Naturally Occurring Cyclohexane Epoxides: Sources, Biological Activities, and Synthesis†

José Marco-Contelles,*,‡ María Teresa Molina,§ and Shazia Anjum‡,||

Laboratorio de Radicales Libres (IQOG, CSIC) and Instituto de Química Médica (CSIC), C/Juan de la Cierva, 3, 28006-Madrid, Spain

Received July 30, 2002

Contents

† This paper is dedicated respectfully to Professor José Luis Soto (Universidad Complutense de Madrid) on the occasion of his retirement and in recognition of both teaching and research in heterocyclic chemistry.

* To whom correspondence should be addressed.
‡ Laboratorio de Radicales Libres (IQOG, CSIC).
§ Instituto de Química Médica (CSIC).
|| Permanent address: PCSIR Laboratories Complex, Karachi-75280, Pakistan.

10.1021/cr980013j CCC: $48.50
Published on Web 04/21/2004

José Marco Contelles studied chemistry at the Universidad Complutense de Madrid (UCM) (graduating with honors), where he obtained his Ph.D. degree under Professor Benjamín Rodríguez (Instituto de Química Orgánica, Consejo Superior de Investigaciones Científicas, CSIC) in 1984. After two years working as a postdoctoral fellow under Dr. H.-P. Husson (Institut de Chimie de Substance Naturelles, CNRS, Gif-sur-Yvette, France) (CNRS methods in asymmetric synthesis) (1984–85), he worked as an associate researcher under Professor Wolfgang Oppolzer (Département de Chimie Organique, Genève, Suisse) (aldol reaction) (1986) and was a visiting professor at the Department of Chemistry, Duke University, NC, working with Professor Fraser-Reid (free radical chemistry; annulated furanoses; formal total synthesis of phyllantocin). In 1986 he was appointed as Associate Researcher, and in 1992 he was promoted to Research Scientist in the CSIC (Spain). He was an Invited Professor at the Université Pierre et Marie Curie, Paris VI (June 2000), at the Université Jules Verne-Picardie (Amiens, France) (May 2003), and at the Okayama University (Faculty of Engineering) (September 2003). In 2002 he was awarded the French–Spanish award of the French Chemical Society. His present interests include the development of new synthetic methodologies in carbohydrates, free radical chemistry, organometallic chemistry (Pauson–Khand reaction, $PtCl_2$-mediated cycloisomerization of polyunsaturated precursors), and synthesis/biological evaluation of heterocyclic systems (CSIC reaction, tacrine analogues). He is the author of 154 scientific articles (146 papers and 8 reviews), 4 chapters in books, and 6 patents.

María Teresa Molina was born in Madrid and studied chemistry (Honors) at the Universidad Complutense de Madrid. She received her Ph.D. degree in 1985 (Institute of Organic Chemistry, CSIC) under the supervision of Professor Francisco Fariña. She was a postdoctoral fellow from CSIC (1985–1986) and a Fulbright-MEC fellow (1986–1988) in the United States working at the Department of Chemistry (Iowa State University) with Professor George Kraus (1985–1987) and at the University of Kansas (Department of Medicinal Chemistry) with Professors Lester Mitscher and Angelo Vedani (1987–88). In 1987 she was appointed as Tenured Scientist working at the Institute of Medicinal Chemistry (CSIC). Her research interests are the synthesis of quinones and heterocyclic systems with biological activity and the development of new synthetic methods.

Shazia Anjum was born in 1972 in Pakistan. Her training as a chemist started at Bahaudin Zakariya University, Multan, and afterward at H. E. J. Research Institute of Chemistry, Karachi University, Pakistan, where she earned her Ph.D. degree under the supervision of Professor Atta-ur Rahman in 1999. Her doctoral thesis concerned structure elucidation and synthesis of bioactive natural products. After a year of working in the Pakistan Council of Scientific and Industrial Research Laboratories, Karachi, as a Senior Scientific Officer, she was appointed as an Assistant Professor in the H. E. J. Research Institute of Chemistry, Karachi University, Pakistan. At present, Dr. Anjum is working on transition-metal-mediated cycloisomerization of enynes, synthetic applications to natural products, with Professor José Luis Marco Contelles as a postdoctoral fellow at the Consejo Superior de Investigaciones Cientificas, Madrid, Spain. Her current research interests have revolved around the design and execution of multistep natural products syntheses with particular emphasis on metal catalysis.

1. Introduction

The frequent natural occurrence of cyclohexane epoxides, coupled with the wide range of interesting biological activities that they display, has made these compounds of considerable interest to biologists, pharmacologists, and synthetic chemists. Exploration of these compounds has been aided by the remarkable advances in the field of asymmetric synthesis

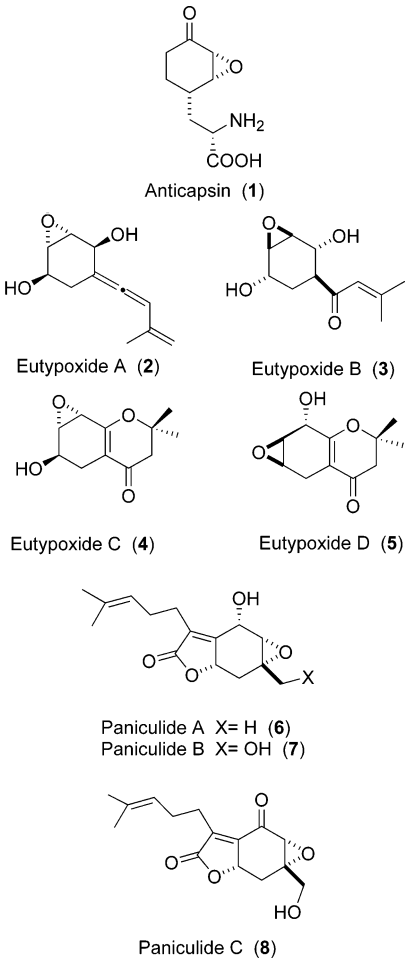


Figure 1. Cyclohexane monoepoxides.

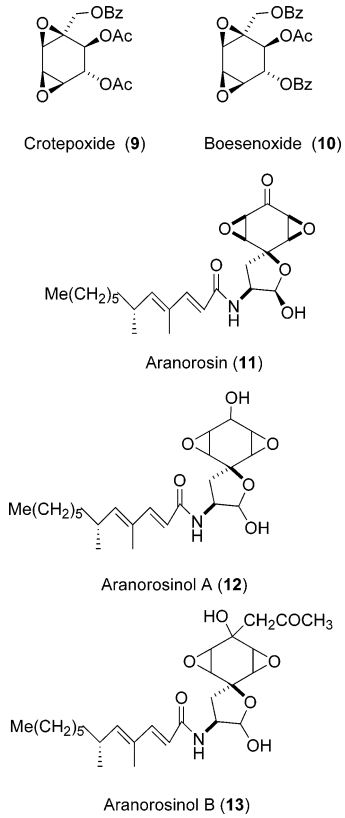


Figure 2. Cyclohexane bisepoxides.

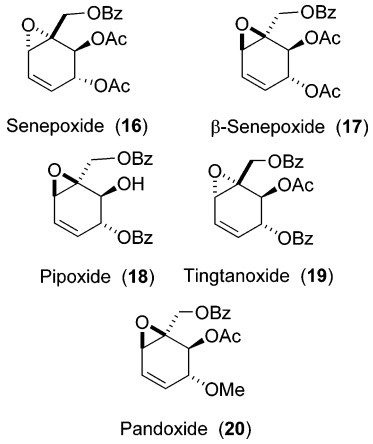


Figure 3. Cyclohexene monoepoxides.

of bioactive natural products with many stereogenic centers that have occurred over the past 30 years. Prior to these advances, syntheses of this type were quite challenging.

The first review of naturally occurring cyclohexene epoxides was published in 1986[1a] and mostly focused on the chemistry and biology of crotepoxide, senepoxide, and pipoxide, which are three, now well-known, members of this group of molecules. In 1990, soon after this initial report appeared, a review dedicated to conduritols and related compounds was published that contained a brief reference to the cyclohexane epoxides.[1b] Finally, a review of cyclophellitol chemistry by one of us appeared in 2001.[2]

Since these pioneering reports, the number of new molecules has considerably increased, their biological activities have been better documented, and significant efforts have been devoted to the synthesis of these molecules in racemic or enantiomerically pure form. Due to these advances, an updated review covering the new developments in this area since 1990 is warranted. This review will emphasize the isolation, biological activities, and syntheses of naturally occurring cyclohexane epoxides, particularly those isolated from fungal sources.

This review has been divided into sections according to the type and number of both epoxides and other significant functional groups found on the cyclohexane ring of the cyclohexane epoxides discussed, as follows: (1) Cyclohexane monoepoxides [anticapsin (**1**), eutypoxides A−D (**2**−**5**), paniculides A−C (**6**−**8**)] (Figure 1); (2) Cyclohexane bisepoxides [crotepoxide (**9**), boesenoxide (**10**), aranorosin (**11**), aranorosinol A (**12**), aranorosinol B (**13**)] (Figure 2); (3) Cyclohexene monoepoxides [senepoxide (**16**), *β*-senepoxide (**17**), pipoxide (**18**), tingtanoxide (**19**), pandoxide (**20**)] (Figure 3); (4) Quinone monoepoxides [eupenoxide (**188**), theobroxide (**189**), asperpentyn (**190**), epoformin (**191**), epiepoformin (**192**), epoxydon (**193**), epiepoxydon (**194**), harveynone (**195**), tricholomenyn A (**196**), phyllostine (**197**), panepoxydon (**247**), isopanepoxydon (**248**), cycloepoxydon (**249**)] (Figure 4), [parasitenone (**261**), terreic acid (**262**), terremutin (**263**), bromoxone (**264**), acetylbromoxone (**265**), shikimic acid derivative (**272**), chaloxone (**273**), epoxydeliquinone (**281**), lachnumon (**282**), lachnumol A (**283**), A80915 (**284**), UCF76 B (**285**)] (Figure 5), [epoxyquinol (**286**), ambuic acid (**287**), flagranones

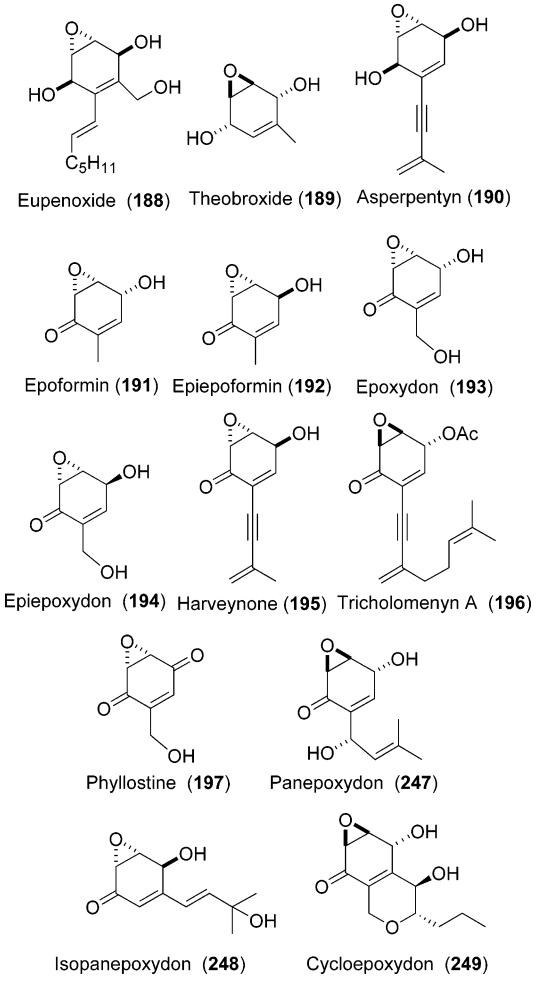


Figure 4.

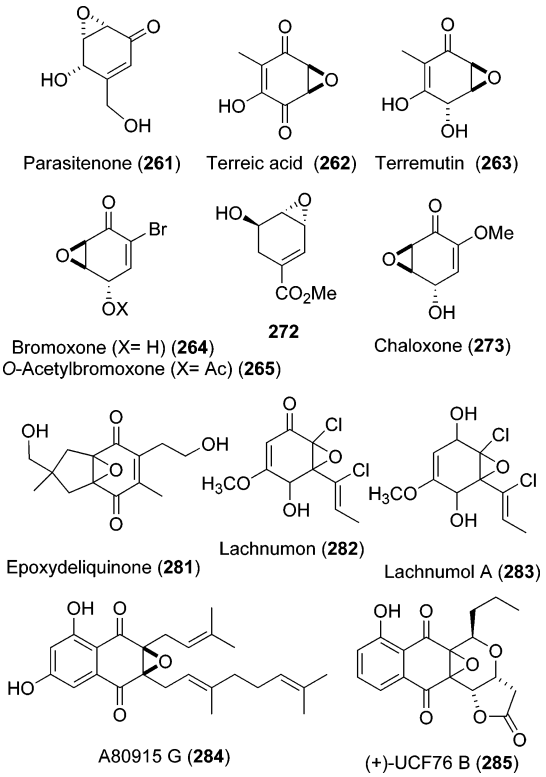


Figure 5.

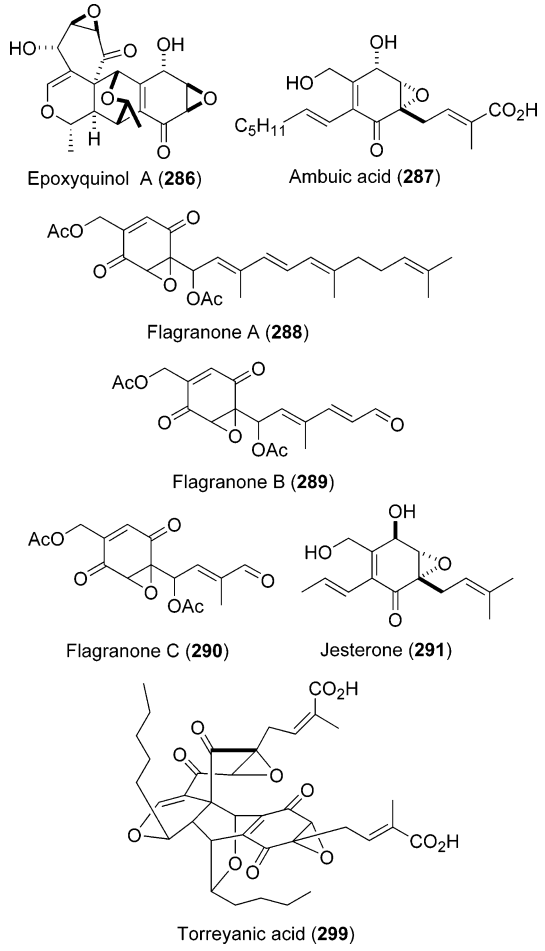


Figure 6.

A−C (**288**−**290**), jesterone (**291**), torreyanic acid (**299**)] (Figure 6), [epoxysorbicillinol (**304**), scyphostatin (**314**), yanuthone A (**331**), oligosporons (**332a**−**c**), macrophorin A (**333**)] (Figure 7); and (5) 2-Aminoepoxyquinones [manumycin A (**334**), MM14201 (**335**), LL-C10037α (**336**), MT 35214 (**337**), G-7063−2 (**338**), 2061-B (**339**), KT 8110 (**340**), epoxyquinomycins A−D (**341**−**344**)] (Figure 8).

The manumycin class of epoxides has been well covered in the literature and therefore is not included in this review. Specifically, the manumycin group of metabolites has been the subject of a review covering the literature up to 1997,[3a] a feature article by Taylor,[3b] and accounts within reviews of polyene natural products published in 2000 by Nájera and Yus[3c] and in 2002 by Thirsk and Whiting.[3d]

Epoxycyclohexane containing natural products isolated from higher plants (for instance, epoxyroyleanone[4a] and the 17-hydroxywithanolides[4b]) comprise a large group of diverse molecules which is also beyond the scope of this review and will not be discussed here. In addition, some marine cyanobacteria have been found to produce epoxycyclohexanes such as those of the malyngamide family (malyngamide C, see Figure 9). These have been the subject of a recent review and will not be discussed here.[5]

Finally, the interested reader is directed to an excellent recent review by Krohn[6] on the epoxycyclohexene natural products derived from naph-

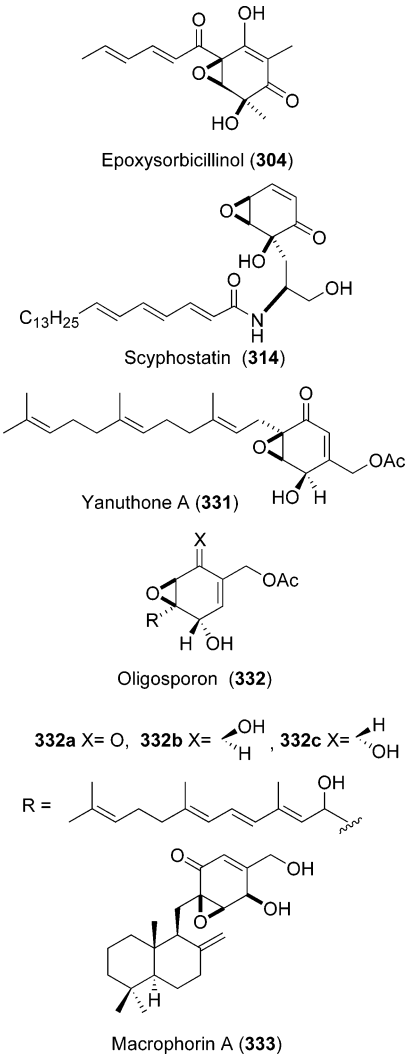


Figure 7.

thalenoid precursors (specifically, palmarumycin C_2, diepoxin α, preussomerin A, cladospirone, and spiroxin A) (Figure 9).

2. Cyclohexane Monoepoxides

2.1. Anticapsin

Anticapsin (**1**) (Figure 1) is an amino acid antibiotic that was isolated in 1970 from *Streptomyces griseoplanus*[7a] and *Bacillus subtilis*[7b] and that inhibits hyaluronic acid capsule formation in *Streptococcus pyogenes*.[7a] Anticapsin is an active-site-directed irreversible inhibitor of glucosamine 6-phosphate synthetase from *Escherichia coli*.[7b] It also occurs as the *C*-terminal amino acid in bacilysin, a substance that is formed by certain bacteria and causes lysis in growing *Staphylococci*.[7b] The structure and absolute configuration of anticapsin was assigned by CD/ORD measurements and ^{1}H NMR analysis.[7b,c] Later research showed that the proposed structure was incorrect and that the actual arrangement of the protons at C-3 and C-4 is cis.[7d,e]

2.2. Eutypoxide B

The fungus *Eutypa lata* is one of the pathogenic agents responsible for the vineyard dieback observed during the late 1970s in Switzerland and France.[8] Biological studies have shown that the disease is linked to a toxic secondary fungal metabolite which

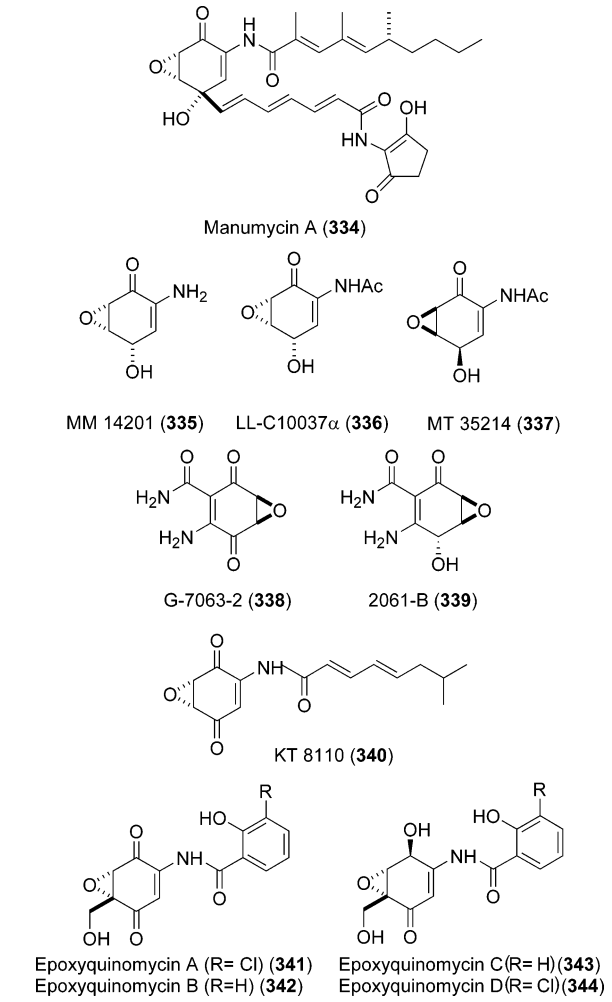


Figure 8.

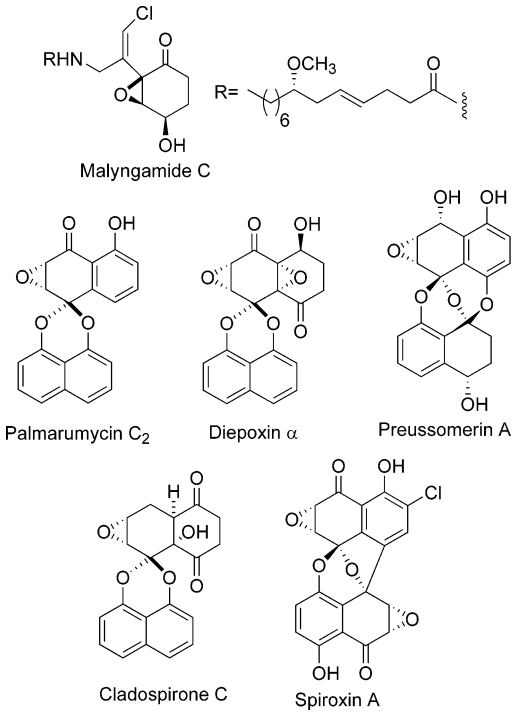


Figure 9.

is transferred by the sap from its point of origin to new branches, causing them to wither and ultimately leading to the death of the plant. This process is known as 'eutypiosis', and there are no known means of controlling it. In a search for the pathogenically active secondary metabolites in the culture medium of *Eutypa lata*, four epoxycyclohexanes have been isolated: eutypoxide A [5-(methylbuta-1,3-dienylidene)-2,3-epoxycyclohexane-1,4-diol] (**2**), (−)-eutypoxide B [1-[3,4-epoxy-2,5-dihydroxycyclohexyl]-3-methyl-2-buten-one] (**3**), eutypoxide C [6-hydroxy-2,2-dimethyl-5,6,7,8-tetrahydro-7,8-epoxychroman-4-one] (**4**), and eutypoxide D [8-hydroxy-2,2-dimethyl-5,6,7,8-tetrahydro-6,7-epoxychroman-4-one] (**5**) (Figure 1). The structures of these molecules were established by a combination of X-ray analysis, spectroscopy, and chemical techniques.[8]

2.3. Paniculides A–C

Callus cultures, which were derived from hypocotyl and stem tissues of *Andrographis paniculata* Nees (Acanthaceae) and grown in liquid-shake culture, produced paniculide A (**6**), paniculide B (**7**), and paniculide C (**8**). These compounds were isolated and characterized by Overton and co-workers in 1968 (Figure 1).[9a] The structures of these highly oxygenated lactones were established by spectroscopic methods,[9a] and an X-ray analysis of paniculide B bis-*p*-bromobenzoate confirmed its structure.[9b] All of these compounds are members of the bisabolane class of sesquiterpenes, since they are structurally related to γ-bisabolene.

3. Cyclohexane Bisepoxides

3.1. Crotepoxide

(+)-Crotepoxide (**9**) (Figure 2) was isolated in the late 1960s from *Croton macrostachys* by Kupchan and co-workers.[10] Almost simultaneously a similar product was found in *Piper futokadzura* by Takahashi and was named "futoxide".[11] The structure of crotepoxide was firmly established by chemical transformations[12] and X-ray analysis.[13] Since then, crotepoxide has also been isolated from *Piper brachystachyum*,[14a] *Piper clarkii*,[14b] *Kaempferia rotunda*,[14c] and *Kaempferia angustifolia*.[14d]

Crotepoxide showed significant inhibitory activity against Lewis lung carcinoma in mice (LL) and Walker intramuscular carcinosarcoma in rats (WM).[12a] It also inhibited the binding of [^{3}H]platelet-activating factor to human platelets and leukocytes.[12b] However, it did not affect platelet aggregation induced by collagen and ADP.[15]

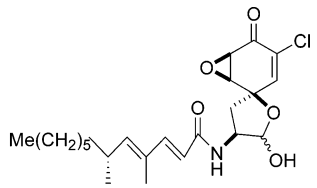
3.2. Boesenoxide

(+)-Boesenoxide (**10**) (Figure 2) and four novel oxygenated cyclohexane epoxide derivatives were isolated from the stem bark of *Monanthotaxis buchananii*.[16a] The new compounds were identified as (+)-pipoxide-2-Me ether, monanthadiepoxide Me ether, epimonanthadiepoxide, and 1α-benzoyloxymethyl-3α-benzoyloxycyclohex-5-en-1β,2β,4β-triol. Boesenoxide was also found in a new *Boesenbergia* species (Zingiberaceae).[16b]

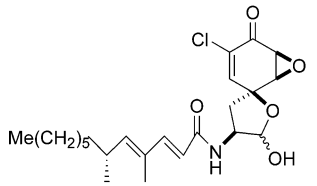
3.3. Aranorosin

Aranorosin (**11**) (Figure 2), which is an antifungal antibiotic, was isolated from the culture filtrate and mycelium of the *Pseudoarachniotus roseus* strain.[17] Aranorosin contains a 1-oxaspiro[4,5]decane ring system. The structure of aranorosin was established by chemical and spectroscopic (mainly NMR) methods,[17a,b] and an X-ray analysis of aranorosin was published by Taylor et al. in 1994.[17d] Two new secondary metabolites, aranorosinol A (**12**) and aranorosinol B (**13**) (Figure 2), were also isolated from a strain of *Pseudoarachniotus roseus*. Their structures were elucidated on the basis of their spectral properties and chemical transformations and were found to be similar to that of aranorosin isolated from the same strain.[17c] Two additional cyclohexane monoepoxide metabolites related to aranorosin (**11**), namely, aranochlor A (**14**) and aranochlor B (**15**) (Chart 1), were isolated from *Pseudoarachniotus roseus*. These compounds inhibit a variety of bacterial and fungal strains.[17e]

Chart 1



Aranochlor A (**14**)



Aranochlor B (**15**)

4. Cyclohexene Monoepoxides

4.1. Senepoxide and β-Senepoxide

(−)-Senepoxide (**16**) (Figure 3) was isolated from *Uvaria catocarpa*.[18] Its structure and absolute configuration were deduced by correlating its spectroscopic and chemical properties with compounds of known stereostructures and were confirmed by X-ray analysis.[19] (+)-β-Senepoxide (**17**) (Figure 3) was isolated from *Uvaria ferruginea* (Annonaceae).[20]

4.2. Pipoxide

The cyclohexane epoxide (+)-pipoxide (**18**) (Figure 3) was first isolated from *Piper hookeri*.[21] The structure proposed for this compound by Atal and coworkers in 1970[21] was revised following detailed spectroscopic analysis by Joshi[22] and Ganem.[23] The absolute configuration of (+)-pipoxide was later assigned by Ganem based on CD spectral studies.[24] The genus *Uvaria* (Annonaceae) has been extensively

studied and continues to yield cyclohexane epoxides, including some which have been previously undiscovered. (−)-Pipoxide has been isolated from the whole plant of *Uvaria pandensis*,[25a] from the chloroform extract of the root bark of *Uvaria dependens*,[25b] and from the rhizomes of *Kaempferia angustifolia*.[25c]

4.3. Tingtanoxide

(−)-Tingtanoxide (**19**) (Figure 3), *β*-senepoxide, and their diene precursors were isolated from *Uvaria ferruginea* (Annonaceae).[20] Their structures and absolute configurations were determined by spectroscopic and chemical correlations with compounds of known stereostructures.

4.4. Pandoxide

The new cyclohexene-type epoxide (+)-pandoxide (**20**) (Figure 3) was isolated from *Uvaria pandensis*, together with the previously mentioned (+)-*β*-senepoxide and (−)-pipoxide.[25a] Their structures and stereochemical configurations were determined by spectroscopic methods.

5. Syntheses of Cyclohexane Monoepoxides, Cyclohexane Bisepoxides, and Cyclohexene Monoepoxides

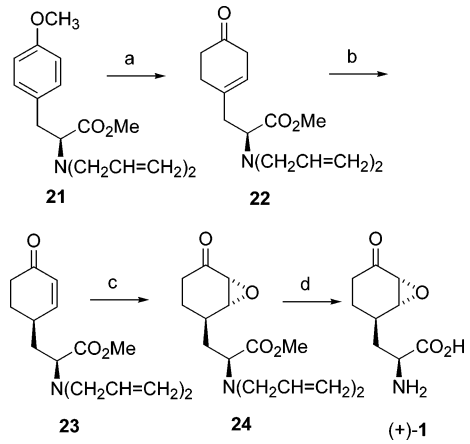
5.1. Synthesis of Anticapsin

Syntheses of anticapsin (**1**) (Figure 1) have been reported by Rickards,[26] Ganem,[27] Souchet,[28] Crossley,[7d] Baldwin,[29] and Wild.[30] However, the first three syntheses[26−28] did not actually make the natural product, since its stereostructure had been misassigned, and they instead made the incorrectly reported stereoisomer. The correct stereochemistry for anticapsin was clarified by Crossley,[7d] who suggested that the epoxide was cis to the pendant side chain. That same year Baldwin and co-workers[7e,29] arrived at an identical conclusion after achieving the enantioselective synthesis of anticapsin. Finally, Wild,[30] in an independent account, reported the total synthesis of anticapsin, bacilysin, and other related analogues.

5.1.1. Ganem's Approach

Previous investigators were concerned that enantiomerically pure tyrosine would not be useful as a starting material for the synthesis of anticapsin, since it could form an intermediate enone and undergo 1,4-addition rather than following the desired reaction pathway. However, Ganem[27] circumvented this potential problem by first protecting the tyrosine as the *N*,*N*-diallyl derivative **21** (Scheme 1) and then submitting it to Birch reaction conditions followed by acid hydrolysis. This method gave product **22** in 83% yield, while forced acid hydrolysis afforded an equilibrium mixture of ketones **22** and **23**, from which **23** was isolated in 32% yield. Carrying out the epoxidation under basic conditions gave a mixture of cis and trans epoxides in a 5:2 ratio. The trans isomer **24** (isolated in 23% yield) was submitted to amine deprotection and ester hydrolysis under basic conditions to give (+)-**1** (Scheme 1). No NMR data for this synthetic *pseudo-anticapsin* were reported, and the optical rotation of this sample {$[\alpha]^{25}_D$ + 4 (*c* 0.2, H_2O}} was quite different from the value reported for natural anticapsin {$[\alpha]^{25}_D$ + 125 (*c* 1, H_2O}} as well as the value measured from an authentic sample {$[\alpha]^{25}_D$ + 21 (*c* 0.2, H_2O}}.[27] However, the authors were confident that they had synthesized natural (+)-anticapsin and suggested that some epimerization could have occurred during the process.[27]

Scheme 1. Ganem's Approach for the Synthesis of (+)-Anticapsin (1)[a]

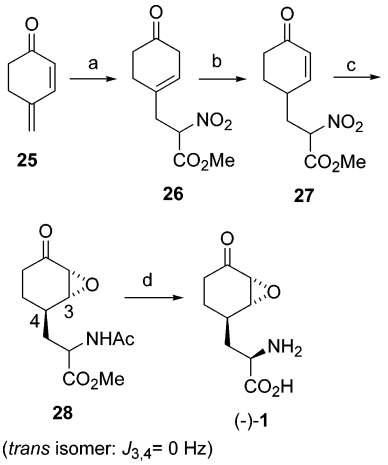


[a] Reagents: (a) (i) Li, NH_3 (83%), (ii) 1% HCl (99%); (b) HCl, DMSO (32%); (c) H_2O_2, MeONa, CH_3OH (23%); (d) (i) $(Ph_3P)_3RhCl$, (ii) NaOH (yield not given).

