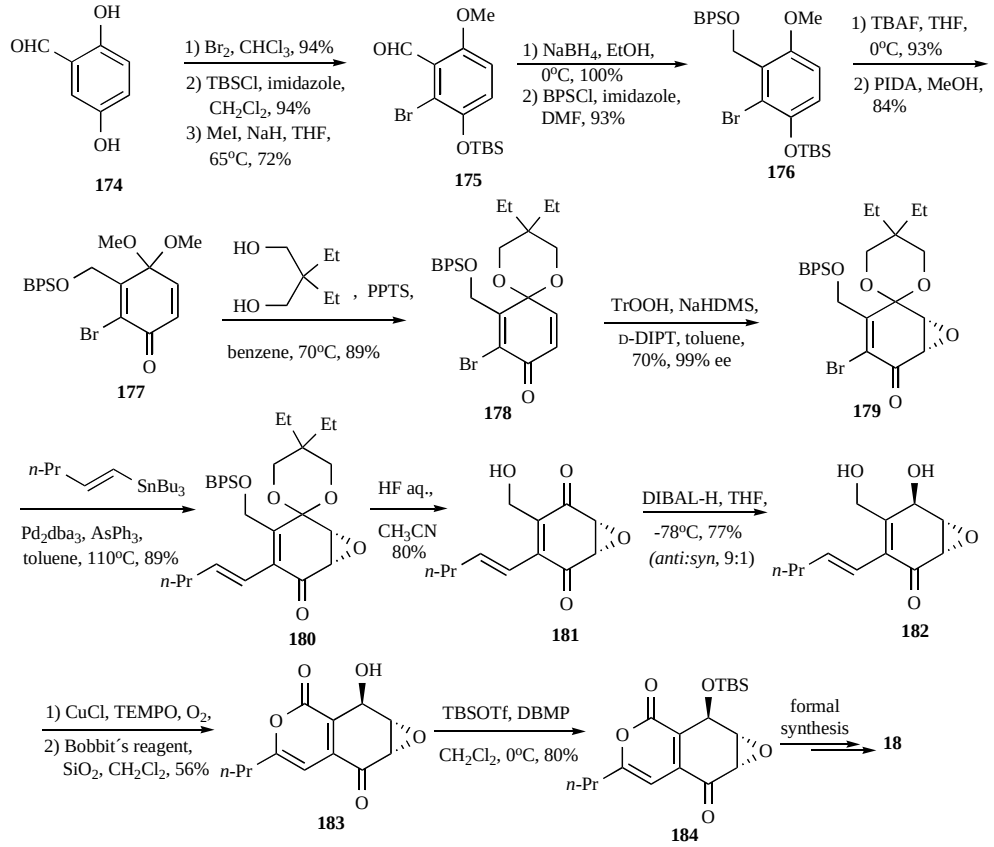
Taylor's synthesis of (-)-harveynone (**11**) [115] (scheme **26**) started with a double oxidation of 3-iodophenol (**170**) with an hypervalent iodine reagent (PIDA) to afford ketal **171**. Epoxide **172** was obtained through a tartrate-mediated asymmetric epoxidation methodology developed by Porco *et al.* [116], which was extensively used by the authors. Porco postulated that NaHMDS and L-DIPT build a cavity that blocks one face of the quinone monoketal, thus allowing the epoxidation through the opposite side. In this synthesis, asymmetric epoxidation afforded **172** in high yield with a 93:7 enantiomeric ratio. Stereoselective reduction with DIBAL-H, followed by montmorillonite K10 deprotection afforded **173** in an 85:15 *anti:syn* ratio. Finally, Stille cross-coupling reaction with the appropriate alkynylstannane delivered (-)-harveynone (**11**) in a short and efficient route.



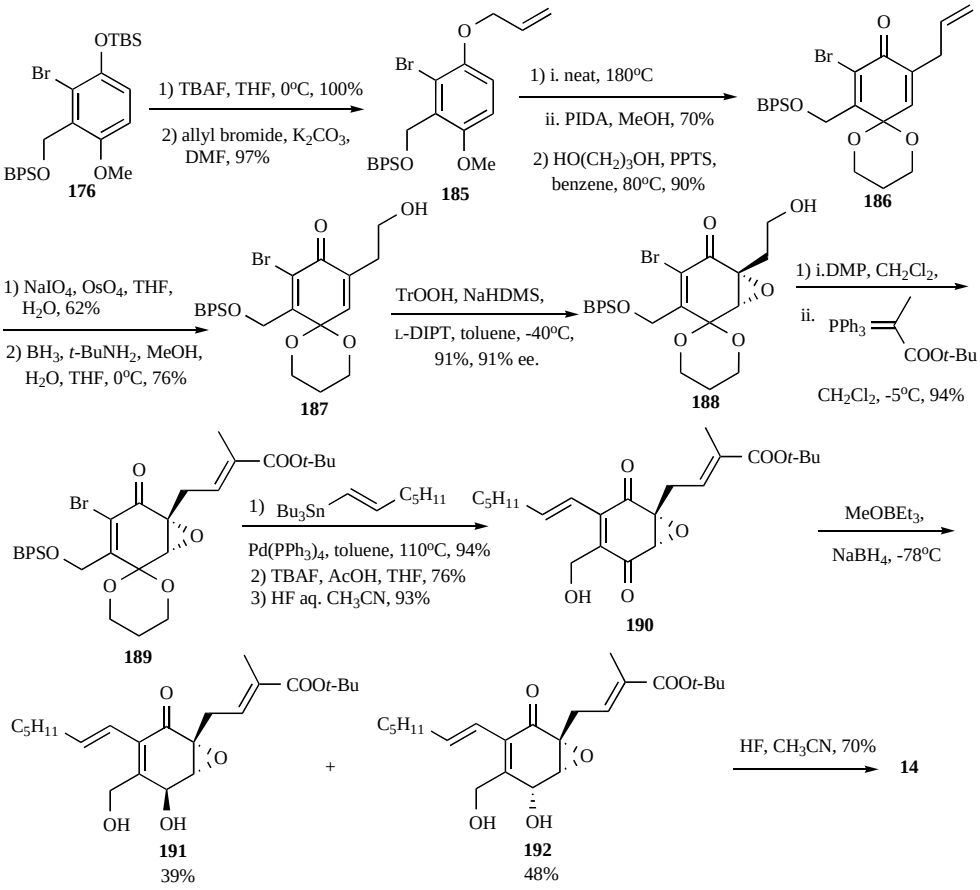
Scheme 26.

Porco's Methodology

Porco's synthesis of (-)-EI-1941-2 (**18**) [117] employed quinone **178** prepared from aromatic compound **174** as previously reported [116,118]. Aromatic compound **174** was (scheme **27**) brominated and selectively protected to yield **175**. Reduction of the aldehyde and protection of the formed alcohol afforded **176**. Desilylation and oxidation gave **177** that when transacetalized, permitted to obtain quinone **178**. In this strategy, a tartrate-mediated nucleophilic epoxidation is used again for the asymmetric construction of the natural product. Compound **178** reacted with tritylhydroperoxide in the presence of NaHDMS and D-DIPT to furnish **179** in a 99% ee. Stille cross-coupling for the insertion of the alkenyl side chain afforded **180**, which upon hydrolysis delivered epoxyquinone **181**. Stereoselective reduction furnished **182** (*anti:syn*, 9:1). Oxidation with CuCl/TEMPO/O_2 followed by reaction with Bobbit's reagent allowed the preparation of **183**. Protection of this compound as silyl ether afforded **184**, which was previously reported by Shoji and Mehta[103,119], thus consisting in a formal synthesis of (-)-EI-1941-2 (**18**).



Scheme 27.

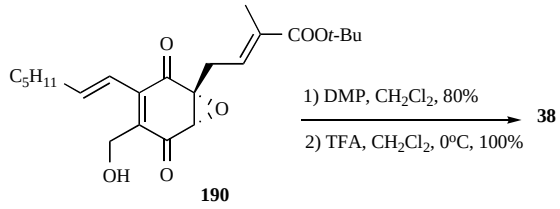


Scheme 28.

Porco's group also completed the first enantioselective synthesis of (+)-ambuic acid (**14**) and its related dimer (+)-torreyanic acid (**38**), confirming their absolute stereochemistry [120]. By using a similar strategy as shown above, ambuic acid synthesis (scheme **28**) started with a selective deprotection and allylation of compound **176** to afford **185**.

Upon Claisen rearrangement at high temperatures compound **185** was transformed to an *ortho*-allylphenol, which was oxidized to quinone and then protected to afford **186**. Oxidative cleavage and further reduction allowed the formation of **187**, which upon nucleophilic epoxidation afforded **188** with excellent yield and 91% ee. Evidence showed that homoallylic alcohol directed the stereochemistry of the epoxidation. Oxidation of this alcohol followed by Wittig reaction allowed the side chain insertion leading to **189**. Stille cross-coupling permitted the insertion of the remaining side chain and further deprotection steps led to key compound **190**. By reduction, a diastereomeric mixture of **191** and **192** was formed (*syn: anti*, 1.2: 1). After separation, the major compound **192** was deprotected furnishing **(+)-**ambuic acid (**14**).

(+)-Torreyanic acid (**38**) was prepared from compound **190** (scheme **29**) by oxidation with Dess-Martin periodinane followed by deprotection, through an oxidative dimerization cascade.



Scheme 29.

Porco and co-workers also prepared by the same strategy ECH (**8**), epoxyquinols A (**28**) and B (**29**), and epoxytwinol A (**31**). [121,122] As shown in scheme **30**, compound **178** was subjected to a tartrate-mediated asymmetric epoxidation to yield epoxide *ent*-**179** with 96% ee. Stille reaction allowed the alkenyl side chain insertion affording **193**. Deprotection followed by stereoselective reduction delivered the monomeric precursor ECH in a high diastereomeric ratio (18:1). Oxidation of hydroxymethyl alcohol allowed the dimerization cascade to afford epoxyquinol A, B and epoxytwinol A, with a solvent dependent ratio.

These authors also reported the synthesis of epoxytwinol A (**31**), from monomeric ECH (**8**), conducted through the formation of an alkoxysilanol to promote a formal [4+4] dimerization [123].

(+)-Hexacyclinol (**32**) was prepared by Porco's group [124], bringing light to the debate of the previous mis-assigned structure of this natural product. Gräfe and co-workers isolated (+)-hexacyclinol from a siberian fungus and proposed the structure shown in figure **5**, containing an epoxyketone and a highly strained

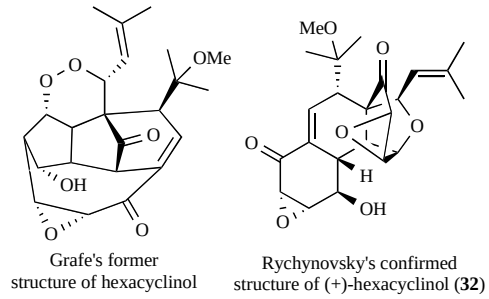


Fig. (5). Former and confirmed structure of (+)-hexacyclinol.

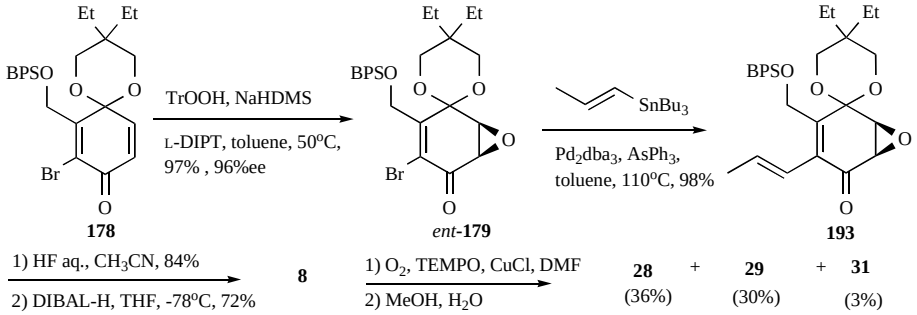
endoperoxide moiety [66]. La Clair's synthesis of this proposed structure [125] gave rise to an academic debate known as the "hexacyclinol dispute'' [69]. Therefore, Rychnovsky proposed an alternative structure [67] (Fig. **5**) based on ^{13}C-NMR chemical shifts calculations. Porco and co-workers reported the first total synthesis of the revised structure of (+)-hexacyclinol along with the unambiguous confirmation of the proposed reassignment for this compound (Scheme **31**) [124].

Porco's synthesis of compound **197** has been previously described by this group for the synthesis of panepophenanthrin (**33**) [126]. It involved an asymmetric epoxidation of **194** that yielded **195** in 95% ee., which by reduction afforded **196**. Mitsunobu inversion produced compound **197**, which was deprotected with montmorillonite to deliver natural product (+)-bromoxone (**5**). Then it was protected as silyl ether **198** followed by Stille reaction to insert the alkenylic side chain to afford **199**. Deprotection and further standing at room temperature allowed the preparation of **"**prehexacyclinol'' (**54**) by a highly diastereoselective Diels-Alder dimerization of the epoxyquinol monomer. S_N2' substitution-cyclization was performed with montmorillonite affording (+)-hexacyclinol (**32**).

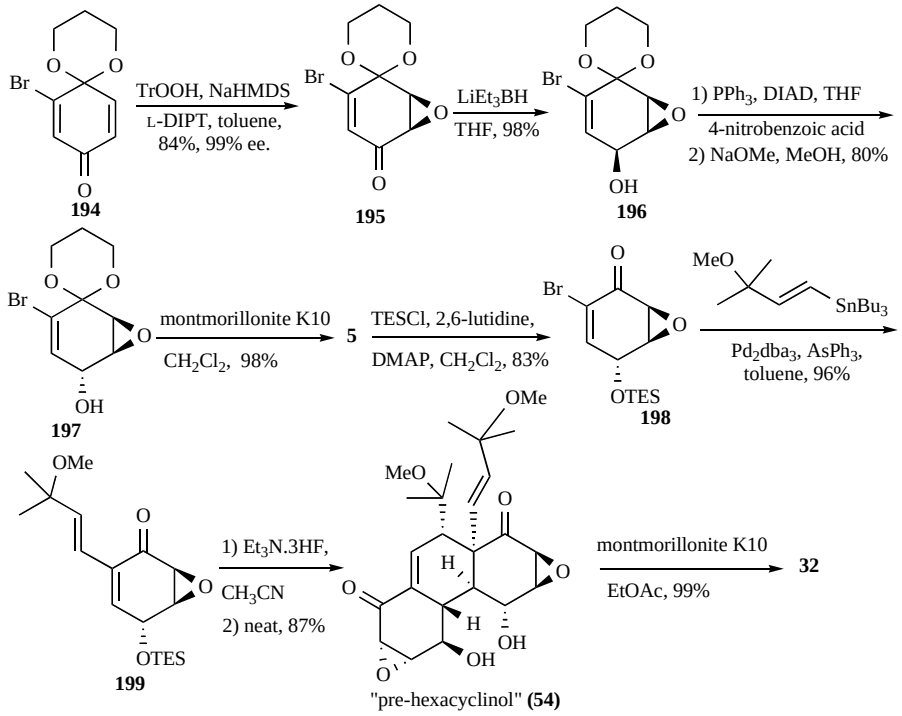
Porco's group also completed the synthesis of the spiroisoxazoline natural product (+)-calafianin (**37**) by using an asymmetric nucleophilic epoxidation and a zirconium-mediated nitrile oxide cycloaddition as the key steps (scheme **32**) [127]. Compound **194** was prepared according to their previously described protocols [126] which upon epoxidation led to *ent*-**195**. Methylenation of epoxyketone afforded **200**. 1,3-Dipolar cycloaddition of vinyl epoxide with Zr(IV) alkoxide allowed spiroisoxazolidine **201** construction in a 1.8:1 dr, favoring the *anti* compound. Diamide **202** was constructed by reaction of **201** and 1,4-diaminobutane with 2-hydroxypyridine as an activator along with Zr(O-*t*-Bu)$_4$ and Zn(OTf)$_2$. Acetal deprotection in aqueous HF completed the synthesis of (+)-calafianin (**37**). Porco and co-workers completed the synthesis of all four stereoisomers of this compound, therefore confirming the stereochemical assignment for the natural product.

