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 desymmetrization and 2) chemically stereocontrolled methodologies. Efficient syntheses starting with enantiomerically pure available synths are also reviewed. Finally, scyphostatin chiral preparations will be separately presented. Epoxycyclohexenones derived from naphthole-noid 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 Phomopsis sp. [10] a secondary metabolite called (+)-epoxydon (3) was isolated, which was described as phytio 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 (Phyllium hemichordata) [12]. The haloepoxycyclohexenone acetate 6 possess antitumor activity in P388 cells (IC50 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 nonpeptide 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]. (+)-Harveyonone (11), a secondary metabolite with phytotoxic activity was isolated from the tea gray blight fungus Pestalotiopsis theae [20]. (-)-Tricholomenyn A (12) showed antimitic activity 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...
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 Lentinia innocua. This mode of action suggests the potential 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 deutermycete strain 45-93 [29] and exhibited activation of NF-kB [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, Kozumi 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 IC50 values of 0.086 and 0.006 μM, respectively. ICE inhibitors have been suggested as potential anti-inflammatory drug candidates [33].

(+)-Scyphostatin (19) was first isolated from a mycelia extract of Dasyscyphus molitissimus Sank 13892 [34]. Up to date, 19 exhibits the most potent (IC50 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-kB [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
culture filtrate of the fungus Lasiidodium 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 cinerea and Bacillus subtilis. 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 stereoisomer. An endophytic fungus of the genus Eupenicillium is the source of an anti-fungal 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 mycelium (MF63896) [59]. Natural integrasone inhibited HIV-1 integrase which is one of the critical enzymes involved in viral replication. (-)-Phyllostine (27) was found in Phylllosticta 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 2,9.03,8.011,16]icosa-3(8),11(16)-diene, inhibited endothelial cell migration stimulated by vascular endothelial growth factor (ED_{50} = 2.6 μM).

The culture of the fungal strain of Panus rudis was the source of a 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 Ogamaño 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 torreynic acid was established as the dimeric quinone 38 that could be biogenerated from ambuc acid (14) as the monomer unit. Torreynic 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 chiral building blocks of microbial origin and the use of lipases for kinetic resolution of enantiomeric mixtures.

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 ambuc acid.

In 2009, Banwell and co-workers started to use these metabolites for the synthesis of natural epoxyquinoids. 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-cyclohexadienols 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.

Applying 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 2.

Scheme 3.
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).
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 regiosomer 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...
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).
(+)-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 4R (88) and 4S (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 93).
that when treated for removal of the silyl group, were trans-
formed 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 amino-
quinoine 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 depro-
tected to furnish 102. Amide formation led to 103. Deprotection and
reduction generated 104. This compound was treated with hexa-
ocan anhydride to give a dihexanoate, which upon enzymatic reso-
lution with Amano lipase (Ampan 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 pre-
paring (-)-bromoxone as the precursor for panepophenanthrin.

Enzymatic resolution of racemic 106 generated compounds (+)-
106 and (+)-107 in optically pure form. Methanolation of (+)-106
produced 108 which upon epoxidation yielded 109. Oxidation fol-
lowed 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 di-
merization 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 reso-
lutions. 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.
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 and 124.
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.
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-hydroxaldehyde 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.

Epoxodon (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 epoxodon (+)-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 (+)-
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 an 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)-, 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
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]. \( \alpha \)-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-
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-pquinol [114] in order to introduce the required asymmetry (scheme 25). p-Benzoxquinone dimethylmonosacetal (163) reacted with the lithium anion of (R)-methyl-p-tolylsulfoxide, and then was subjected to hydrolysis of the acetal to afford sulfoxide 164. Diastereoselective addition of AlMe3 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-tolylsulfonyl 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-hydroxysulfone 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 trartate-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.

**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 triarylborane 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/O2 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 (+)-ambucic acid (14) and its related dimer (+)-torreyanic acid (38), confirming their absolute stereochemistry [120]. By using a similar strategy as shown above, ambucic 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 (+)-ambucic 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 epoxywinol A (31). 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 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 epoxywinol A, with a solvent dependent ratio.