5.1.2. Rickards' Approach

Rickards[26] synthesis of anticapsin started from enone **25** (Scheme 2), which he reacted with methyl nitroacetate to produce ketone **26** in 95% yield. Equilibration of this ketone under mild acid conditions gave a mixture of **26** and the *α*,*β*-unsaturated ketone **27** (1:1 ratio). Ketone **27** (as a 1:1 mixture of isomers) was transformed into an epoxide, which after hydrogenation and acetylation afforded compound **28** as a mixture of separable cis and trans isomers (4:1 ratio) in 35% yield. The cis isomers (1:1

Scheme 2. Rickards' Approach for the Synthesis of (+)-Anticapsin (1)[a]



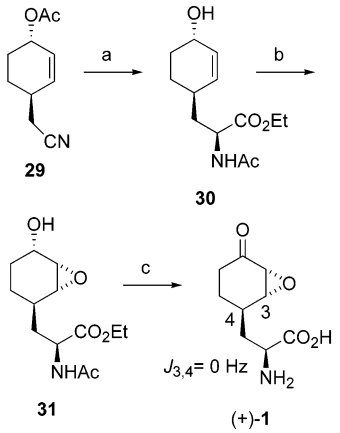
[a] Reagents: (a) methyl nitroacetate (95%); (b) 1%HCl, DMSO; (c) (i) H_2O_2, NaOH, CH_3OH (79%), (ii) H_2, Ac_2O (35%); (d) (from pure trans isomer) (i) NaOH, (ii) porcine kidney acylase (9%).

ratio) showed coupling constants of 2.0 Hz between H-3 and H-4, while the trans isomers showed virtually no coupling between these hydrogens. Since the natural product had been incorrectly reported to also show no coupling between these hydrogens, the authors were led to select the wrong isomer and synthesize a final product that was not anticapsin. After ester hydrolysis of *trans*-**28** in basic medium, followed by enzyme-mediated *N*-deacetylation, a product mixture containing 87% of (−)-**1** was obtained. (No optical rotation was given for this product.) Even if this synthetic scheme had not been plagued by an incorrect structural assignment, it would still be of limited use because it exhibited poor stereocontrol and some racemization occurred in the final step.

5.1.3. Souchet's Approach

Souchet's approach[28] to synthesizing anticapsin (Scheme 3) relied on the preparation of compound **29**, which was obtained from 1,3-cyclohexadiene according to Bäckvall's method,[31] followed by DIBALH reduction of **29** and Strecker synthesis to give racemic **30** with the *S*/*R* configuration in the α-amino acid side chain. Hydroxyl-directed epoxidation from the α-face of pure racemic compound *S*-**31**, followed by oxidation, yielded compound (+)-**1**, which was isolated using the final steps described by Rickards.[26]

Scheme 3. Souchet's Approach for the Synthesis of (+)-Anticapsin (1)[a]

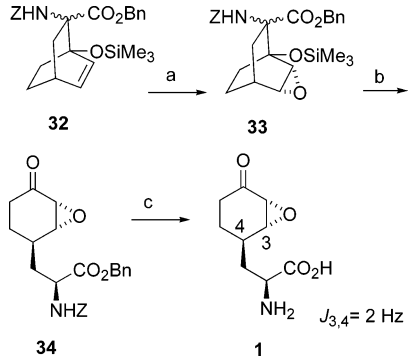


[a] Reagents: (a) (i) DIBALH, (ii) TMSCN (75%), (iii) HCl, EtOH, (iv) Ac_2O (55%); (b) MCPBA (73%); (c) (i) Collins reagent (70%), (ii) 0.1 N NaOH, (iii) porcine kidney acylase (30%).

5.1.4. Crossley's Approach

Crossley's[7d] approach to synthesizing anticapsin is shown in Scheme 4. The Diels−Alder reaction of *N*-benzyloxycarbonyldehydroalanine benzyl ester and 1-trimethylsilyloxycyclohexa-1,3-diene gave a 2:1 mixture of isomers **32** in 80% yield, which, when epoxidized without prior separation, stereoselectively produced the *endo*-epoxides **33**. Quantitative desilylation followed by a base-promoted retro-aldol reaction afforded a mixture of **34** and its α-amino acid side chain epimer in a 1:1 ratio. After crystallization, compound **34** was obtained in pure form and its trans arrangement at carbons C-3 and C-4 was confirmed by X-ray analysis. Finally, mild basic hydrolysis and hydrogenolysis of **34** afforded a compound that

Scheme 4. Crossley's Approach for the Synthesis of (+)-Anticapsin (1)[a]



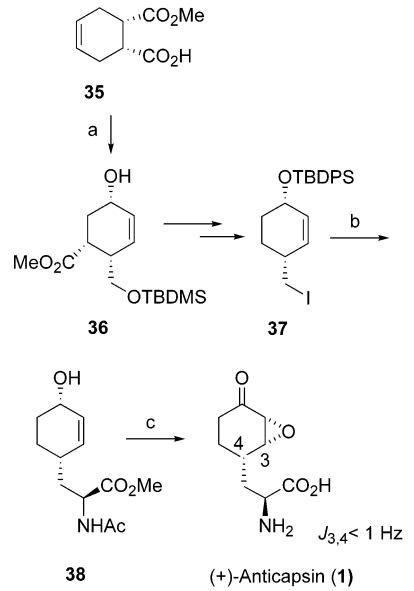
[a] Reagents: (a) (i) MCPBA (86%); (b) *t*-BuOK (94%); (c) (i) 0.2 M NaOH (99%), (ii) 2.0 M HCO_2H, Pd/C (99%).

showed a $J_{3,4}$ coupling constant equal to 2.0 Hz. This is different from the value observed for the natural product anticapsin ($J_{3,4}$ = 0 Hz), which led the authors to suggest that anticapsin has a cis arrangement between the side chain and the epoxide, as shown in compound **1**. Surprisingly, previous researchers who had attempted to synthesize this molecule[26−28] claimed to have prepared the trans product but assigned it a vicinal coupling constant that was not only incorrect, but it did not even correspond to the value found for the natural product. In his full paper,[7d] Crossley claimed that synthesis of compound **1** that would confirm the revised structure, "is well advanced and will be reported shortly";[7d] however, this report has not yet become available.

5.1.5. Baldwin's Approach

The same year that Crossley's paper appeared, Baldwin communicated the first total, enantioselective synthesis of (+)-anticapsin (**1**). His work confirmed that the previously assigned structure was

Scheme 5. Baldwin's Synthesis of (+)-Anticapsin (1)[a]



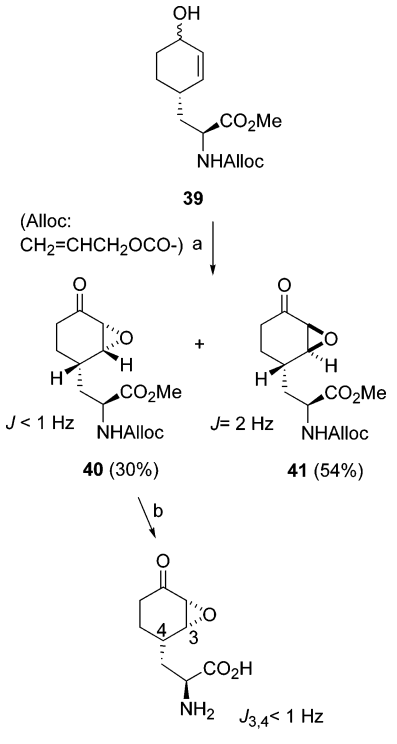
[a] Reagents: (a) ref 32; (b) (i) ref 33 (68%), (ii) HCl then Ac_2O (82%), (iii) NH_4F (88%); (c) (i) MCPBA (88%), (ii) TPAP cat., NMO (89%), (iii) pronase E, then acylase I (80%).

incorrect and should be revised.[29] Baldwin's synthesis began with the chiral, commercially available compound **35** (Scheme 5), from which ester **36**[32] was prepared following the method described by Ohno. The transformation of **36** into derivative **37** then took place in six steps with a 38% yield. Compound **37** was then transformed into the acetamide **38** by subjecting it to an α-amino acid synthesis according to Schöllkopf's methodology,[33] followed by acid hydrolysis, acetylation, and reaction with tetrabutylammonium fluoride. The epoxidation of **38** occurred from the α-face as expected. From there, oxidation and enzyme-catalyzed hydrolysis gave natural anticapsin (**1**) in an elegant synthetic sequence.

5.1.6. Wild's Approach

Wild[30] independently reported the synthesis of anticapsin (Scheme 6), and his conclusions regarding the absolute and relative configuration of this molecule were in good agreement with those reported by Baldwin.[29] (Wild also described the synthesis of the related metabolites chlorotetaine and bacilysin.[30]) The critical intermediate in Wild's path to anticapsin was a mixture of allylic alcohols **39** [which were prepared from the same ketone **25** (Scheme 2) as that used by Rickards[26] in his attempted synthesis of anticapsin]. The epoxidation and oxidation of this material gave a separable mixture of ketoepoxides **40** and **41**, whose relative configurations at carbons C-3 and C-4 were easily assigned from the usual spectroscopic data. The cis isomer **40** was transformed into natural anticapsin (**1**) after standard manipulations.

Scheme 6. Wild's Synthesis of (+)-Anticapsin (1)[a]



[a] Reagents: (a) (i) MCPBA, (ii) CrO_3; (b) (i) $Pd(PPh_3)_4$, (ii) NaOH (58%).

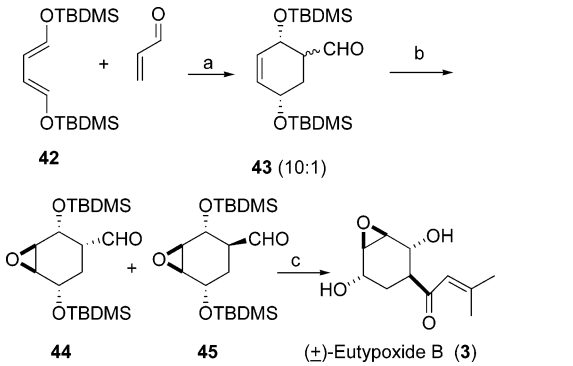
5.2. Synthesis of Eutypoxide B

The synthesis of eutypoxide B (**3**) (Figure 1) has been reported four times. The first synthesis of racemic eutypoxide B was reported by Tabacchi.[8b] Takano then described the asymmetric synthesis of both enantiomers,[34a] while Maycock described the asymmetric synthesis of (+)-eutypoxide B.[35] Finally, Okamura again reported the asymmetric synthesis of both enantiomers.[36]

5.2.1. Tabacchi's Approach

Tabacchi and co-workers described the first synthesis of eutypoxide B (**3**) (Figure 1) in racemic form in 1992.[8b] As shown in Scheme 7, the synthetic sequence started with the Diels−Alder reaction of (*E*,*E*)-1,4-bis{[(*tert*-butyl)dimethylsilyl]oxy}buta-1,3-diene (**42**) and acrolein to give the product **43** as a mixture of epimers in a 10:1 ratio in 76% yield. All efforts to epoxidize this mixture were fruitless, so the aldehyde was reduced, acetylated, and then submitted to epoxidation. Next, the mixture was deacetylated and reoxidized to afford the readily separable compounds **44** and **45** in a 10:1 ratio. In both of these compounds the epoxide was trans to the silyloxy group, so that they differed only in their configuration at C-1, as demonstrated by careful NMR analysis. The synthesis was continued using the minor isomer **45**, which had the correct relative stereochemistry at C-1 and C-2. Reaction of this isomer with 1-lithio-2-methylprop-1-ene, followed by oxidation and then treatment with tetrabutylammonium fluoride, gave eutypoxide B (**3**). Although the chemical yields in this sequence were good, the process seems tedious and had a low overall efficiency due to only the minor intermediate leading to the desired racemic eutypoxide B product.

Scheme 7. Tabacchi's Synthesis of (±)-Eutypoxide B (3)[a]

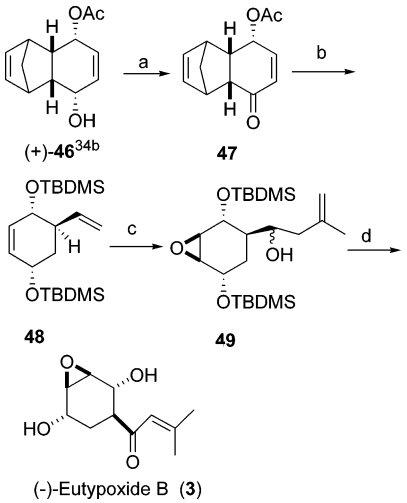


[a] Reagents: (a) 50 °C (76%); (b) (i) $NaBH_4$ (90%), (ii)Ac_2O (89%), (iii) MCPBA (82%), (iv) LiOH (67%), (v) CrO_3 (75%); (c) (from **45**) (i) 1-lithio-2-methyl-propene (84%) (ii) Dess−Martin periodinane (72%), (iii) Bu_4NF (no yield reported).

5.2.2. Takano's Approach

In 1993 Takano published a preliminary report[34a] of the synthesis of enantiomerically pure eutypoxide B (**3**). The general strategy used in his synthesis is similar to that used by Ogasawara for the synthesis of pipoxide (see below, Scheme 35).[58] In this strategy, one of the double bonds of a 1,4-cyclohexadiene was "protected" in the form of a Diels−Alder adduct,

Scheme 8. Takano's Synthesis of (−)-Eutypoxide B (3)[a]



[a] Reagents: (a) PCC (91%); (b) (i) CH_2═$CHMgBr$ (81%), (ii) $NaBH_4$ then K_2CO_3 (92%), (iii) diphenyl ether (73%), (iv) TBDMSCl (94%); (c) (i) MCPBA (74%), (ii) prop-2-enylmagnesium bromide then PCC (89%); (d) (i) DBU (91%), (ii) Bu_4NF (63%).

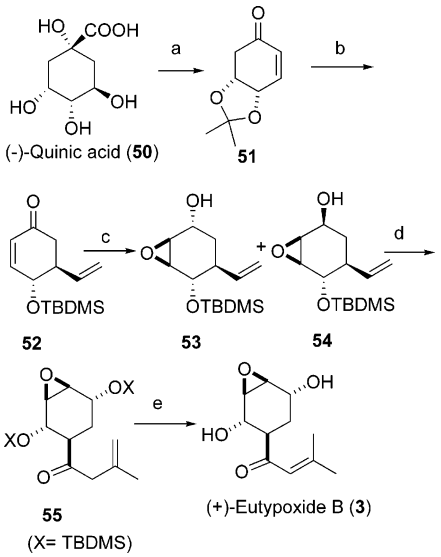
leaving the other double bond free to incorporate the necessary functionality for the synthesis of the target molecule. Steric hindrance from the Diels−Alder adduct promoted stereoselective *exo*-induced reactions at the other double bond in the cyclohexane system. After functionalization of the free double bond, a retro-Diels−Alder reaction restored the "latent" double bond, which was then conveniently manipulated to finish the synthesis of the target molecule. In addition, the starting material **46** was obtained in enantiomerically pure form by lipase-mediated asymmetrization.[34b] The synthetic sequence for the formation of eutypoxide B from **46** is shown in Scheme 8. Natural eutypoxide B (**3**) was obtained in 11 steps from compound **46**, via intermediates **47**−**49**, with a 14% overall yield.

5.2.3. Maycock's Approach

Maycock described the asymmetric synthesis of nonnatural (+)-eutypoxide B (**3**) starting from (−)-quinic acid (**50**) (Scheme 9).[35] As will be seen later, Shing[54] also successfully used compound **50** as a convenient and readily available starting material in his approach to synthesizing mono- and bisepoxycyclohexanes. In addition, Maycock has written a series of papers describing the asymmetric synthesis of other quinone epoxyclohexanes (see below) from (−)-quinic acid (**50**).

(−)-Quinic acid is well suited as a starting material because it not only has the hydroxyl group at C-4 with the correct configuration, but also incorporates a cyclohexane ring with additional functional groups that can be further manipulated. In Maycock's synthesis, compound **51** underwent vinyl addition and formation of the double bond at C-2/C-3 to yield **52**. Compound **52** then underwent epoxidation from the less hindered, β-face followed by reduction of the keto group to give a mixture of allylic alcohols **53** and **54** in a 1:1 ratio. After separation, compound **53** was protected and submitted to side-chain elongation, followed by a series of simple, high-yielding steps, to

Scheme 9. Maycock's Synthesis of (+)-Eutypoxide B (3)[a]



[a] Reagents: (a) (i) acetone, HCl (89%), (ii) Ac_2O, Py (92%), (iii) $LiAlH_4$, then $NaIO_4$ (91%), (iv) Ac_2O, *i*-Pr_2NEt (99%); (b) (i) $(CH_2$═$CH)_2CuCNLi_2$, (ii) NaOH, (iii) TBDMSCl (60% total yield); (c) (i) *t*-BuOOH (94%), (ii) $NaBH_4$, $CeCl_3$ (98%); (d, from **53**) (i) TBDMSCl (99%), (ii) O_3, then Ph_3P (92%), (iii) prop-2-enylmagnesium bromide (96%), (iv) Dess−Martin periodinane (99%); (e) (i) DBN (99%), (ii) Bu_4NF (93%).

give intermediate **55**. After further manipulation of **55**, (+)-eutypoxide B (**3**) was obtained in the efficient and elegant approach shown in Scheme 9.

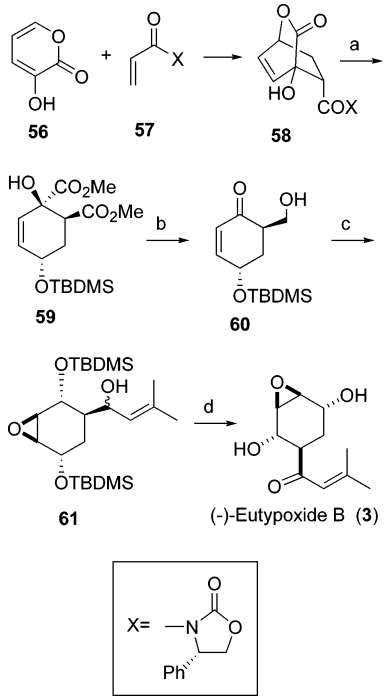
5.2.4. Okamura's Approach

Okamura's approach[36] to the synthesis of eutypoxide B was based on the asymmetric Diels−Alder reaction between 3-hydroxy-2-pyrone (**56**) and the optically active acrylate (−)-**57** (Scheme 10). Compound **58** was isolated from this reaction in almost diastereomerically pure form (de 95%) in 74% yield. After simultaneous lactone opening and ester hydrolysis to liberate the chiral auxiliary, the homochiral intermediate **59** was obtained. In the next set of steps reduction of two carbomethoxy groups and oxidative cleavage of the resulting 1,2-diol afforded the unsaturated ketone **60** in good yield. After reduction, protection, and epoxidation, the free primary alcohol was obtained. Swern oxidation of this alcohol afforded an aldehyde, which underwent the typical side-chain elongation to give product **61**. Finally, oxidation of the secondary alcohol and cleavage of the silyl ether provided natural (−)-eutypoxide B (**3**). Remarkable stereochemical control was observed during the formation of the stereocenters in each step of the synthesis. The authors also described the preparation of (+)-eutypoxide B (**3**) via the same synthetic sequence but by employing enantiomerically pure (+)-**57** as the chiral inductor.[36]

5.3. Syntheses of Paniculides A–C

The paniculides A (**6**), B (**7**), and C (**8**) (Figure 1) have been the subject of continuous interest by several different laboratories over the last 20 years. In chronological order, these efforts have resulted in the synthesis of racemic paniculides A (**6**), B (**7**), and

Scheme 10. Okamura's Synthesis of (−)-Eutypoxide B (3)[a]



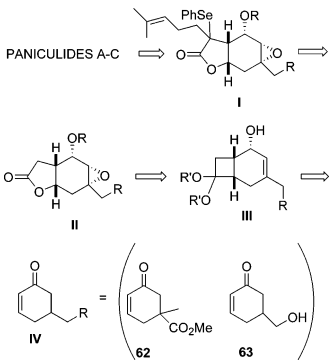
[a] Reagents: (a) (i) MeONa, then TBDMSCl (74%); (b) (i) $LiAlH_4$, then $NaIO_4$ (71%); (c) (i) $NaBH(OAc)_3$ (95%), (ii) TBDMSCl, then MCPBA (77%), (iii) Swern oxidation (66%), (iv) 2-methylpropenylmagnesium bromide (96%); (d) (i) PDC (50%), (ii) Bu_4NF (94%).

C (**8**) (A. B. Smith),[37] the synthesis of racemic paniculide A (A. Yoshikoshi),[38] the formal total synthesis of racemic paniculides B and C (R. Baker),[39] the formal total synthesis of racemic paniculide A (P. A. Jacobi),[40] a formal total synthesis of enantiomeric paniculide B from D-glucose (K. Tadano),[41] the total synthesis of (+)-paniculide A via a catalytic asymmetric Diels−Alder reaction (K. Narasaka),[42] and the formal total synthesis of (+)-paniculide A from D-glucose (N. Chida).[43]

5.3.1. Smith's Method

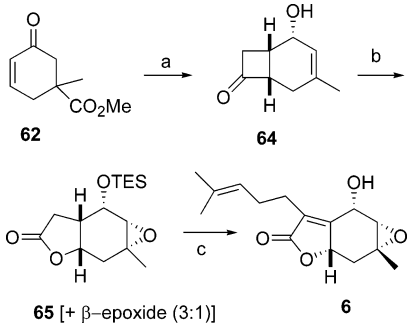
In a piece of pioneering work, A. B. Smith reported a common strategy for the preparation of each of the paniculides.[37] Smith's general retrosynthetic analysis is shown in Scheme 11 and can be summarized as follows: the target molecules could be obtained after selenoxide elimination from bicyclic α-phenylseleno,

Scheme 11. Retrosynthetic Analysis for Paniculides A−C (Smith)[53]



butyrolactones **I** preceded by α-alkylation of bicyclic α-phenylseleno,butyrolactones **II**. Compound **II** could be prepared by Baeyer−Villiger reaction of a bicyclic cyclobutanone, which could in turn be obtained after acid hydrolysis of ketal **III**. Compound **III** could result from a [2+2] cycloaddition of a disubstituted ethylene and an α,β-unsaturated ketone **IV**. In Smith's synthesis of paniculide A the necessary ketone (**IV**) was compound **62**, while for paniculides B and C it was compound **63** (Scheme 11). For simplicity, only the synthetic sequence for paniculide A (**6**) will be commented on here (Scheme 12).

Scheme 12. Smith's Synthesis of (±)-Paniculide A (6)[a]



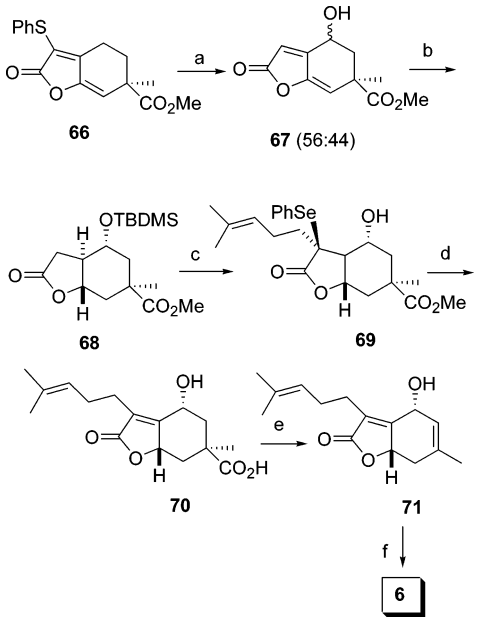
[a] Reagents: (a) (i) hν, 1,1-diethoxyethylene (84%), (ii) NaOH, then $Pb(OAc)_4$ (42%), (iii) $NaBH_4$, (iv) $AcOH/H_2O$ (98%); (b) (i) MCPBA (84%), (ii) (from α-epoxide) TESCl; (c) (i) LDA, 2-methyl-5-iodo-2-pentene (71%), (ii) LiTMP, PhSeCl (49%), (iii) $NaIO_4$ (72%).

The [2+2] cycloaddition of ketone **62** and 1,1-diethoxyethylene gave an adduct which, after standard manipulation, yielded allylic alcohol **64**. Thereafter, the reaction of **64** with MCPBA simultaneously produced the γ-lactone and epoxidized the double bond. This gave a mixture of readily separable epimers (in a 3:1 ratio), wherein the major epimer was the α-epoxide **65**, after protection of the secondary alcohol, as expected. In the following steps, the secondary alcohol was protected and the side chain and phenylselenide group were incorporated by sequential α,α′-dialkylation. Final treatment of the resulting intermediate with sodium periodate not only resulted in formation of the butenolide, but also deprotected the hydroxyl group. Thus, racemic paniculide A was obtained in 10 steps with a 4.2% total yield from ketone **64**. This synthesis has become a key reference for authors working on the synthesis of these molecules. These later authors prepared some of the intermediates described in Smith's pioneering report, in either racemic or enantiomerically pure form, therefore achieving formal total synthesis of the indicated natural products.

5.3.2. Yoshikoshi's Method

Yoshikoshi's approach to paniculide A (**6**) is shown in Scheme 13.[38] He began with bicyclic lactone **66**, which contains suitable functionality to allow additional groups to be incorporated. This adduct was the result of a new vinylfuranone annelation[38c] that combined methyl α-formylpropionate and 2,5-dihydro-3-phenylthio-4-vinylfuran-2-one. Allylic oxidation of **66** with MCPBA followed by treatment with

Scheme 13. Yoshikoshi's Synthesis of (±)-Paniculide A (6)[a]



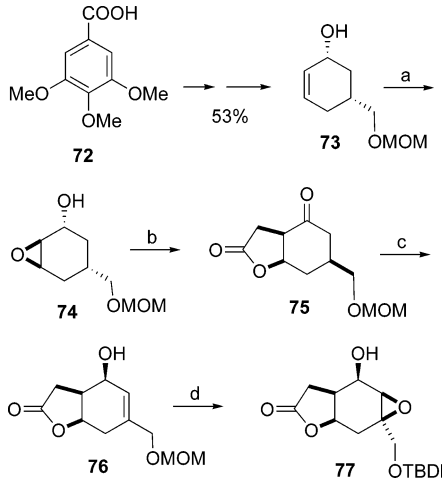
[a] Reagents: (a) MCPBA, then Py/H_2O (62%); (b) (i) (from α-epimer) TBDMSCl, then H_2 (57%); (c) (i) LDA, 2-methyl-5-iodo-2-pentene (81%), (ii) Bu_4NF, then LDA, PhSeCl (62%); (d) KOH, then H_2O_2 (69%); (e) (i) Ac_2O, then $Pb(OAc)_4$ (12%), (ii) K_2CO_3; (f) *t*-BuO_2H (30%).

base gave product **67** as a mixture of α- and *β*-epimers in a 56:44 ratio. Although this step is at the beginning of the synthesis where high yields are particularly desirable, it is the first weak point in Yoshikoshi's synthesis of paniculide A. The synthesis was continued using the α-epimer **67**, from which lactone **68** was isolated after *O*-silylation and stereoselective hydrogenation. Compound **68** then underwent sequential α-alkylation with 1-iodo-4-methylpent-3-ene, reaction with tetrabutylammonium fluoride, and α-alkylation with phenylselenenyl chloride to afford alcohol **69** in good yield. Molecule **69** is well set up for base hydrolysis of the ester followed by selenoxide formation and elimination to give the olefin **70**. After achieving this transformation, compound **70** was acetylated and submitted to oxidative decarboxylation with lead tetraacetate. This is the second weak point in the synthesis, as the yield of compound **71** was only 12%. After deacetylation and hydroxy-directed epoxidation, compound (±)-**6** was finally obtained in 15 steps and 0.2% overall yield, which compares unfavorably with Smith's approach.[37]

5.3.3. Baker's Method

In 1984 Baker and co-workers published, first in preliminary form and later in a full paper,[39] the stereoselective synthesis of lactone **77** (Scheme 14). This lactone was prepared some years earlier by Smith and Richmond, although by a different route, in their total synthesis of paniculides B (**7**) and C (**8**).[37b] As a consequence, Baker's synthesis of lactone **77** constituted a formal total synthesis of these natural products. In Scheme 14 we show the most significant intermediates along this simple, stereocontrolled route to product **77**. Alcohol **73**, obtained

Scheme 14. Baker's Synthesis of Compound 77[a]



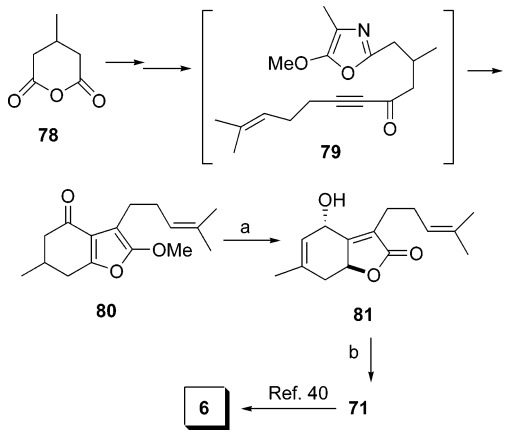
[a] Reagents: (a) (i) TMSCl, (ii) MCPBA, (iii) NH_4Cl (90%); (b) (i) $LiCH_2CO_2Li$ (93%), (ii) PCC (81%); (c) (i) PhSeCl, then H_2O_2 (85%), (ii) $LiEt_3BH$ (92%); (d) (i) HBr (72%), (ii) TBDMSCl (70%), (iii) MCPBA (81%).

in good yield from 3,4,5-trimethoxybenzoic acid (**72**), was protected with a bulky group ($SiMe_3$) in order to direct the epoxidation from the opposite face, so that after acid hydrolysis only epoxide **74** was obtained. The epoxide was opened using dilithioacetate to give the expected lactone, which after oxidation afforded ketone **75**. The reduction of **75** proceeded from the α-face to give an allylic alcohol whose hydroxy-directed epoxidation cleanly provided almost pure epoxide **77** in good yield.