Shoji's Methodology

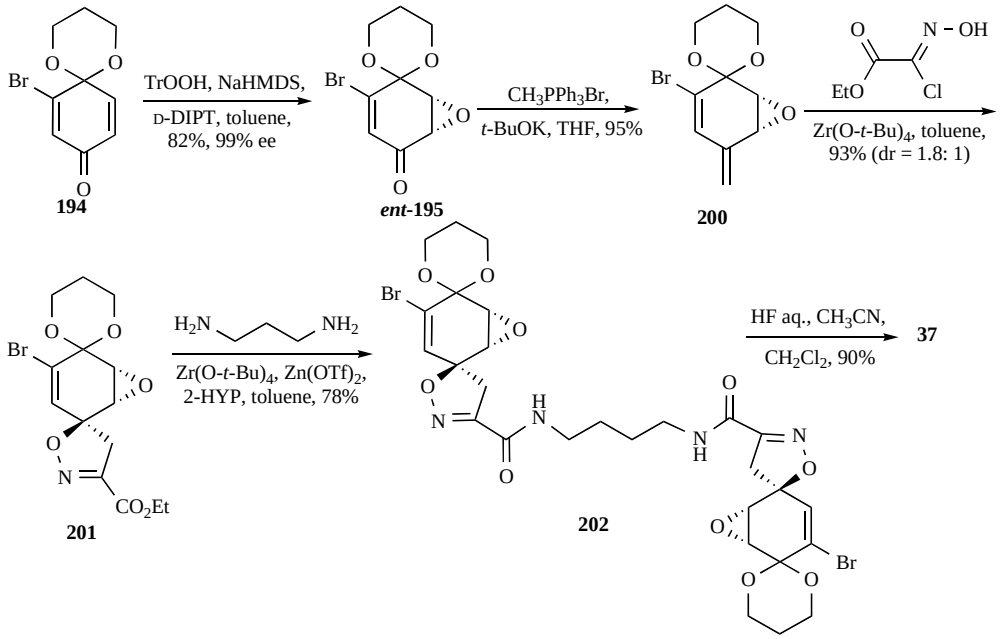
Shoji's first generation syntheses of ECH (**8**) and epoxyquinols A (**28**) and B (**29**), employed a hafnium-mediated diastereoselective



Scheme 30.

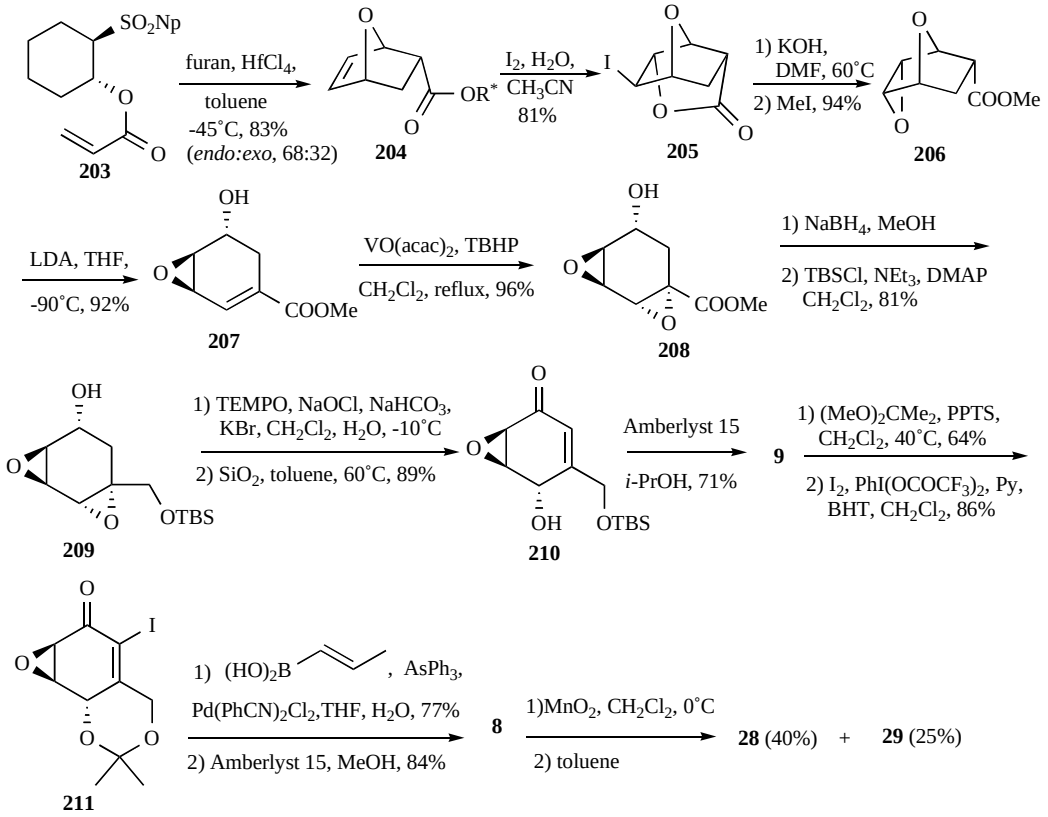


Scheme 31.

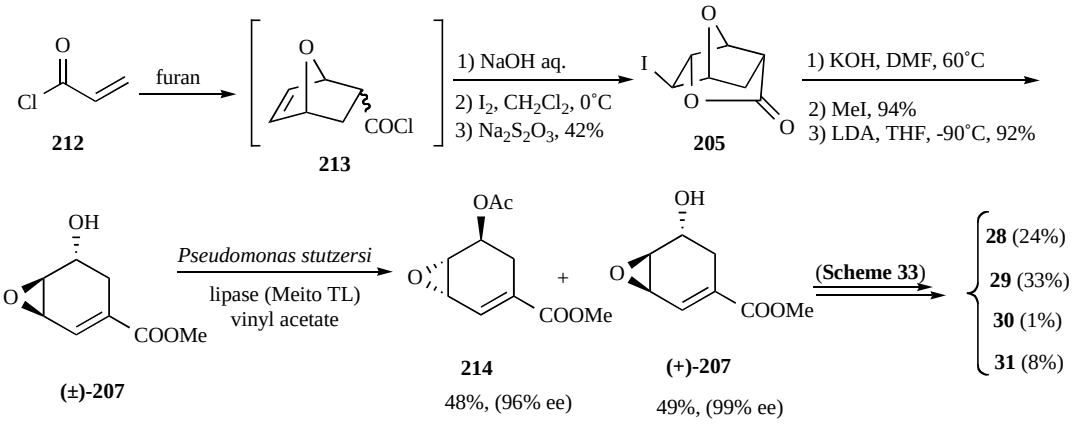


Scheme 32.

Diels-Alder reaction in the presence of a chiral auxiliary to generate the required asymmetry (scheme **33**) [128-130]. Diels-Alder reaction between furan and chiral acrylate **203**, derived from Corey's chiral auxiliary, in the presence of $HfCl_4$ at low temperature, preferentially yielded the *endo* adduct **204** with high diastereoselectivity. Iodolactonization of this compound allowed the recovery of the chiral auxiliary and recrystalization afforded **205** with 99% ee. Lactone hydrolysis permitted epoxide formation by nucleophillic displacement and further esterification gave epoxymethylester **206**. β-Elimination rendered **207**, and then Sharpless epoxidation produced **208** as a single isomer. Reduction and protection delivered **209**, which upon oxidation and SiO_2 treatment, underwent elimination with oxirane opening to construct the enone moiety. Deprotection of **210** allowed the synthesis of the ECH analog, RKTS-33 (**9**). Protection followed by α-iodination afforded **211**. Suzuki cross-coupling with 1-propenylborate followed by deprotection gave the monomeric ECH (**8**), which upon oxidation of the hydroxymethyl chain triggered the biomimetic cascade involving a 6π-electrocyclization and Diels-Alder dimerization [130] to form epoxyquinols A (**28**) and B (**29**). The authors also described the preparation of several ECH analogues with different side chain motifs, by variation of the cross-coupling partners at the Suzuki reaction step [17]. Evaluation of biological properties and structure-activity relationship of these ECH-related molecules, defined as



Scheme 33.

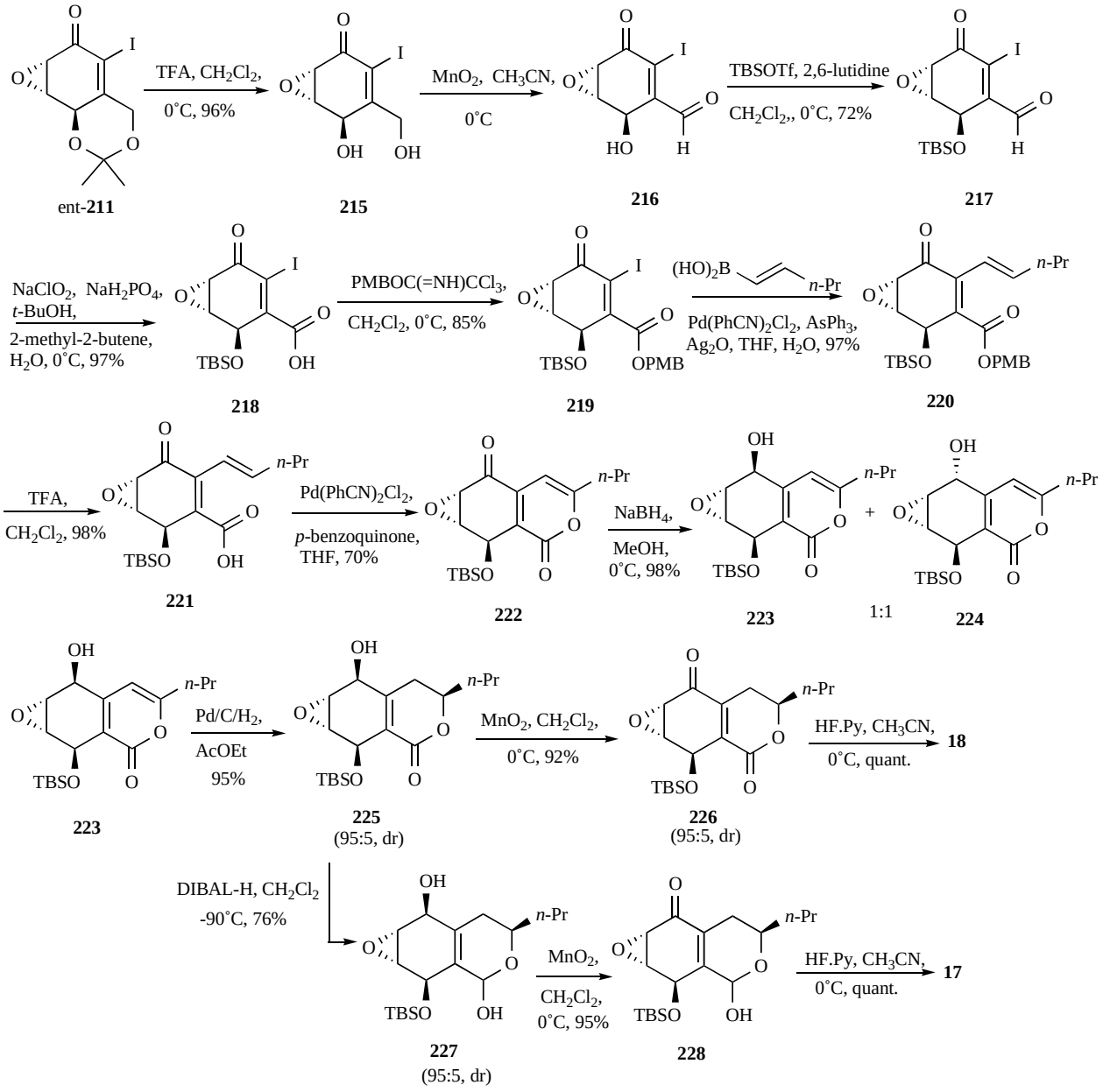


Scheme 34.

RKTS, showed that RKTS-33 (**9**) and RKTS-34 (**10**) proved to be more effective than ECH towards Fas-mediated apoptosis.

In Shoji's second generation synthesis of these compounds, the authors included a chromatography-free preparation of iodolactone **205** and the introduction of chirality was achieved by a lipase-mediated kinetic resolution of cyclohexenol **207** (scheme **34**) [65,129,131,132]. Diels-Alder reaction between furan and acryloyl chloride (**212**) furnished **213**, which upon hydrolysis and iodolactonization afforded compound **205**, pure enough to be used in the next reaction. Lactone hydrolysis with epoxidation, followed by esterification and β-elimination were performed with high yields. Racemic **207** was subjected to kinetic resolution with Meito TL lipase, which proceeded with high efficiency affording **(+)-207** in 99% ee, and its corresponding acetate antipode **214**. Enantiomerically pure (+)-**207** was then transformed into ECH (**8**) and epoxyquinols following their previous synthetic sequences shown in scheme **33**. This second generation synthesis, suitable for large-scale preparations, allowed in this case the formation of the minor products epoxyquinol C (**30**) and epoxytwinol A (**31**) along with the previously synthesized natural products.

Shoji´s group also completed the first asymmetric synthesis of EI-1941-1 (**17**) and EI-1941-2 (**18**), featuring an intramolecular carboxypalladation via a 6 π -endo cyclization mode followed by β-hydride elimination (scheme **35**) [119]. Compound *ent*-**211** was readily synthesized from **205** (see scheme **33**) [132]. Cleavage of the acetonide afforded **215**, which upon selective oxidation of the primary alcohol gave **216.** Protection of the secondary alcohol generated **217** and oxidation under Kraus´s conditions yielded **218**, which was protected as it *p*-methoxybenzyl ester **219**. Introduction of a side chain by Suzuki coupling produced **220**. Acid treatment afforded **221**, which was subjected to intramolecular cyclization through carboxypalladation and β-hydride elimination to afford



Scheme 35.