These authors also reported the synthesis of epoxywinol A (31), from monomeric ECH (8), conducted through the formation of an alkoxy silanol 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. Grafe and co-workers isolated (+)-hexacyclinol from a siberian fungus and proposed the structure shown in figure 5, containing an epoxyketone and a highly strained 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, Rychynovsky proposed an alternative structure [67] (Fig. 5) based on 13C-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 alkenyl side chain to afford 199. Deprotection and further standing at room temperature allowed the preparation of “pre-hexacyclinol” (54) by a highly diastereoselective Diels-Alder dimerization of the epoxyquinol monomer. S$_2$2’ 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. Methylation of epoxyketone afforded 200. 1,3-Dipolar cycloaddition of vinyl epoxide with Zr(IV) alkoxide allowed spiroisoxazoline natural product (+)-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
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 HfCl₄ at low temperature, preferentially yielded the endo adduct 204 with high diastereoselectivity. Iodolactonization of this compound allowed the recovery of the chiral auxiliary and recrystallization afforded 205 with 99% ee. Lactone hydrolysis permitted epoxide formation by nucleophilic 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 SiO₂ 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
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 6π-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 205. 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...
Reduction of the carbonyl generated 222 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-cyclohexanediol 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 generated epoxynone 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.
ozonolysis, and was then subjected to an intramolecular aldol condensation and elimination to deliver enone \( \text{241} \). Stereoselective epoxidation with \( \text{t-butylhydroperoxide} \) gave \( \text{242} \) quantitatively as a single stereoisomer. Completion of the epoxycyclohexenone core was achieved through an \( \alpha \)-selenylation followed by oxidative elimination. \( \alpha \)-Bromination of \( \text{243} \) permitted Stille cross-coupling over \( \text{244} \) for the insertion of alkenyl side chain. Deprotection of the hydroxyl groups afforded the monomeric \( \text{ECH} \) (8). Finally epoxynolns 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 \( \text{250} \). It was prepared from commercially available diol \( \text{245} \), em-
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 CH2Cl2 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 MnO2, 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, 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, which was used for the preparation of the antitumor agent (+)-ottelione A [138].
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].
**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 stereocore 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 acetone 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 stoichiometric reductant. Optimization of Ru(p-cymene)((S,S)-TsDPEN) percentage was also described. Typical retro Diels-Alder conditions (heating at 170°C) 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 epoxyquinone 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].
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].

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. Deoxegenation followed by cleavage of the cyclopropane ring gave the iodoketone 290. Deiodination, retro Diels-Alder reaction, mesylation, acetone 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.
Enantioselective Synthesis of Natural Epoxyquinoids

Scheme 47.

Scheme 48.
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-isopropylidene 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 methodology 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-Benzooquinone (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-
Enantioselective Synthesis of Natural Epoxyquinoids

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 $\pi$-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,
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,
treatment with \( p \)-MeOC\(_6\)H\(_4\)OH, 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-catalyzed 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 bromoacetdehyde 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.
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 rearrangement 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 vinilologous 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.
Isariotin E (364) is a spiro-epoxyenone (Fig. 6) isolated from entomopathic 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].

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...
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 monosubstituted 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.

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LIST OF ABBREVIATIONS

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Ac = acetyl
acac = acetylacetonyl
AIBN = azobisisobutyronitrile
aq. = aqueous
BHT = 2,6-di-r-butyl-p-cresol
Boc = t-butoxy carbonyl
BPS = t-butyldimethylsilyl
cryst. = crystallization
CSA = camphorsulphonic acid
Cy = cyclohexyl
dba = dibenzylideneacetone
DBMP = 2,6-di-r-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
DIEA = diisopropylethylamine
DIPT = diisopropyl tartrate
DMAP = N,N-4-dimethyaminopyridine
DME = 1,2-dimethoxyethane
DMF = N,N-dimethylformamide
DMP = Dess-Martin periodinane
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 diisopropylamide
m-CPBA = m-chloroperoxybenzoic 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 = phenylidonium 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-toluenesulphonate
p-TsOH = p-toluenesulphonic acid
Py = pyridine
PyBop = (benzotriazol-1-yl-oxy)tripyrrolidinophosphoniumhexafluorophosphate
quant. = quantitative
rt = room temperature
TBAF = tetra-n-butylammonium fluoride
TBHP = r-butyl hydroperoxide
TBME = r-butylmethylether
TBS = r-butylmethylsilyl
TEMPO = 2,2,6,6-tetramethyl-1-piperidyloxy free radical
TES = triethylsilyle
TF = trifluoromethanesulfonyl
TFAA = trifluoroacetic acid
THF = tetrahydrofuran
TMS = trimethylsilyl
TPAP = tetrapropylammonium perruthenate
Tr = triphenylmethyl```

Enantioselective Synthesis of Natural Epoxyquinoids


Troc = trichloroethoxycarbonyl
TSDEN = N-tyosyl-1,2-diphenylethylene-1,2-diamine
Δ = heat

REFERENCES


Pandoli et al.
Enantioselective Synthesis of Natural Epoxyquinoids