5.3.4. Jacobi's Method

Jacobi's approach to the synthesis of paniculide A (**6**) involved the construction of its skeleton by a new methodology.[40] This was accomplished in a very elegant manner, as shown in Scheme 15. 3-Methylglutaric anhydride (**78**) underwent cycloaddition via intermediate **79** to produce compound **80**, which was isolated in 61% from **78**. Compound **80** was then transformed into product **81** (Scheme 13) by α-alkylation with phenylselenenyl chloride, followed by kinetic deprotonation−protonation, DIBALH reduc-

Scheme 15. Jacobi's Synthesis of (±)-Paniculide A (6)[a]



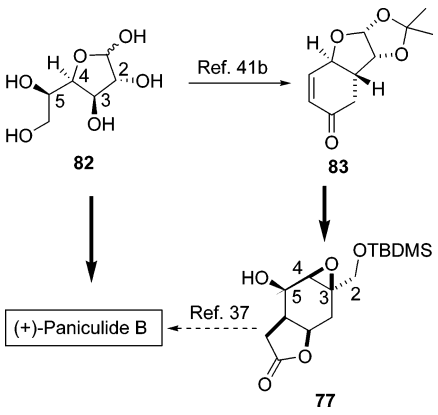
[a] Reagents: (a) (i) LDA, PhSeCl, then LDA, AcOH (94%), (ii) DIBALH, pH 5 (71%), (iii) $NaIO_4$, then Na_2CO_3 (82%); (b) (i) CrO_3/Py, (ii) $NaBH_4$ (90%).

tion, acid hydrolysis, selenoxide formation, and finally elimination. The configuration of **81** at the secondary alcohol was inverted by an additional oxidation and reduction, after which the final transformation of the resulting intermediate **71** was performed as previously described[38a] to give compound **6**.

5.3.5. Tadano's Method

Following the work of Baker and co-workers,[39] who prepared **77** by a different route, Tadano prepared intermediate **77** in enantiomerically pure form[41] in a process that can be considered to be the first chiral approach to this molecule. Tadano's synthesis therefore constitutes a formal chiral, total synthesis of paniculide B (**7**), since, as mentioned above, Smith and Richmond already described the transformation of **77** into paniculide B (Chart 2).[37] Tadano's approach

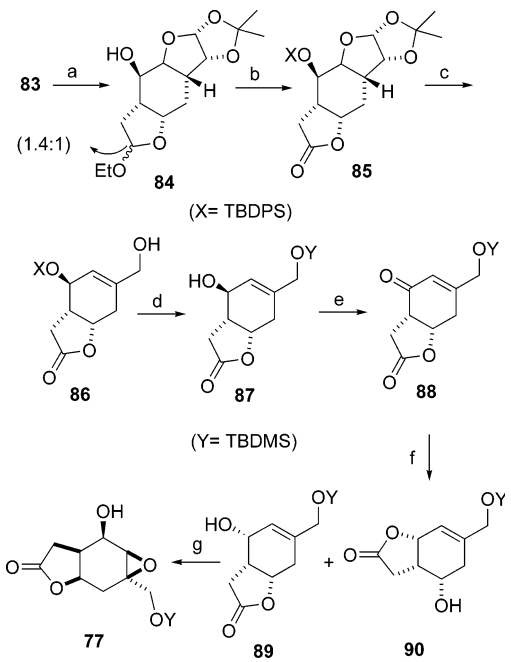
Chart 2



started from D-glucose (**82**) and proceeded via intermediate **83** (Chart 2). Interestingly, none of the stereogenic centers in D-glucose were conserved in product **77**; all of them, except for the configuration at C-5, which was inverted, were destroyed and subsequently restored as the necessary functionality was incorporated. Furthermore, only carbons C-2 to C-5 in D-glucose were preserved in compound **77**.

As shown in Scheme 16, the ketone in product **83** was reduced to form an intermediate allylic alcohol, which underwent palladium-mediated lactol formation with ethyl vinyl ether followed by hydroboration from the less hindered β-face, to give a mixture of compounds **84**. Subsequent protection and oxidation of **84** gave lactone **85**. With this compound in hand, the authors manipulated the 1,2-*O*-isopropylidene group to give alcohol **86** in 59% yield after four steps. The next steps in the synthesis were dedicated to adjusting the protecting groups so that **87** could be obtained. Oxidation of the secondary allylic alcohol in **87** gave ketone **88**. The reduction of the keto group then gave an inseparable mixture of products **89** and **90** in a 1.2:1 ratio. The authors could not find a way to prevent the undesirable side reaction that led to **90** from occurring, and consequently, this step caused a considerable drop in the efficiency of the synthetic scheme. The efficiency was also negatively affected by the number of steps required for protection and deprotection of the hydroxyl groups, as is often a

Scheme 16. Tadano's Synthesis of Compound (+)-77[a]



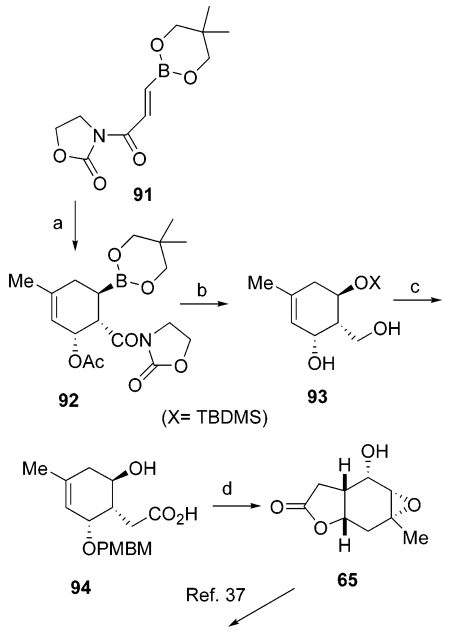
[a] Reagents: (a) (i) $NaBH_4$, (ii) ethyl vinyl ether, $Pd(OAc)_2$ (62%), (iii) B_2H_6, H_2O_2 (74%); (b) TBDPSCl (68%), (ii) Jones reagent (73%); (c) (i) AcOH, (ii) $NaIO_4$, (iii) DBU, (iv) $NaBH_4$ (59%); (d) (i) Bu_4NF, (ii) TBDMSCl (76%); (e) (i) PCC; (f) $NaBH_4$ (79%); (g) (from **89**) MCPBA (93%).

problem when dealing with sugar-derived intermediates. After separation, compound **89** was epoxidized to give product **77**, which showed identical spectroscopic data to those described by Smith.[37] In summary, this is an interesting example of the chiral pool of natural products, specifically D-glucose (**82**), being utilized for the synthesis of an advanced intermediate on the path to paniculide B (**7**).

5.3.6. Narasaka's Method

Narasaka's approach to paniculide A (**6**)[42a] was part of a program directed at applying the chiral, densely functionalized cyclohexane derivative **92** (Scheme 17) to organic synthesis. Compound **92** was obtained from the catalytic Diels−Alder reaction of 3-(3-borylpropenoyl)-1,3-oxazolidin-2-one (**91**) and 1-acetoxy-3-methyl-1,3-butadiene in the presence of a titanium complex prepared from dichlorodiisopropoxytitanium and TADOL.[42b] As shown, compound **92** was readily transformed to incorporate diverse functional groups, culminating in the installation of the lactone and the epoxide, through a series of high-yielding reactions that proceeded via intermediates **93** and **94** (Scheme 17). Finally, enantiomerically pure epoxide **65** was obtained and shown to be identical to the product prepared by Smith and Richmond during their synthesis of paniculide A.[37] Having made compound **65**, the authors completed the first formal total synthesis of paniculide A; however, they repeated the process,[37] with slight modification, to actually obtain synthetic (+)-paniculide A (**6**). The complete synthesis, beginning from starting material **91**, took 19 steps and gave a 7% overall yield of (+)-paniculide A.

Scheme 17. Narasaka's Synthesis of Compound (−)-65[a]

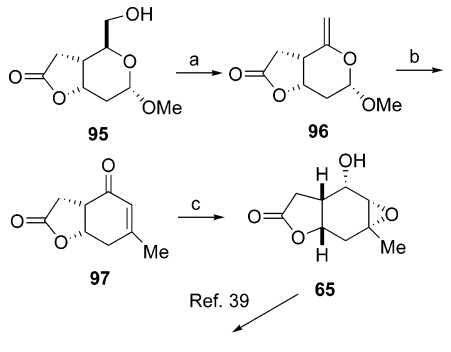


[a] Reagents: (a) 1-acetoxy-3-methyl-1,3-butadiene, TADOL, $TiCl_2(O\textit{i}\text{-}Pr_2)$ (82%); (b) (i) MCPBA, Li_2CO_3 (98%), (ii) TBDMSCl (91%), (iii) $CH_3(CH_2)_7SLi$ (90%), (iv) $LiAlH_4$ (71%); (c) (i) TsCl (89%), (ii) *p*-methoxybenzyl chloride (98%), (iii) NaCN (89%), (iv) Bu_4NF (99%), (v) KOH (97%); (d) (i) DEAD, Ph_3P (99%), (ii) DDQ (87%), (iii) $NaBH_4$, $CeCl_3$ (98%), (iv) MCPBA (52%).

5.3.7. Chida's Method

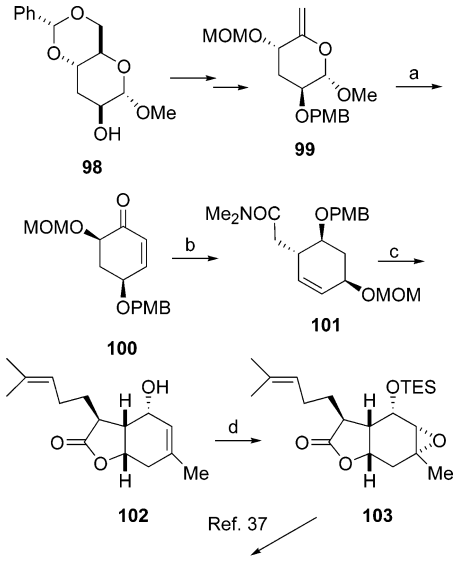
Chida and co-workers also reported a chiral formal total synthesis of (−)-paniculide A (**6**) by performing the synthesis of compound (−)-**65** (Scheme 18).[43] Like Tadano,[41] they used D-glucose (**82**) as their starting material. They also used the Ferrier reaction[44] to prepare the chiral cyclohexane ring system via intermediate **96**, which was in turn prepared from the known lactone **95** as described by Corey and co-workers.[45] The resulting α,β-unsaturated ketone was subjected to the typical protocol for the synthesis of β-methyl α,β-unsaturated ketone **97** as described by Saegusa.[46] Further reduction and epoxidation of the secondary allylic alcohol gave product **65**, which was identical to the product reported by Smith[37] and

Scheme 18. Chida's Synthesis of Compound (−)-65[a]



[a] Reagents: (a) (i) I_2 (85%), (ii) DBU (82%); (b) (i) $Hg(OCOCF_3)_2$ (10−60%), (ii) MsCl, Py (76%), (iii) MeMgBr, TMSCl, $Pd(OAc)_2$ (58%); (c) (i) $NaBH_4$, $CeCl_3$, (ii) MCPBA (38%).

Scheme 19. Chida's Total Synthesis of (+)-Paniculide A (6)[a]



[a] Reagents: (a) (i) $Hg(OCOCF_3)_2$, MsCl, Et_3N (67%), (ii)DBU (62%); (b) (i) $NaBH_4$, $CeCl_3$ (86%), (ii) $CH_3(OCH_3)_2CNMe_2$, Δ (89%); (c) (i) I_2, Bu_3SnH (94%), (ii) LHMDS, 5-iodo-2-methyl-2-pentene (71%), (iii) AcCl, MeOH (93%), (iv) MsCl, (v) DDQ (63%), (vi) PCC (99%), (vii) Me_2CuLi, TMSCl, $Pd(OAc)_2$ (67%), (viii) $NaBH_4$, $CeCl_3$ (70%); (d) (i) *t*-BuOOH (72%), (ii) TESOTf (95%).

Tadano.[41] However, the authors found that with compound **96** the Ferrier reaction was capricious, giving variable yields. They therefore questioned the efficacy of this synthesis and considered an alternative strategy in which the lactone moiety was elaborated using a Claisen rearrangement on a preformed cyclohexene ring.[47] This ring was also obtained via a Ferrier reaction,[44] only on a conveniently functionalized sugar derivative **99** (Scheme 19) that was prepared from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-arabinopyranoside (**98**).[48] The Ferrier reaction on **99**, followed by epimerization at C-2, gave ketone **100**. Reduction of **100** then gave an allylic alcohol that underwent Claisen−Eschenmoser rearrangement to incorporate the two-carbon side chain **101** needed for the lactone formation. After several steps the α-alkylated lactone **102** was obtained from precursor **101** in good yield and without problems. A final stereoselective epoxidation and hydroxyl group protection afforded the known intermediate **103**[37] in 12 steps with a 3.9% overall yield. Having thus synthesized intermediate **103**, the authors achieved a chiral formal synthesis of paniculide A (**6**). Nevertheless, they repeated the described procedure to actually prepare natural compound paniculide A (**6**).

5.4. Syntheses of Crotepoxide, Boesenoxide, β-Senepoxide, Pipoxide, and Tingtanoxide

The syntheses of the cyclohexane bisepoxides crotepoxide (**9**) and boesenoxide (**10**) and the cyclohexene monoepoxides senepoxide (**16**), β-senepoxide (**17**), pipoxide (**18**), and tingtanoxide (**19**) (Figure 3) are usually reported using similar synthetic strategies and common intermediates and, in some cases, by hemisynthesis from natural compounds. In this section we will present an integrated view of the

different synthetic approaches and the key intermediates that have been used for the preparation of these molecules.

(±)-Crotepoxide (**9**) was first prepared by Ichihara in 1975[49] and subsequently prepared by White[50] and Matsumoto.[51] Schlessinger[52] described a formal total synthesis of the racemic mixture, while Ogawa[53] prepared (+)-crotepoxide (**9**) for the first time in enantiomerically pure form from *β*-senepoxide (**17**). In 1996 Shing described the first enantiospecific synthesis of crotepoxide (**9**) and *iso*-crotepoxide from (−)-quinic acid (**50**).[54]

(±)-Senepoxide (**16**) was also prepared for the first time by Ichihara in 1974[55] and subsequently prepared by Ganem[56] and Schlessinger.[52]

Ogawa[57] and Shing[54b] were the first to synthesize (+)-*β*-senepoxide and (−)-*β*-senepoxide (**17**), respectively.

The first total synthesis of (±)-pipoxide (**18**) was achieved by Ganem in 1979.[23] In 1981 a formal total synthesis of (±)-pipoxide was described by Schlessinger.[52] However, only Ogawa[57] and Ogasawara[58] reported the synthesis of enantiomerically pure (+)-pipoxide. Shing, meanwhile, described the synthesis of (+)-pipoxide acetate.[54]

Last, (−)-boesenoxide (**10**) and (−)-tingtanoxide (**19**) have also been prepared by Shing from (−)-quinic acid (**50**) (Scheme 9).[54b] However, no synthesis of pandoxide (**20**) (Figure 3) has yet been reported.

The nonnatural epimers of this series, *iso*-crotepoxide and *ent*-senepoxide, have also been prepared. Specifically, White reported the racemic preparation of *epi*-crotepoxide and *iso*-crotepoxide,[52] Shing reported preparing (−)-*iso*-crotepoxide,[54] and Müller described the synthesis of enantiomerically pure *iso*-crotepoxide and *ent*-senepoxide.[59]

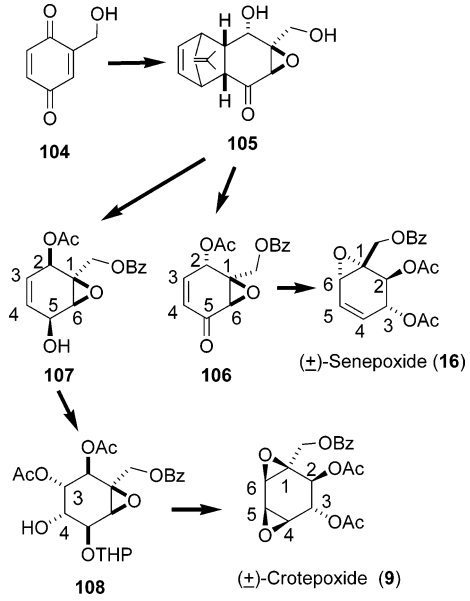
We will describe here, in chronological order, the diverse strategies employed for the preparation of these targets.

5.4.1. Ichihara's Method

Ichihara described, in preliminary form[49a,b] and later in a full paper,[49c] a common strategy for the syntheses of the closely related compounds racemic crotepoxide (**9**) and senepoxide (**16**) using 2-hydroxymethyl-1,4-benzoquinone (**104**) as the common starting material. Ichihara was the first to synthesize the epoxide rings by epoxidizing a "protected quinone" followed by base-promoted intramolecular nucleophilic displacement in a conveniently functionalized 1-hydroxy-2-mesylate derivative. The key reaction in his strategy was the Diels−Alder reaction of compound **104** with dimethylfulvene to "protect" the less substituted double bond, so that the *endo* product would be exclusively obtained. *exo*-Mediated hydrogen peroxide oxidation was used to incorporate one of the final epoxides into the molecule, after which regioselective hydroxyl-directed reduction of one of the carbonyl groups afforded intermediate **105**. Intermediate **105** was then used for the synthesis of crotepoxide (**9**) and senepoxide (**16**) (Scheme 20).

For the synthesis of senepoxide (**16**), the primary and secondary hydroxyl groups were selectively protected as a benzoate and an acetate, respectively,

Scheme 20. Ichihara's Approach for the Synthesis of (±)-Senepoxide (16) and (±)-Crotepoxide (9)



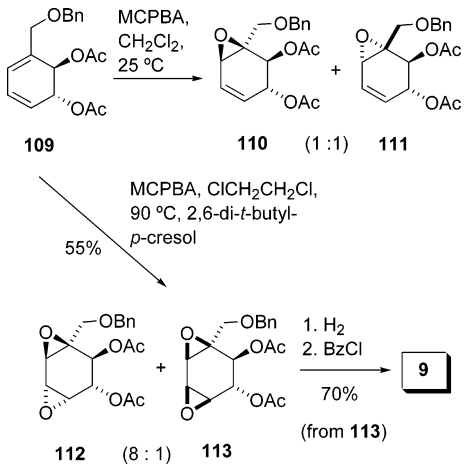
after which a retro-Diels−Alder[49d] reaction gave key intermediate **106**. Epoxidation of **106** occurred as desired from the less sterically hindered *β*-face. Hydrazine-mediated reaction of the α-ketoepoxide moiety then afforded the allylic alcohol with the correct stereochemistry at C-3, which after acetylation led to senepoxide (**16**). This is a simple yet very efficient synthesis (10 steps) providing remarkable control of the relative configurations at the newly formed stereocenters. Unfortunately, it is impossible to know what the overall yield of this synthesis was, since yields were not reported for some of the steps.

The synthetic scheme is longer for crotepoxide (**9**) since the relative configuration of the epoxide at C-1/C-6 is opposite to that of senepoxide (**16**) and an additional contiguous epoxide ring has to be formed. In this case, the secondary hydroxyl group in intermediate **105** (Scheme 20) was benzoylated; then after a retro-Diels−Alder reaction, stereoselective reduction of the keto group and subsequent acetolysis, the intermediate **107** was obtained. The next steps in the synthesis protected the secondary hydroxyl group and osmylated the double bond to give product **108**. The osmylation occurred with complete stereoselection from the less hindered α-face. The acetylation also occurred selectively at C-3, possibly because the hydroxyl group at this carbon was in an equatorial orientation, which allowed it to react in preference to the hydroxyl group at C-4. The final steps in the synthesis required adjustment of the functional groups so that they ended up with the correct placement to afford (±)-crotepoxide (**9**). The synthetic sequence required 13 steps, but it was again impossible to determine the overall chemical yield from the report as the yields were not documented for some of the steps.

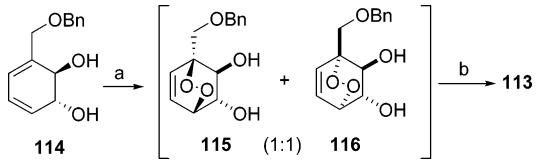
5.4.2. White's Method

White's[50] and Matsumoto's[51] (see below) proposals for the synthesis of cyclohexane epoxides have been successfully applied to different substrates by Shing[54]

Scheme 21. White's Synthesis of (±)-Crotepoxide (9)



Scheme 22. White's Alternative Synthesis of Compound 113[a]



[a] Reagents: (a) O_2, *hν* (52%); (b) (i) Ac_2O, Na_2CO_3, (ii) $C_2H_4Cl_2$, 2,6-di-*tert*-butyl-*p*-cresol, reflux (24% from **114**).

and Ganem.[56] Briefly, their approach utilized singlet oxygen photooxygenation of 1,4-cyclohexadienes[60] to give bicyclic endoperoxides, whose controlled transformation is known to selectively afford differently substituted cyclic mono-[61] or bisepoxides.[62]

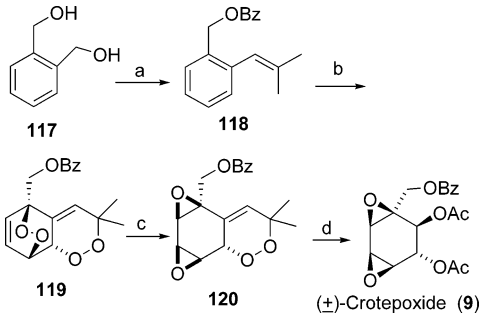
In White's strategy,[50] (±)-crotepoxide (**9**) [and also some nonnatural epimers, such as (±)-epicrotepoxide and (±)-*iso*-crotepoxide] was prepared from a 1-substituted-1,3-cyclohexadiene by using either epoxidation or photooxygenation to incorporate the epoxides into the ring. Although these protocols resulted in low chemical yields of the desired products, White nevertheless was the first to propose that 1,3-cyclohexadienes would be ideal intermediates for the synthesis of molecules of this type. More recently, Shing[54] also photooxygenated cyclohexadiene substrates to more efficiently synthesize cyclohexane epoxides.

White's pioneering studies also provided useful information about the epoxidation of allylic alcohols in unsaturated cyclohexanes. For instance, diacetate **109** (obtained in 32% yield from benzoic acid) yielded the monoepoxides **110** and **111** in a 1:1 ratio (Scheme 21). Under forcing conditions, the bisepoxides **112** and **113** were obtained in moderate yield. The stereoselectivity of this reaction was better than that obtained for the monoepoxides, but unfortunately the undesired epimer was favored (Scheme 21). As a result, (±)-crotepoxide (**9**) was obtained in 4% yield from compound **109**. A better overall yield of **9** (17%) was obtained from diol **114** using the photooxygenation method (Scheme 22). Interestingly, diacetate **109** was unreactive under these conditions, but diol **114** gave a mixture of the unstable endoperoxides **115** and **116** in a very unselective process. After acetylation and thermal isomerization, **115** and **116** afforded only compound **113** (Scheme 21), which was transformed as described above into (±)-crotepoxide (**9**). The authors suggested that the epimeric α-endoperoxide may have produced a secondary aromatic side product during the thermal isomerization due to the favored stereochemical arrangement of substituents in the endoperoxide. Unfortunately no full paper is available, and this proposal was not further elucidated.

5.4.3. Matsumoto's Method

In 1977 Matsumoto's group described the synthesis of (±)-crotepoxide (**9**) in a preliminary communication.[51] The steps and experimental conditions of this attractive method are shown in Scheme 23. Matsumoto's approach used a styrene building block as the substrate for a double peroxide formation, which occurred both inside and outside the aromatic ring and afforded an intermediate with suitable functionality to enable it to be used for the synthesis of the target molecule. The singlet oxygen photooxygenation of *β*,*β*-dimethylstyrene **118**, which was obtained from phthalyl alcohol (**117**) in three steps (42% total yield), gave the desired product **119** (13% yield). This product was easily separated from its allylic-position epimer, which was also obtained from the reaction and isolated in 21% yield. Thermal isomerization of **119** occurred with retention of configuration to give the bisepoxide **120** in 56% yield. The final steps of the sequence were trivial and afforded (±)-crotepoxide (**9**) after only eight steps, but with a low (2%) overall chemical yield.

Scheme 23. Matsumoto's Approach for the Synthesis of (±)-Crotepoxide (9)[a]

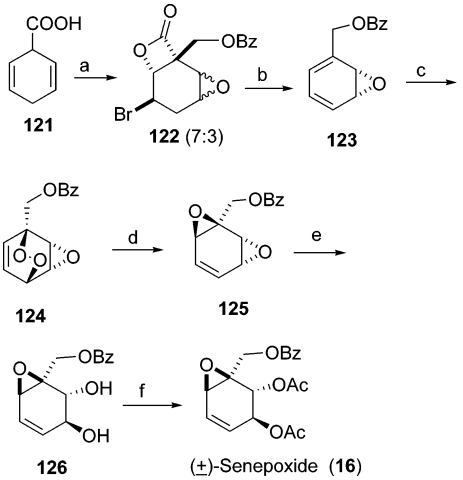


[a] Reagents: (a) (i) BzCl, Et_3N (63%), (ii) MnO_2 (82%), (iii) $(CH_3)_2C{=}PPh_3$ (80%); (b) O_2, *hν* (13%); (c) Δ (56%); (d) (i) O_3, (ii) $NaBH_4$, (iii) H_2 (39%); (iv) AcCl, Py (99%).

5.4.4. Ganem's Method

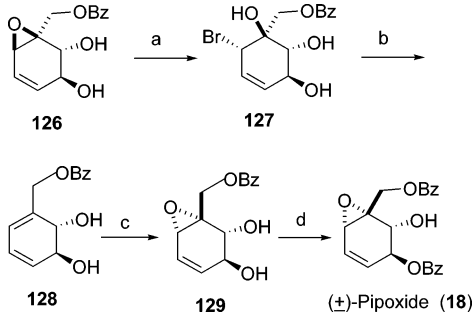
Ganem's approach to (±)-senepoxide (**16**) was published in 1978 in preliminary form[56a] and later as a full paper.[56b] Ganem's strategy follows a biogenetic hypothesis which suggests that arene oxides could be utilized as possible intermediates.[56c] Accordingly, Ganem and co-workers designed the synthesis of key intermediate **123** [prepared from 1,4-dihydrobenzoic acid (**121**) in four steps; intermediate **122** was obtained in 63% yield and cleanly afforded **123** by dehydrobromination (Scheme 24)].[56] It is noteworthy that this intermediate is related to the 1,3-cyclohexadiene **109** (Scheme 21) used in White's synthesis of

Scheme 24. Ganem's Approach for the Synthesis of (±)-Senepoxide (16)[a]



[a] Reagents: (a) (i) LDA, CH_2O (85%), (ii) Br_2 (90%), (iii) BzCl, Py(98%); (iv) CF_3CO_3H (63%); (b) (i) DBU, (ii) Δ (total yield for two steps = 90%); (c) O_2, *hν* (80%); (d) $P(OMe)_3$, benzene (88%); (e) THF/10% AcOH (30%); (f) Ac_2O, Py (94%).

Scheme 25. Ganem's Approach for the Synthesis of (±)-Pipoxide (18)[a]



[a] Reagents: (a) HBr (95%); (b) Zn, AcOH, EtOH (10%); (c) MCPBA (74%); (d) BzCl, Py (yield not reported).

(±)-crotepoxide (**9**)[50] but with the 1,2-diol moiety replaced by an epoxide ring. Singlet oxygen photooxygenation gave the endoperoxide **124**, which after treatment with trimethylphosphite afforded bisepoxide **125**. The acid hydrolysis of this intermediate is the weak point in this scheme, since even under the best conditions the desired diol **126** was obtained in only 30% yield. Following standard acetylation, (±)-senepoxide (**16**) was finally obtained in 10 steps from intermediate **121** with a 9% overall chemical yield.

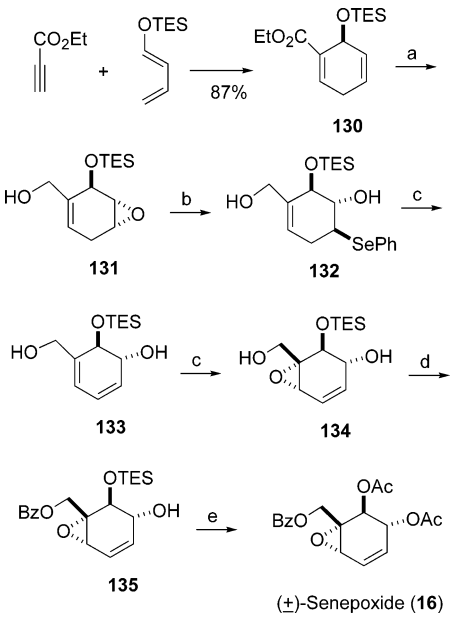
In a 1979 preliminary communication, Ganem not only revised the structure of pipoxide, but described the first synthesis of racemic pipoxide (**18**).[23] The synthesis was performed as shown in Scheme 25 using diol **126** as the starting material. This diol had been previously synthesized by the same group in their approach to (±)-senepoxide (see above). By opening the epoxide with hydrobromic acid, bromohydrin **127** was formed, after which its treatment with zinc led to the 1,3-cyclohexadiene **128**, although in very low yield (10%). The most substituted double bond of this 1,3-cyclohexadiene was epoxidized from the α-face to give product **129** in a regio- and stereoselective manner. Finally, after standard benzoylation, a synthetic sample of pipoxide (**18**) was isolated. The spectroscopic data for this synthetic sample proved to be identical to that of the naturally occurring sample.

5.4.5. Schlessinger's Method

In Schlessinger's strategy[52] for the synthesis of (±)-senepoxide (**16**), 1,3-cyclohexadiene **133** (Scheme 26), which is related to compounds **114**[50] and **123**[56] that were reported by White and Ganem, respectively, was crucial for the success of the synthesis. However, instead of being prepared from benzoic acid derivatives as White's and Ganem's compounds were,[50,56] this compound was prepared from dihydrobenzene derivative **130**, which was synthesized from ethyl propiolate and 1-(triethylsilyloxy)buta-1,3-diene. Compound **133** was obtained in three steps with a 67% total yield by epoxidation of **130** from the α face. This gave the major epoxide **131**, which yielded alcohol **132** after reduction with DIBALH. Alcohol **132** was reacted with sodium phenylselenide, followed by selenoxide formation and in situ elimination, to provide diene **133** (Scheme 26). The low overall yield described by White[50] for the photooxygenation plus thermal isomerization of analogous intermediate **114** (Scheme 22) prompted these authors to test the epoxidation of compound **133** using MCPBA at −40 °C. Only epoxide **134** resulted, and total control of the regio- and stereoselectivity occurred. The final steps of the synthesis consisted of benzoylation, acid hydrolysis of benzoate **135**, and acetylation to give (±)-senepoxide (**16**) in 37% overall yield. This is an elegant and short (seven steps from ethyl propiolate) synthetic sequence with a very good total chemical yield; however, no full paper has been published to date.