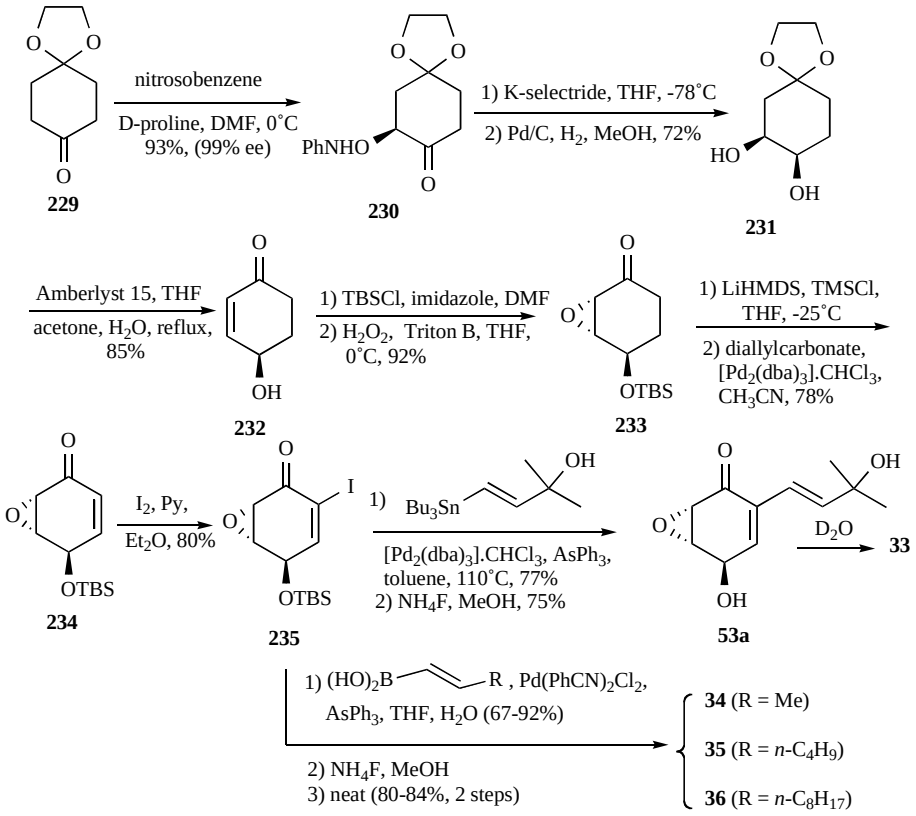
222. Reduction of the carbonyl generated **223** and **224** which were separated by column chromatography. Hydrogenation of **223** proceeded stereoselectively, affording **225** with high diastereoselectivity. Oxidation and deprotection of this compound allowed the preparation of EI-1942-2 (**18**). Reduction of compound **225**, followed by oxidation and deprotection completed the synthesis of EI-1941-1 (**17**). The authors also completed the synthesis of EI-1941-2 *non*-natural stereoisomers through similar strategies [133].

This group also completed the synthesis of (+)-panepophenanthrin (**33**) and analogues, through a catalytic asymmetric α-aminoxylation followed by several diastereoselective Diels-Alder reactions, including a biomimetic Diels-Alder reaction in water (scheme **36**) [134]. α-Aminoxylation of 1,4-cyclohexanedione monoethylene ketal **229** with nitrosobenzene and D-proline afforded **230** with excellent ee. Regioselective reduction followed by reductive cleavage produced **231**. Removal of acetal and dehydration afforded **232**. Formation of silyl ether and epoxidation yielded **233**. Double bond formation generated epoxyenone **234**. α-Iodination led to **235** and further Stille side chain insertion and deprotection afforded monomer **53a**. Diels-Alder dimerization in deuterium oxide produced **(+)**-panepophenanthrin (**33**).

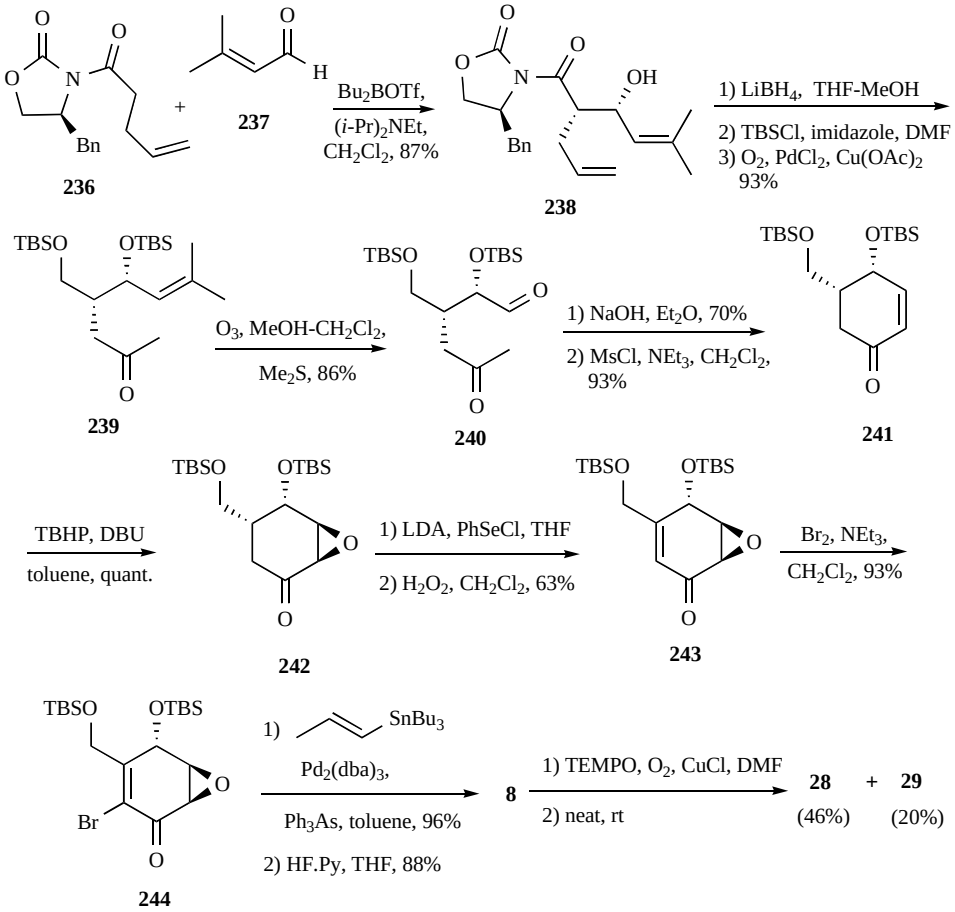
The authors also reported the Suzuki reaction of **235** with different cross-coupling partner followed by deprotection and dimerization allowing the preparation of panepophenanthrin analogues RKTS-80 (**35**), -81 (**36**) and -82 (**37**)**,** along with the study of their biological properties.

Kuwahara's Synthesis of Epoxyquinols A and B

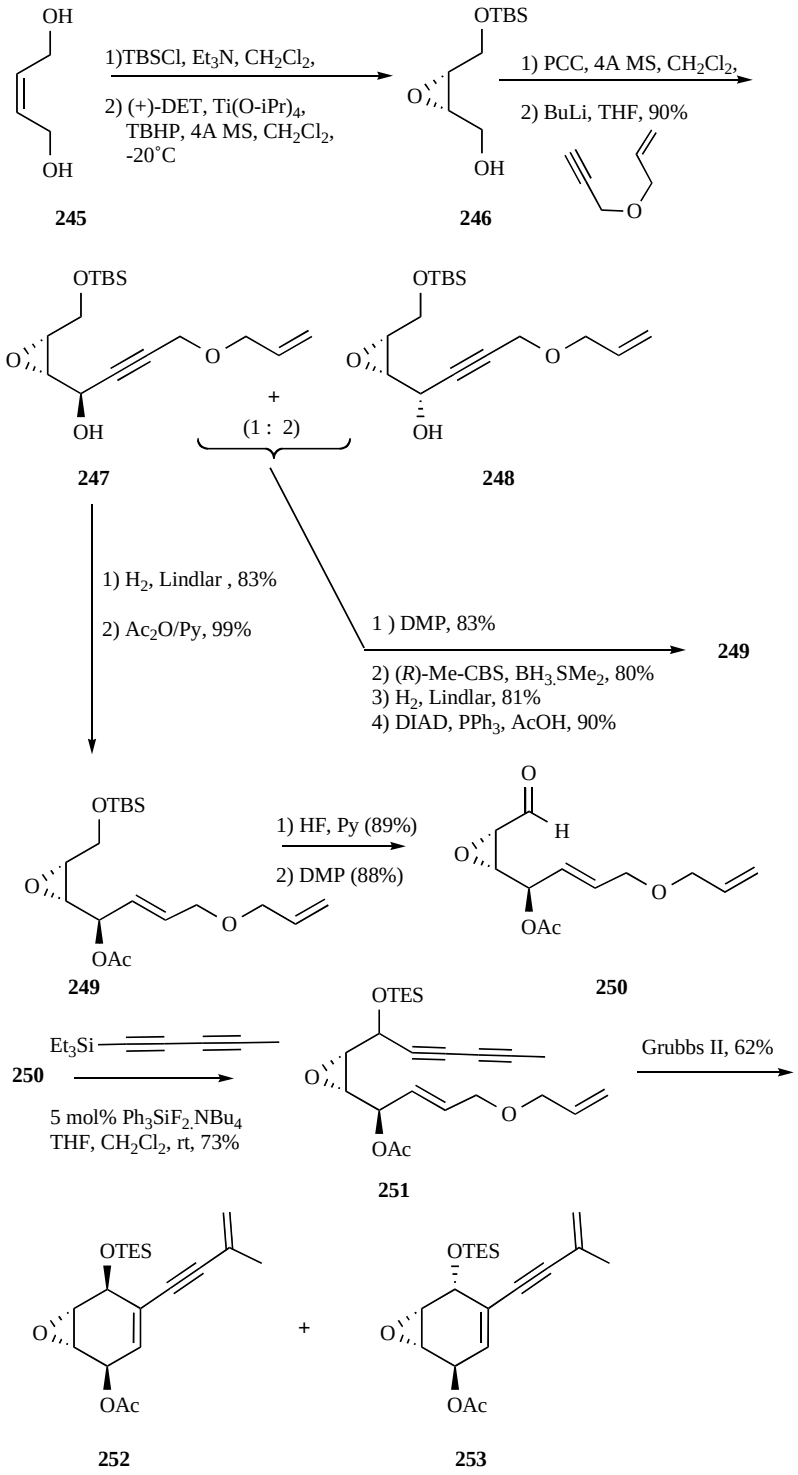
Kuwahara *et al*. prepared epoxyquinols A (**28**) and B (**29**) through an Evans asymmetric aldol reaction as the key step (scheme **37**) [134]. Reaction between oxazolidinone **236** and aldehyde **237** afforded stereoselectively *syn*-aldol **238**. Removal of chiral auxiliary under reductive conditions, followed by protection of the hydroxyl groups, allowed a Wacker oxidation at the terminal olefin to obtain **239** in high yields. Aldehyde **240** was obtained by



Scheme 36.



Scheme 37.

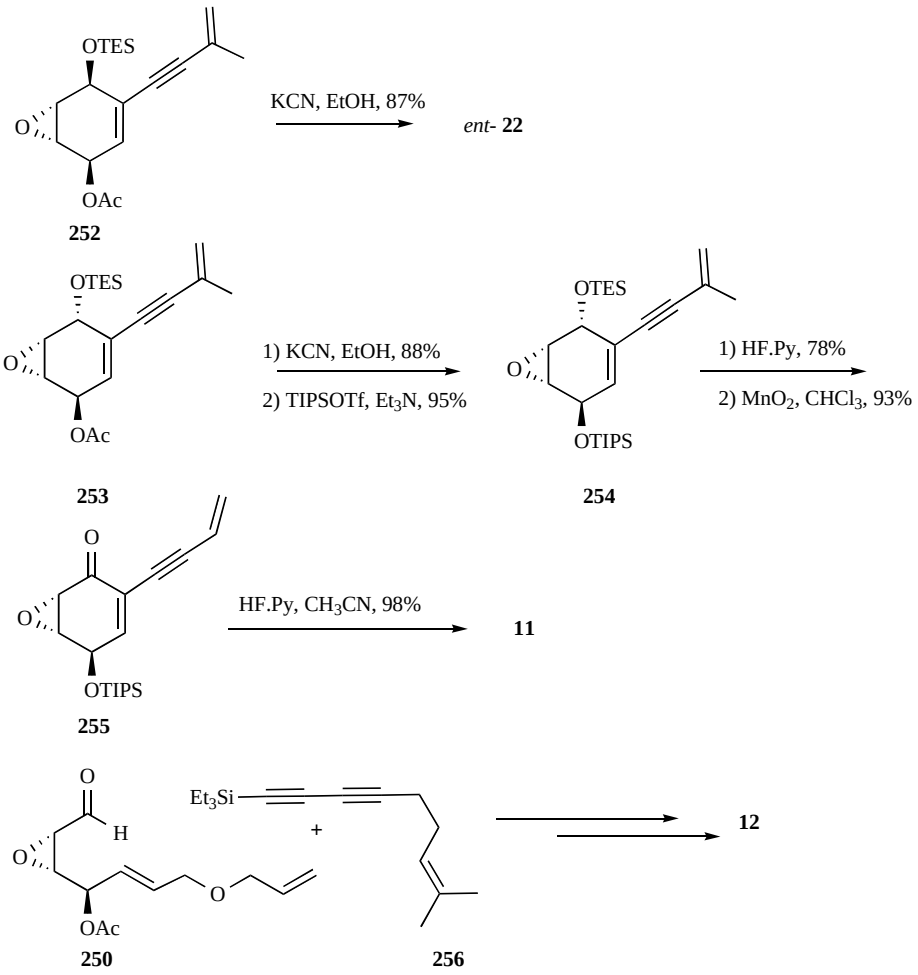


Scheme 38.

ozonolysis, and was then subjected to an intramolecular aldol condensation and elimination to deliver enone **241**. Stereoselective epoxidation with *t*-butylhydroperoxide gave **242** quantitatively as a single stereoisomer. Completion of the epoxycyclohexenone core was achieved through an α-selenylation followed by oxidative elimination. α-Bromination of **243** permitted Stille cross-coupling over **244** for the insertion of alkenyl side chain. Deprotection of the hydroxyl groups afforded the monomeric ECH (**8**). Finally epoxyquinols A (**28**) and B (**29**) were prepared by chemoselective oxidation of the primary hydroxyl group and then by leaving the neat product at room temperature to trigger the electrocyclization/Diels-Alder dimerization cascade.

Lee´s Methodology

Lee developed a strategy based on the sequence enyne ring-closing metathesis (RCM) followed by metallotropic [1,3]-shift, to install the 1,5-dien-3-yne moiety of (+)-asperpentyn (*ent*-**22**), (-)-harveynone (**11**) and (-)-tricholomenyn A (**12**) [135]. The common intermediate to obtain these three natural products was aldehyde **250**. It was prepared from commercially available diol **245**, em-



Scheme 39.

ploying in the first step a Sharpless asymmetric epoxidation to afford epoxide **246** (scheme **38**). Separable diastereomeric alcohols **247** and **248** were obtained in a 1:2 ratio when aldehyde derived from **246** was subjected to acetylide addition in basic media. Lindlar hydrogenation of the correct epimer **247**, followed by acetylation gave **249** with high yield.