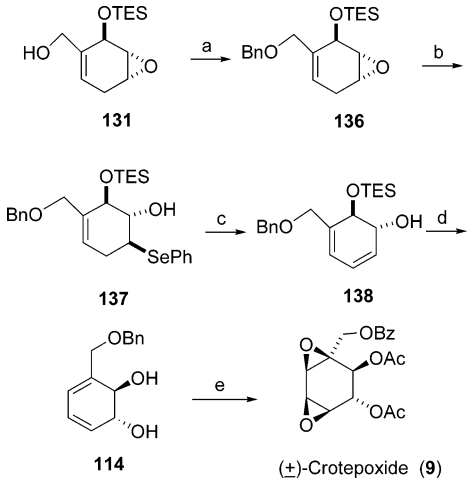
The same authors, in the same publication, also used intermediate **131** for the formal total synthesis

Scheme 26. Schlessinger's Approach for the Synthesis of (±)-Senepoxide (16)[a]



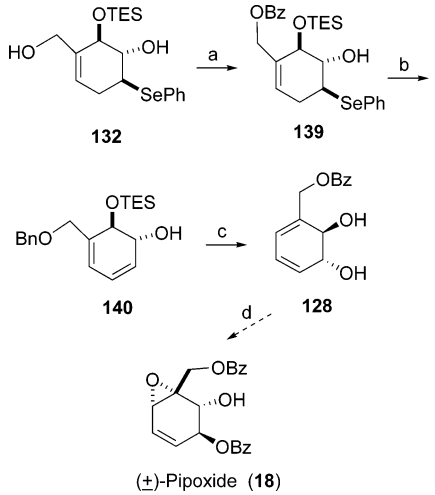
[a] Reagents: (a) (i) MCPBA, (ii) DIBALH (85%); (b) NaSePh(82%); (c) MCPBA (from **132** to **133** = 95%; from **133** to **134** = 77%); (d) BzCl, Et_3N (85%); (e) (i) HCl, MeOH, (ii) Ac_2O, DMAP (83% from **135**).

Scheme 27. Schlessinger's Approach for the Formal Total Synthesis of (±)-Crotepoxide (9)[a]



[a] Reagents: (a) *n*-BuLi, BnBr, HMPA, −78 °C (67%); (b) NaSePh (80%); (c) MCPBA (87%); (d) HCl, MeOH (99%); (e) ref 50 (see Schemes 21 and 22).

Scheme 28. Schlessinger's Approach for the Formal Total Synthesis of (±)-Pipoxide (18)[a]



[a] Reagents: (a) BzCl, Et_3N (95%); (b) MCPBA; (c) HCl, MeOH (78%); (d) ref 23 (see Scheme 25).

of (±)-crotepoxide (**9**) (Scheme 27). This was achieved after preparation of diene **114** (Scheme 22), which was previously synthesized by White[50] in his approach to (±)-crotepoxide. Diene **114** was prepared by benzylation of the primary hydroxyl group of compound **131** to afford epoxide **136**, which was then opened with sodium phenylselenide to give **137**. Further oxidation of **137** to give the selenoxide followed by its elimination furnished **138**. Finally, after desilylation the authors accomplished the synthesis of diene **114**.

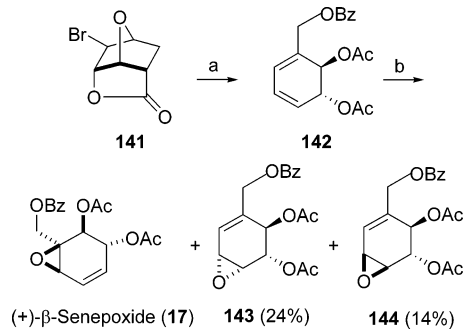
Similarly, a formal total synthesis of (±)-pipoxide (**18**), as shown in Scheme 28, was achieved after the synthesis of product **128** from intermediate **132**.[52] Compound **128** has been previously transformed into (±)-pipoxide by Ganem and co-workers.[23] The protocol that was used for the formation of **128** was just simple benzoylation, selenoxide formation, elimination to form the 1,3-diene, and desilylation.

5.4.6. Ogawa's Method

Ogawa's group has the distinction of being the first to prepare any natural cyclohexane epoxide in enantiomerically pure form. In 1985 Ogawa reported the asymmetric synthesis of (+)-pipoxide (**18**) and (+)-*β*-senepoxide (**17**)[57a] from optically pure bromolactone **141** (Scheme 29). Compound **141** was submitted to a series of transformations, which were previously developed in Ogawa's laboratory,[57b−d] to give diacetate **142**. Subsequent epoxidation of this 1,3-cyclohexadiene proceeded from the less hindered *β*-face to give (+)-*β*-senepoxide (**17**) (Scheme 29), along with two other monoepoxides (**143** and **144**), which resulted from epoxidation of the less substituted double bond. The epoxidation of product **142** gave (+)-*β*-senepoxide (**17**) in poor yield (19%).[57a]

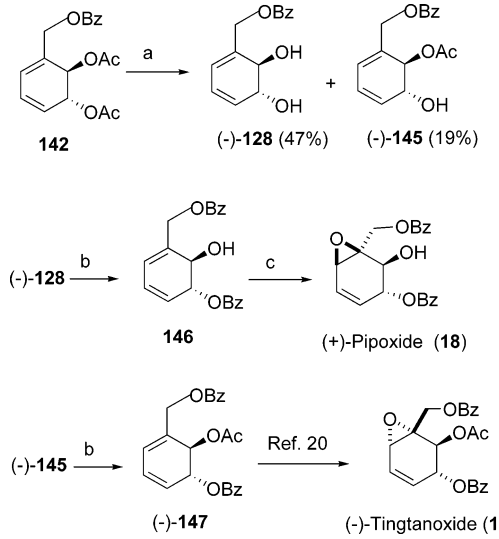
For the synthesis of (+)-pipoxide (**18**), diacetate **142** was deacetylated to give diol (−)-**128** and monoacetate **145** in 19% yield (Scheme 30). It should be noted that racemic **128** had been previously prepared by Ganem (Scheme 25)[23] for the synthesis of (±)-pipoxide (**18**). However, Ogawa changed the order of the reactions in the first steps of the synthesis, benzoylating the less hindered secondary allylic alcohol first to give dibenzoate **146** in moderate yield

Scheme 29. Ogawa's Approach for the Synthesis of (+)-*β*-Senepoxide (17)[a]



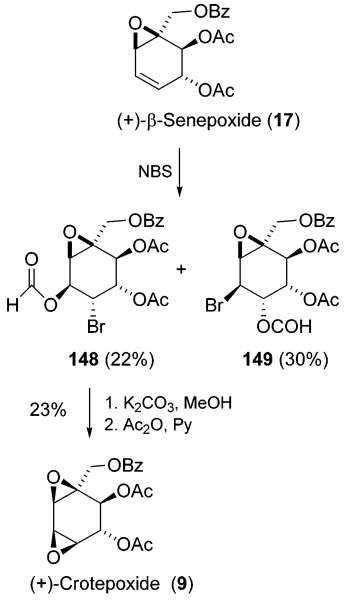
[a] Reagents: (a) refs 57b−d; (b) MCPBA (19%).

Scheme 30. Ogawa's Approach for the Synthesis of (+)-Pipoxide (18) and (−)-Tingtanoxide (19)[a]



[a] Reagents: (a) *p*-TsOH; (b) BzCl, Py (from **128** to **146** = 46%; from **145** to **147** = 95%); (c) MCPBA (87%).

Scheme 31. Ogawa's Approach for the Synthesis of (+)-Crotepoxide (9) from (+)-β-Senepoxide (17)



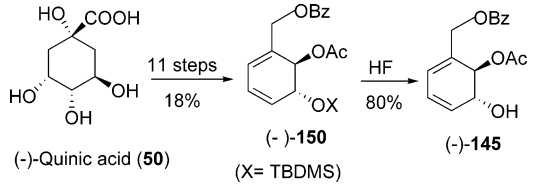
while carrying out the epoxidation later. This reversal of the sequence caused the epoxidation to take place from the β-face, due to the directing effect of the allylic hydroxyl group, to give natural (+)-pipoxide (**18**) in good yield (Scheme 30). Finally, the benzoylation of alcohol **145** afforded product **147**, diene previously used in the synthesis of (−)-tingtanoxide (**19**),[20] thus constituting a formal total synthesis of compound **19**.

Ogawa was also the first to report the synthesis of (+)-crotepoxide (**9**) in enantiomerically pure form from synthetic (+)-β-senepoxide (**17**),[53] which was prepared as described above. Scheme 31 shows the three steps of this synthetic sequence. The reaction of (+)-β-senepoxide (**17**) with aqueous NBS gave a mixture of bromoformates **148** and **149** in moderate yield and in an almost equimolar ratio. Minor isomer **148**, after treatment with potassium carbonate and acetylation, produced (+)-crotepoxide (**9**). The overall yield of **9** was 5% from compound **17**.

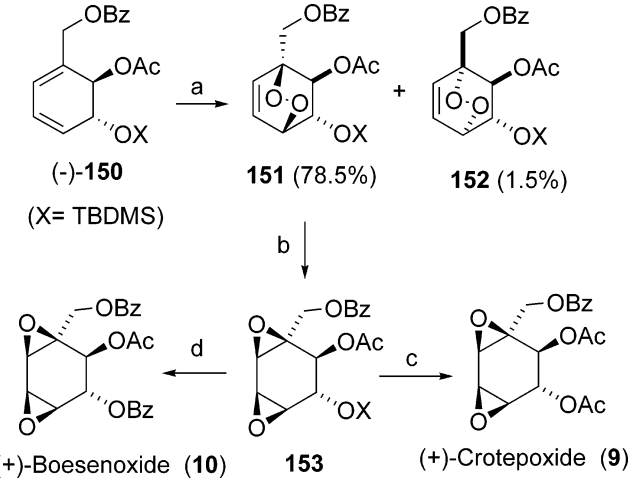
5.4.7. Shing's Method

Shing and co-workers described a new asymmetric synthesis for (+)-crotepoxide (**9**). They also reported for the first time the synthesis of (+)-boesenoxide (**10**), (−)-senepoxide (**16**), and (−)-tingtanoxide (**19**) in enantiomerically pure form from commercially available (−)-quinic acid (**50**).[54] Shing's choice for the best intermediate and the most convenient strategy for synthesizing these compounds benefited from the enormous amount of information previously reported and summarized here (see above). In 1996 it seemed clear that the best possible intermediate for the synthesis of this type of molecule was a 1,3-cyclohexadiene and that the best synthetic strategy by far involved singlet oxygen photooxygenation. Consequently, the only task remaining was to select and design the correct *O*-protecting groups. With this in mind, Shing prepared compound **150**, which has a *tert*-butyldimethylsilyl as the *O*-protecting group, as

Scheme 32. Synthesis of Compounds 150 and 145 from (−)-Quinic Acid (50) (Ref 54)



Scheme 33. Shing's Approach for the Synthesis of (+)-Crotepoxide (9) and (+)-Boesenoxide (10)[a]



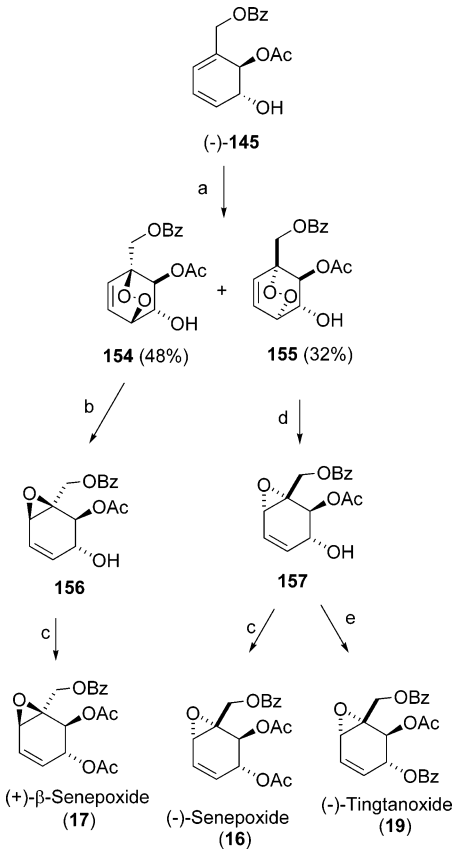
[a] Reagents: (a) O_2, $h\nu$; (b) (from pure **151**) CoTPP (99%); (c) (i) HF, Py (85%), (ii) Ac_2O, Py (99%); (d) (i) HF, Py (85%), (ii) BzCl, Py (99%).

the key intermediate. The synthesis began with (−)-quinic acid (**50**), required 11 steps to complete, and proceeded with an 18% overall yield (Scheme 32). For details of this synthesis, the reader is directed to the original paper.[54] Herein we will only address the subsequent transformation of this molecule into the naturally occurring cyclohexane epoxides.

Photooxygenation of diene **150** afforded compounds **151** and **152**, the major endoperoxide **151** in good yield (Scheme 33) as the result of an attack from the less hindered β-face. After reaction with cobalt−*meso*-tetraphenylporphyrin (CoTPP), **151** gave the rearranged bisepoxide **153** in quantitative yield. The acylation of this intermediate provided (+)-crotepoxide (**9**) (15 steps, 9% overall yield) or (+)-boesenoxide (**10**) (15 steps, 9% overall yield) (Scheme 33), depending on the reagents used.

To synthesize the natural α-epoxides, such as senepoxide (**16**) or tingtanoxide (**19**), Shing had to change the functionalization of the 1,3-cyclohexadiene such that the key intermediate was now **145** rather than **150**. Benzoate **145** had previously been prepared in poor yield by Ogawa[57a] from the corresponding diacetate precursor (Scheme 30). Shing obtained this molecule in better yield from **150** by desilylation (Scheme 32). As expected, the photooxygenation of **145** was less stereoselective and yielded both of the endoperoxides β-**154** and α-**155** in practical chemical yields. These intermediates were then transformed by the usual methodology into isomers **156** and **157**, which after acetylation gave (+)-β-senepoxide (**17**) (15 steps, 6% overall yield from **50**) or (−)-senepoxide (**16**) (15 steps, 4% overall yield)

Scheme 34. Shing's Approach for the Synthesis of (+)-β-Senepoxide (17), (−)-Senepoxide (16), and (−)-Tingtanoxide (19)[a]



[a] Reagents: (a) O_2, *hν*; (b) $P(OMe)_3$ (85%); (c) Ac_2O, Py (99%); (d) CoTPP (84%); (e) BzCl, Py (99%).

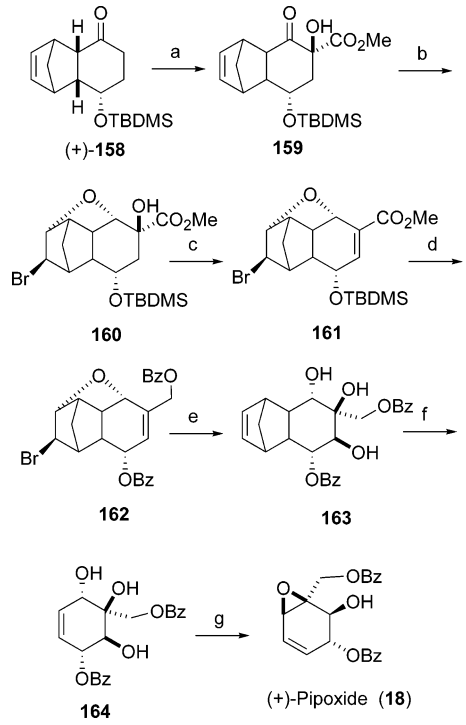
and (−)-tingtanoxide (**19**) (15 steps, 3% overall yield from quinic acid), respectively (Scheme 34).

5.4.8. Ogasawara's Method

Ogasawara's group also made interesting contributions to the synthesis of pipoxide and related compounds. In this section we will comment on the preliminary results published for the synthesis of (+)-pipoxide (**18**).[58a] The reported strategy rests on the use of the well-known, chiral, synthetic intermediate **158**[58b,c] (Scheme 35), which was developed in Ogasawara's laboratory and largely employed by his group in the synthesis of other natural products.

Sequential α-methoxycarbonylation and α′-hydroxylation of ketone **158** afforded only compound **159**, which has the free hydroxyl group in a β-orientation as a result of the *exo* hydroxylation being preferred. However, the orientation of this hydroxyl group is trivial because this stereocenter is destroyed in the following steps in order to install a double bond. Ketone reduction and protection of the secondary alcohol by intramolecular ether formation gave product **160**, which was dehydrated to afford alkene **161**. Thereafter, reduction, desilylation, and benzoylation of **161** gave dibenzoate **162** in good yield. Compound **162** then underwent osmylation from the less hindered β-face and Zn-mediated liberation of the secondary alcohol to produce triol **163**. At this point, a retro-Diels−Alder reaction[49d] performed on a **163** derivative rendered cyclohexene **164**, which was ready for the final Mitsunobu reaction. In this manner, (+)-pipoxide (**18**) was obtained in 14 steps and with a remarkable 28% overall yield from compound **158**. It is noteworthy that this methodology is reminiscent of Ichihara's approach, in the sense that a Diels−Alder-type adduct is used to "protect" one of the double bonds of an intermediate quinone.

Scheme 35. Ogasawara's Approach for the Synthesis of (+)-Pipoxide (18)[a]

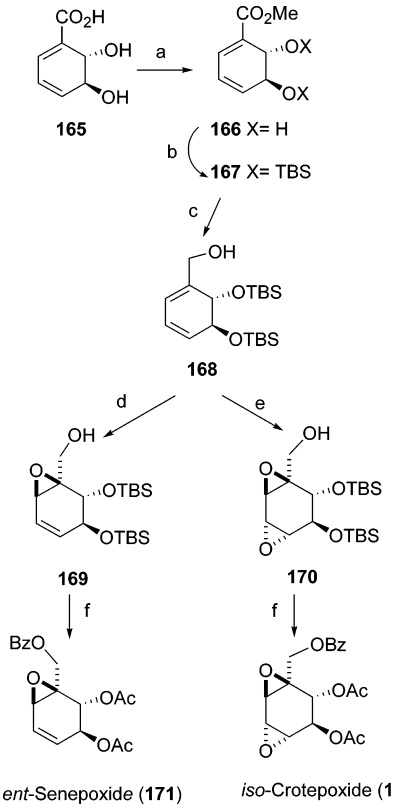


[a] Reagents: (a) (i) NaH, $(MeO)_2CO$ (89%), (ii) O_2, KF (82%); (b) (i) $NaBH_4$, (ii) NBS (96%); (c) $POCl_3$ (84%); (d) (i) DIBALH, (ii) Bu_4NF, (iii) BzCl, Py (97%); (e) (i) OsO_4, (ii) Zn (96%); (f) (i) TMSCN, (ii) diphenyl ether, (iii) HF (83%); (g) DEAD, PPh_3, THF (62%).

5.4.9. Müller's Method

Müller very recently described the syntheses of enantiomerically pure *iso*-crotepoxide and *ent*-senepoxide.[59] Although both are nonnatural products, we will describe these interesting syntheses as they complement the efforts of other authors in this area. Müller's methodology starts from *trans*-cyclohexadienediol **165**, which was isolated in enantiomerically pure form from *E. coli* and produced in multigram quantities in a metabolic engineered microbial process. As shown in Scheme 36, when compound **168**, which was prepared in three steps from **165** via compounds **166** and **167**, was submitted to epoxidation under mild or forcing conditions, it yielded monoepoxide **169** or bisepoxide **170** in good yields. These were the only isomers formed at the new stereocenters. Intermediates **169** and **170** were the precursors for *ent*-senepoxide (**171**) and *iso*-crotepoxide (**172**), obtained in seven steps with overall yields of 26% and 24%, respectively.

Scheme 36. Müller's Approach for the Synthesis of *iso*-Crotepoxide (172) and *ent*-Senepoxide (171)[a]



[a] Reagents: (a) $TMSCHN_2$ (81%); (b) TBSTfO (95%); (c) DIBALH (88%); (d) MCPBA, room temperature (91%); (e) MCPBA, 50 °C (79%); (f) (i) BzCl, Py, (ii) TBAF, (iii) Ac_2O, Py (from **169** to **171** = 41%; from **170** to **172** = 44%).

5.5. Synthesis of Aranorosin

In 1993 Wipf[63] and McKillop-Taylor[64] described the total synthesis of natural aranorosin (**11**) (Figure 2) in enantiomerically pure form. Previously, in 1991, Rama Rao and co-workers published a synthetic study directed at aranorosin,[65] but no full paper ever appeared. Completing the total synthesis of aranorosin enabled Wipf[63] to assign its absolute configuration at C-6′ as *R*, which no one previously had been able to establish.

The retrosynthetic analyses put forth by Wipf, McKillop-Taylor, and Rama Rao were all based on the amide disconnection, a protocol that implies condensation between acid **173** (Figure 10) and a

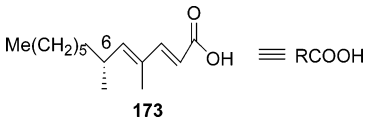
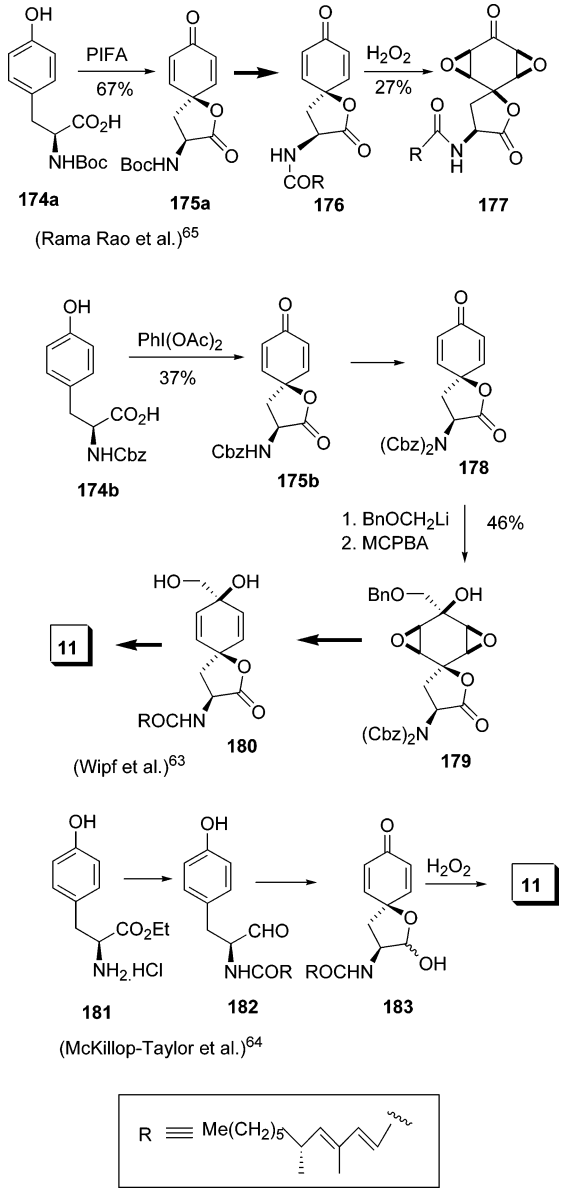


Figure 10.

convenient carbocyclic intermediate. The synthesis of (6*R*)-**173** and its enantiomer will not be presented here, and we will only comment on the synthesis of the cyclohexane bisepoxide moiety of aranorosin. All of the synthetic endeavors referenced above shared the same method for the synthesis of the 1-oxaspiro-[4,5]decane ring, specifically, the oxidative cyclization of tyrosine derivatives. The differences in the synthetic schemes lie in which tyrosine derivative was

Scheme 37. Synthesis of Aranorosin (11)



utilized, how acid **173** was incorporated, and whether the ketone in the cyclohexane ring was preserved in the synthetic sequence. These points are highlighted in Scheme 37.

In Rama Rao's approach[65] (Scheme 37) the reaction of compound **174a** with iodobenzene bis(trifluoroacetate) (PIFA) gave product **175a** in good yield and as the only observed diastereoisomer. After a series of steps for protection, followed by amidation with acid **173** (Figure 10), substrate **176** was isolated and submitted to epoxidation with H_2O_2 to give compound **177**. Compound **177** was obtained in poor yield but with complete stereocontrol over the formation of the new stereocenters.

To circumvent the problems leading to the low yield of **177**, Wipf[63] (Scheme 37) devised a strategy in which ketone **178** was transformed into a compound with α-hydroxy and α′-benzyloxymethyl functional groups capable of hydrogen bonding, which served inter alia to control the attack of MCPBA from the β-face to give intermediate **179**. The presence of the carbobenzyloxy (Cbz) protecting group instead of the

Boc group at the nitrogen in intermediates **174b** and **175b** also seemed to play a crucial role in the success of these reactions, and the introduction of a second *N*-Cbz protecting group proved to be necessary, since the addition of organolithium reagents to **175b** led to significant lactone opening. Finally, once the side chain was incorporated, the keto group at C-8 was reinstalled to provide natural product **11** via compound **180**. This strategy provided an elegant solution to the problems that originated from the presence of the keto group in the synthetic sequence, although at the cost of increasing the number of steps required.

In this sense, McKillop-Taylor's[64] approach is by far the shortest (four steps!) (Scheme 37). In their analysis the tyrosine-protected aldehyde **182** was used to directly give lactol **183** after oxidative cyclization. This is a remarkable strategy; unfortunately, the epoxidation of the double bonds, as before, gave a poor yield that lowered the total overall yield to 4% for the synthesis of aranorosin (**11**). However, this expeditious procedure was applied by the authors to the preparation of several aranorosin analogues.

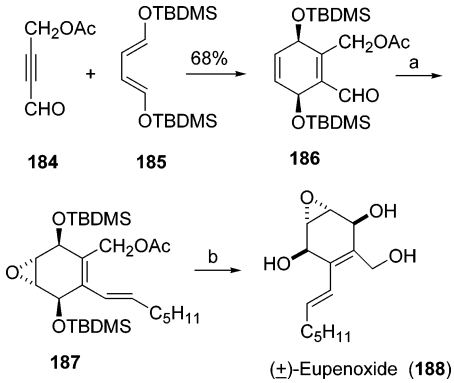
6. Quinone Monoepoxides

6.1. Eupenoxide

Eupenoxide (**188**) (Figure 4) is an antifungal agent produced by a fungus assigned to the genus *Eupenicillium*.[66]

The only synthesis of racemic eupenoxide to date has been reported by Duke and Rickards (Scheme 38).[66] The Diels−Alder reaction of aldehyde 4-acetoxybut-2-ynal (**184**) and 1,4-[bis(*tert*-butyldimethylsilyloxy)]buta-1,3-diene (**185**) gave adduct **186** in 68% yield. The epoxidation of this compound was totally stereoselective and afforded the α-epoxide, although in low yield due, most likely, to decomposition. The α-epoxide was submitted to a Wittig reaction, which exclusively gave the *Z* (**187**) isomer. Subsequent photochemical isomerization gave a mixture of *Z* and *E* isomers in a 1:3 ratio, which after recrystallization provided pure *E* (**187**) in 50% yield. The final steps were trivial but allowed the authors to generate racemic eupenoxide (**188**) in six steps with a 5% total yield.

Scheme 38. Rickards' Total Synthesis of (±)-Eupenoxide (188)[a]



[a] Reagents: (a) (i) *p*-Nitroperoxybenzoic acid (26%), (ii) $C_5H_{11}CH{=}PPh_3$ (70%), (iii) I_2, *hν* (50%); (b) (i) NH_3, MeOH (98%), (ii) Bu_4NF (87%).

6.2. Theobroxide

(−)-Theobroxide (**189**) (Figure 4) is an epoxy cyclohexene (or a reduced-quinone epoxide) that is isolated from the culture filtrate of the fungus *Lasiodiplodia theobromae* and induces potato microtuber formation in vitro.[67a] Theobroxide spray treatment also produced flower buds in morning glory plants kept under non-inducing conditions (i.e., long days). Furthermore, under inducing conditions (i.e., short days), the number of flowers produced by seedlings sprayed with theobroxide was about 1.5 times that produced by unsprayed controls.[67b] The structure of theobroxide was assigned mostly on the basis of spectroscopic analysis.[67a]

6.3. Asperpentyn

(−)-Asperpentyn (**190**) (Figure 4) has been isolated from the antimicrobial extracts of *Aspergillus duricaulis*.[68]

6.4. Epoformin ("Deoxyepoxydon")

Epoformin (**191**) (Figure 4) is an antibiotic and cytotoxic substance isolated from the culture broth of *Penicillium claviforme*.[69] Only weak antimicrobial activity was exhibited by epoformin. Although its cytotoxic activity was strong against PS cells, epoformin showed less activity against L-1210 than epoxydon. *Phoma sorghina* is a newly described leaf spot pathogen on pokeweed, which produced phytotoxins in liquid culture. These phytotoxins were isolated and structurally identified as epoformin, epoxydon, phyllostine, and epoxydon 6-methylsalicylate ester. The cell-free culture filtrate, as well as each of the toxins, caused necrosis when spotted on pokeweed leaves and eight other weed species; thus, these toxins were nonspecific phytotoxins. Epoxydon and epoformin showed strong antimicrobial properties against all the bacteria and fungi tested. In addition, epoxydon, deoxyepoxydon, and phyllostine were isolated from *Ophiosphaerella herpotricha*, which is a cause of spring dead spot (SDS) on Bermuda grass. All of these isolated metabolites caused necrosis when spotted onto leaves of Bermuda grass and other plant species. Bermuda grass cultivars varied in their sensitivity to epoxydon, which was the major metabolite isolated. However, there was no correlation between the amount of leaf necrosis caused by epoxydon and the resistance of the cultivars to SDS in the field.[69b] The structures of these new metabolites were assigned by analyses of their MS and NMR spectra.

6.5. Epiepoformin

(+)-Epiepoformin (**192**) (Figure 4) was separated from a culture of an unidentified fungus on diseased crape myrtle (*Lagerstroemia indica*) leaves. Neutral fractions of the media containing this compound markedly inhibited the germination of lettuce seeds.[70] (+)-Epiepoformin proved to be very active, providing

complete control of redroot pigweed and 88% control of white mustard when applied at 4.4 kg/ha.

6.6. Epoxydon ("Epoxydone", "Phyllosinol")

Epoxydon (**193**) (Figure 4) (and phyllostine, see below) is a phytotoxic metabolite isolated from a culture filtrate of *Phyllosticta sp S 1019*, which is a pathogenic fungus of red clover. Epoxydon (**193**) is the principal toxic compound that causes wilting and simultaneous dark discoloration of leafy stem cuttings from the host plant.[71a] Epoxydon was also isolated from *Phoma sp*. as a cytotoxic compound.[71b]

6.7. Epiepoxydon

Epiepoxydon (**194**) (Figure 4) was initially obtained as a synthetic artifact,[72a] together with epoxydon, and later characterized as a phytotoxin. Epiepoxydon, obtained from an unidentified fungus that was separated from diseased crape myrtle (*Lagerstroemia indica* L.) leaves[72b] and then identified as an intermediate in the patulin pathway in *Penicillium urticae*, was likewise characterized as a phytotoxin.[72c]

6.8. Harveynone ("PT-Toxin")

(+)-Harveynone (**195**) (Figure 4) has been isolated from the tea gray blight fungus *Pestalotiopsis theae* and shown to be a phytotoxin.[73a] Its relative structure was based on a comparison of its ^{1}H and ^{13}C NMR data with those of (+)-epiepoxydon (**194**) (Figure 4). Its enantiomer, (−)-harveynone (**195**), was isolated from *Curvularia harvey* and found to possess antitumor activity.[73b]

6.9. Tricholomenyn A

Tricholomenyn A (**196**) (Figure 4) was isolated from the fruiting bodies of the mushroom *Tricholoma acerbum* and is a mitotic inhibitor.[74] Its relative structure, which has an enyne side chain on the polyoxygenated cyclohexene framework, was assigned mostly by NMR spectroscopy, while its absolute configuration was tentatively assigned by correlating its CD spectrum with those of simpler natural products possessing the same epoxyclohexane chromophore.