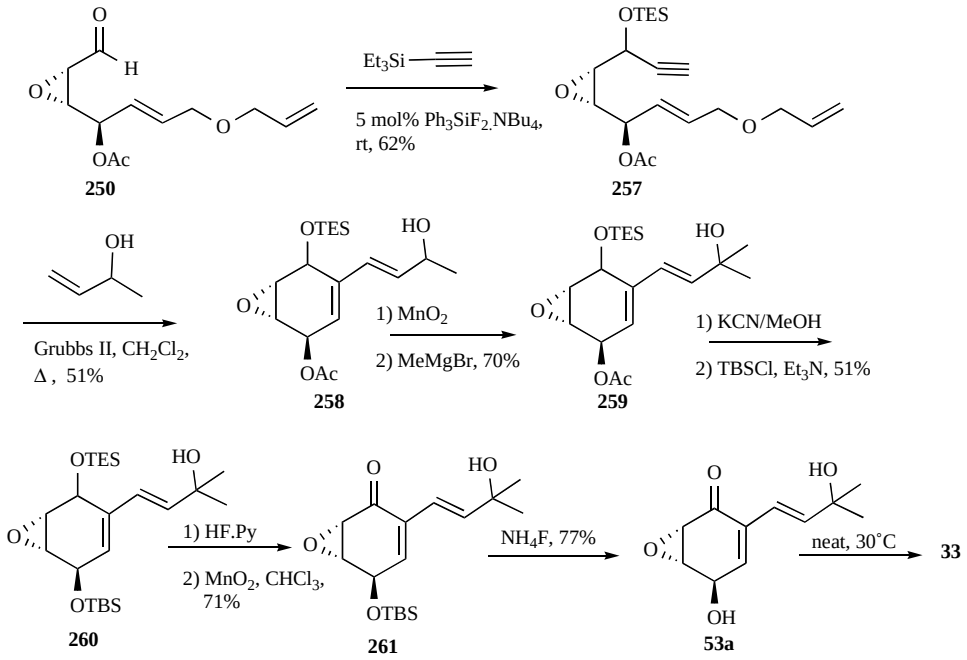
Lee also reported an efficiently method to obtain **249** from the epimers mixture (**247** + **248**). This strategy included Dess-Martin oxidation of the mixture, followed by an asymmetric reduction using (*R*)-Me-CBS as a chiral auxiliary. The authors clarified that the use of this auxiliary provided the *non*-desirable epimer but increased the stereoselectivity for the major product in a ratio of 10:1. They obtained **249** after Lindlar hydrogenation and inversion at C4 according to Mitsunobu`s protocol with acetic acid. Desilylation followed by oxidation of the primary alcohol afforded **250**.

The key step in this strategy was the RCM of enyne **251** followed by a metallotropic [1,3]-shift, as shown in scheme **38**. A second-generation Grubbs catalyst was added to **251** as a diluted solution in CH_2Cl_2 to obtain a mixture of epimers (**252** and **253**). Complete deprotection of **252** afforded (+)-asperpentyn (*ent*-**22**) (scheme **39**). After selective deprotection of TES group, followed by oxidation with MnO_2, the authors reported that C4-acetate could not be removed. To address this problematic protective group manipulation, the researchers converted **253** into **254**. Selective deprotection of **254** followed by oxidation gave **255**, which was deprotected to afford (-)-harveynone (**11**). Natural tricholomenyn A (**12**) was also synthesized according to a similar procedure using common intermediate **250** and the appropriated endiyne **256**.

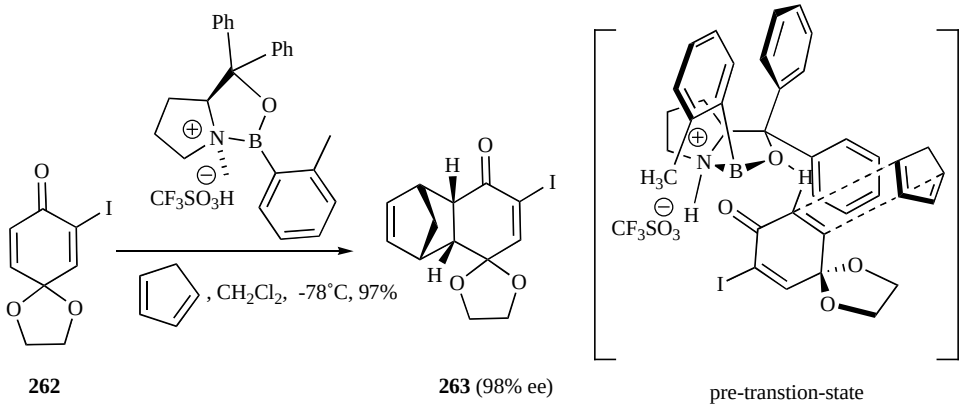
One year later Lee and co-workers [136] reported details of the synthesis of natural (+)-panepophenanthrin (**33**) based on tandem metathesis strategy. With the common intermediate **250** in their hands a silyl ether was installed together with an acetylene group to obtain **257** according to scheme **40**. Cross-metathesis between **257** and 3-buten-2-ol afforded **258**. The authors also suggested a mechanism for this transformation. Considering the previous C4-deacetylation difficulties, they decided to transform **259** into silyl ether **260**. Selective deprotection, followed by manganese oxide oxidation and secondary alcohol deprotection yielded monomer **261** as a precursor of (+)-panepophenanthrin. Cleavage of the silyl ether and a highly stereoselective intramolecular Diels-Alder reaction on neat **53a** yielded (+)-panepophenanthrin (**33**).

Ryu's Methodology

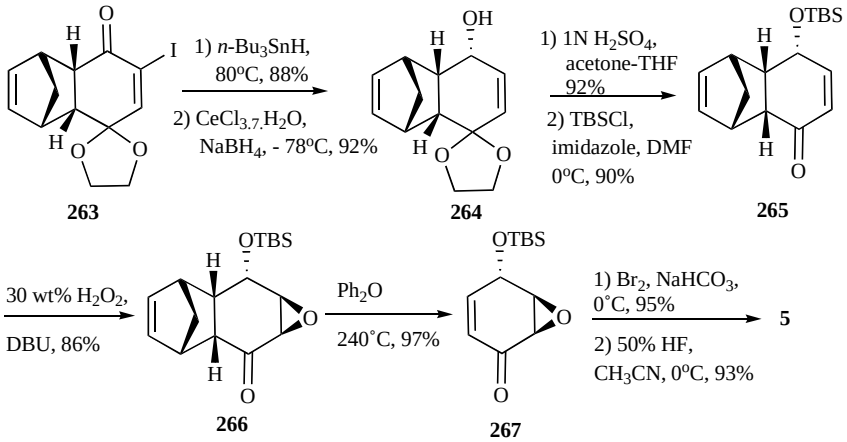
A catalytic enantioselective Diels-Alder strategy was achieved by Ryu's group towards the synthesis of several natural epoxycyclohexenones. In 2010 they reported the first chemocatalytic enantioselective process for the synthesis of natural bromoxone (**5**), epiepoxydon (**4**) and epiepoformin (**2**) [137]. The authors have previously developed an oxazaborolidium chiral catalyst, which was used for the preparation of the antitumor agent (+)-ottelione A [138]. Cyclopentadiene and 2-iodo-1,4-quinone monoketal (**262**) in the presence of catalytic amounts of oxazaborolidium chiral catalyst at -78ºC afforded only the *endo*-cycloadduct **263** with 98% ee. Transition state shown in scheme **41** explained the high sterecontrol of the reaction. Halogen was removed from **263** by treatment with tributyltin hydride, and then reduction yielded the correct epimer



Scheme 40.



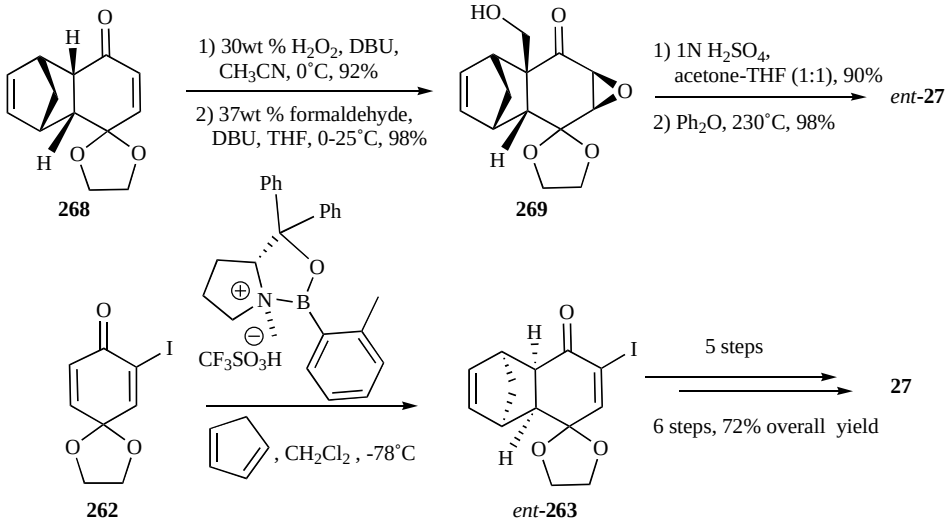
Scheme 41.



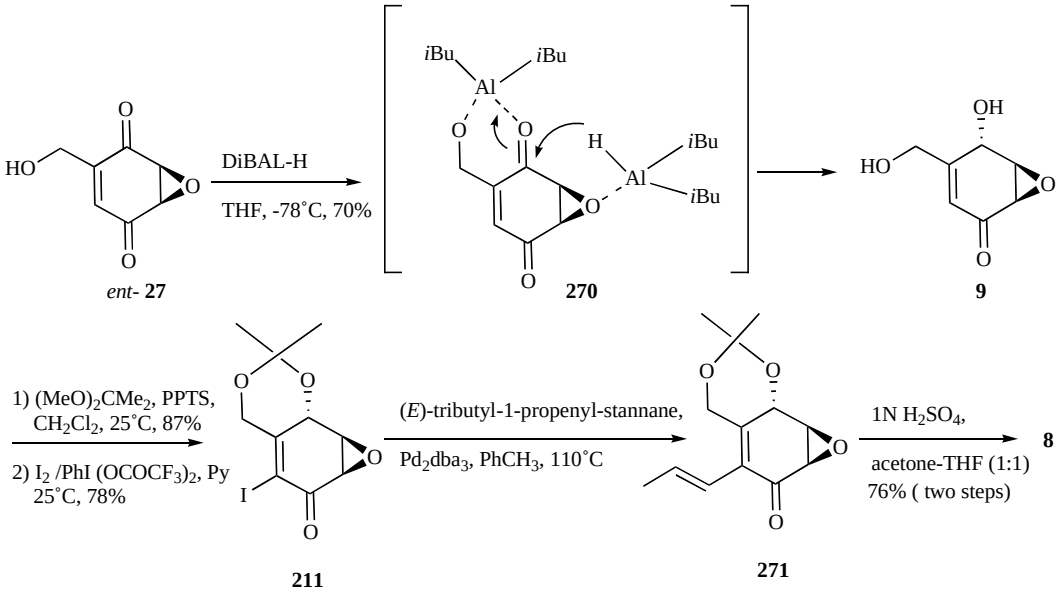
Scheme 42.

264 as shown in scheme **42**. It was first deprotected in acidic conditions to give the corresponding ketone and the secondary hydroxyl group was protected as TBS silyl ether to give **265**. The bulky group induced the correct stereochemistry at the next epoxidation reaction to generate **266**. A retro Diels-Alder reaction took place when **266** was heated at 240ºC in diphenylether affording **267**. Addition-elimination reaction of bromine, followed by deprotection led to natural bromoxone (**5**).

Using Ogasawara's previously reported protocol, the authors also obtained (+)-epiepoxydon and (+)-epiepoformin from **266** [139,140].



Scheme 43.



Scheme 44.

ent-Phyllostine (*ent*-**27**) was obtained starting from the *endo* Diels-Alder adduct **268** that was obtained by deiodinating **263** [141]. Hydrogen peroxide epoxidation of enantiomerically pure intermediate **268** gave the desirable *exo*-epoxide and a subsequent stereoselective hydroxymethylation afforded **269.** Deprotection under acidic conditions and typical retro Diels-Alder reaction gave *ent*-**27** (scheme **43**).

Using an *ent*-oxazaborolidium catalyst, Ryu obtained *ent*-**263**, which was used in a similar route to prepare natural phyllostine (**27**)

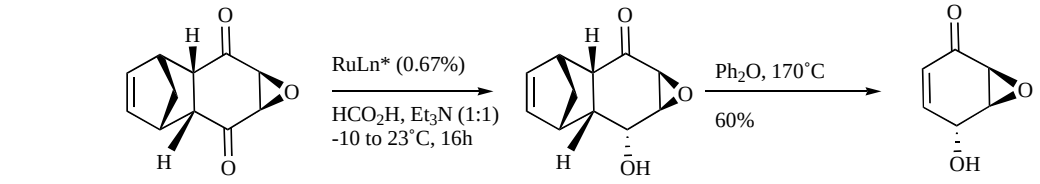
ECH (**8**) was also synthesized by Ryu and co-workers in the cited article [141]. Using *ent*-phyllostine (scheme **44**) as a precursor, under regioselective and stereoselective reduction conditions (Kiyooka's protocol), the authors obtained alcohol RKTS-33 (**9**). The total stereocontrol of this reduction could be explained through the intermediacy of the aluminium complex **270**. According to Shoji´s methodology **(**see scheme **33**), protection of **9** as acetonide followed by α-iodination, afforded the halogenated partner **211** necessary for the Stille cross-coupling reaction. **211** was coupled with (*E*)-1-tributyl-propenyl stannane to afford **271** and its deprotection under acidic conditions gave ECH (**8**).

McIntosh's Method (the Noyori Desymmetrization)

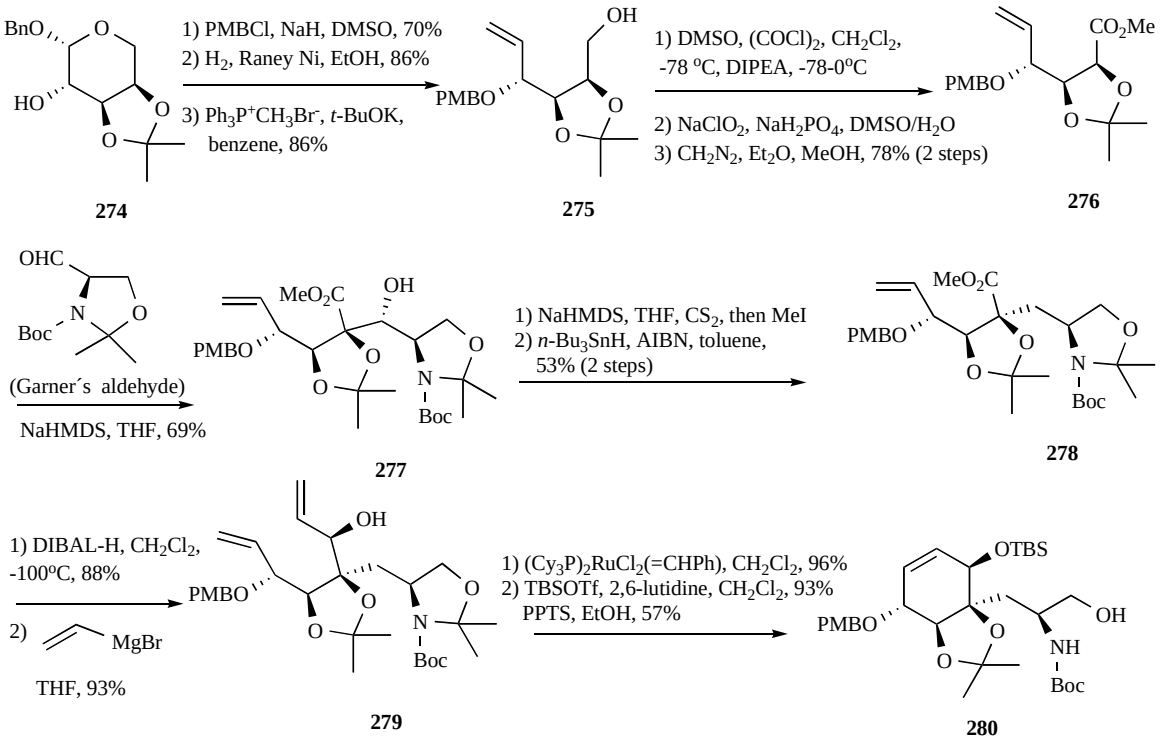
Enantioselective reduction of epoxydiketone **113** based on Noyori desymmetrization was reported by McIntosh in 2011[142]. This article included studies in different solvents, scale-up conditions, and ratio formic acid/trialkyl amine as stoichometric reductant. Optimization of Ru(*p*-cymene)[(*S*,*S*)-TsDPEN] percentage was also described. Typical retro Diels-Alder conditions (heating at 170ºC) of **272** completed the preparation of epoxyquinol **273** (scheme **45**).