6.10. Phyllostine

Phyllostine (**197**) (Figure 4) is a phytotoxic metabolite isolated from *Phyllosticta* sp.[75a] This epoxyquinone possessed antibiotic activity against *Bacillus subtilis* and was approximately 80% as active as patulin.[75b]

6.11. Syntheses of Theobroxide, Asperpentyn, Epoformin, Epiepoformin, Epoxydon, Epiepoxydon, Harveynone, Tricholomenyn A, and Phyllostine

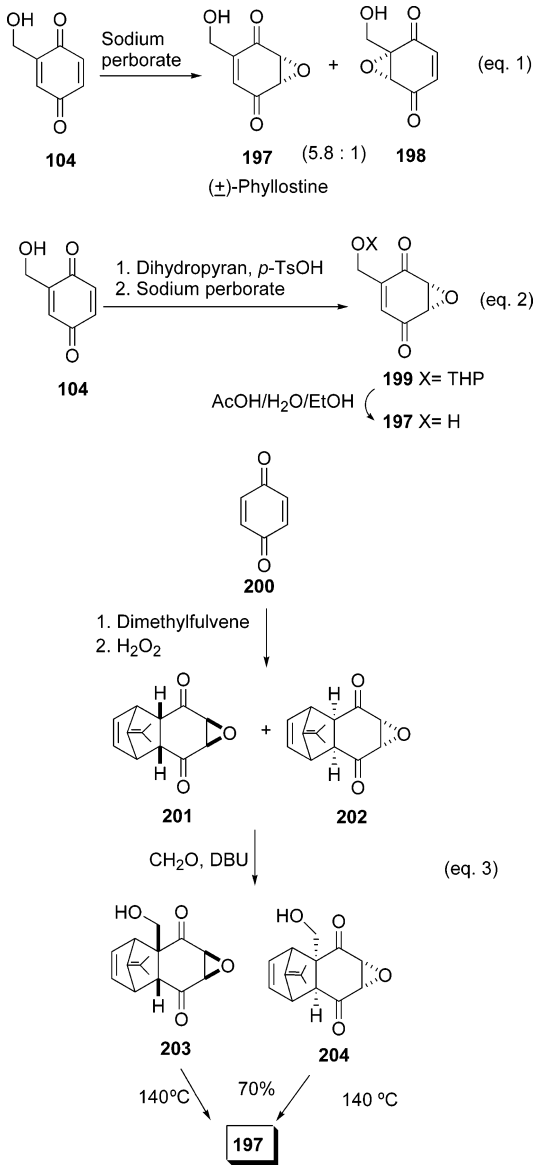
In this section we will discuss the synthesis of quinone monoepoxides **189**−**197**. These compounds have been synthesized using common strategies and intermediates, although the syntheses were performed by different laboratories. Natural (−)-theobroxide (**189**) was synthesized by Ogasawara[76] and Maycock,[77] while unnatural (+)-theobroxide (**189**) has been prepared by Ogasawara.[76] (−)-Asperpentyn (**190**) has been prepared only once and in enantiomerically pure form from (−)-quinic acid (**50**) by Maycock.[77] (±)-Epoformin (**191**) was one of the first compounds in this group to be synthesized, first by Ichihara[78] and later by Maycock.[79] Epiepoformin (**192**) has been produced by Ichihara,[78] Ogasawara,[76] Maycock,[77] and recently Okamura.[80] Related epoxydon (**193**), epiepoxydon (**194**), and phyllostine (**197**) are usually prepared together and have been described by Ichihara,[81] Ogasawara,[82] and Taylor.[83] Harveynone (**195**) has been synthesized by Taylor in racemic form[84] and by both Ogasawara[85] and Maycock in enantiomerically pure form.[77] The synthesis of tricholomenyn A (**196**) has been reported by Ogasawara[86] and Taylor,[87] while Johnson[88] and Negishi[89] described the syntheses of compounds **195** and **196**. In the following sections we will present details of the different synthetic sequences leading to these compounds.

6.11.1. Ichihara's Approach

Ichihara described three approaches to synthesizing (±)-phyllostine (**197**) (Scheme 39). The first synthesis was nonselective and used as the starting material 2-hydroxymethyl-1,4-benzoquinone (**104**), which was obtained by oxidation of the expensive substrate gentisyl alcohol with lead tetraacetate. After several unsuccessful trials, the epoxidation of **104** with sodium perborate gave an inseparable mixture of phyllostine (**197**) and compound **198** (eq 1, Scheme 39)[81b] which was treated with cyclopentadiene. As a result, compound **198** afforded a Diels−Alder adduct, which was easily separated from phyllostine (**197**), obtained in 22% yield. Better results were obtained when the primary alcohol in product **104** was first pyranylated by treatment with dihydropyran to increase the steric hindrance on the trisubstituted double bond. As a result of this hindrance, the epoxidation was cleanly directed to the correct place giving product **199**, which released phyllostine after acid hydrolysis of the directing group, in 31% total yield (eq 2, Scheme 39).[81a,b] The third approach used the same strategy as had been reported by Ichihara for the synthesis of crotepoxide (Scheme 20). Starting from 1,4-benzoquinone (**200**), the Diels−Alder reaction with dimethylfulvene followed by epoxidation gave the epoxides **201** and **202** (eq 3, Scheme 39). These molecules underwent aldol reactions with formaldehyde to afford intermediates **203** and **204**, after which the retro-Diels−Alder reactions of these intermediates gave phyllostine (**197**).[81c,d]

Ichihara developed two approaches to the synthesis of epoxydon (**193**). In the first synthesis[81a,b] (eq 1, Scheme 40), compound **199** was reduced and peracetylated to give diacetate **205**. A short (1 h) mild acid hydrolysis of this compound afforded alcohol **206**, which on treatment with potassium carbonate underwent regioselective hydrolysis of the proximal acetate leading to diol **207**. After tritylation, oxidation, and full deprotection, **207** and **208** provided

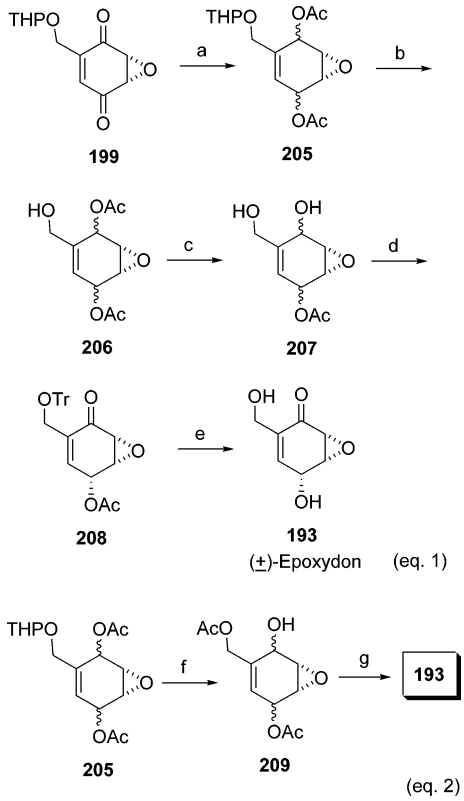
Scheme 39. Ichihara's Synthesis of (±)-Phyllostine (197)



epoxydon (**193**) in 8% total yield from compound **205**. It is interesting to note that the reduction of quinone **199** afforded a mixture of diastereomers, but no separation was attempted. Apparently, in the synthetic sequence, epimerization took place to give diastereomerically pure epoxydon. Incidentally, the authors found that if the acid hydrolysis of product **205** was prolonged (12 h), acetyl migration took place giving diacetate **209** (eq 2, Scheme 40), whose oxidation and hydroxyl deprotection gave epoxydon in a shorter sequence and in better total yield from **199** (16%).

The second of Ichihara's approaches to epoxydon (**193**) is shown in Scheme 41. This approach was so flexible that it allowed the authors to also prepare epiepoxydon (**194**).[81d] As in his other synthesis, Ichihara successfully employed the Diels–Alder and retro-Diels–Alder reactions on conveniently functionalized quinone derivatives to yield both **193** and **194**. Reduction of the "protected" quinone epoxides **201** (eq 1, Scheme 41) and **202**[81e] (eq 2, Scheme 41) gave the corresponding pairs of epoxyalcohols (**210**/**211** and **212**/**213**), which were treated with formaldehyde to give compounds **214**/**215** and **216**/**217**. After thermal treatment, these compounds provided epoxydon and epiepoxydon. When this synthetic scheme was applied to benzoquinone, epoxydon was obtained in 10% yield, which is a notable improvement over a previous synthesis reported by this group where the starting material was gentisyl alcohol (1%, Scheme 39).

Scheme 40. Ichihara's Synthesis of (±)-Epoxydon (193)[a]



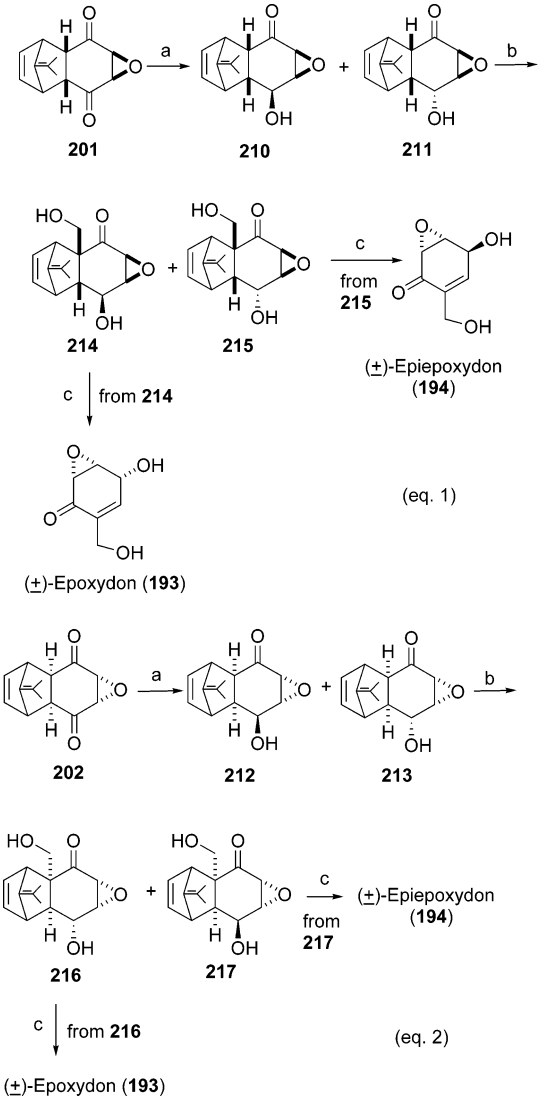
[a] Reagents: (a) (i) $NaBH_4$ (63%), (ii) Ac_2O, Py (99%); (b)MeOH, *p*-TsOH, 1 h (70%); (c) $KHCO_3$, 48 h; (d) (i) $ClC(C_6H_5)_3$ (60%), (ii) MnO_2 (88%); (e) MeOH, *p*-TsOH; (f) EtOH, *p*-TsOH, 12 h; (g) (i) MnO_2, (ii) MeOH, *p*-TsOH.

Ichihara also described the synthesis of epoformin (**191**) and epiepoformin (**192**),[78] as shown in Scheme 42. In this approach the ketones of the known intermediates **212** and **213** (see Scheme 41) were alkylated with methyl iodide instead of formaldehyde. Molecular models showed that only cis stereoisomers should be observed at the fused ring in products **218** and **219**. The trans isomers were determined to be unlikely due to their highly strained structure.

6.11.2. Ogasawara's Approach

As in his syntheses of (+)-pipoxide (**18**) (Scheme 35) and (−)-eutypoxide B (**3**), performed by Takano (Scheme 8), Ogasawara's strategy for the syntheses of (+)-epiepoxydon, (−)-phyllostine, (−)-tricholomenyn A, and (+)/(−)-harveynone relied on Ichihara's concept of using Diels–Alder adducts to "protect" one of the double bonds of the 1,4-benzoquinone product, then developing the necessary functionality at the other available double bond, and

Scheme 41. Ichihara's Synthesis of (±)-Epoxydon (193) and (±)-Epiepoxydon (194)[a]



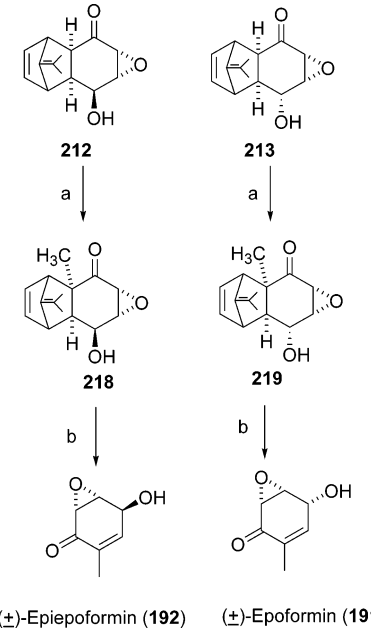
[a] Reagents: (a) $NaBH_4$; (b) CH_2O, DBU (86−90%); (c) Δ (60−76%).

finally performing a retro-Diels−Alder reaction to restore the masked alkene. Ogasawara's group is credited with the preparation of enantiomerically pure (+)- and (−)-**46**[34b] for achieving these goals.

(+)-Epiepoxydon (**194**)[82] was synthesized from compound (−)-**46** as shown in Scheme 43. After a series of standard steps for protection, deprotection, and oxidation, the important ketone **220** was prepared. Next, the β-face was epoxidized, which, when followed by an aldol reaction with formaldehyde and thermal treatment, afforded epoxyketone **222** in good yield. Desilylation gave (+)-epiepoxydon (**194**), and the selective oxidation of (+)-epiepoxydon (**194**) with PDC in DMF provided (−)-phyllostine (**197**) in 37% yield (Scheme 43).[82]

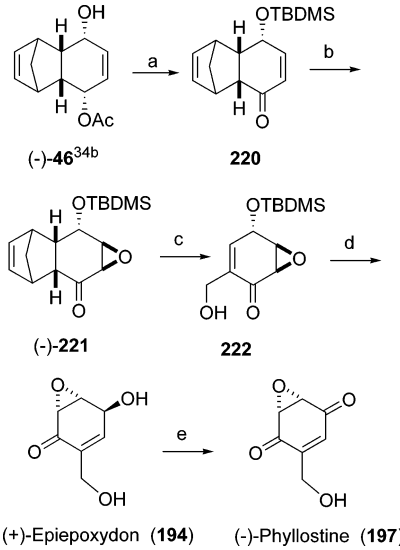
The synthesis of natural (−)-theobroxide (**189**) has been performed from intermediate (−)-**221** (Scheme 43) using concepts and methods analogous to those previously employed for the syntheses of (+)-epiepoxydon and (−)-phyllostine.[76] In this case, however, the α-alkylation had to be carried out using methyl iodide (Scheme 44). The reduction of epoxyketone **223**

Scheme 42. Ichihara's Synthesis of (±)-Epoformin (191) and (±)-Epiepoformin (192)[a]



[a] Reagents: (a) (i) Ac_2O, Py, (ii) MeI, *t*-BuOK, (iii) KOH; (b) Δ (50% overall yield from **213**).

Scheme 43. Ogasawara's Synthesis of (+)-Epiepoxydon (194) and (−)-Phyllostine (197)[a]

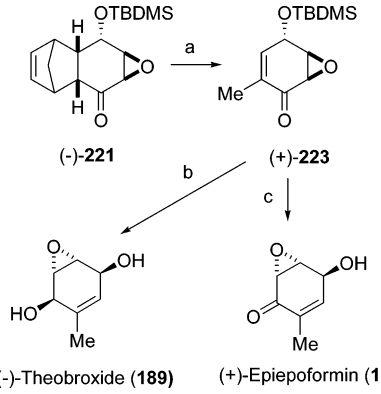


[a] Reagents: (a) (i) TBDMSCl; (ii) K_2CO_3, MeOH, then PDC; (b) H_2O_2 [80% from (−)-**46**]; (c) (i) CH_2O, DBU (98%), (ii) diphenyl ether, Δ (87%); (d) HF−MeCN (86%); (e) PDC, DMF (37%).

afforded a mixture of separable allylic alcohols, of which the major epimer gave (−)-theobroxide (**189**) (80%) after desilylation. Direct desilylation of compound **223**, as opposed to reduction, gave (+)-epiepoformin (**192**).

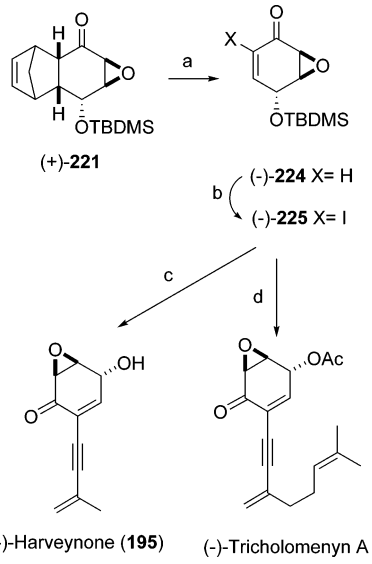
Finally, Ogasawara described the syntheses of natural (−)-harveynone (**195**)[85] and (−)-tricholomenyn A (**196**).[86] Starting from intermediate (−)-**221** (Scheme 45), the common intermediate α-iodoenone (−)-**225** was prepared via epoxyketone (−)-**224** in good yield and enantiomerically pure form. From this compound the authors prepared (−)-harveynone (**195**)[85] and (−)-tricholomenyn A (**196**)[86] in moderate to good yields by utilizing a one-step Stille[90] reaction with stan-

Scheme 44. Ogasawara's Synthesis of (−)-Theobroxide (189) and (+)-Epiepoformin (192)[a]



[a] Reagents: (a) (i) KH, MeI (87%), (ii) diphenyl ether, Δ (94%); (b) $NaBH_4$, $CeCl_3$, then HF−MeCN (80% from **223**); (c) HF−MeCN (93%).

Scheme 45. Ogasawara's Synthesis of (+)-Harveynone (195) and (−)-Tricholomenyn A (196)[a]



[a] Reagents: (a) diphenyl ether (93%); (b) I_2 (89%); (c) (i) **226a**, $PdCl_2(PPh_3)_2$, CuI, *N*-methylpyrrolidone (82%), (ii) HF−MeCN (87%); (d) (i) **227a**, $PdCl_2(PPh_3)_2$, CuI, *N*-methylpyrrolidone (39%), (ii) HF−MeCN (86%); (iii) Ac_2O, Py (59%).

nanes **226a** and **227a** (Figure 11). Surprisingly, Sonogashira reaction[91] between acetylenes **226b** and **227b** (Figure 11) and iodoenone (−)-**225** failed to give the cross-coupling product. This problem was solved by using the alcohol obtained by reduction of iodoenone (−)-**225**, instead of **225** itself, which under the Sonogashira reaction conditions gave the desired intermediates but at the cost of lengthening the synthetic sequence.[85] Ogasawara also described the synthesis of enantiomeric (+)-**224,** which, following the same protocol, afforded (+)-harveynone (**195**).[85]

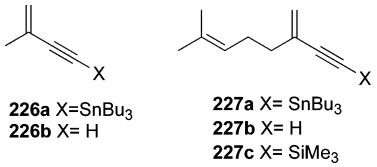


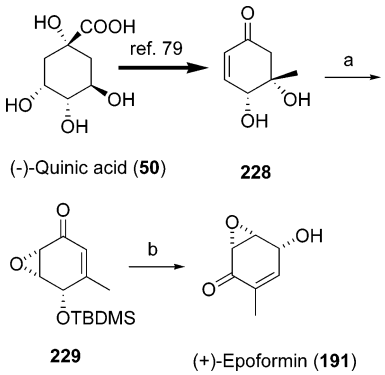
Figure 11.

6.11.3. Maycock's Approach

Maycock and co-workers synthesized a number of natural products of this quinone monoepoxide family in enantiomerically pure form by starting from (−)-quinic acid (**50**). Their work continues the research in this area that started with the synthesis of eutypoxide B (**3**) (Scheme 9).

(+)-Epoformin (**191**) was prepared for the first time in optically pure form, as shown in Scheme 46.[79] α,β-Unsaturated ketone **228**, prepared in several steps from quinic acid (**50**), was silylated at the secondary alcohol, and the epoxidation then occurred from the plane of the molecule occupied by the silyloxy group. This unexpected result may be due to the directing effect of the tertiary alcohol and was fortuitous, as product **229** contained all the appropriate functional groups with the correct stereochemistry needed to synthesize (+)-epoformin (**191**). Reduction of ketone **229** gave the alcohol that resulted from hydride attack on the β-face; then, finally, after acetylation, desilylation, oxidation, and deacetylation, (+)-epoformin (**191**) was efficiently obtained.

Scheme 46. Maycock's Synthesis of (+)-Epoformin (191)[a]



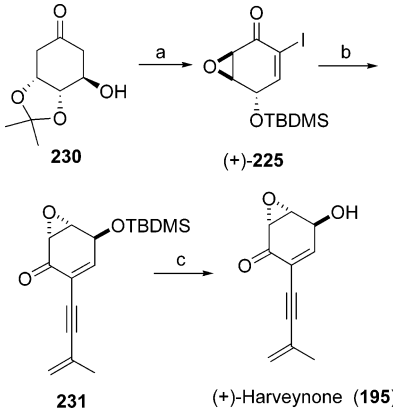
[a] Reagents: (a) (i) TBDMSCl (79%), (ii) H_2O_2 (92%), (iii) Tf_2O(57%); (b) (i) L-selectride, then Ac_2O, diisopropylethylamine (73% two steps), (ii) Bu_4NF (98%), (iii) Dess−Martin periodinane (99%), (iv) KOH (95%).

In their next communication on this subject, Maycock and co-workers described the preparation of (−)-asperpentyn, (+)-harveynone, (+)-epiepoformin, and (−)-theobroxide.[77] The most interesting aspect of this new report was that the methyl or unsaturated side chain in the α-iodoenone intermediate (+)-**225** (which is the same intermediate prepared two years earlier by Ogasawara;[85] see Scheme 45) was incorporated via a Stille coupling,[90] based on (−)-quinic acid (**50**). The result was that compound (+)-**225** was synthesized from hydroxyketone **230**[35] (Scheme 47). Stille coupling[90] of stannane **226a** (Figure 11) with α-iodoenone (+)-**225** gave intermediate **231**, which after desilylation furnished (+)-harveynone (**195**).

The reduction of compound **231** with sodium borohydride in the presence of cerium trichloride afforded a mixture of allylic alcohols in a 2.7:1 ratio. The major alcohol, after separation and desilylation, gave (−)-asperpentyn (**190**) (Scheme 48).

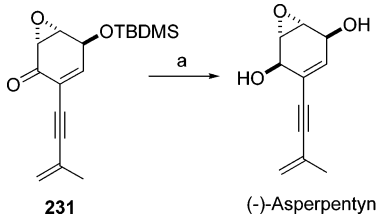
Stille coupling[90] of tetramethylstannane with α-iodoenone (+)-**225** gave intermediate **232**, which after

Scheme 47. Maycock's Synthesis of (+)-Harveynone (195)[a]



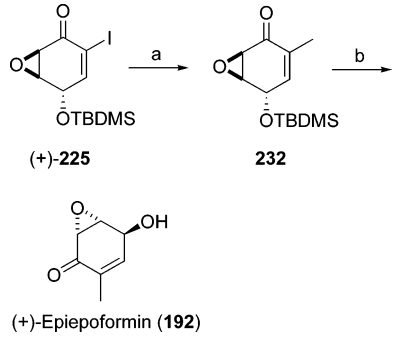
[a] Reagents: (a) (i) TBDMSCl (98%), (ii) NaOH (41%), (iii) H_2O_2 (89%), (iv) Ac_2O, diisopropylethylamine (44%), (v) I_2 (93%); (b) **226a**, CuI, $AsPh_3$, $Pd(PPh_3)_2Cl_2$ (98%); (c) HF (92%).

Scheme 48. Maycock's Synthesis of (−)-Asperpentyn (190)[a]



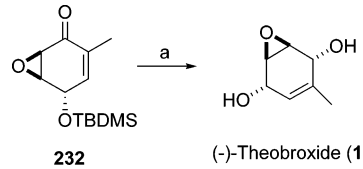
[a] Reagents: (a) (i) $NaBH_4$, $CeCl_3$ (99%), (ii) HF (99%).

Scheme 49. Maycock's Synthesis of (+)-Epiepoformin (192)[a]



[a] Reagents: (a) Me_4Sn, $AsPh_3$, $Pd_2(dba)_3$, $CHCl_3$, CuI (91%); (b) HF (99%).

Scheme 50. Maycock's Synthesis of (−)-Theobroxide (189)[a]



[a] Reagents: (a) (i) $NaBH_4$, $CeCl_3$ (92%), (ii) HF (99%).

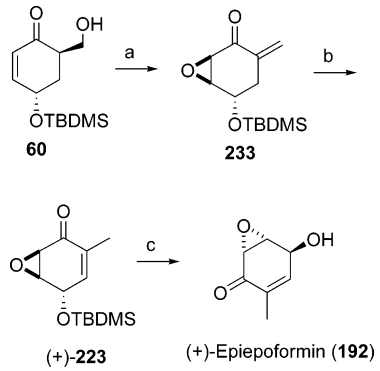
desilylation produced (+)-epiepoformin (**192**) in excellent yield (Scheme 49).

Finally, the reduction of intermediate **232** with sodium borohydride in the presence of cerium trichloride afforded an inseparable mixture of allylic alcohols, which after desilylation and chromatography afforded (−)-theobroxide (**189**) (Scheme 50) in 84% yield.

6.11.4. Okamura's Approach

Okamura described the asymmetric synthesis of (+)-epiepoformin (**192**), beginning with compound **60** and proceeding via intermediate **233** (Scheme 51).[80] Compound **60** (Scheme 10) was crucial in Okamura's synthesis of eutypoxide B (**3**), and this new report also marked its successful use for the preparation of epoxide (+)-**223**, which was previously reported by Ogasawara in his approach to (+)-epiepoformin (**192**).[76]

Scheme 51. Okamura's Synthesis of (+)-Epiepoformin (192)[a]

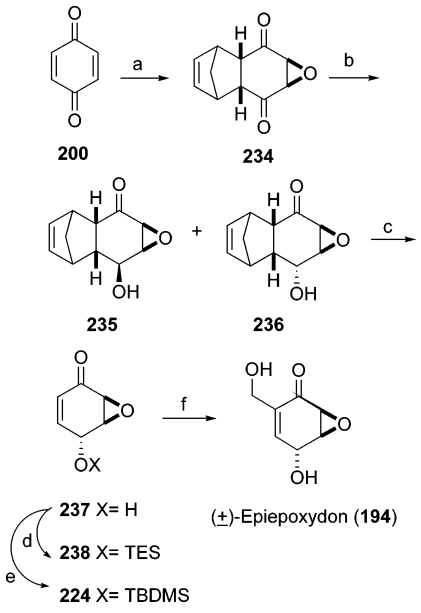


[a] Reagents: (a) (i) H_2O_2 (92%), (ii) TsCl, Et_3N (94%); (b) Pd/C (70%); (c) HF (99%).

6.11.5. Taylor's Approach

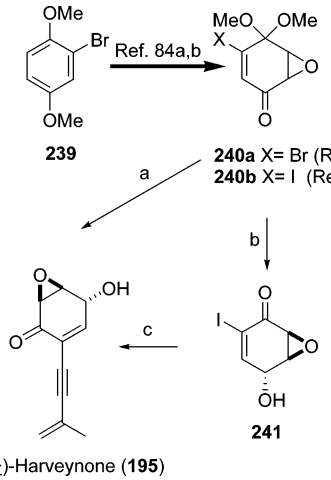
Very recently, Taylor described the synthesis of epiepoxydon (**194**)[83] based on the Baylis−Hillman reaction[92] of formaldehyde with racemic epoxy-α,β-unsaturated ketones **224** (Scheme 45) and **238**, both of which were prepared from alcohol **237**, as shown in Scheme 52. The known cycloaddition of 1,4-benzoquinone (**200**) and cyclopentadiene[93] exclusively

Scheme 52. Taylor's Synthesis of (±)-Epiepoxydon (194)[a]



[a] Reagents: (a) (i) Cyclopentadiene, MeOH (74%), (ii) *t*-BuOOH (85%); (b) *n*-Bu_4NBH_4 (64%); (c) (from **236**) diphenyl ether (94%); (d) Et_3SiCl (86%); (e) TBDMSOTf (43%); (f) (from **238**) (i) CH_2O, Et_3Al, n-Bu_3P (44%), (ii) HF−Py (70%).

Scheme 53. Taylor's Synthesis of (±)-Harveynone (195)[a]



[a] Reagents: (a) (from **240a**) (i) **226b**, $PdCl_2(PPh_3)_2$, CuI, diisopropylamine (41%); (from **240b**) (i) **226b**, $Pd(OAc)_2$ (68%), (ii) DIBALH, then montmorillonite K10 (43%); (b) (from **240b**) (i) DIBALH, then montmorillonite K10 (74%); (c) **226a**, $PdCl_2(PPh_3)_2$, CuI, (74%).

afforded the *endo*-adduct, whose epoxidation then gave epoxide **234** with total *exo*-selectivity.[94] Under the best conditions, the reduction of this ketone produced a mixture of separable epoxyalcohols **235** and **236** in a 1:6.4 ratio. The major isomer, **236**, was then submitted to a retro-Diels−Alder reaction[49d] to produce alcohol **237**, which was routinely transformed into the precursors **238** and **224** that were required for the Baylis−Hillman reaction. This transformation of **238** and **224** into **194** proved to be very sensitive to the reaction conditions and, even after optimization, gave the α-alkylated products in only moderate yield. The overall yields were higher when **238** was used as starting material, instead of **224**. The first steps in Taylor's synthesis of intermediate **237** are similar to those developed by Ichihara in his synthesis of epoxydon and epiepoxydon (Scheme 41), although Taylor's differs in that he uses cyclopentadiene as the diene partner. Interestingly, Ichihara commented[81e] that he rejected using cyclopentadiene for this task because it is well-known that strong conditions are required for the retro-Diels−Alder reactions of adducts of this type.[95]

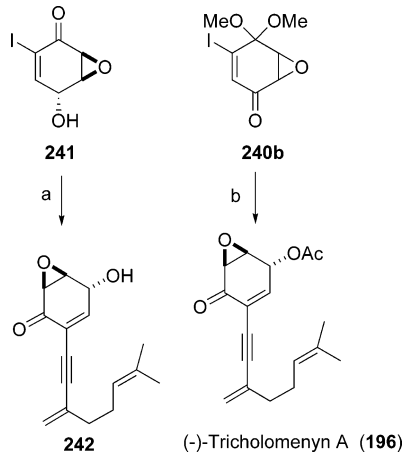
Lubineau[96] also recently described a synthetic sequence identical to that depicted in Scheme 52, but he was unable to separate alcohols **235** and **236**. Fortunately, thermolysis of this mixture afforded compound **237**, along with unreacted adduct **235**.