Syntheses of Scyphostatin

Finally, it's scyphostatin's turn. Scyphostatin (**19**) deserves its own "chapter" in this review. Due to its complex structure and in concordance with the subject of this revision, we are going to focus on the introduction of chirality and preparation of the epoxyenone central core, without going into details concerning the construction of the chiral fatty acid side chain. Scyphostatin has been isolated in 1997 [34], but no chiral preparation (either total or partial) was reported until 2004, when Katoh and co-workers published the first synthesis [143].



Scheme 45.



Scheme 46.

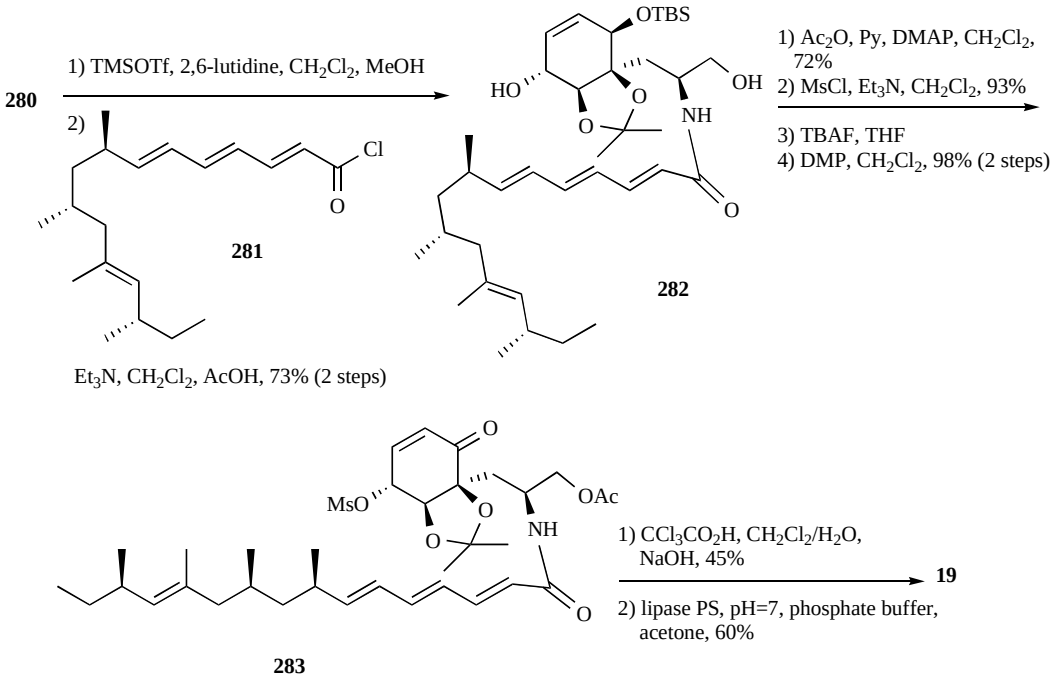
The chiral starting material for the cyclohexenone moiety was D-arabinose. When this sugar is *O*-benzylglycosydated and the acetonide is formed, compound **274** is obtained. This was the starting material in this case (scheme **46**). Protection-deprotection steps, followed by Wittig olefination yielded alcohol **275** that when oxidized and esterified, was converted into **276**. At this point, the crucial aldol addition with Garner aldehyde could be performed with good results. Alcohol **277** was obtained as a single diastereomer.

Further deoxygenation provided compound **278** and reduction-Grignard sequence over the ester group yielded diene **279**. Ring closing methatesis proceeded successfully in the presence of Grubbs catalyst. Final manipulation of the protective groups led to **280** that represents the cyclohexene segment to be coupled with the corresponding fatty acid chloride segment **281** (scheme **47**). This one was efficiently prepared from a chiral well known aldehyde [144].

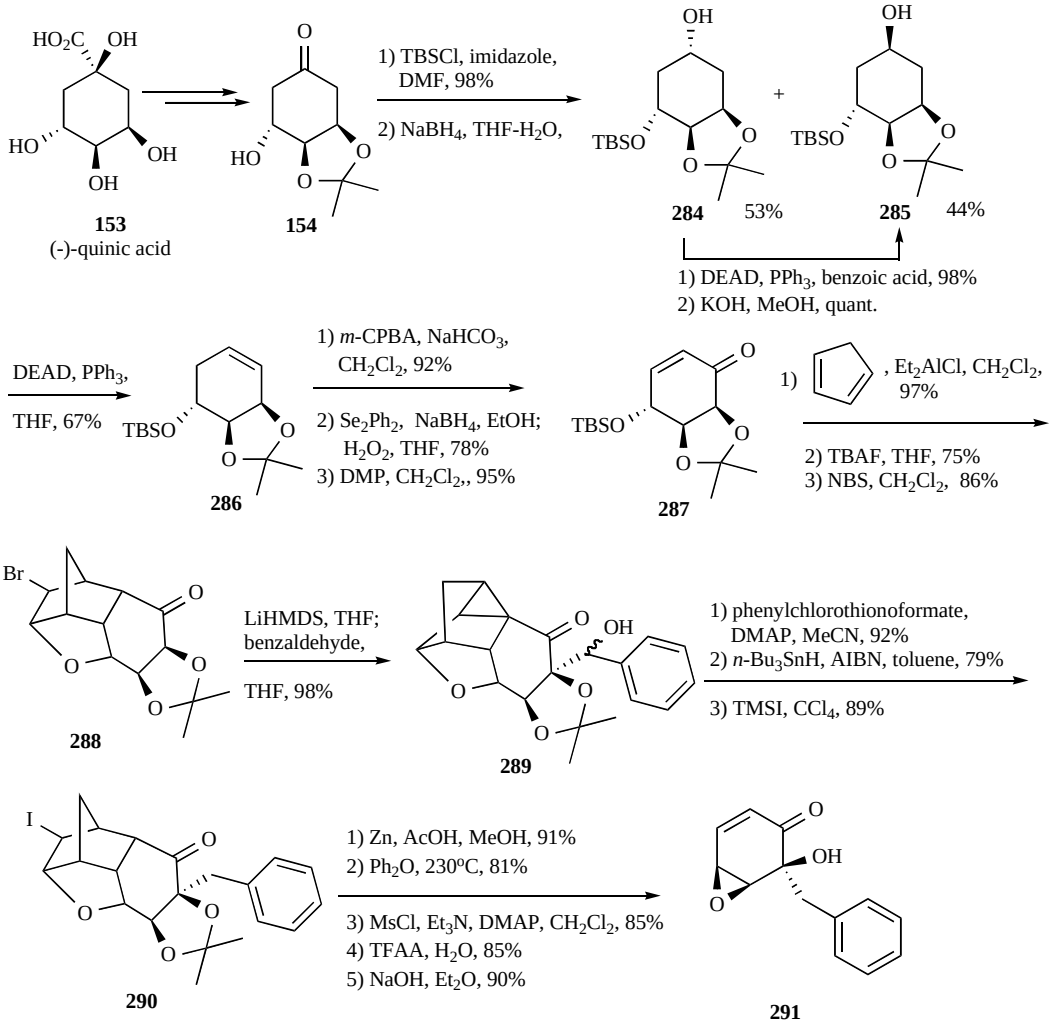
The fatty acid chloride **281** was efficiently bonded to **280** and the amide **282** was obtained. Acetylation of primary hydroxyl group, mesylation of the secondary one and desilylation-oxidation of the protected one gave compound **283**. Acetonide cleavage permitted oxirane ring closure. Finally, lipase hydrolysis of the acetate led to (+)-scyphostatin after 24 reaction steps. This first total enantioselective synthesis was also discussed in 2007 [145].

Katoh and his group continued working on this molecule. In 2006 they published an extensive work concerning an enantiocontrolled synthesis of the epoxycyclohexenone moiety [146]. This time, the starting material was (-)-quinic acid (scheme **48**).

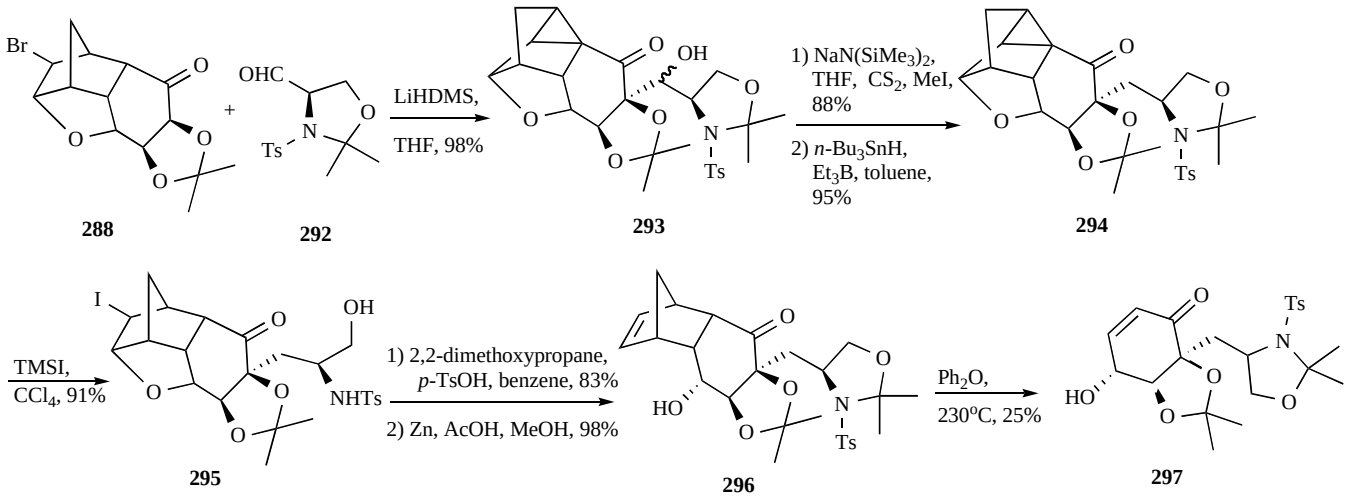
The conversion of (-)-quinic acid (**153**) into ketone **154** has been reported previously [146]. Protection of free hydroxyl group and reduction of the carbonyl provided the mixture of epimers **284** and **285**. As elimination of hydroxyl group was not possible with **284**, it was converted into **285** and then the olefin **286** could be obtained. Diastereoselective epoxidation, followed by Sharpless protocol (ring opening and elimination of phenylselenoxide) and oxidation of the allylic alcohol yielded the key intermediate **287**. As aldol addition of benzaldehyde failed, the double bond was masked as the Diels-Alder bromo adduct **288** that was obtained through a sequence Diels-Alder-desilylation-bromoetherification from **287**. The aldol addition yielded the rearranged compound **289** successfully. Deoxygenation followed by cleavage of the cyclopropane ring gave the iodoketone **290**. Deiodination, retro Diels-Alder reaction, mesylation, acetonide removal and epoxide formation permitted to obtain epoxycyclohexenone moiety **291**. Once the methodology was proven, the authors decided to synthesize a fully functionalized epoxycyclohexenone moiety. This time, **288** was coupled with aldehyde **292** as shown in scheme **49**.



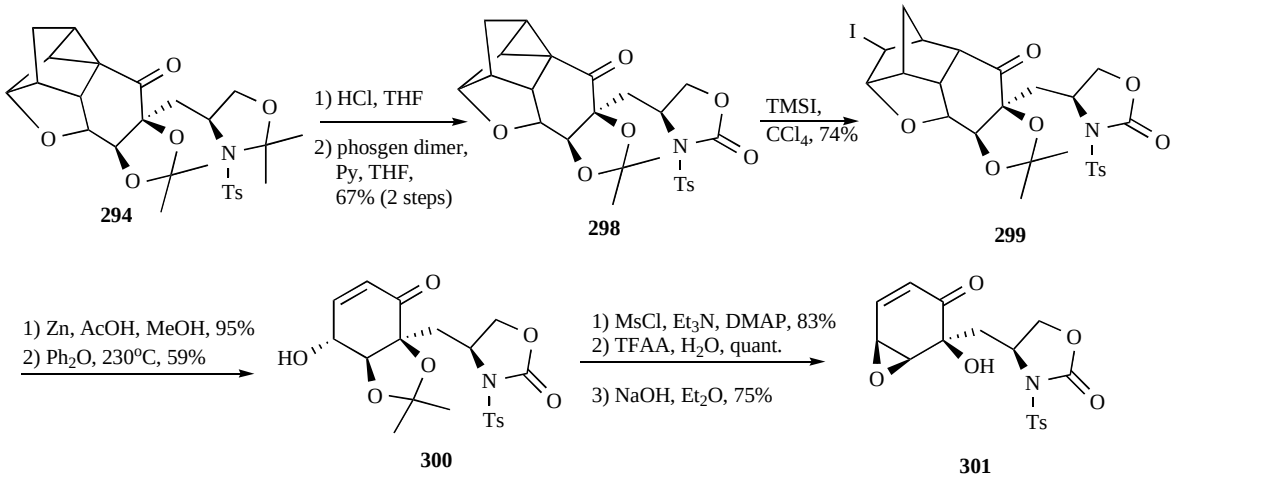
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.

Compound **293** was obtained with an excellent yield as an inseparable mixture of epimers. Deoxygenation yielded **294** and treatment with TMSI gave the iodo compound **295**. Reaction with 2,2-dimethoxypropane furnished an acetonide that when treated with zinc powder was transformed into **296**. Retro Diels-Alder reaction to obtain **297** proceeded with very poor yield. Therefore, the *N,O*-isopropylidene group had to be replaced via a carbamate, as shown in scheme **50**.

With **294** in their hands, the authors exchanged the *N,O*-isopropyplidene moiety with the corresponding cyclic carbamate, obtaining **298**. Treatment with TMSI gave **299** that was subsequently converted, with a 59% yield for the retro Diels-Alder reaction, into **300**. Mesylation of the free alcohol, followed by removal of acetonide and oxirane ring closure furnished **301**, a fully functionalized epoxyenone moiety of scyphostatin.

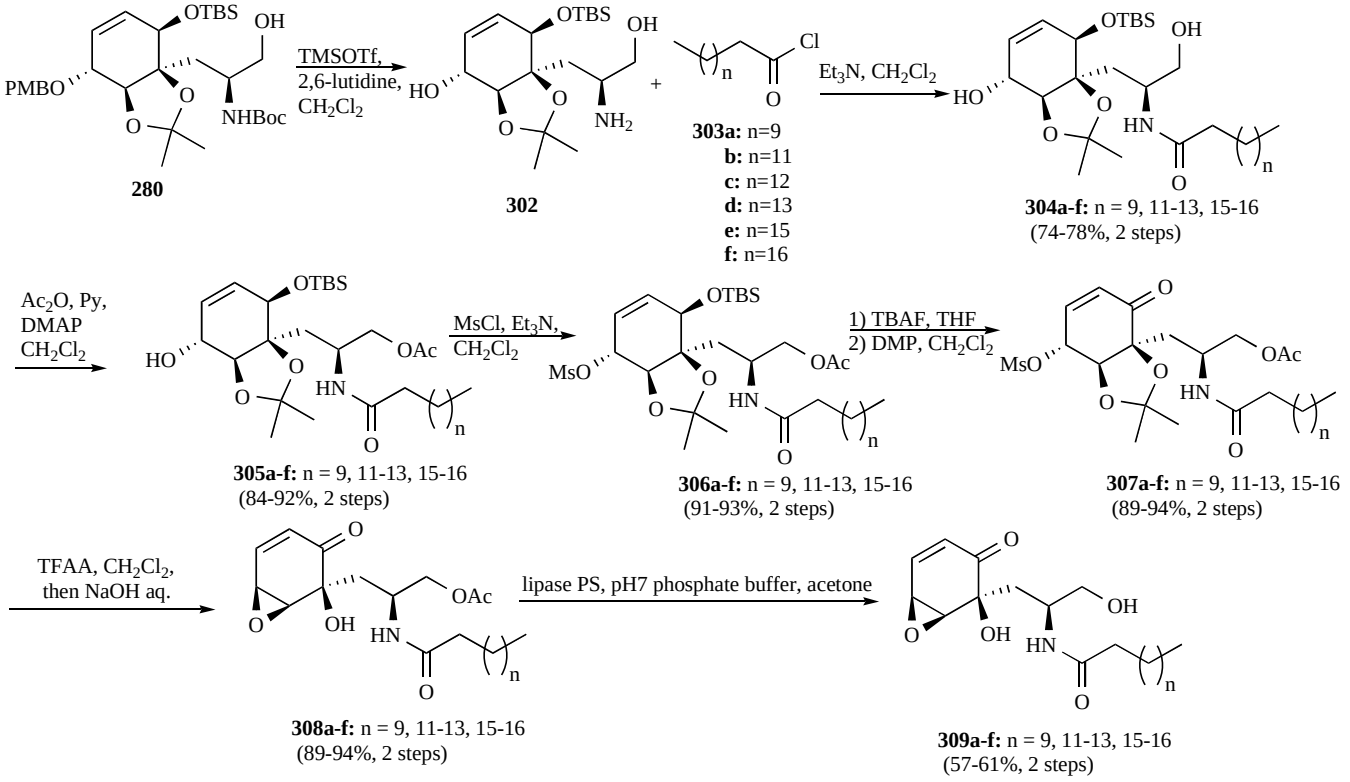
After this fruitful work, Katoh and his group published a study concerning the preparation of scyphostatin analogs with different saturated fatty acid chains [147], aiming to improve the stability of scyphostatin. Intermediate **280** was the cyclohexene moiety used to couple with the fatty acids, and has been previously prepared by the authors (see scheme **46**). Six analogs of scyphostatin were obtained, as it is shown in scheme **51**.

Protective groups Boc and PMB were simultaneously removed to give **302**. The free amino group was then coupled with fatty acid chlorides **303a-f** to give the corresponding amides **304a-f** with excellent yields. The primary hydroxyl group was then acetylated to afford **305a-f** and subsequently the secondary alcohol was mesylated to give **306a-f**. Silyl ether removal followed by oxidative conditions permitted to obtain the cyclohexenones **307a-f**. Cyclohexenones **307a-f** yielded epoxycyclohexenones **308a-f** when treated under acidic conditions to remove acetonide and then treated with base. Enzymatic hydrolysis of the acetate group afforded the six targeted scyphostatin analogs **309a-f**.

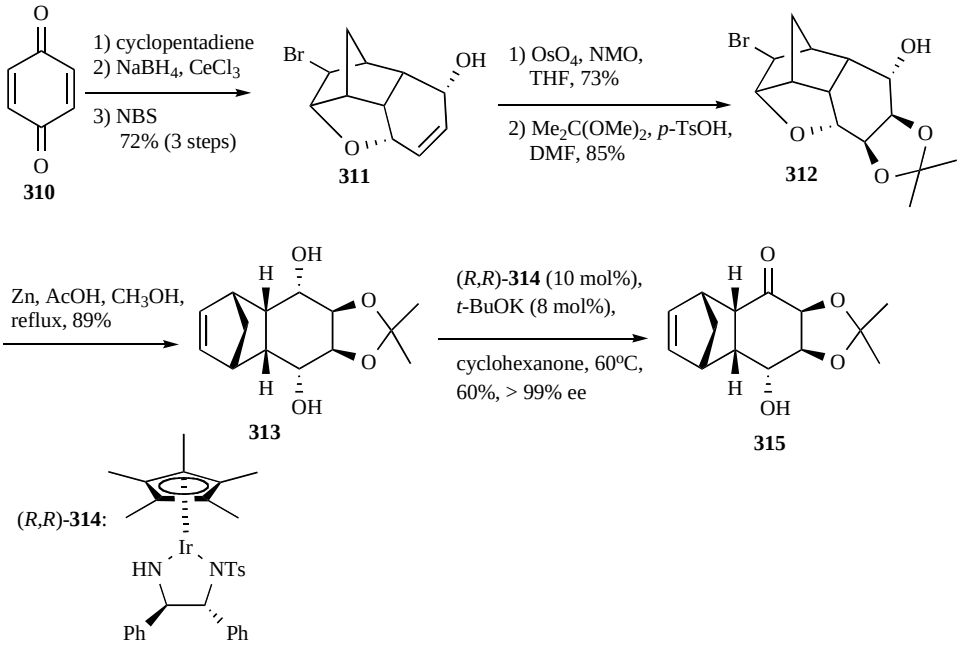
A very interesting alternative to the use of quinic acid as the source of chirality in Katho´s strategy was proposed by the same group in 2009 [148]. This work is about a new methology for desymmetrization of *meso*-diols, based on the use of a chiral iridium catalyst, that was applied to the preparation of a common intermediate of ottelione and scyphostatin. The synthetic route is shown in scheme **52**.

p-Benzoquinone (**310)** was easily transformed into **311**. Dihydroxylation and protection of the diol functionality rendered **312**, that was debrominated to yield **313**. This diol was desymmetrized with the aid of the iridium catalyst (*R,R*)-**314**. Hydroxyketone **315** was obtained in an enantiomerically pure form, and constitutes a value intermediate for the synthesis of scyphostatin as well as ottelione.

In 2005, the enantioselective synthesis of a scyphostatin analogue was reported [149]. As shown in scheme **53**, cyclohexanone (**316**) was coupled with Garner´s aldehyde and then the aldol ob-



Scheme 51.

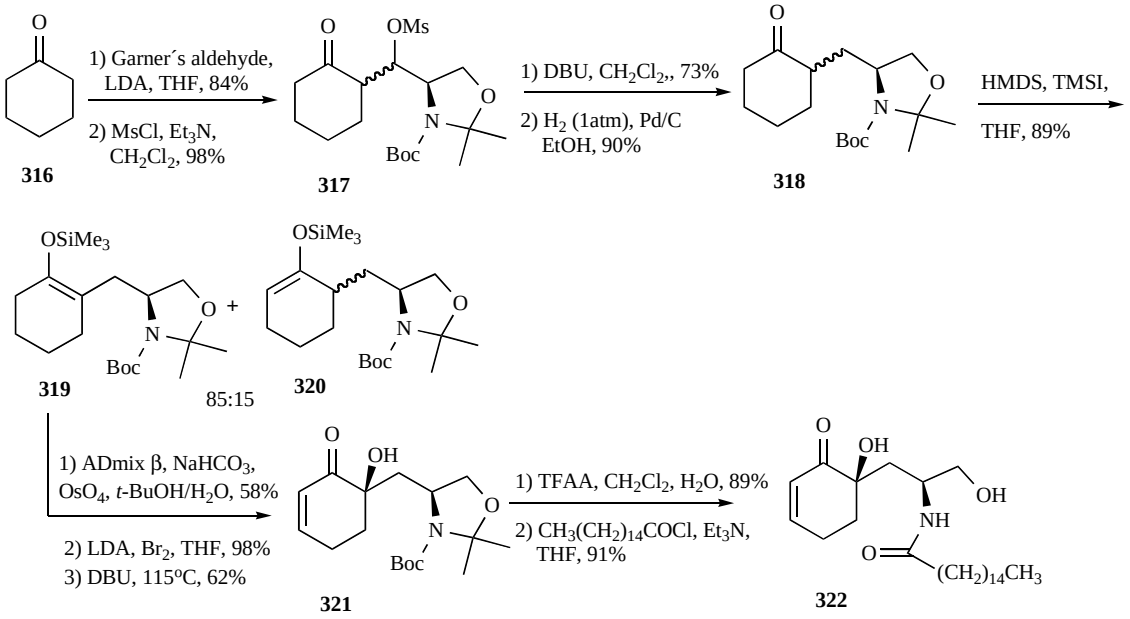


Scheme 52.

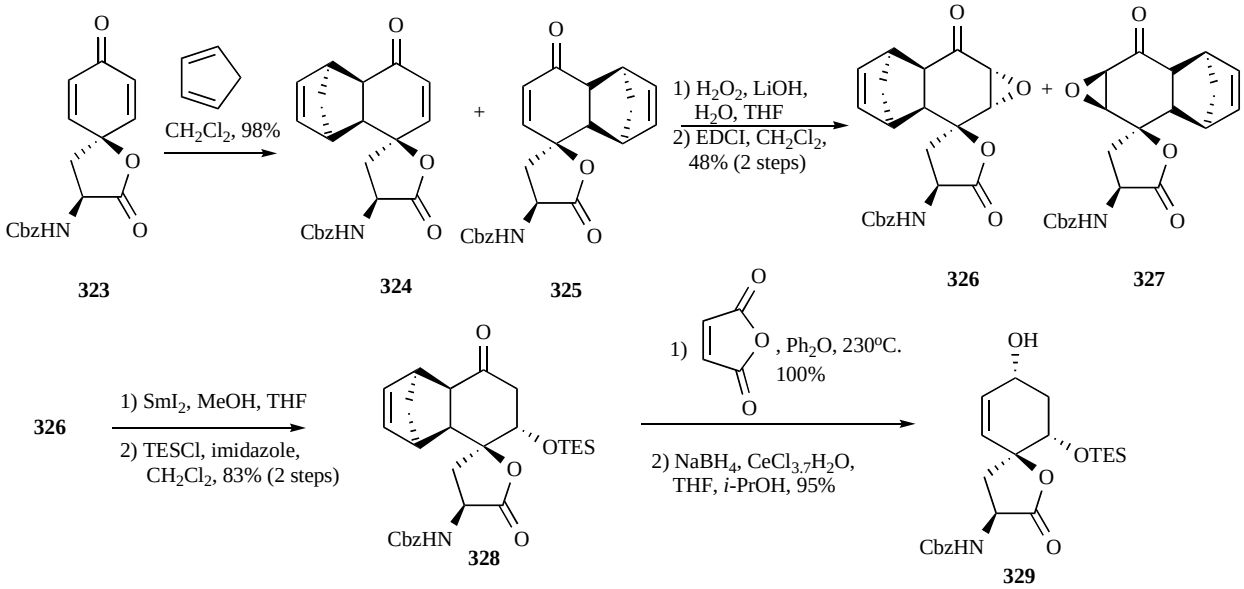
tained was mesylated to give **317**. After elimination/hydrogenation steps, deoxygenated compound **318** was obtained. Silyl enol ethers **319** and **320** were obtained in a 85:15 ratio. Silyl enol ether **319** reacted under asymmetric Sharpless hydroxylation conditions to yield **321** with 86% of diastereomeric excess. Fully deprotected **321** reacted with palmitoyl chloride to give **322**, a simplified scyphostatin analogue.

In 2007, Takagi and co-workers reported the second total synthesis of (+)-scyphostatin [150]. As in Katoh's case, the starting material was a natural chiral product. In this work, L-tyrosine was used to prepare chiral spirolactone **323**, according to a procedure previously reported [151]. The spirolactone reacted with cyclopentadiene with high π-facial selectivity to give a 1:1 mixture of the *endo* aducts **324** and **325**. The first part of the synthesis is shown in scheme **54**.

The mixture of Diels-Alder products gave a mixture of epoxides (**326** and **327**), easy to separate. Epoxide **326** was opened in the presence of SmI_2 and after protection of the hydroxyl group,



Scheme 53.



Scheme 54.

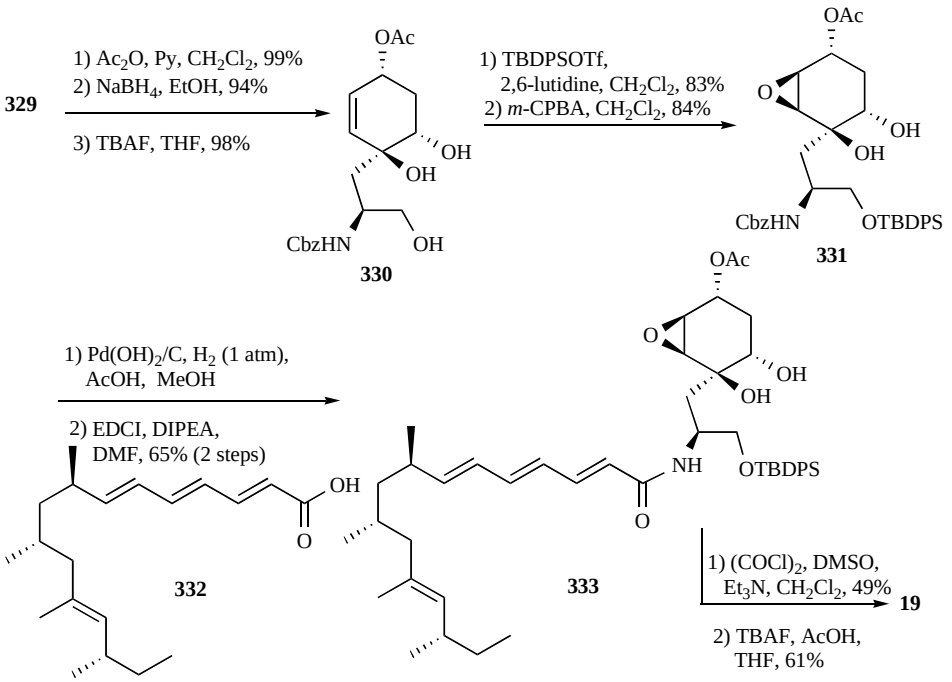
compound **328** was obtained. Retro Diels-Alder reaction followed by ketone reduction provided **329**. As epoxidation of **329** gave the incorrect stereochemistry, it was kept for later steps. The highlights of the synthesis are illustrated in scheme **55**.

Alcohol **329** was acetylated and then lactone ring was reductively opened. After desilylation triol **330** was obtained. The primary alcohol was protected and then the epoxidation underwent with the correct orientation to give epoxide **331**. Nitrogen was deprotected and the amide **333** was formed straightforward with fatty acid **332** [152]. Oxidation of the secondary alcohol followed by deprotection of the primary one, permitted to accomplish the total synthesis of (+)-scyphostatin. A similar strategy, but racemic, was previously applied by Ohkata´s group for the preparation of scyphostatin analogs [153,154].