Compound **237** has also been prepared from anthracene-like adducts by Australian researchers using the same strategy.[97]

Finally, on this subject, Ogasawara also reported the synthesis of compound **224** in both enantiomeric forms (Scheme 45) by using related cyclopentadiene adducts as chiral intermediates.[85,86]

Taylor and co-workers reported routes to racemic harveynone (**195**)[84a] and tricholomenyn A (**196**)[87] in 1996 and 1997, respectively. As shown in Scheme 53, the selected methodology consisted of Sonogashira[91] or Stille[90] couplings between compounds **240**−**241** and acetylenic or stannane intermediates, respectively. As occurred previously, Ogasawara described similar, independent methodologies almost simultaneously.[85,86] The required α-halogenated enone precursors, compounds **240a**,[84a] **240b**,[84b] and **241**,[84a] were prepared from commercially available 1-bromo-2,5-dimethoxybenzene **239** (Scheme 53). Sonogashira coupling between 2-methyl-1-buten-3-yne (**226b**) (Figure 11) and precursor **240a** produced the corresponding adduct in low yield (41%), and the yield of this coupling reached 68% when the crystalline and stable iodide **240b** was used as starting material in the Sonogashira reaction. After reduction of this adduct with DIBALH, followed by acetal hydrolysis with montmorillonite K10, harveynone (**195**) was obtained along with some epimeric alcohol. A better result (74%) was obtained by coupling precursor **241** with stannane **226a** (Figure 11).

Scheme 54. Taylor's Synthesis of (±)-Tricholomenyn A (196)[a]



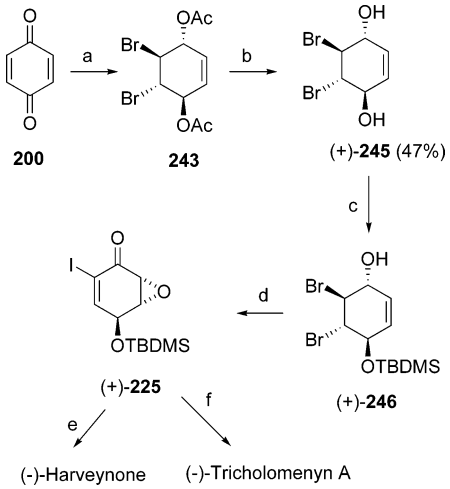
[a] Reagents: (a) **227a**, $PdCl_2(PPh_3)_2$, CuI (20%); (b) (i) **227c**, Bu_4NF, SiO_2, $Pd(OAc)_2$, CuI (86%), (ii) $LiEt_3BH$, then Ac_2O, Py, and montmorillonite K10 (57%).

Conversely, for the preparation of tricholomenyn A (**196**),[87] the Stille coupling between **241** and stannane **227a** (Figure 11) gave compound **242** in very poor yield (20%) (Scheme 54), while the reaction between acetylene **227c** (Figure 11) and the α-iodoenone **240b** provided the desired adduct in good yield (86%). Complete stereoselective reduction and hydrolysis of this adduct furnished racemic tricholomenyn A (**196**) in good overall yield.

6.11.6. Johnson/Negishi's Approaches

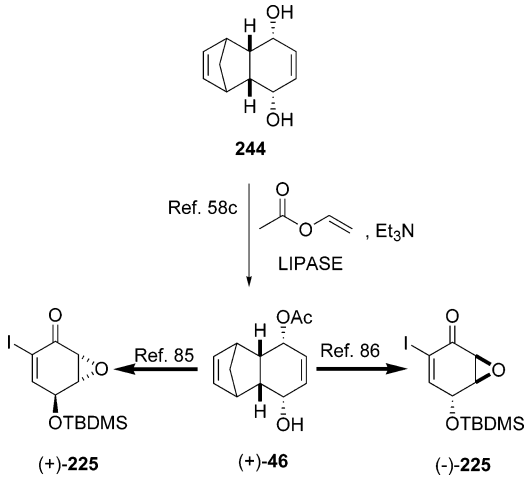
Johnson[88a,c] and Negishi's[89] approaches to harveynone (**195**) and tricholomenyn A (**196**) used similar precursors but different methodologies. Because of their similarities, we will discuss them here together. Johnson's intermediate was the enantiomerically pure compound (+)-**225** obtained by enzymatic resolution of compound **243**[88b] and subsequent manipulation of conveniently functionalized derivatives (Scheme 55). It is remarkable that Ogasawara also prepared product **225** in both enantiomeric forms from *meso*-tricyclic ene-1,4-diol (**244**) by reacting it with vinyl acetate in tetrahydrofuran containing triethylamine in the presence of immobilized lipase. The reaction proceeded via intermediate (+)-**46** (Chart 3).[58c] Contrary to previous reports from Ogasawara[85,86] and

Scheme 55. Johnson's Synthesis of (−)-Harveynone (195) and (−)-Tricholomenyn A (196)[a]



[a] Reagents: (a) (i) Br_2, (ii) $NaBH_4$ (62%), (iii) Ac_2O, Et_3N (72%); (b) Amano PS-30; (c) TBDMSOTf (45%); (d) (i) CF_3CO_3H (84%) (ii) Zn (81%), (iii) PCC (82%), (iv) I_2 (77%); (e) (i) **226b**, $PdCl_2(PPh_3)_2$, CuI, diisopropylamine (52%), (ii) H_2SiF_6 (81%); (f) (i) **227b**, $PdCl_2(PPh_3)_2$, CuI, diisopropylamine (54%), (ii) H_2SiF_6 (79%), (iii) DCC, AcOH (92%).

Chart 3



Taylor,[84] which speculated that Sonogashira coupling was not viable in substrate **225**, possibly because of aromatization side reactions, Johnson[88] was able to demonstrate that this reaction was possible and afforded enantiomerically pure (−)-harveynone (**195**) and (−)-tricholomenyn A (**196**) in 52% and 54% yields, respectively. The Sonogashira coupling reactions proceeded faster with diisopropylamine than with triethylamine, and the workup conditions proved critical, being necessary to carefully remove all traces of amine promoters.

Recently, Negishi[89] significantly improved these yields by utilizing the Pd-catalyzed cross-coupling of racemic **225** with suitable alkynylzinc reagents [73% yield for harveynone (**195**) and 80% yield for tricholomenyn A (**196**)].

6.12. Panepoxydon/Isopanepoxydon/Cycloepoxydon

Panepoxydon (**247**) (Figure 4; for other related natural metabolites, such as panepoxydione, neopanepoxydon, neopanepoxydol, and 7-deoxypanepoxydol,[98a] see Figure 12) and isopanepoxydon (**248**) (Figure 4) were the major metabolites obtained from *Panus rudis* and *Panus conchatus*.[98a] Panepoxydon has been isolated from fermentations of the basidiomycete *Lentinus crinitus* and inhibits the NF-κB-activated expression of SEAP (secreted alkaline phosphatase) with an IC_{50} of 1.5−2 μg/mL (7.15−9.52 μM). No inhibition of AP-1-mediated expression of the reporter gene could be observed at a concentration up to 5 μg/mL of panepoxydon (**247**). Panepoxydon (**247**) strongly reduced the TPA-, TNF-α-, and okadaic acid-mediated binding of NF-κB to the high-affinity consensus sequence in COS-7 and HeLa S3 cells as confirmed by EMSA's. Panepoxydon inhibits IκB phosphorylation and, therefore, sequesters the NF-κB complex in an inactive form.[98b] In a screening for new inhibitors of NF-κB- and AP-1-mediated signal transduction pathways in COS-7 cells using SEAP as a reporter gene, cycloepoxydon (**249**)[99] (Figure 4) was isolated from fermentations of the deuteriomycete strain 45−93. Cycloepoxydon inhibits the TPA-induced NF-κB- and AP-1-mediated SEAP expression with an IC_{50} of 1−2 μg/mL (4.2−8.4 μM) and 3−5 μg/mL (12.6−21 μM), respectively. In COS-7 and HeLa S3 cells electrophoretic mobility shift assays showed that cycloepoxydon strongly reduced the TPA- and TNF-α-mediated binding of NF-κB to a high-affinity consensus sequence. This effect was due to the inhibition of phosphorylation within the protein IκB.[99a] The structure of cycloepoxydon (**249**) was determined by spectroscopic techniques.[99b]

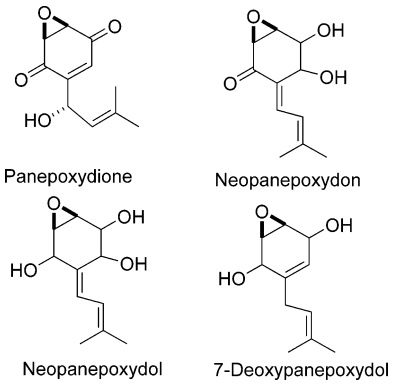
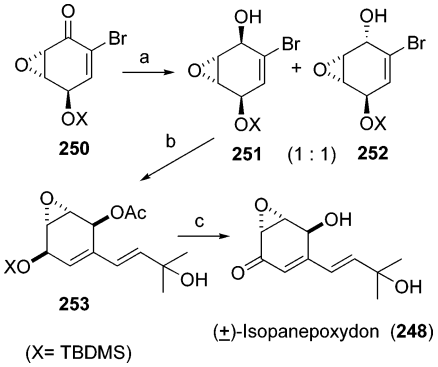


Figure 12. [98a]

The first and only known total syntheses of racemic panepoxydon (**247**) and isopanepoxydon (**248**) have been described by Wood and co-workers as outlined in Schemes 56 and 57.[100] The reduction of α-bromo enone **250** (Scheme 56) gave two allylic alcohols, **251** and **252**, in a 1:1 ratio, which after chromatographic separations were used to produce isopanepoxydon (**248**) and panepoxydon (**247**). As shown in Scheme 56, the acetylated derivative of compound **251** underwent Heck reaction to afford intermediate **253**, which was transformed into isopanepoxydon (**248**) after standard treatment.

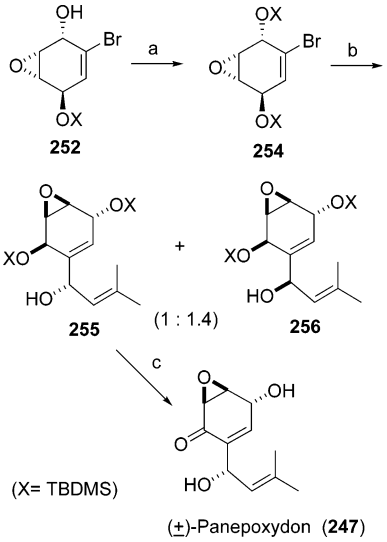
For the synthesis of racemic panepoxydon (**247**) (Scheme 57), compound **252** was silylated to give product **254**, which after lithiation and reaction with crotonaldehyde afforded alcohols **255** and **256** in a

Scheme 56. Crews/Wood's Synthesis of (±)-Isopanepoxydon (248)[a]



[a] Reagents: (a) $NaBH_4$, $CeCl_3$ (91%); (b) (i) Ac_2O, DMAP (93%), (ii) (from **251**) 2-methyl-3-buten-2-ol, $Pd(OAc)_2$ (89%); (c) (i) Bu_4NF, then Dess−Martin periodinane (93%), (ii) NH_3, MeOH (69%).

Scheme 57. Crews/Wood's Synthesis of (±)-Panepoxydon (247)[a]

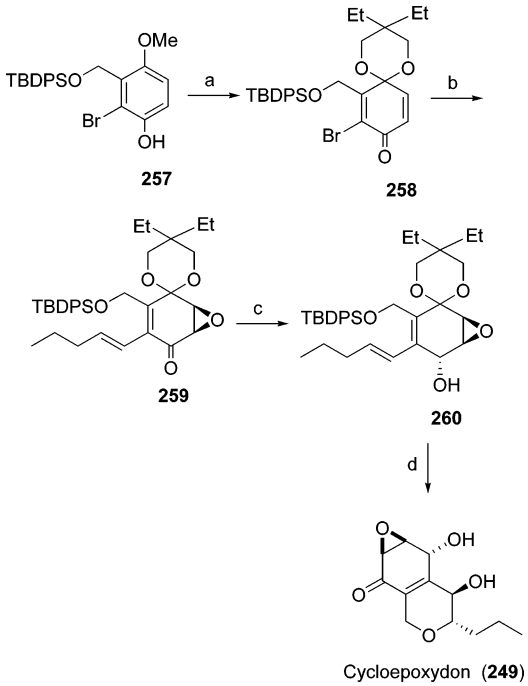


[a] Reagents: (a) TBDMSCl; (b) *t*-BuLi, crotonaldehyde (80%); (c) (i) NaH, (ii) Dess−Martin periodinane, (iii) HF (52%).

1:1.4 ratio. Pure **255** was processed under standard conditions to eventually lead to the target molecule. In summary, isopanepoxydon was synthesized in six steps (24% overall yield from **250**) and panepoxydon in 11% yield from **250**, also in six steps. The synthetic process served to assign the correct stereochemistry of both natural products.

Porco et al. accomplished the first stereoselective total synthesis of cycloepoxydon (**249**), an inhibitor of NF-κB.[101] To do so they employed a tartrate-mediated, asymmetric nucleophilic epoxidation of a quinone monoacetal. Their synthetic strategy started with protected hydroquinone **257** (Scheme 58), which they transformed into ketone **258** by hypervalent iodine oxidation and further acetalization. Asymmetric nucleophilic epoxidation and Stille coupling of **258** then gave epoxy ketone **259**, which after reduction and deprotection yielded epoxyquinol **260**. Finally, the desired (−)-cycloepoxydon (**249**) was obtained, after eight steps and in 21% overall yield, by sequential epoxidation, tandem deprotection, and cyclization of epoxyquinol **260**.

Scheme 58. Porco's Synthesis of (−)-Cycloepoxydon (249)[a]



[a] Reagents: (a) (i) $PhI(OAc)_2$ (84%), (ii)2,2-diethyl-1,3-propanediol, PPTS (89%); (b) (i) NaHMDS, L-DIPT, Ph_3CO_2H (97%, 96% ee), (ii) (*E*)-tributyl-1-pentenyl-stannane, $Pd_2dba_3{\cdot}CHCl_3$, $ClCH_2$-CH_2Cl (81%); (c) (i) DIBALH (88%), (ii) HF-MeCN (92%); (d) (i) MCPBA (85%), (ii) HF−MeCN (53%).

6.13. Parasitenone

Parasitenone (**261**) (Figure 5) was isolated as a fairly unstable epoxycyclohexanone from the marine algicolous fungus *Aspergillus parasiticus*.[102]

6.14. Terreic Acid

Terreic acid (**262**) (Figure 5) is a quinone monoepoxide[103a] that was obtained from the submerged culture fermentation broth of *Aspergillus terreus*.[103b] It was found to be active against HeLa cells in tissue and Ehrlich carcinoma cells in vitro.[103c] The biosynthesis of terreic acid has also been studied.[103d]

6.15. Terremutin

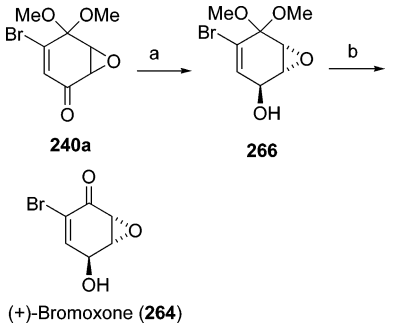
Terremutin is a metabolite isolated from *Aspergillus terreus* that was first structurally characterized by Miller.[104a] Miller's original structure was revised and assigned as **263** (Figure 5) by Read and Ruiz based on its unequivocal synthesis via sodium borohydride reduction of terreic acid (**262**), followed by a comparison of the synthetic compound with the natural product.[104b]

6.16. Bromoxone

Bromoxone (**264**) and its acetate (**265**) (Figure 5) were isolated from marine acorn worms (*Phyllum hemichordata*) by Higa and co-workers in 1987.[105] The structure of bromoxone was confirmed by an X-ray analysis of its acetate. Compound **265** showed antitumor activity in P388 cells (IC_{50} 10 ng/mL).

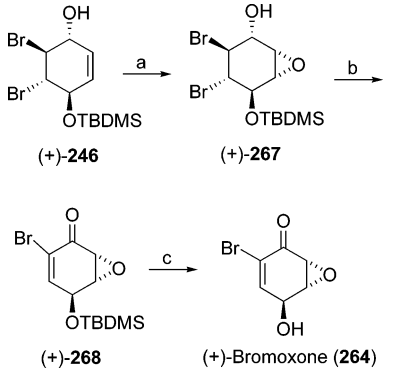
Bromoxone (**264**) has been prepared in racemic form by Taylor and co-wokers[84b] and in enantiomeri-

Scheme 59. Taylor's Synthesis of (±)-Bromoxone (264)[a]



[a] Reagents: (a) DIBALH; (b) Montmorillonite K10 (53% overall yield).

Scheme 60. Johnson's Synthesis of (+)-Bromoxone (264)[a]



[a] Reagents: (a) CF_3CO_3H (84%); (b) CrO_3·Py (89%); (c)H_2SiF_6 (74%).

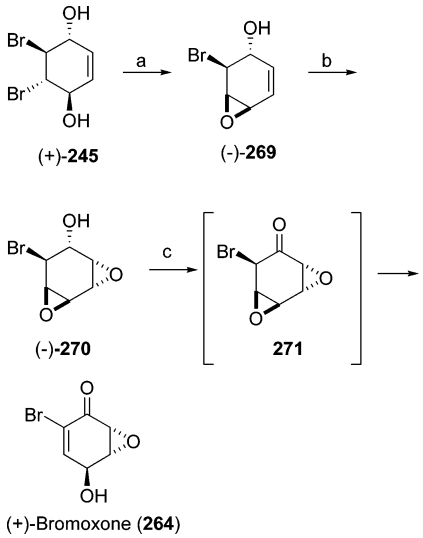
cally pure form in both Johnson's[88b] and Altenbach's laboratories.[106]

Taylor's approach to synthesizing bromoxone is shown in Scheme 59. The reduction of intermediate **240a** (Scheme 53) gave a mixture of alcohol **266** and its epimer in a 9:1 ratio (Scheme 59). This mixture was deprotected and easily separated by chromatography. The major isomer **266** gave (±)-bromoxone (**264**) in five steps (15% overall yield) from commercial 1-bromo-2,5-dimethoxybenzene **239**.

In 1995 Johnson reported the synthesis of both enantiomeric forms of bromoxone (**264**). We will only describe the synthesis of (+)-bromoxone (**264**).[88b] Compound (+)-**246** was again the key intermediate in this synthesis, just as it had been in Johnson's synthesis of tricholomenyn A (**196**) and harveynone (**195**) (Scheme 55). As outlined in Scheme 60, epoxidation of the double bond from the α-face afforded exclusively epoxide **267**. The oxidation conditions that compound **267** was subjected to not only introduced the ketone, but also promoted the elimination of hydrobromic acid to give, after desilylation, the desired (+)-bromoxone (**264**).

In 2000 Altenbach reported[106a] details concerning the asymmetric synthesis of (+)-bromoxone (**264**) from compound (+)-**245**. Product (+)-**245** was prepared by a similar route to that shown in Scheme 55 from racemic **243** by enzymatic resolution with PPL, thus using the same methodology that Johnson, who had used lipase Amano PS-30, had implemented for the preparation of these molecules. However, Altenbach actually originated these concepts, which he had developed and exemplified in previous reports.[106b,c] Altenbach's synthesis of (+)-bromoxone is shown in Scheme 61. It is very efficient and shorter than other routes. The reaction of lithium hydroxide with compound (+)-**245** gave exclusively epoxide **269**, which after further epoxidation with MCPBA furnished bisepoxide **270**. As in Johnson's method, Dess–Martin oxidation of **270** directly gave (+)-bromoxone (**264**) in 31% overall yield from **245**. The intermediate diepoxyketone **271** could be detected by NMR but during the workup rearranged to **264**.

Scheme 61. Altenbach's Synthesis of (+)-Bromoxone (264)[a]



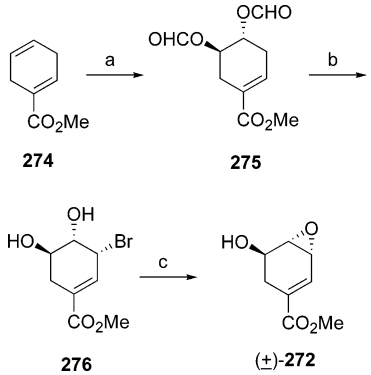
[a] Reagents: (a) LiOH (90%); (b) MCPBA (67%); (c) Dess–Martin periodinane (52%).

6.17. Chaloxone

Epoxide **272** (no common name given), which is a derivative of shikimic acid, and chaloxone (**273**) (Figure 5) are fungal metabolites that were isolated in 1981 from *Chalara microspora*. These compounds were readily characterized by their spectroscopic data[107] and by independent synthesis.[107a,108]

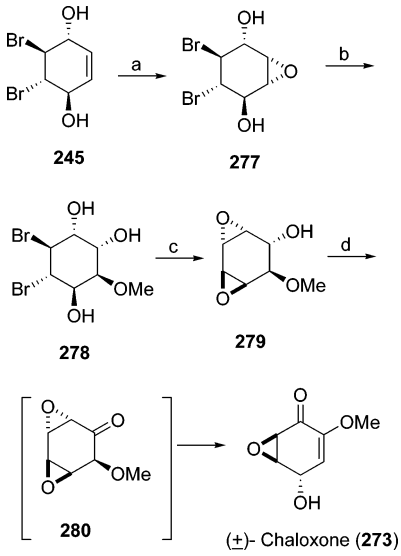
Epoxide **272** has been prepared by Fex as shown in Scheme 62. Starting from methyl 1,4-cyclohexadien-1-carboxylate (**274**) and following literature procedures,[107b,c] precursor **275** was obtained and

Scheme 62. Fex's Synthesis of Epoxide (±)-272[a]



[a] Reagents: (a) ref 107; (b) NBS, then MeOH (16%); (c) Na_2CO_3, acetone (81%).

Scheme 63. Fex's Synthesis of (±)-Chaloxone (273)[a]



[a] Reagents: (a) MCPBA (ref 106d); (b) MeOH, $BF_3 \cdot Et_2O$(90%); (c) *t*-BuOK, *t*-BuOH (89%); (d) $CrO_3 \cdot Py$ (40%).

submitted to allylic bromination to give bromodiol **276**. After base treatment, compound **276** yielded the target molecule.[107a]

Fex also described the synthesis of racemic chaloxone (**273**) as outlined in Scheme 63.[108] Starting with racemic diol **245** (Scheme 61), compound **277** was obtained according to the method reported by Altenbach.[106d] The reaction of **277** with methanol in the presence of a Lewis acid catalyst opened the epoxide trans diaxially to give ether **278**. Base-mediated bisepoxide formation gave product **279**, which was oxidized to form the intermediate ketone **280**. Ketone **280** underwent in situ opening of the epoxide to finally yield racemic chaloxone (**273**).

6.18. Epoxydeliquinone

2,9-Epoxydeliquinone (**281**) (Figure 5) has been isolated from intact injured fruit bodies of *Russula delica* (*Russulaceae*). Its relative configuration could not be established from spectroscopic data.[109]

6.19. Lachnumon/Lachnumol A

Lachnumon (**282**) and lachnumol A (**283**) (Figure 5), isolated from *Lachnum papyraceum*, were found to be new fungal metabolites with cytotoxic, nematicidal, and antimicrobial activities.[110a] The structures of these biologically active, chlorinated metabolites have been assigned by NMR and mass spectroscopy.[110b]

6.20. A80915

A80915 factor G (**284**) (Figure 5) has been isolated from the fermented broth of *Streptomyces aculeolatus*.[111]

6.21. UCF76-B

UCF76-B (**285**) (Figure 5) was isolated while searching for farnesyltransferase inhibitors in *Streptomyces* species. It is structurally related to the pyranonaphthoquinone antibiotics nanaomycin, frenolicin, and kalafungin. Farnesyltransferase inhibition by UCF76-B was weak, with IC_{50} values of 25 μM.[112]

6.22. Epoxyquinol A

Epoxyquinol A (**286**) (Figure 6) was produced by an unidentified fungus isolated from a soil sample. It was obtained during the course of a research program directed at identifying angiogenesis inhibitors of microbial origin. Its structure was established by extensive analysis of its spectroscopic data and by X-ray analysis.[113] Epoxyquinol possesses an unique carbocyclic ring structure, essentially formed by two 2*H*-pyran monomers. The biological activities of this compound seem very promising because epoxyquinol A (**286**) inhibited VEGF (vascular endothelial growth factor) induced cell migration.

6.23. Ambuic Acid

Ambuic acid (**287**) (Figure 6), which is a highly functionalized cyclohexenone, was isolated from *Pestalotiopsis* and *Monochaetia* species and characterized.[114] These two species are biologically related endophytic fungi that are associated with many tropical plant species. Ambuic acid (**287**) was found in representative isolates of these fungal species that were obtained from rainforest plants located on several continents.

6.24. Flagranones A–C

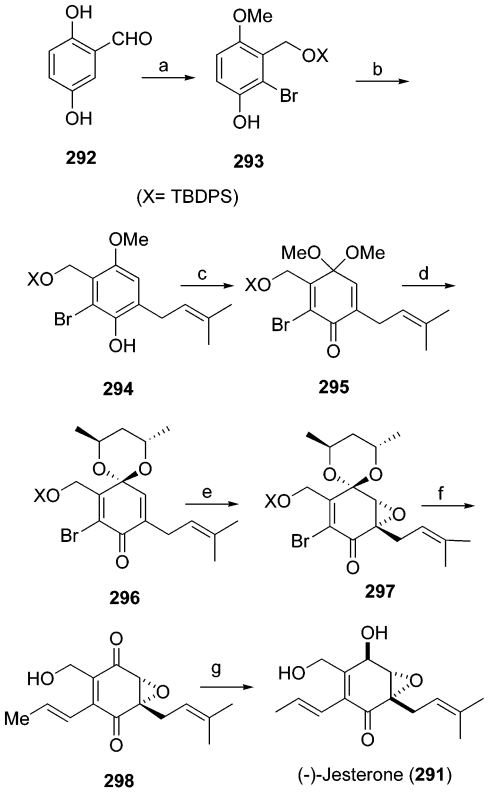
Flagranones A (**288**), B (**289**), and C (**290**) (Figure 6) are metabolites isolated from the nematode-trapping fungus *Duddingtonia flagrans*.[115] These antibiotics are structurally related to the farnesylated cyclohexenoxides of the oligosporon group, which were recently isolated from the nematode-trapping fungus *Arthrobotrys oligospora*, and they show similar antimicrobial activity.

6.25. Jesterone

(−)-Jesterone (**291**) (Figure 6) and hydroxy−jesterone are novel, highly functionalized cyclohexenone epoxides isolated from the newly described endophytic fungal species *Pestalotiopsis jesteri*.[116] They were purified from cultures of the fungus by bioassay-guided fractionation using *Pythium ultimum* as the indicator organism. Jesterone (**291**) is particularly noted for displaying selective antimycotic activity against the oomycetous fungi, which are some of the most plant pathogenic fungi known.

Porco and co-workers recently reported the asymmetric synthesis of natural (−)-jesterone (**291**) (Scheme 64).[117] Commercially available 2,5-dihydroxybenzaldehyde (**292**) was transformed into intermediate **293** in six steps (53% overall yield). The first step of the synthesis was a prenylation reaction that was effected by *O*/*C* alkylation at the phenol moiety in compound **293**. This process yielded the *C*-alkylated compound **294** in 49% yield, along with the *O*-alkylated derivative (not shown). The *O*-alkylated derivative was isomerized to **294** by treatment with

Scheme 64. Porco's Synthesis of (−)-Jesterone (291)[a]



[a] Reagents: (a) (i) Br_2 (94%), (ii) TBDMSCl (94%), (iii)MeI, NaH (72%), (iv) $NaBH_4$ (99%), (v) TBDPSCl (93%), (vi) Bu_4NF (93%); (b) NaH, prenyl bromide (60%); (c) $PhI(OAc)_2$ (83%); (d) (2*S*,4*S*)-(+)-pentanediol (80%); (e) Ph_3COOH (80%); (f) (i) (*E*)-tributyl-1-propenylstannane, $Pd(PPh_3)_4$ (88%), (ii) HF (82%); (g) DIBALH (84%).

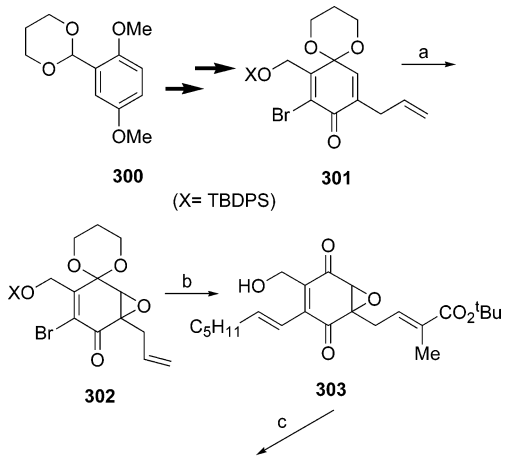
montmorillonite, raising the total yield for compound **294** to 60%. Next, the monoprotected hydroquinone functionality of **294** was converted into the 1,4-keto dimethyl acetal of compound **295** after hypervalent iodine oxidation. The acetal generated in this step is conveniently located such that the transacetalation reaction with chiral 2*S*,4*S*-(+)-pentanediol gives product **296**, which is ready for substrate-directed asymmetric epoxidation. This process was totally stereocontrolled, as only enantiomerically pure epoxide **297** was isolated. This product was subjected to a second prenyl incorporation via a Stille reaction.[90] Finally, desilylation and DIBALH-chelate-directed reduction of the ketone **298** afforded (−)-jesterone (**291**) in a very elegant and efficient synthetic sequence. In biological assays, not only jesterone (**291**), but its epimer and precursor **298**, displayed potent antifungal activity.

6.26. Torreyanic Acid

In 1996 Clardy and co-workers described the isolation and characterization of the quinone epoxide dimer torreyanic acid (**299**) (Figure 6) from the fungus *Pestalotiopsis microspora*.[118] This compound was cytotoxic to tumor cells and 5−10 times more potent in cell lines that were sensitive to protein kinase C agonists.

Racemic torreyanic acid (**299**) has been synthesized by Porco and co-workers (Scheme 65).[119] Starting

Scheme 65. Porco's Synthesis of (±)-Torreyanic Acid (299)[a]



[a] Reagents: (a) Ph_3COOH (81%); (b) (i) OsO_4, NMO,then $Pb(OAc)_4$ (96%), (ii) $Ph_3P{=}C(CH_3)CO_2tBu$ (64%), (iii) (*E*)-tributyl-1-heptenyl stannane, $Pd(PPh_3)_4$ (97%), (iv) Bu_4NF (72%), (v) HF (93%); (c) (i) Dess−Martin periodinane (39%), (ii) CF_3CO_2H (99%).

with the 1,3-dioxane derivative **300** and following a synthetic protocol similar to that previously described for the synthesis of jesterone (**291**) (see above), compound **301** was readily obtained. Epoxidation and Stille reaction[90] of this compound afforded the key monomer **302**, which was conveniently manipulated to afford intermediate **303**. This intermediate was dimerized after Dess−Martin oxidation, which afforded two dimeric products in a 1:1 ratio. A final hydrolysis of the mixture provided torreyanic acid (**299**) and its stereoisomer (*iso*-torreyanic acid).