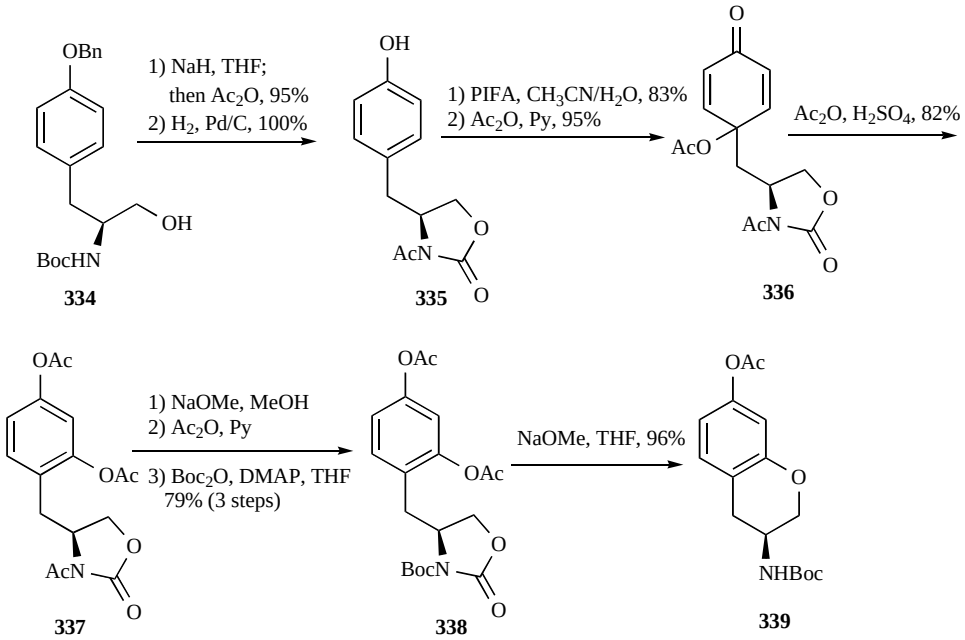
Pitsinos and co-workers published in 2007 the chiral synthesis of an advanced intermediate towards the total synthesis of scyphostatin [155]. The strategy was based in a previous work in which the same group prepared the polar core of scyphostatin in a racemic way [156]. Once again, L-tyrosine was the source of chirality. This time it was used to prepare the starting material **334** as it was previously reported [157]. The synthetic sequence is shown in scheme **56**.

Enantiopure **334** was easily transformed into oxazolidinone **335**. Oxidation and acetylation yielded the *p*-quinol **336**. A rearranged aromatic compound **337** was obtained by means of a treatment with sulphuric acid and acetic anhydride. Protection-deprotection steps afforded **338** which under basic conditions was transformed into the target compound **339**, a chiral benzopyran *en route* to (+)-scyphostatin. In 2010, this compound was successfully used by the same group as starting material for the total synthesis of scyphostatin [158] that is shown in scheme **57**.

The Boc group was replaced by trichloroacetate, and then the aromatic ring was oxidized. The product was quinol **340** that was subsequently hydrolyzed and reduced to give **341**. After reduction,



Scheme 55.

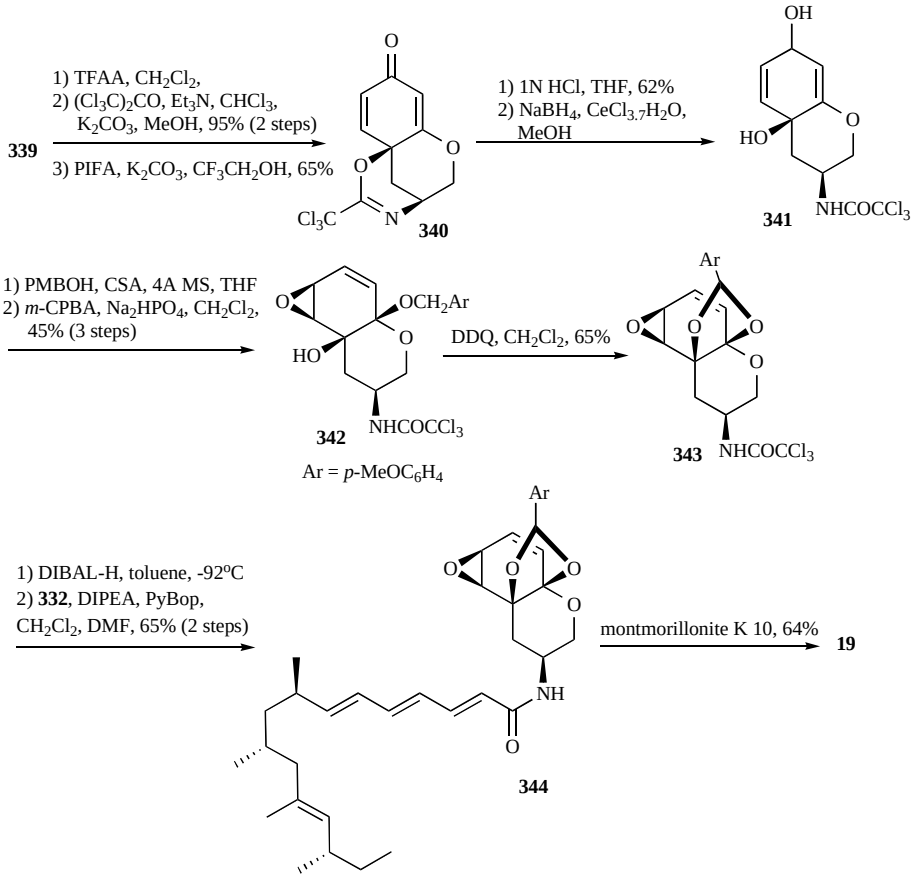


Scheme 56.

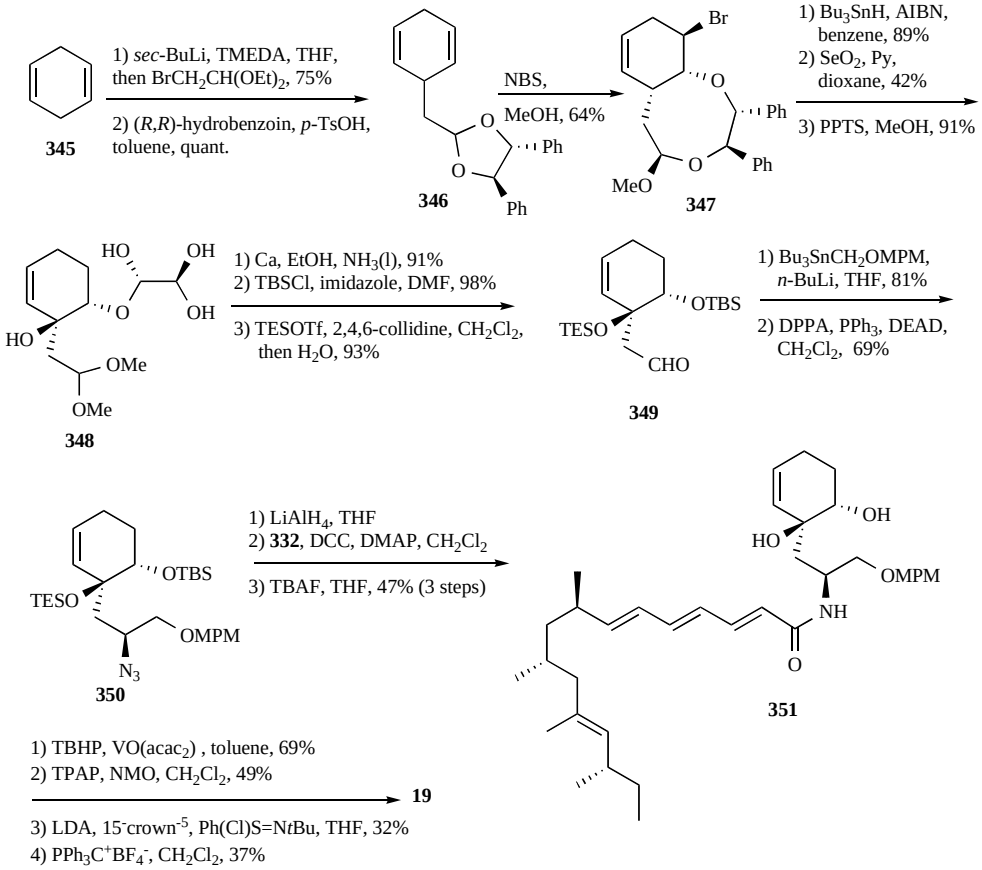
treatment with *p*-$MeOC_6H_4OH$, in the presence of CSA proceeded with allylic rearrangement. Epoxidation of the double bond yielded compound **342** and further oxidation with DDQ yielded **343**. Removal of trichloroacetate permitted the assembly with fatty acid **332** to yield **344**. This time, an interesting carboalumination Zr-catalized was used during the synthesis of the chiral fatty acid moiety [159]. When **344** was hydrolyzed in the presence of montmorillonite K10, the total synthesis of scyphostatin was achieved.

The next total synthesis we are going to analyze was published by Kita in 2007 [160]. The "first generation" synthetic strategy is shown in scheme **58**.

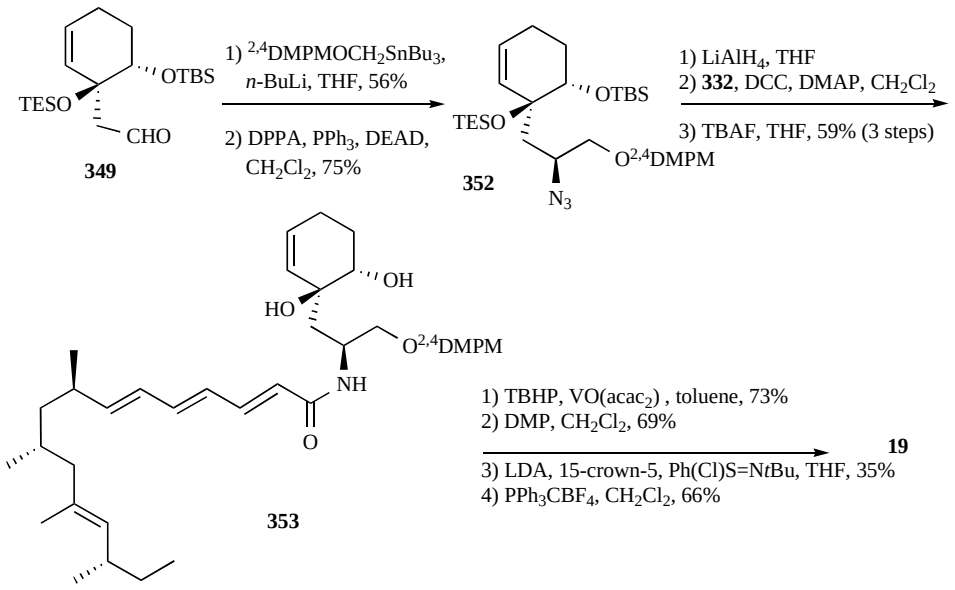
1,4-Cyclohexadiene (**345**) was coupled with bromoacetaldehyde diethyl acetal, and then the chiral auxiliary (*R*,*R*)-hydrobenzoin was introduced to give acetal **346**. Bromoetherification with NBS gave bromide **347**, which was debrominated, oxidized and hydrolyzed to yield **348**. The chiral auxiliary was removed, the alcohols were protected and the aldehyde was deprotected to obtain **349**. The alcohol produced by addition of 4-methoxyphenylmethyloxymethyl lithium to the aldehyde was converted into azide **350** under Mitsunobu conditions. The azide was reduced to the amine that was coupled with **332** (prepared as described by Hoye and Tennakoon [161]) and desilylated to give **351**. To obtain (+)-scyphostatin epoxidation, oxidation, double bond formation and deprotection were successfully performed. After several studies for improvement of yields and optimization of various synthetic steps, a second generation total asymmetric synthesis of **19** could be accomplished. This second generation strategy is shown in scheme **59**.



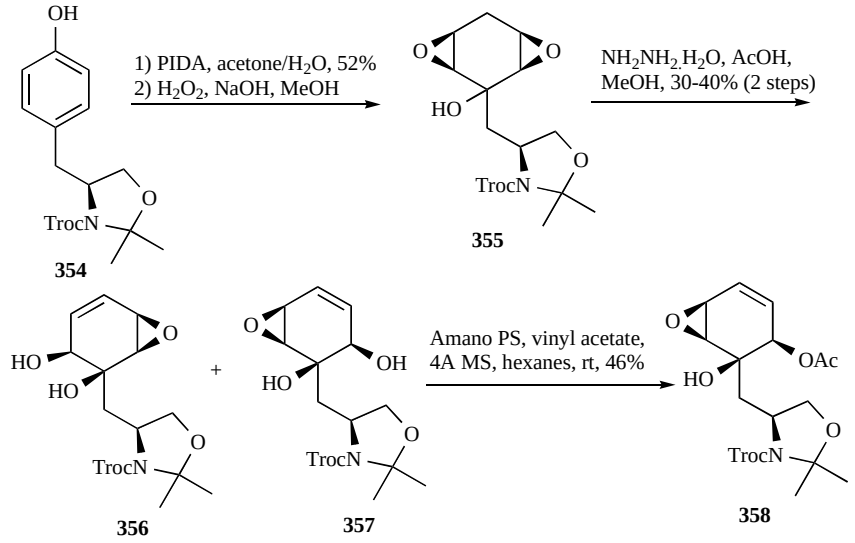
Scheme 57.



Scheme 58.



Scheme 59.



Scheme 60.

Starting from aldehyde **349**, the nucleophile was changed into 2,4-dimethoxyphenylmethylmethyloxymethyl lithium. After Mitsunobu inversion azide **352** was obtained. The following steps are equivalent to the ones of the first generation synthesis, obtaining **353** and (+)-scyphostatin in 17 steps with an improved yield.

In 2010, Hoye´s group published another approach to the polar core of scyphostatin [162]. Again, the source of chirality was a phenol derived from L-tyrosine (**354**). As it is illustrated in scheme **60**, the phenol was oxidized and the quinol formed was bis-epoxidated to give **355**. Wharton rearrengement of **355** produced a 1:1 mixture of alcohols **356** and **357**. HPLC separation of these diastereomers resulted in a return to the mixture, thus suggesting a vinilogous Payne rearrangement as the cause of the equilibration.