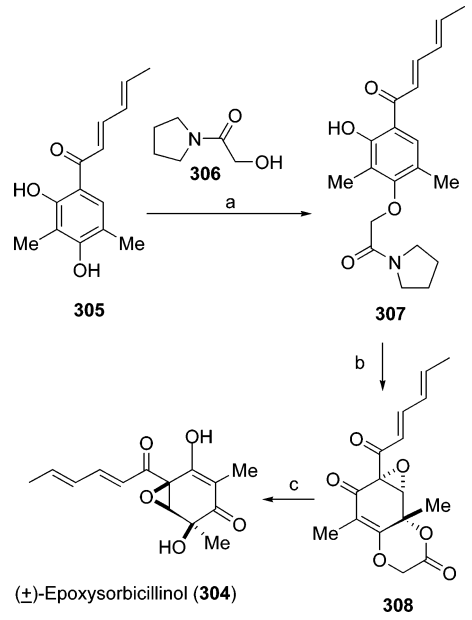
6.27. Epoxysorbicillinol

Recent interest in the saltwater culture of a sponge-derived *Trichoderma longibrachiatum* has led to the isolation of (+)-epoxysorbicillinol (**304**) (Figure 7).[120] This compound represents the first isolated vertinoid polyketide possessing an epoxide functional group. Two synthesis for racemic epoxysorbicillinol (**304**) have been reported.[121,122]

The reported synthesis of racemic epoxysorbicillinol (**304**) by Pettus and co-workers (Scheme 66) is extremely simple and elegant.[121] It is noteworthy that the hypervalent iodine oxidation of intermediate **307** (obtained by Mitsunobu reaction of sorbicillin **305** with amide **306**) in one step afforded compound **308**, which has all of the necessary functional groups for the target molecule located in the correct place and with the appropriate configuration. Vinyl ether **308** proved quite resistant to hydrolysis conditions, and therefore, the lactone was submitted to a Weinreb procedure to yield the amide, which, after acid cleavage, finally yielded racemic epoxysorbicillinol (**304**).

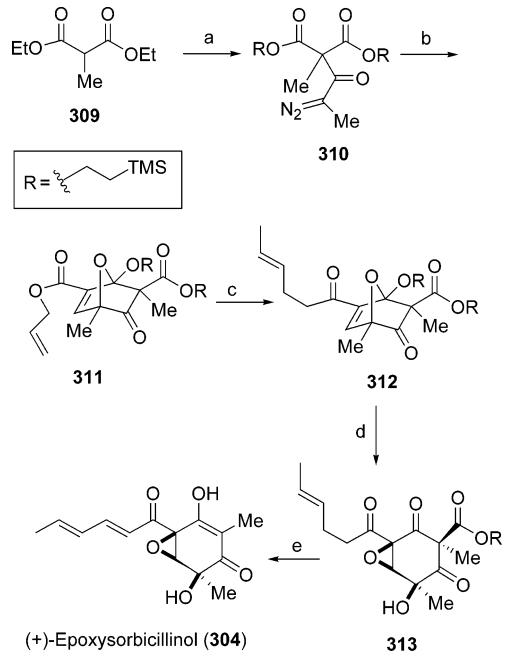
In the same year that Pettus's report appeared, Wood and co-workers also disclosed the total synthesis of epoxysorbicillinol (**304**) in 13 steps from diethyl methyl malonate (**309**) (Scheme 67).[122] Knowing the propensity of the sorbyl side chain to undergo polymerization led the authors to delay the incorporation of this functionality until the last steps of the

Scheme 66. Pettus' Synthesis of (±)-Epoxysorbicillinol (304)[a]



[a] Reagents: (a) DEAD, PPh_3 (90%); (b) $PhI(OCOCF_3)_2$ (40%); (c) (i) dimethylaluminum amide (90%), (ii) $SnCl_4$ (80%).

Scheme 67. Wood's Synthesis of (±)-Epoxysorbicillinol (304)[a]



[a] Reagents: (a) (i) β-trimethylsilylethanol, (ii) NaH, pyruvoyl chloride, (iii) tosylhydrazine, (iv) Al_2O_3 (71% from **304**); (b) allyl propiolate, $Rh_2(OAc)_4$ (73%); (c) (i) $Pd(PPh_3)_4$, $C_5H_{11}N$, (ii) HNMe(OMe), (iii) 3-pentenyllithium (41%); (d) (i) CF_3CO_2H, (ii) t-BuOOH (62%); (e) (i) CF_3CO_2H (81%), (ii) DDQ (30−40%).

sequence. After a series of trials, the best route to the target molecule was determined to proceed by the novel and very efficient 1,3-dipolar cycloaddition of α-diazoketone **310** and allyl propiolate to form the bicyclic acetal **311**, where compound **311** represents the carbocyclic core of epoxysorbicillinol (**304**). The unsaturated side chain was incorporated by applying Weinberg's methodology to yield ketone **312**. Compound **312** was submitted to acid hydrolysis and epoxidation to provide precursor **313**, which on acid hydrolysis and DDQ treatment to effect the desired dehydrogenation afforded the target product **304**. The last step proceeded in a modest 30−40% yield, which confirmed the sensitivity of the side chain in the reaction conditions.

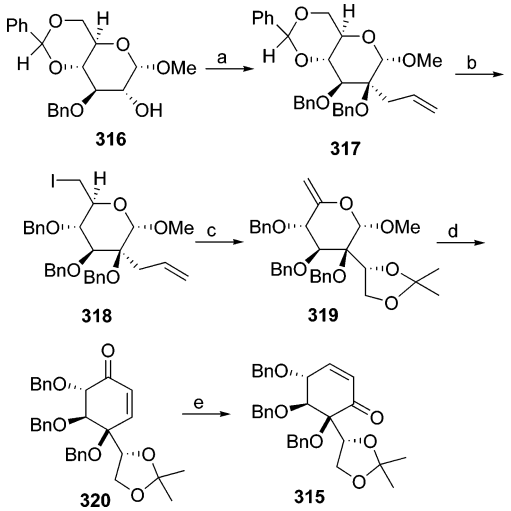
6.28. Scyphostatin

Scyphostatin (**314**) (Figure 7) was first isolated in 1997 by Ogita and co-workers from a mycelial extract of the microorganism *Trichopeziza mollissima* SANK 13892.[123] This discomycete had been previously named as *Dasyscyphus mollissimus*.[123a] Scyphostatin was found to exhibit selective inhibitory activity against the enzyme neutral sphingomyelinase (N-SMase) and thus far remains the most potent (IC_{50} 1.0 μM) of the few known inhibitors of this enzyme. It is believed that inhibition of N-SMase may lead to treatment for inflammatory and autoimmune disorders. Its structure and absolute configuration were determined by extensive spectroscopic analysis,[123a,b] degradation, and correlation with known compounds[124] and finally by unequivocal synthesis of the C(1′)−C(20′) trienoyl fragment.[125]

The total synthesis of scyphostatin (**314**) still remains elusive, and only a few reports concerning the synthesis of its analogues[126−128] or structural fragments[129−131] have been published.

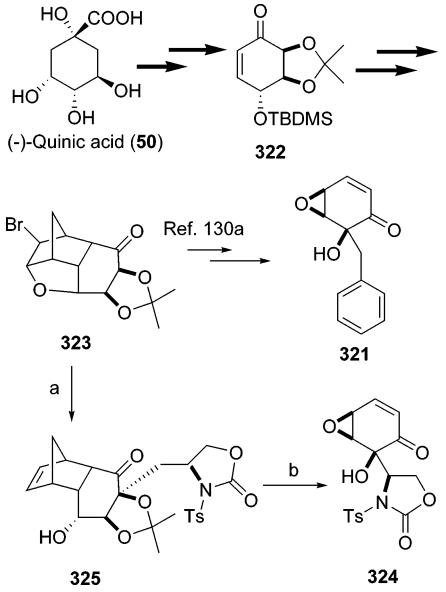
Gurjar and Hotha[129] reported the synthesis of compound **315** (Scheme 68) from D-glucose using a Ferrier reaction[44] to prepare the cyclohexenone ring. Note that this fragment has all of the necessary functional groups in the correct position and with the appropriate configuration for the final synthesis of scyphostatin in enantiomerically pure form. Beginning with the known intermediate **316**, the major branched *C*-sugar **317** was readily obtained along with its epimer at the newly formed stereocenter in a 4:1 ratio. After separation and routine transforma-

Scheme 68. Synthesis of Product 315[a]



[a] Reagents: (a) (i) Swern oxidation (89%), (ii) allylmagnesium-bromide (68%), (iii) NaH, BnBr (97%); (b) (i) $LiAlH_4$, $AlCl_3$ (90%), (ii) I_2 (95%); (c) (i) AD-mix-α, *t*-BuOH (89%), (ii) DMP (98%), (iii) DBU (48%); (d) (i) $Hg(OAc)_2$ (80%), (ii) MsCl, Et_3N (85%); (e) (i) H_2O_2 (65%), (ii) $NaBH_4$ (93%), (iii) ImC(S)Im (98%), (iv) Bu_3SnH (30%), (v) MnO_2 (87%).

Scheme 69. Synthesis of Product 324[a]

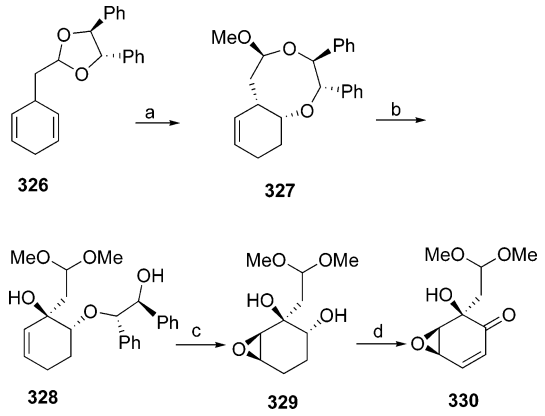


[a] Reagents: (a) (i) LHMDS, (*R*)-*N*-(*p*-toluenesulfonyl)-*N*,*O*-isopropylidene serinal (95%), (ii) NHMDS, CS_2, MeI(88%), (iii) Bu_3SnH (95%), (iv) HCl, then $Cl_3COCOCl$ (67%), (v) TMSI (74%), (vi) Zn, MeOH (95%); (b) (i) diphenyl ether (59%), (ii) MsCl, Py (83%), (iii) CF_3CO_2H (99%), (iv) NaOH (75%).

tions, the iodo derivative **318** was submitted to a Sharpless dihydroxylation reaction,[132] which afforded a mixture of epimers in a 4:1 ratio. The major epimer, whose absolute configuration at the newly formed stereocenter was predicted based on the Sharpless hypothesis, afforded intermediate **319** following standard manipulation. Ferrier rearrangement of **319** and further dehydration cleanly gave product **320**. This enone underwent epoxidation followed by reduction, yielding an epoxyalcohol which was subjected to Barton's α-epoxy radical opening reaction,[133] in order to translocate the α,*β*-unsaturated system.

Izuhara and Katoh reported the synthesis of epoxycyclohexenone **321** (Scheme 69), which is a model compound for the total synthesis of scyphostatin.[130a] This compound was prepared from (−)-quinic acid (**50**) via intermediate **323,** which was obtained from cyclohexenone **322**. In a recent paper these authors also reported the synthesis of the scyphostatin fragment **324**[130b] from intermediate **323** by following a similar strategy to that described for the preparation of the model product **321**.[130a] Compound **324** is the most advanced intermediate prepared to date for the synthesis of scyphostatin (**314**). As shown, it has both the complete functionality and the absolute stereochemistry that are present in the natural product and is ready for the side-chain polyene to be incorporated. The synthesis of **324** started with the reaction of ketone **323** with a serinal derivative to give an aldol product, which was then deoxygenated under Barton conditions via the corresponding xanthate. After a series of steps in which one of the isopropylidene groups was removed and an oxazolidinone put in its place, the free hydroxy group was "unblocked" using Zn. Compound **325** was then isolated and submitted to the retro-Diels−Alder reaction that liberated the "masked" cyclohexenone. In the final steps of the

Scheme 70. Kita's Synthesis of Compound 330[a]



[a] Reagents: (a) (i) NBS (63%), (ii) Bu_3SnH (89%); (b) (i) SeO_2, Py (42%), (ii) MeOH, PPTS (91%); (c) (i) $VO(acac)_2$, *t*-BuOOH (82%), (ii) Ca, liquid NH_3, −78 °C (70%); (d) (i) TPAP, NMO (80%), (ii) LDA, *N*-*tert*-butylphenylsulfinimidoyl chloride (55%).

synthesis, the free hydroxyl group was mesylated to prepare it for the epoxide formation reaction and the 1,2-diol protecting group hydrolyzed to give the precursor to compound **324**.

Very recently, Fujioka and Kita[131] published a short asymmetric synthesis of compound **330**, which is the cyclohexenone core of scyphostatin (Scheme 70). Instead of using "chirons" such as glucose or quinic acid, they prepared a chiral acetal **326**, which was obtained from cyclohexa-2,5-dienylethanal diethylacetal and (*R*,*R*)-hydrobenzoin. After intramolecular bromoetherification in the presence of methanol, acetal **326** afforded a bromo acetal, which was then reduced by radical methodology to furnish acetal **327**. SeO_2 oxidation of acetal **327** and further deprotection led to intermediate **328**, which underwent a Sharpless epoxidation followed by Birch reduction to give epoxy alcohol **329**. Finally, oxidation of secondary alcohol **329** with TPAP and subsequent LDA treatment with *N*-*tert*-butylphenylsulfinimidoyl chloride produced enone **330**. The stereochemistry at every step of the synthesis was ascertained by nOe experiments or X-ray analysis. The main feature of this method is that the acetal works not only as a chiral auxiliary for the discrimination of two olefins and to protect the alcohols, but also as a template for the stereoselective selenium dioxide oxidation. Furthermore, every reaction proceeds in a stereoselective manner. The overall yield of **330** from this synthesis was 6.6%, and fewer steps were required than in Katoh's procedure.[130] However, compound **330** lacks the additional amino functionality that is present in natural scyphostatin (**314**).

6.29. Yanuthone A

Yanuthone A (**331**) (Figure 7) is a typical example of a series of metabolites (there are others, specifically yanuthones B−E) recently isolated from *Aspergillus niger*.[134] These epoxy cyclohexenones are closely related to oligosporons and macrophorins.

6.30. Oligosporons

The oligosporons [oligosporon (**332a**), oligosporol (**332b**), and oligosporol B (**332c**)] (Figure 7) are a

group of metabolites isolated from *Arthrobotrys oligospora*,[135] whose structures are related to those of the yanuthones (**331**). These compounds exhibit weak antibacterial, antiyeast, cytotoxic, and haemolytic effects.

6.31. Macrophorins

Macrophorins A−D are drimane-type sesquiterpenyl metabolites isolated from *Macrophoma* or *Eupenicillium* sp.[136] Macrophorin A (**333**)[136b] (Figure 7) is active against strains of *Staphylococcus aureus* (MIC 25 μM) and *Trichophyton* spp. (MIC 6.2−25 μM), and its cytotoxicity for mouse tumor cells (L-5178Y) is very high (IC_{50} 0.3 μM).

7. 2-Amino-epoxyquinones

The manumycin group of 2-amino-epoxyquinones, including such compounds as manumycin A (**334**) (Figure 8), is a large family of natural products isolated from *Streptomyces* species.[4] Most of the manumycins exhibit a range of biological effects including antibiotic, antifungal, cytotoxic, and elastase inhibitory activities. In addition, manumycins have recently been identified as potent and selective inhibitors of Ras farnesyltransferase.[137] Structurally, they are characterized by a central aminoepoxycyclohexenone core with "southern" and "eastern" polyunsaturated side chains linked to C-4 and to the amine substituent, respectively. In addition to the manumycins, a series of smaller *meta*-substituted aniline (*m*C_7N) antibiotics also have been recently identified. Some representative examples are shown in Figure 8 [MM 14201 (**335**), LL-C10037α (**336**), MT 35214 (**337**), G-7063-2 (**338**), 2061-B (**339**), KT 8110 (**340**), and epoxyquinomycins A−D (**341**−**344**)] and will be presented and discussed here. The methodologies applied to the syntheses of these small compounds are those typically used in the preparation of the central carbocyclic motif in the manumycin-type molecules.

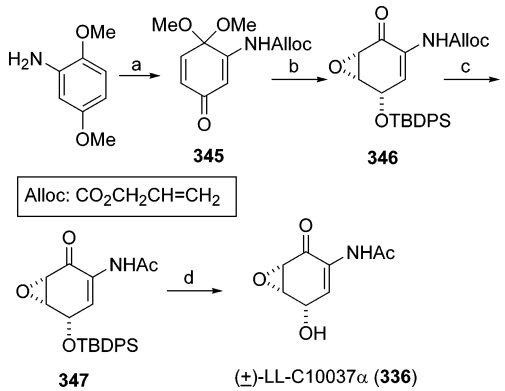
7.1. MM 14201

MM 14201 (**335**) is an antibiotic that has been detected in a culture of *Streptomyces* species NCIB 11813. MM 14201 has broad-spectrum antibacterial activity and is most effective against *Serratia* and *Pseudomonas* species.[138]

7.2. LL-C10037α

LL-C10037α (**336**) is an antitumor antibiotic isolated from the fermentation filtrate of a *Streptomyces* species by adsorption, partition, and reverse-phase column chromatography. Its chemical structure was established from ^{1}H NMR, ^{13}C NMR, UV, IR, and mass spectral data.[139a] The structure of antibiotic LL-C10037α was eventually revised on the basis of a single-crystal X-ray diffraction analysis.[139b] Gould and co-workers also established that the biosynthesis of this antibiotic occurs from 3-hydroxyanthranilic acid via the shikimic acid pathway.[139c] The synthesis of LL-C10037α has been reported several times in either racemic or enantiomerically pure form by Wipf,[140] Taylor,[141] Johnson,[142] and Altenbach.[106a]

Scheme 71. Wipf's Synthesis of (±)-LL-C10037α (336)[a]



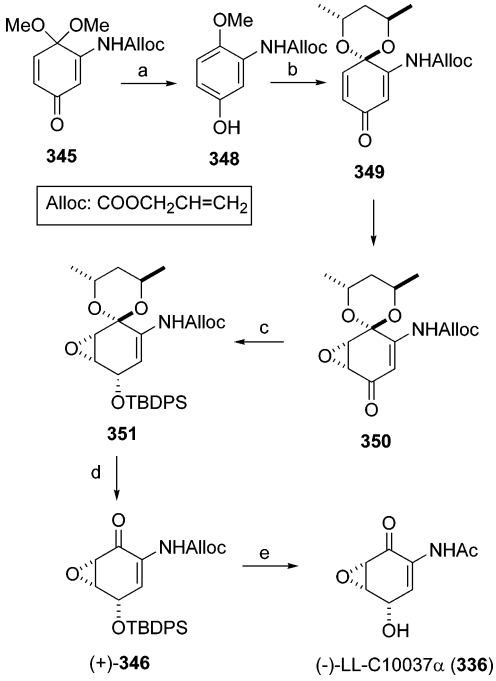
[a] Reagents: (a) AllocCl, then $PhI(OAc)_2$ (59%); (b) (i) H_2O_2, then $NaBH_4$ (60%), (ii) TBDPSCl (91%), (iii) *p*-TsOH (81%); (c) (i) Ac_2O, DMAP (64%), (ii) $PdCl_2(PPh_3)_2$, Bu_3SnH (81%); (d) HF−MeCN (58%).

7.2.1. Wipf's Approach

The first synthesis of racemic LL-C10037α (**336**) was described by Wipf in 1994.[140a] Taylor subsequently applied Wipf's strategy to the synthesis of **336**[141] and related products (see below). As shown in Scheme 71, the synthesis began with commercially available 2,5-dimethoxyaniline, which underwent *N*-protection and iodine hypervalent oxidation, to yield quinone acetal **345**. Epoxidation and sodium borohydride reduction of **345** (under the best conditions, the alcohols were obtained in a 5.3:1 ratio), followed by silylation, gave two alcohols which were separated by chromatography. Hydrolysis of the acetal group in the major epimer led to **346,** and then *N*-acetylation furnished intermediate **347**. The *N*-Alloc group was removed from **347** using palladium catalysis. A final acid hydrolysis provided LL-C10037α (**336**) in nine steps with an 8% overall yield.

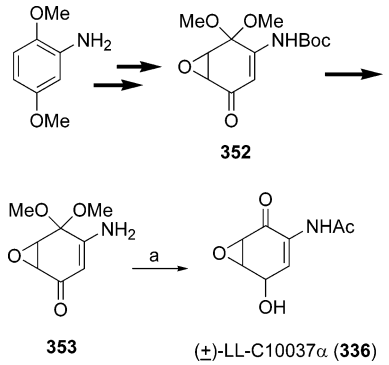
Wipf also designed a chiral synthesis of (−)-LL-C10037α (**336**)[140b] (Scheme 72). This synthesis followed a strategy similar to that used in his earlier nonchiral synthesis but incorporated a chiral auxiliary in the quinone acetal **349**. Quinone **349** was formed during the iodine hypervalent oxidation of compound **348** in the presence of enantiomerically pure pentane-2,4-diol and further acid treatment. Its asymmetric epoxidation gave a mixture of epoxides in a 4.5:1 ratio, where the major product had the required configurations at the newly formed stereocenters. In this step, the chiral acetal restricted the access from the sterically more hindered β-face, and thus, α-epoxidation was preferred. This intermediate **350** was reduced, then the resulting mixture of alcohols (obtained in a 3.1:1 ratio) was silylated, and the products were separated. After acid hydrolysis, the major product, compound **351**, gave known compound **346** in optically pure form. Compound **346** was subsequently manipulated, as shown in Scheme 71 for the synthesis of the racemic compound, to finally afford (−)-LL-C10037α (**336**).

Scheme 72. Wipf's Synthesis of (−)-LL-C10037α (336)[a]



[a] Reagents: (a) $NaBH_4$; (b) (i) $PhI(OAc)_2$, (2*R*,4*R*)-pentane-2,4-diol, then PPTS, (ii) H_2O_2 (21% from **348**); (c) (i) $NaBH_4$, (ii) TBDPSCl (56% from **350**); (d) PPTS (78%); (e) see Scheme 71.

Scheme 73. Taylor's Synthesis of LL-C10037α (336)[a]



[a] Reagents: (a) (i) AcCl, *t*-BuOLi (65%), (ii) $NaBH_4$, then *p*-TsOH, PPTS (49%).

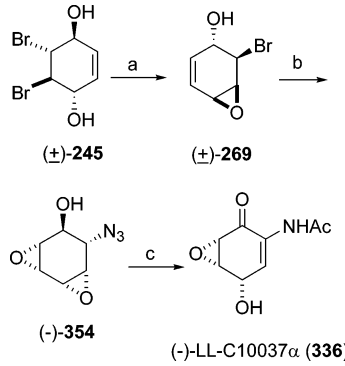
7.2.2. Taylor's Approach

Taylor also described a protocol for the preparation of racemic LL-C10037α (**336**)[141] based on Wipf's strategy[140a] and his own work on bromoxone (Scheme 59).[84b] He was able to improve on Wipf's synthesis by reducing the number of steps in the sequence to seven and increasing the overall, unoptimized, yield to 10%. However, no experimental details are currently available. Taylor prepared intermediate **352**, which is analogous to product **345** (Scheme 71) but has a Boc as the nitrogen-protecting group, and submitted it to acid hydrolysis to give the free amino derivative **353**. This amine is the key intermediate in the present synthesis and was used by the authors for the incorporation of other acyl substituents as well. As shown in Scheme 73, the acetylation of **353**, followed by ketone reduction and acid hydrolysis, rendered a separable mixture of LL-C10037α (**336**) and its epimer in a 3:1 ratio.

7.2.3. Johnson's Approach

In a continuation of his previous work on the preparation of enantiomerically pure cyclohexane epoxides by enzymatic resolution,[88] Johnson described the synthesis of LL-C10037α (**336**) from benzoquinone. The synthesis proceeded via intermediate (±)-**245** (Scheme 55),[142] which was prepared according to the literature protocol,[106d] and intermediate (±)-**269**. On treatment with *Candida rugosa* lipase, the racemic monoepoxide (**269**) gave acetylated (−)-**269** (Scheme 61) in high yield and enantiomerically pure form (Scheme 74) along with unreacted (+)-**269**. After reaction of the (+)-**269** enantiomer with sodium azide, hydroxyl-directed epoxidation with MCPBA, and treatment with potassium hydroxide, bisepoxide **354** was obtained. In the remaining steps of the synthesis the azide was reduced, the amine was acetylated, and the alcohol was oxidized to give a ketone which was transformed in situ into LL-C10037α (**336**).[142] This method was extremely efficient comprising 10 steps and 20% overall yield from benzoquinone, including the enzymatic resolution step.

Scheme 74. Johnson's Synthesis of (−)-LL-C10037α (336)[a]

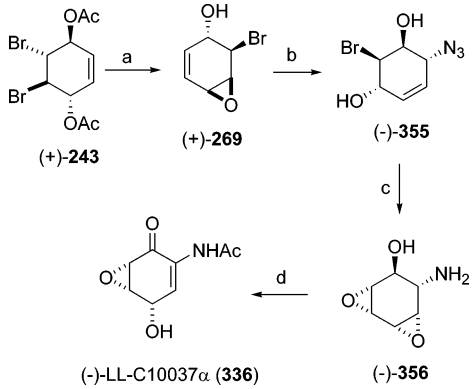


[a] Reagents: (a) KOH, 0 °C (92%); (b) (i) *Candida rugosa* lipase (47%), (ii) NaN_3 (95%), (iii) MCPBA (94%), (iv) KOH (86%); (c) (i) H_2, then Ac_2O, Et_3N (84%), (ii) Dess−Martin periodinane (87%).

7.2.4. Altenbach's Approach

Altenbach and co-workers developed a synthesis of (−)-LL-C10037α (**336**) (Scheme 75)[106a] using an approach similar to Johnson's, which proceeded via the known intermediates (+)-**243** and (+)-**269**. These intermediates had been previously used in the preparation of (+)-bromoxone[106a] (see Schemes 55 and 61). The reaction of epoxide (+)-**269** with sodium azide occurred at the allylic position to give product **355**, which after epoxidation, base-promoted epoxide formation, and hydrogenation afforded amino alcohol **356**. After regioselective acetylation of **356** at the nitrogen, oxidation produced the ketone and caused in situ opening of the epoxide to furnish the target molecule, just as it had in other similar cases described by Fex[108] and Johnson.[142]

Scheme 75. Altenbach's Synthesis of (−)-LL-C10037α (336)[a]

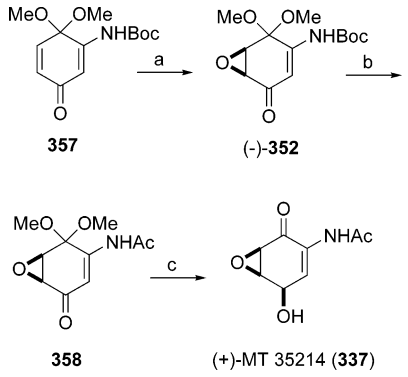


[a] Reagents: (a) LiOH (90%); (b) NaN_3 (78%); (c) (i) CF_3CO_3H (82%), (ii) KOH (84%), (iii) H_2 (79%); (d) (i) Ac_2O, MeOH (81%), (ii) Dess−Martin periodinane (52%).

7.3. MT 35214

MT 35214 (**337**) (Figure 8) is the enantiomer of (−)-LL-C10037α (**336**). The only reported synthesis of this compound (Scheme 76) has been described by Taylor.[143] His asymmetric synthesis of this target molecule relies on the enantioselective chiral phase-transfer epoxidation[144] of quinone acetal **357** (Scheme 73) using *tert*-butyl hydroperoxide in the presence of commercially available *N*-benzylcinchonidinium chloride. Under these conditions compound (−)-**352** was isolated in 71% yield and 89% ee. This compound was then transformed into (+)-MT 35214 (**337**) as described above for the synthesis of its enantiomer (Scheme 73). Note, however, that in this case the ketone reduction of acetamide **358** was performed using $LiEt_3BH$ and afforded only the syn isomer (Scheme 76). Overall, the synthesis of (+)-MT 35214 (**337**) took place in seven steps (10% overall yield) which compared favorably to Wipf's synthesis of (−)-LL-C10037α (**336**) (12 steps, 1.3% overall yield).[140b]

Scheme 76. Taylor's Synthesis of (+)-MT 35214 (337)[a]



[a] Reagents: (a) *t*-BuOOH, NaOH, *N*-benzylcinchonidinium chloride (71%, 89% ee); (b) (i) CF_3CO_2H (95%), (ii) AcCl, *t*-BuOLi (65%); (c) (i) $LiEt_3BH$ (89%), (ii) Montmorillonite K10 (90%).

7.4. G-7063-2 and G-2061-B

G-7063-2 (**338**) and G-2061-B (**339**) (Figure 8) are two antibacterial antibiotics belonging to the epoxydon group that were isolated from the *Streptomyces* species designated No. 2061 FCE. These compounds showed moderate to weak activity against Gram-positive and Gram-negative bacteria in vitro experiments.[145]

7.5. KT 8110

(+)-KT 8110 (**340**) (Figure 8) showed inhibitory potency to interleukine-converting enzyme (ICE).[146] Altenbach and co-workers reported the synthesis of (+)-KT 8110 (**340**)[106a] via acylation and oxidation of intermediate (−)-**356** (Scheme 75).

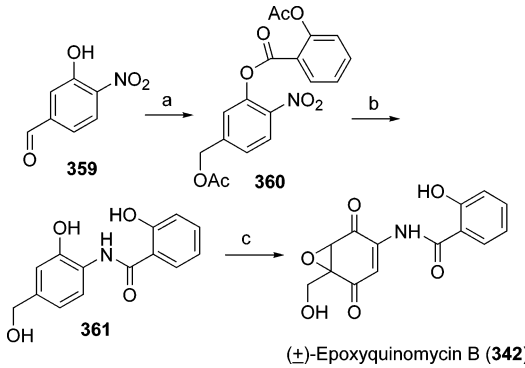
7.6. Epoxyquinomycins A–D

Epoxyquinomycins A (**341**), B (**342**), C (**343**), and D (**344**) (Figure 8) have been isolated from the culture broth of *Amycolatopsis* sp.[147a] The structures of these molecules have been assigned by spectroscopic and X-ray analysis.[147b] All of these antibiotics exhibited antiinflammatory activities and low toxicity. Compounds **341** and **342** showed weak antimicrobial activity against Gram-positive bacteria, while products **343** and **344** showed almost no antimicrobial activity.[147a]

Only the synthesis of epoxyquinomycin B (**342**) in racemic form has been reported.[148,149] Epoxyquinomycin B (**342**) was found to exhibit a potent inhibitory effect on type II collagen-induced arthritis in vivo,[148b] so it could be used in the treatment of rheumatic diseases.