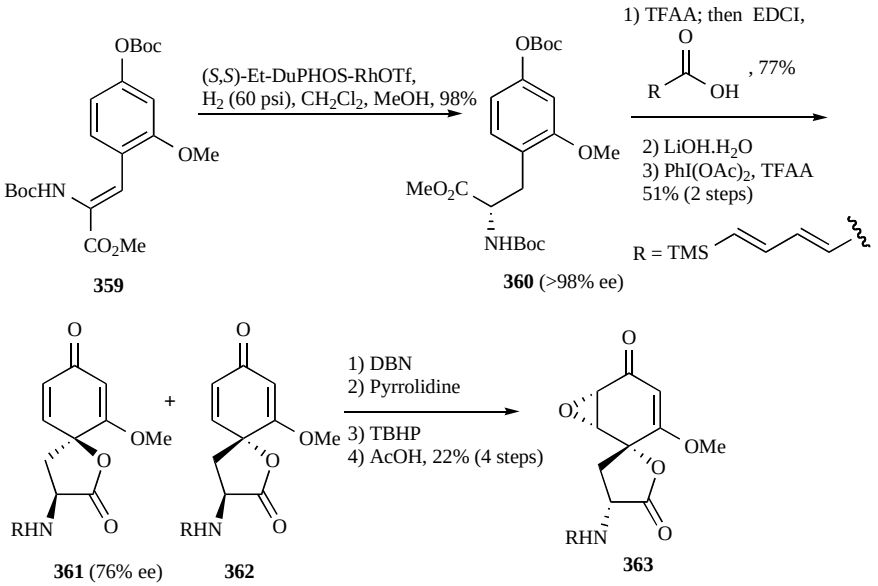
When the mixture was treated with vinyl acetate in the presence of a lipase, dynamic kinetic resolution worked, and a single acetate **358** was produced, consisting in an advanced intermediate towards the synthesis of the central core of (+)-scyphostatin.

The last and more recent article concerning scyphostatin was published this year [163]. It consists in an extensive work for the racemic synthesis of scyphostatin analogs that includes an enantioselective access, which is described in scheme **61**.

Hydrogenation of the double bond present in the starting material **359** was run in the presence of Burk´s Et-DuPHOS ligand to yield enantiopure **360**. Boc groups were then removed and an analogue of the side chain of scyphostatin was introduced. Ester hydrolysis and oxidative dearomatization yielded a 1:1.3 mixture of **361** (desired S, S) and **362**, with some loss of enantioselectivity. Treatment with DBN of **362** permitted epimerization to give the (*R*, *R*) diastereomer with >97% ee. Further treatment with pyrrolidine, *t*-butylhydroperoxide and acetic acid yielded **363**, thus demonstrating that the enantiodivergent strategy for the synthesis of scyphostatin analogs, including enantiomeric molecules, was successful.

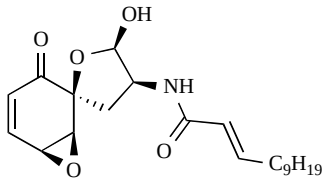
PERSPECTIVES

In this section we describe reported epoxyquinoids that have not yet been enantioselectively synthesized. Some of them were prepared in racemic form and due to their biological properties are expected to be synthesized in optically pure form in the near future.



Scheme 61.

Isariotin E (**364**) is a spiro-epoxyenone (Fig. **6**) isolated from entomophatic fungi-afflicting insects [164]. It has been proposed that isariotin E could be the biosynthetic progenitor of isariotin F and TK-57-164A, another isolated metabolites. Pettus and co-workers recently reported the first total synthesis of these compounds in a racemic fashion [165].



isariotin E (**364**)

Fig. (6). Structure of isariotin E.

A group of molecules that resemble the structure of harveynone have been recently prepared by Taylor and co-workers through racemic synthesis [166]. Speciosins A-F (**365**-**370**, Fig. **7**) were isolated by Jiang *et al*. from the chinese fungus *Hexagonia speciosa* [167]. Ghisalberti described the isolation of the plant growth promoting, anti-fungal metabolite from an ectotrophic australian fungus, SDEF 678 (**371**) [168].

In 2000, Ireland and co-workers [169] reported the isolation and structure elucidation of eight bioactive farnesylated epoxycyclohexenoids (Fig. **8**) from an *Aspergillus niger* isolate, obtained from tissue homogenates of an orange *Aplidium* sp. ascidian. These compounds were denominated yanuthones A-D (**372**-**376**), 1-hydroxyyanuthone A and C (**377**-**378**), and 22-deacetylyanuthone A (**379**), and they exhibited weak antimicrobial activity against methicillin resistant *Staphilococcus aureus* and vancomycin resistant *Enterococcus*. Also, deacetoxyyanuthone A (**380**), was isolated

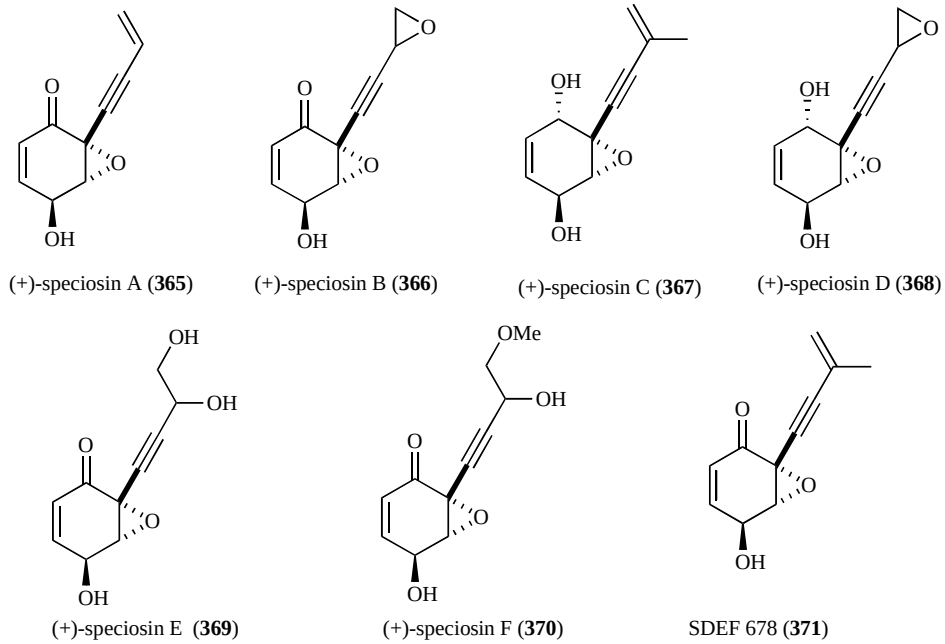
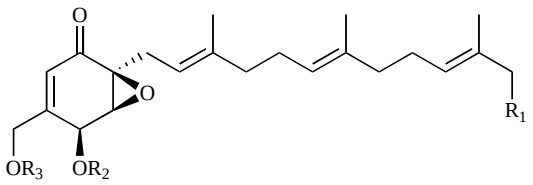


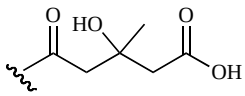
Fig. (7). Structures of speciosins A-F and SDEF 678.



yanuthone A (**372**): R_1= H, R_2= H, R_3= Ac

yanuthone C (**373**): R_1= H, R_2= Ac, R_3= H

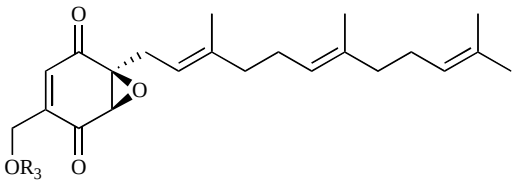
yanuthone E (**374**): R_1= H, R_2= H, R_3=



1-hydroxyyanuthone A(**377**): R_1= OH, R_2= H, R_3= Ac

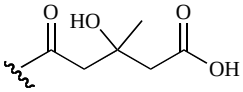
1-hydroxyyanuthone C (**378**): R_1= OH, R_2= Ac, R_3= H

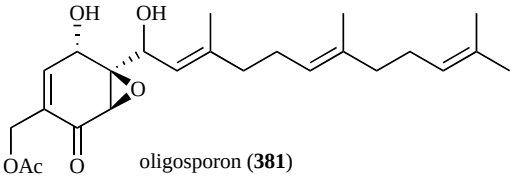
22-deacetylyanuthone A (**379**): R_1= H, R_2= H, R_3= H



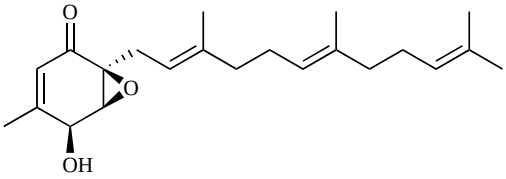
yanuthone B(**375**): R_3= Ac

yanuthone D (**376**) R_3=

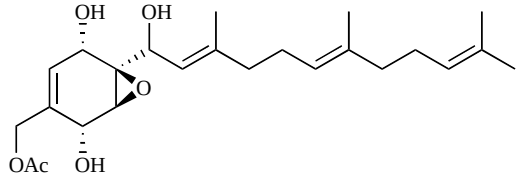




oligosporon (**381**)

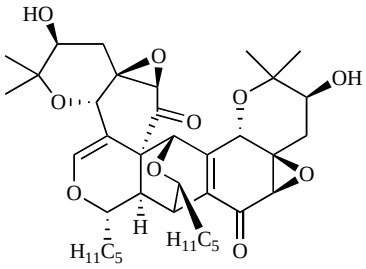


deacetoxyyanuthone A (**380**)

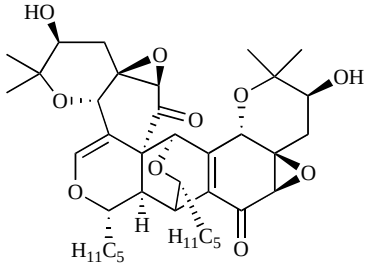


oligosporol B (**382**)

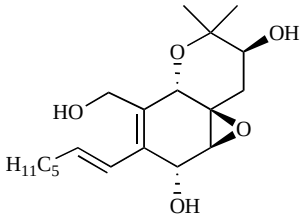
Fig. (8). Farnesyl epoxycyclohexenoids.



pestaloquinol A (**383**)



pestaloquinol B (**384**)



cytosporin D (**385**)

Fig. (9). Epoxyquinoids derived from *Pestalotiopsis* sp..

from a marine isolate of genus *Penicillium* sp., which displayed mild antimicrobial activity against methicillin resistant and multidrug resistant *S. aureus* [170]. Furthermore, oligosporon (**381**) and oligosporol B (**382**), structurally related farnesyl epoxycyclohexenoids, were isolated from *Arthrobotrys oligospora* [171]. Mehta *et al*. reported in 2005 the total synthesis of yanuthones A, B, C and 22-deacetylyanuthone A in racemic form [172].

In 2011, Cha and co-workers reported the isolation of pestaloquinols A and B (**383**-**384**), along with cytosporin D (**385**), their putative biosynthetic precursor, from the plant endophytic fungus *Pestalotiopsis* sp. (Fig. **9**) [173]. Resemblance of these structures with antiangiogenic epoxyquinol A and related dimers, added to their reported cytotoxicity against HeLa cells, surely will turn these compounds attractive for synthetic chemistry.

CONCLUSION

Almost 50 papers have been published since 2004 concerning chiral synthesis of epoxyquinoids. The volume of published work shows that this is a field of great interest for the synthetic community, that needed to be reviewed. Enzymatic and chemical methods for introduction of chirality have been developed and improved during this period of time. Enzymatic methods have been used for the preparation of enantiopure starting materials as well as for the resolution of racemic mixtures. In particular, lipase mediated kinetic resolutions has been widely used by several authors, specially by Mehta. Concerning microbially prepared chiral compounds, cyclohexadiene-*cis*-diols obtained from monosustituted benzenes have been used by Banwell´s and our own group for the preparation of 10 molecules of this family.

With reference to chemical methods, the use of natural compounds from the chiral pool has been extensively applied. Many synthesis of natural epoxyquinoids started form L-tyrosine, D-arabinose and (-)-quinic acid, among others. Nevertheless, the use of chiral auxiliaries and asymmetric catalysis have also found a place in the desymmetrization processes discussed.

Almost all the molecules included are interesting not only from a synthetic point of view, but also regarding the biological activities they display, as antibiotic, antiangiogenic and enzyme inhibitors, among others.

We expect that the analysis of the synthetic challenges presented, will be helpful to encourage synthetic organic chemists to go on deepening the knowledge on this attractive and interesting area.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

The authors thank ANII (Agencia Nacional de Investigación e Innovación), PEDECIBA (PNUD/URU/06/004) and CSIC-UdelaR for financial support.

LIST OF ABBREVIATIONS

Ac	=	acetyl
acac	=	acetylacetonyl
AIBN	=	azobisisobutyronitrile
aq.	=	aqueous
BHT	=	2,6-di-*t*-butyl-*p*-cresol
Boc	=	*t*-butoxy carbonyl
BPS	=	*t*-butyldimethylsiliyl
cryst.	=	crystallization
CSA	=	camphorsulphonic acid
Cy	=	cyclohexyl
dba	=	dibenzylideneacetone
DBMP	=	2,6-di-*t*–butyl-4-methylpyridine
DBN	=	1,5-diazabicyclo(4.3.0)non-5-ene
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	=	dicyclohexylcarbodiimide
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	diethyl azodicarboxylate
DET	=	diethyl tartrate
DHMEQ	=	dehydromethylepoxyquinomicin
DIAD	=	diisopropyl azodicarboxylate
DIBAL-H	=	diisobutylaluminium hydride
DIPEA	=	diisopropylethylamine
DIPT	=	diisopropyl tartrate
DMAP	=	*N*,*N*-4-dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	*N*,*N*-dimethylformamide
DMP	=	Dess-Martin periodinane
^{2,4}DMPM	=	2,4-dimethoxyphenylmethyl
DPPA	=	diphenylphosphoryl azide
dr	=	diastereomeric ratio
EDCI	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	=	enantiomeric excess
HMDS	=	bis(trimethylsilyl)amide
2-HYP	=	2-hydroxypyridine
IBX	=	*o*-iodoxybenzoic acid
K-10	=	a type of montmorillonite clay
LDA	=	lithium diisopropylamine
m-CPBA	=	*m*-chloroperbenzoic acid
Me-CBS	=	methyl oxazaborolilidine
MPM	=	*p*-methoxyphenylmethyl
Ms	=	methansulphonyl
MS	=	molecular sieves
NBS	=	*N*-bromosuccinimide
NMO	=	*N*-methylmorpholine-*N*-oxide
NMP	=	*N*-methyl-2-pyrrolidinone
NMR	=	nuclear magnetic resonance
Np	=	naphthalene
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PIDA	=	phenyliodonium diacetate
PIFA	=	phenyl iodonium bis(trifluoroacetate)
PMB	=	*p*-methoxybenzyl
p-MBDA	=	*p*-methoxybenzaldehyde dimethyl acetal
PNBA	=	*p*-nitrobenzoic acid
PPL	=	porcine pancreas lipase
PPTS	=	pyridinium *p*-toluenesulfonate
p-TsOH	=	*p*-toluenesulphonic acid
Py	=	pyridine
PyBop	=	(benzotriazol-1-yloxy)tripyrrolidinophosphoniumhexafluorophosphate
quant.	=	quantitative
rt	=	room temperature
TBAF	=	tetra-n-butylammonium fluoride
TBHP	=	*t*-butyl hydroperoxide
TBME	=	*t*-butylmethylether
TBS	=	*t*-butyldimethylsilyl
TEMPO	=	2,2,6,6-tetramethyl-1-piperidyloxy free radical
TES	=	triethylsilyl
Tf	=	trifluoromethanesulfonyl
TFAA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
THS	=	thexyltrimethylsilyl
TIPS	=	triisopropylsilyl
TMEDA	=	tetramethylethylenediamine
TMS	=	trimethylsilyl
TPAP	=	tetrapropylammonium perruthenate
Tr	=	triphenylmethyl

Troc	=	trichloroethyloxycarbonyl
TsDPEN	=	*N*-tosyl-1,2-diphenylethane-1,2-diamine
Δ	=	heat

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