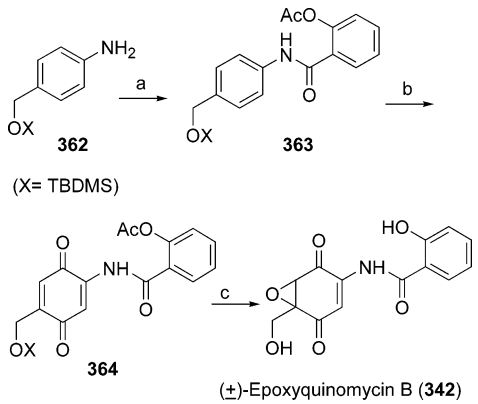
The synthesis of epoxyquinomycin B (**342**), which was reported by Matsumoto,[148a] is outlined in Scheme 77. Commercially available 3-hydroxy-4-nitrobenzaldehyde **359** was reduced at the aldehyde moiety, then acetylated, regioselectively hydrolyzed at the phenolic acetate, and finally acylated with acetylsalicyloyl chloride to give nitrobenzene derivative **360**. During the catalytic hydrogenation of **360**, the salicyloyl group migrated to the amino function to give an amide, which was hydrolyzed to compound **361**. Final oxidation to generate the quinone moiety and epoxidation yielded epoxyquinomycin B (**342**) in eight steps with a 22% overall yield from starting material **359**. This procedure has been applied by the authors to the synthesis of simpler derivatives.[148b]

Scheme 77. Matsumoto's Synthesis of (±)-Epoxyquinomycin B (342)[a]



[a] Reagents: (a) (i) $NaBH_4$, (ii) Ac_2O, Py, (iii) $KHCO_3$, (iv) acetylsalicyloyl chloride (50% from **359**); (b) (i) H_2, (ii) NaOH (64% two steps); (c) (i) Fremy's salt (82%), (ii) H_2O_2 (85%).

Scheme 78. Nicolaou's Synthesis of (±)-Epoxyquinomycin B (342)[a]



[a] Reagents: (a) acetylsalicyloyl chloride, Et_3N (99%); (b) Dess−Martin periodinane (43%); (c) (i) H_2O_2 (95%), (ii) HF−Py (95%).

More recently, Nicolaou and co-workers described the shortest route to this type of compound thus far reported.[149] The synthetic sequence that they employed is shown in Scheme 78. After only four steps, epoxyquinomycin B (**342**) was obtained in 38% overall yield from aniline **362**. Nicolaou applied his new method for generating *o*-imidoquinones by oxidation of anilides with Dess−Martin periodinane (DMP) and water to this latest synthesis. Thus, aniline **362** was acylated to afford anilide **363**, which upon treatment with DMP rendered **364**. Final epoxidation and deprotection of **364** led to the target epoxyquinomycin B (**342**).

8. Conclusions

In this account we have given an updated perspective on naturally occurring epoxycyclohexane derivatives isolated from various organisms such as fungi, bacteria, worms, and mushrooms. Most of these compounds display interesting pharmacological and biological properties, such as antibiotic, antibacterial, and antitumor activities.

Particular emphasis has been placed on the strategies developed for the synthesis of these molecules. In the past few years new methodologies have been successfully applied to the asymmetric synthesis of these products, including drawing starting materials from the chiral pool of readily available natural products (i.e., quinic acid or D-glucose) and utilizing enzymatic resolution of racemic mixtures. The application of iodine hypervalent mediated oxidation of aromatic derivatives for the synthesis of quinone-like advanced intermediates has been particularly relevant and useful in this area.

It is evident from the present review that cyclohexane epoxides represent an important class of compounds on which can be implemented elegant strategies for the introduction of relevant functionalities in regio- and stereoselective manners. It is expected that the results collected here will be useful in spurring on new improvements and developments in this active and attractive area of the organic synthesis of natural products.

9. Addendum

After the writing of this review, some major advances, especially in the area of quinone epoxides, have been reported.

Thus, it has been found that the inductive effect of theobroxide (**189**) (Figure 4) on potato tuber formation is probably achieved by stimulating jasmonic acid and tuberonic acid synthesis, enhancing lipoxygenase activity.[150]

Kitahara published the enantioselective total synthesis of (+)-epiepoformin (**192**) (Figure 4), (+)-epiepoxydon (**194**) (Figure 4), and (+)-bromoxone (**264**) (Figure 5) using the same chiral building block, ethyl (1*R*, 2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate. These synthetic routes also provided useful intermediates to achieve a formal total synthesis of (−)-theobroxide (**189**), (−)-phyllostine (**197**) (Figure 4), (+)-harveynone (**195**) (Figure 4), and (−)-asperpentyn (**190**) (Figure 4).[151]

Okamura published the full report of his synthesis of (+)-epiepoformin (**192**)[152] (Figure 4), featuring the use of a common intermediate **233**[80] (Scheme 51), also amenable to the synthesis of (−)-phyllostine (**197**) (Figure 4).

Maycock and co-workers also reported the synthesis of (+)-bromoxone (**264**) (Figure 5) using an aziridine to direct the epoxidation of a double bond. The synthetic sequence is extremely efficient with an overall yield of 24% from an enone derived from quinic acid (**50**) (Scheme 9), being the only asymmetric synthesis of bromoxone that does not rely on an enzymatic resolution.[153]

Crews and Wood[154] applied the chemistry developed in the synthesis of isopanepoxydone (**248**) (Figure 4) and panepoxydone (**247**) (Figure 4) in the preparation of a number of NF-κB-signaling inhibitors,[155] finding that a biotinylated isopanepoxydone affinity reagent can be useful in the labeling of a cellular protein.

The synthesis and isolation of epoxyquinols has received considerable attention because of their potent antiangiogenic activity,[156] and so, the metabolite epoxyquinol B (Figure 13) has been isolated from a cultured fungal strain and its structure elucidated by spectroscopic methods.[157] Interestingly, epoxyquinol B has the same molecular formula as epoxyquinol A (**286**) (Figure 6) but opposite configurations at C-17, C-18, and C-19, and these differences of stereochemistry play an important role in the biological activity, since epoxyquinol B is 10 times more potent (IC_{50} 0.4 μM) than **286** in the VEGF (vascular endothelial growth factor) cell migration assay. The structure and stereochemistry of these compounds was confirmed by total synthesis using a biomimetic oxidative dimerization,[113] which had been postulated as the biosynthetic pathway for the formation of these products. Thus, a quinone monoepoxide monomer unit, with similar framework to those of epoxydon (**193**) (Figure 4) and parasitenone (**261**) (Figure 5), was subjected to intermolecular Diels−Alder reaction followed by oxidation with MnO_2.[158] The same authors later published a practical total synthesis of both enantiomers of epoxyquinols A and B using a lipase-mediated kinetic resolution of a cyclohexenol

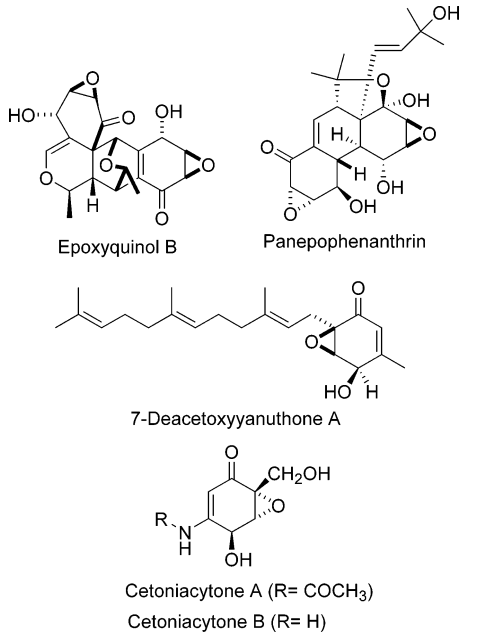


Figure 13.

derivative.[159] In addition to the intensive synthetic efforts reported by Kakeya and Hayashi's groups, they recently published a critical analysis of the different reaction modes of the oxidative dimerization cascade, concluding the crucial role played by hydrogen bonds and solvent effects in the stereochemical outcome of these reactions.[160] Porco also published an elegant synthesis of epoxyquinol A (**286**) (Figure 6) relying on his previous efforts in the area, namely, in the synthesis of torreyanic acid (**299**) (Figure 6), jesterone (**291**) (Figure 6), and cycloepoxydon (**249**) (Figure 4). He used a derivative of **258** (Scheme 58) which after several transformations underwent the electrocyclization-Diels−Alder dimerization to give epoxyquinol A (**286**) (Figure 6), although the last step took place in 26% yield.[161] Mehta[162] recently published an efficient synthesis of racemic epoxyquinols employing a different route for the preparation of the key chiral monoepoxide utilized by Porco in his synthesis.

Porco's group also reported a full paper on the asymmetric total synthesis of (+)-torreyanic acid (**299**)[163] (Figure 6), describing in the same paper the first total synthesis of (+)-ambuic acid (**287**) (Figure 6), which confirmed the stereochemistry previously assigned to the natural product.[114] (+)-Ambuic acid (**287**) (Figure 6) has been established as the monomer unit which by oxidation affords torreyanic acid in the biosynthetic pathway of these compounds. In addition, recent stereochemical analysis of ambuic acid by solid-state NMR has confirmed its relative stereochemistry.[164]

In his reported synthesis of (−)-jesterone (**291**)[117] (Figure 6), Porco also described the preparation of a compound obtained by oxidative Diels−Alder dimerization, jesterone dimer, which has been the subject of exhaustive biological investigations[165] finding that the synthetic dimer is a potent inhibitor of the activation of the transcription factor NF-κB whereas its parent compound **292** does not block activation.

Culminating his massive efforts in the synthesis of epoxyquinoids, Porco recently disclosed the total synthesis of natural (+)-panepophenanthrin (Figure 13), utilizing again a highly stereoselective Diels−Alder dimerization.[166] Panepophenanthrin had been isolated in 2002 from the mushroom strain *Panus rudis* Fr. IFO8994,[167] its structure being characterized by spectroscopic methods. This is the first known inhibitor of the ubiquitin-activating enzyme, which is indispensable for the ubiquitin−proteasome pathway. The synthesis of racemic panepophenanthrin had been previously achieved by Baldwin[168] in an extremely efficient biomimetic-type synthesis proceeding in only three steps from racemic bromoxone (**264**)[106a,b] (Figure 5) and with a 60% overall yield, featuring again a dimerization reaction under reflux of toluene. However, a related dimerization approach attempted by Couladouros[169] in his route to epoxysorbicillinol (**304**) (Figure 7) failed.

Another area of intensive research in this short period has been the biological and synthetic investigations on scyphostatin (**314**) (Figure 7), the most potent inhibitor of neutral sphingomyelinase.[170] Scyphostatin has been claimed as an inhibitor of nerve growth factor in hippocampal neurons[171] and also inhibited sphyngomyelin/lysocholinephospholipids−phospholipase C (SM/LCPL-PLC), and thus, it could be useful in the treatment of malaria.[172] Ohkata and co-workers reported the preparation of a hydrophilic analogue of scyphostatin lacking the hydrophobic side chain,[173] and O'Brien-Taylor,[174] using an enone previously prepared by Maycock[175] from quinic acid (**50**) (Scheme 9), performed a sequence of eight steps to afford the core of scyphostatin in enantiomerically pure form.

A derivative of yanuthone A (**331**) (Figure 7), 7-deacetoxyyanuthone (Figure 13), has been recently isolated by Son and co-workers[176] from a marine-derived fungus of the genus *Penicillium* showing moderate in vitro cytotoxicity in a panel of five human tumor cell lines and also mild in vitro antibacterial activity. Its structure was ascertained by spectroscopic methods.

In the area of 2-aminoepoxyquinones, Whiteley[177] published a study on the inhibitors of the enzymes involved in the biosynthesis of the antitumor antibiotic LL-C10037 (**336**) (Figure 8), but the most important advances have been disclosed by Umezawa's group in the case of epoxyquinomycins, because of their NF-κB effect with potential against inflammatory diseases such as rheumatoid arthritis and neoplastic ailments. Specifically, dehydroxymethylepoxyquinomycin (DHMEQ), a synthetic derivative of epoxyquinomycin C (**343**) (Figure 8), has been found as a potent and specific inhibitor of NF-κB and has been tested in unilateral urethral obstruction, being effective in the prevention of inflammatory kidney diseases.[179] The same group also disclosed the synthesis and structure−activity relationships of DHMEQ analogues, concluding that the hydroxyl group at the 2-position of the benzamide moiety was essential for the inhibitory activity.[180]

Finally, two new metabolites, cetoniacytones A and B (Figure 13), structurally related to epoxyquino-

mycins, have been produced by culture broths of *Actinomyces* sp. (strain Lu 9419), which was isolated from the intestines of a rose chafer (*Cetonia aureata*), and cetoniacytone A showed a significant growth inhibition against HEP G2 (hepatocellular carcinoma, GI_{50} 3.2 μM) and MCF 7 (breast adenocarcinoma, GI_{50} 4.4 μM).[181]

10. Acknowledgments

J.M.C. thanks Professors Yus and Krohn for kindly sending us copies of their papers. J.M.C. thanks DGICYT (BQU2000-1495) and EU (COST D12 and COST D13) for financial support. M.T.M. thanks DGICYT for financial support (SAF-99-061).

11. References

(1) (a) Thebtaranonth, Ch.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84. (b) Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715.
(2) Marco-Contelles, J. *Eur. J. Org. Chem.* **2001**, 1607.
(3) (a) Sattler, I.; Thiericke, R.; Zeeck, A. *Nat. Prod. Rep.* **1998**, *15*, 221. (b) Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Wei, X.; Lewis, N. *Synthesis* **1998**, 775. (c) Nájera, C.; Yus, M. Natural Products with Polyene Amide Structures. In *Studies in Natural Products Chemistry;* 2000; Vol. 21, p 373. (d) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999.
(4) (a) Rueedi, P. *Helv. Chim. Acta* **1984**, *67*, 1116. (b) Su, B.-N.; Misico, R.; Park, E. J.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *Tetrahedron* **2002**, *58*, 3453.
(5) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347.
(6) Krohn, K. Natural Products Derived from Naphthalenoid Precursors by Oxidative Dimerization. In *Prog. Chem. Org. Nat. Prod.;* Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Tamm, Ch., Eds.; Springer, New York, 2003; Vol. 85, p 1.
(7) (a) Shah, R.; Neuss, N.; Gorman, M.; Boeck, L. D. *J. Antibiot.* **1970**, *23*, 613. (b) Walker, J. E.; Abraham, E. P. *Biochem. J.* **1970**, *118*, 563. (c) Neuss, N.; Molloy, B. B.; Shah, R.; De la Higuera, N. *Biochem. J.* **1970**, *118*, 571. (d) Crossley, M. J.; Stamford, A. W. *Aust. J. Chem.* **1993**, *46*, 1443. (e) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1322.
(8) (a) Renaud, J.-M.; Tsoupras, G.; Stoeckli-Evans, H.; Tabacchi, R. *Helv. Chim. Acta* **1989**, *72*, 1262. (b) Defrancq, E.; Gordon, J.; Brodard, A.; Tabacchi, R. *Helv. Chim. Acta* **1992**, *75*, 276.
(9) (a) Allison, A. J.; Butcher, D. N.; Connolly, J. D.; Overton, K. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1493. (b) Anastasis, P.; Freer, I.; Gilmore, C.; Mackie, H.; Overton, K. H.; Swanson, S. *J. Chem. Soc., Chem. Commun.* **1982**, 268.
(10) Kupchan, S. M.; Hemingway, R. J.; Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 2982.
(11) Takahashi, S. *Phytochemistry* **1969**, *8*, 321.
(12) (a) Kupchan, S. M.; Hemingway, R. J.; Smith, R. M. *J. Org. Chem.* **1969**, *34*, 3898. (b) Shen, T. Y.; Hussaini, I.; Hwang, S. B.; Chang, M. N. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1989**, *19*, 359.
(13) Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Chem. Soc. B* **1969**, 534.
(14) (a) Jagdev, S.; Atal, C. K. *Indian J. Pharm.* **1969**, *31*, 129. (b) Pancharoen, O.; Tuntiwachwuttikul, P.; Taylor, W. C. *Phytochemistry* **1989**, *28*, 1143. (c) Boll, P. M.; Hald, M.; Parmar, V. S.; Tyagi, O. D.; Bisht, K. S.; Sharma, N. K.; Hansen, S. *Phytochemistry* **1992**, *31*, 1035. (d) Pai, B. R.; Rao, N. N.; Wariyar, N. S. *Indian J. Chem.* **1970**, *8*, 468.
(15) Ganem, B.; Holbert, G. W.*Bioorg. Chem.* **1977**, *6*, 393.
(16) (a) Liang, G. Y.; Gray, A. I.; Thomas, D. W.; Waterman, P. G. *Phytochemistry* **1988**, *27*, 3857. (b) Tuntiwachwuttikul, P.; Pancharoen, O.; Bubb, W. A.; Hambley, T. W.; Taylor, W. C.; Reutrakul, V. *Aust. J. Chem.* **1987**, *40*, 2049.
(17) (a) Fehlhaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Ganguli, B. N. *J. Am. Chem. Soc.* **1988**, *110*, 8242. (b) Fehlhaber, H. W.; Kogler, H.; Mukhopadhyay, T.; Vijayakumar, E. K. S.; Roy, K.; Rupp, R. H.; Ganguli, B. N. *J. Antibiot.* **1988**, *41*, 1785. (c) Roy, K.; Vijayakumar, E. K. S.; Mukhopadhyay, T.; Chatterjee, S.; Bhat, R. G.; Blumbach, J.; Ganguli, B. N. *J. Antibiot.* **1992**, *45*, 1592. (d) Haltiwanger, R. C.; Eggleston, D. S.; McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1994**, *C50*, 274. (e) Mukhopadhyay, T.; Bhat, R. G.; Roy, K.; Vijayakumar, E. K. S.; Ganguli, B. N. *J. Antibiot.* **1998**, *51*, 439.
(18) Hollands, R.; Becher, D.; Gaudemer, A.; Polonsky, J. *Tetrahedron* **1968**, *24*, 1633.
(19) Ducruix, A.; Pascard, C.; Polonsky, J. *Acta Crystallogr., Sect. B* **1976**, *B32*, 1589.
(20) Kodpinid, M.; Sadavongvivad, Ch.; Thebtaranonth, Ch.; Thebtaranonth, Y. *Tetrahedron Lett.* **1983**, *24*, 2019.
(21) Singh, J.; Dhar, K. L.; Atal, C. K. *Tetrahedron* **1970**, *26*, 4403.
(22) Joshi, B. S.; Gawad, D. H.; Fuhrer, H. *Tetrahedron Lett.* **1979**, *20*, 2427.
(23) Holbert, G. W.; Ganem, B.; Van Engen, D.; Clardy, J.; Borsub, L.; Chantrapromma, K.; Sadavongvivad, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1979**, *20*, 715.
(24) Schulte, G. R.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 4299.
(25) (a) Nkunya, M. H. H.; Weenen, H.; Koyi, N. J.; Thijs, L.; Zwanenburg, B. *Phytochemistry* **1987**, *26*, 2563. (b) Nkunya, M. H. H.; Waibel, R.; Achenbach, H. *Phytochemistry* **1993**, *34*, 853. (c) Pancharoen, O.; Tuntiwachwuttikul, P.; Taylor, W. *Phytochemistry* **1989**, *28*, 1143.
(26) Rickards, R. W.; Rodwell, J. L.; Schmalzl, K. J. *J. Chem. Soc., Chem. Commun.* **1977**, 849.
(27) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483.
(28) Souchet, M.; Baillargé, M.; Le Goffic, F. *Tetrahedron Lett.* **1988**, *29*, 191.
(29) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *Tetrahedron* **1995**, *51*, 5193.
(30) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.
(31) Bäckvall, J. E.; Nyström, J. E.; Norberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
(32) Kobayashi, S.; Kamiyama, K.; Ohno, M. *Chem. Pharm. Bull.* **1990**, *38*, 350.
(33) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65.
(34) (a) Takano, S.; Moriya, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 614. (b) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 177.
(35) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984.
(36) Shimizu, H.; Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *57*, 1903.
(37) (a) Smith, A. B.; Richmond, R. E. *J. Org. Chem.* **1981**, *46*, 4814. (b) Smith, A. B.; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575.
(38) (a) Kido, F.; Noda, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1982**, 1209. (b) Kido, F.; Noda, Y.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 5467. (c) Kido, F.; Noda, Y.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1982**, *104*, 5509.
(39) (a) Baker, R.; Gibson, C. L.; Swain, C. J.; Tapolczay, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 619. (b) Baker, R.; Gibson, C. L.; Swain, C. J.; Tapolczay, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1509.
(40) (a) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, *25*, 4859. (b) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475.
(41) (a) Tadano, K.; Miyake, A.; Ogawa, S. *Tetrahedron* **1991**, *47*, 7259. (b) Tadano, K.; Ueno, Y.; Fukabori, C.; Hotta, Y.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1727.
(42) (a) Yamamoto, I.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3327. (b) Narasaka, K.; Yamamoto, I. *Tetrahedron* **1992**, *48*, 5743.
(43) Amano, S.; Takemura, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Tetrahedron* **1999**, *55*, 3855.
(44) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.
(45) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.
(46) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(47) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.
(48) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
(49) (a) Oda, K.; Ichihara, A.; Sakamura, S. *Tetrahedron Lett.* **1975**, 3187. (b) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron* **1980**, *36*, 183. (c) Ichihara, A. *Synthesis* **1987**, 207. (d) Rickborn, B. *Org. React.* **1998**, *52*, 1.
(50) Demuth, M. R.; Garrett, P. E.; White, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 634.
(51) Matsumoto, M.; Dobashi, S.; Kuroda, K. *Tetrahedron Lett.* **1977**, 3361.
(52) Schlessinger, R. H.; Lopes, A. *J. Org. Chem.* **1981**, *46*, 5252.
(53) Ogawa, S.; Takagaki, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 800.
(54) (a) Shing, T. K. M.; Tam, E. K. W. *Tetrahedron: Asymmetry* **1996**, *7*, 353. (b) Shing, T. K. M.; Tam, E. K. W. *J. Org. Chem.* **1998**, *63*, 1547.
(55) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron Lett.* **1974**, 4235.
(56) (a) Holbert, G. W.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 352. (b) Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483. (c) Ganem, B.; Holbert, G. W. *Bioorg. Chem.* **1977**, *6*, 393. (d) See also: Ganem, B. *Tetrahedron* **1978**, *34*, 3353.

(57) (a) Ogawa, S.; Takagaki, T. *J. Org. Chem.* **1985**, *50*, 2356, (b) Suami, T.; Ogawa, S.; Nakamoto, K.; Kasahara, I. *Carbohydr. Res.* **1977**, *58*, 240. (c) Ogawa, S.; Kasahara, I.; Suami, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 118. (d) Ogawa, S.; Toyokuni, T.; Ara, M.; Suetsugu, M.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1710.

(58) (a) Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1999**, 2197. (b) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287. (c) Konno, H.; Ogasawara, K. *Synthesis* **1999**, 1135.

(59) Lorbach, V.; Franke, D.; Nieger, M.; Müller, M. *Chem. Commun.* **2002**, 494.

(60) Wasserman, H. H. *Tetrahedron* **1981**, *37*, 1825.

(61) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641.

(62) See, for instance: Bartlett, P. D.; Baumstark, A. L.; Landis, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6486.

(63) (a) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649. (b) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.

(64) (a) McKillop, A.; McLaren, L.; Watson, R. J.; Taylor, R. J. K.; Lewis, N. *Tetrahedron Lett.* **1993**, *34*, 5519. (b) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385. For other reports from this group on this subject, see: (c) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1992**, 1589. (d) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 201. (e) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 1005.

(65) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A. *Tetrahedron Lett.* **1991**, *32*, 6613.

(66) Duke, R. K.; Rickards, R. W. *J. Org. Chem.* **1984**, *49*, 1898.

(67) (a) Nakamori, K.; Matsuura, H.; Yoshihara, T.; Ichihara, A.; Koda, Y. *Phytochemistry* **1994**, *35*, 835. (b) Yoshihara, T.; Ohmori, F.; Nakamori, K.; Amanuma, M.; Tsutsumi, T.; Ichihara, A.; Matsuura, H. *J. Plant Growth Regul.* **2000**, *19*, 457.

(68) Mühlenfeld, A.; Achenbach, H. *Phytochemistry* **1988**, *27*, 3853.

(69) (a) Yamamoto, I.; Mizuta, E.; Henmi, T.; Yamano, T.; Yamatodani, S. *Takeda Kenkyusho Ho* **1973**, *32*, 532; *Chem. Abstr.* **1974**, *80*, 106812. (b) Venkatasubbaiah, P.; Tisserat, N. A.; Chilton, W. S. *Mycopathologia* **1994**, *128*, 155.

(70) Nagasawa, H.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1303.

(71) (a) Sakamura, S.; Niki, H.; Obata, Y.; Sakai, R.; Matsumoto, T. *Agric. Biol. Chem.* **1969**, *33*, 698. (b) Closse, A.; Mauli, R.; Sigg, H. P. *Helv. Chim. Acta* **1966**, *49*, 204.

(72) (a) Ichihara, I.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, 4741. (b) Nagasawa, H.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1303. (c) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445.

(73) (a) Nagata, T.; Ando, Y.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810. (b) Kawazu, K.; Kobayashi, A.; Oe, K. JP 03 41,075, 1991; *Chem. Abstr.* **1991**, *115*, 181517.

(74) Garlaschelli, L.; Magistrali, E.; Vidari, G.; Zuffardi, O. *Tetrahedron Lett.* **1995**, *36*, 5633.

(75) (a) Sakamura, S.; Ito, J.; Sakai, R. *Agric. Biol. Chem.* **1971**, *35*, 105. (b) Sekiguchi, J.; Gaucher, G. M. *Biochemistry* **1978**, *17*, 1785.

(76) Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685.

(77) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem. Eur. J.* **2000**, *6*, 3991.

(78) Ichihara, A.; Moriyasu, K.; Sakamura, S. *Agric. Biol. Chem.* **1978**, *42*, 2421.

(79) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233.

(80) Shimizu, H.; Okamura, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *42*, 8649.

(81) (a) Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, *13*, 5105. (b) Ichihara, A.; Oda, K.; Sakamura, S. *Agric. Biol. Chem.* **1974**, *38*, 163. (c) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, *17*, 4741. (d) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Agric. Biol. Chem.* **1982**, *46*, 1879. (e) Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S.; Sakai, R. *Tetrahedron* **1979**, *35*, 2861.

(82) Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499.

(83) Genski, T.; Taylor, R. J. K. *Tetrahedron Lett.* **2002**, *43*, 3573.

(84) (a) Graham, A. E.; McKerrecher, D.; Davies, D. H.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445. (b) Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Tetrahedron Lett.* **1994**, *35*, 8759. For the preparation of some key intermediates in the synthesis of **234b**, see also: (c) Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 5008. (d) Gautier, E. C. L.; Lewis, N. J.; McKillop, A.; Taylor, R. J. K. *Synth. Commun.* **1994**, *24*, 2989.

(85) Kamikubo, T.; Ogasawara, K. *Heterocycles* **1998**, *47*, 69.

(86) Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679.

(87) Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087.

(88) (a) Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582. (b) Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674. (c) Kohrt, J. T.; Gu, J.-X.; Johnson, C. R. *J. Org. Chem.* **1998**, *63*, 5088.

(89) Negishi, E.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.

(90) (a) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(91) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(92) Ciganek, E. *Org. React.* **1997**, *51*, 201.

(93) Benkhoff, J.; Boese, R.; Klärner, G. *Liebigs Ann. Chem.* **1997**, 501.

(94) Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543.

(95) Alder, K.; Flock, F. H.; Beumling, H. *Chem. Ber.* **1960**, *93*, 1896.

(96) Lubineau, A.; Billault, I. *Carbohydr. Res.* **1999**, *320*, 49.

(97) Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1991**, *44*, 61.

(98) (a) Kis, Z.; Closse, A.; Sigg, H. P.; Hruban, L.; Snatzke, G. *Helv. Chim. Acta* **1970**, *53*, 1577. (b) Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214.

(99) (a) Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *J. Antibiot.* **1998**, *51*, 455. (b) Gehrt, A.; Erkel, G.; Anke, H.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 259.

(100) Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639.

(101) Li, C.; Pace, E. A.; Liang, M.-C.; Lobkovsky, E.; Gilmore, T. D.; Porco, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11308.

(102) Son, B. W.; Choi, J. S.; Kim, J. C.; Nam, K. W.; Kim, D.-S.; Chung, H. Y.; Kang, J. S.; Choi, H. D. *J. Nat. Prod.* **2002**, *65*, 794.

(103) (a) Sheehan, J. C.; Lawson, W. B.; Gaul, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 5536. (b) Kaplan, M. A.; Hooper, I. R.; Heinemann, B. *Antibiot. Khimioterap.* **1954**, *4*, 746. (c) Takahashi, S. *J. Antibiot. Ser. B* **1961**, *14*, 49. (d) Read, G.; Westlake, D. W. S.; Vining, L. C. *Can. J. Biochem.* **1969**, *47*, 1071.

(104) (a) Miller, M. W. *Tetrahedron* **1968**, *24*, 4839. (b) Read, G.; Ruiz, V. M. *J. Chem. Soc. C* **1970**, 1945.

(105) Higa, T.; Okuda, R. K.; Severns, R. M.; Scheuer, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.

(106) (a) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716. (b) Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262. (c) Altenbach, H.-J. In *Antibiotics and Antiviral Compounds;* Krohn, K., Kirst, H., Mass, H., Eds.; VCH Verlag: Weinheim, 1993; p 359. (d) Altenbach, H.-J.; Stegelmeier, H.; Vogel, E. *Tetrahedron Lett.* **1978**, *19*, 3333.

(107) (a) Fex, T.; Trofast, J.; Wickberg, B. *Acta Chem. Scand. B* **1981**, *35*, 91. (b) Fex, T.; Wickberg, B. *Acta Chem. Scand. B* **1981**, *35*, 97. (c) Grewe, R.; Kersten, S. *Chem. Ber.* **1967**, *100*, 2546.

(108) Fex, T. *Tetrahedron Lett.* **1981**, *22*, 2707.

(109) Clericuzio, M.; Han, F.; Pan, F.; Pang, Z.; Sterner, O. *Acta Chem. Scand.* **1998**, *52*, 1333.

(110) (a) Stadler, M.; Anke, H.; Arendholz, W. R.; Hansske, F.; Anders, U.; Sterner, O.; Bergquist, K.-E. *J. Antibiot.* **1993**, *46*, 961. (b) Stadler, M.; Anke, H.; Bergquist, K.-E.; Sterner, O. *J. Antibiot.* **1993**, *46*, 968.

(111) Fukuda, D. S.; Mynderse, J. S.; Baker, P. J.; Berry, D. M.; Boeck, L. D.; Yao, R. C.; Mertz, F. P.; Nakatsukasa, W. M.; Mabe, J. *J. Antibiot.* **1990**, *43*, 623.

(112) Hara, M.; Soga, S.; Shono, K.; Eishima, J.; Mizukami, T. *J. Antibiot.* **2001**, *54*, 182.

(113) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496.

(114) Li, J. Y.; Harper, J. K.; Grant, D. M.; Tombe, B. O.; Bashyal, B.; Hess, W. M.; Strobel, G. A. *Phytochemistry* **2001**, *56*, 463.

(115) Anderson, M. G.; Rickards, R. W.; Lacey, E. *J. Antibiot.* **1999**, *52*, 1023.

(116) Li, J. Y.; Strobel, G. A. *Phytochemistry* **2001**, *57*, 261.

(117) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A. *Org. Lett.* **2001**, *3*, 1649.

(118) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.

(119) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484.

(120) Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011.

(121) Pettus, L. H.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2001**, *3*, 905.

(122) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097.

(123) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871.

(124) Saito, S.; Tanaka, N.; Fujimoto, K.; Kogen, H. *Org. Lett.* **2000**, *2*, 505.

(125) Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481.

(126) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237.

(127) Arenz, C.; Gartner, M.; Wascholowski, V.; Giannis, A. *Bioorg. Med. Chem*. **2001**, *9*, 2901.
(128) Izuhara, T.; Yokota, W.; Inoue, M.; Katoh, T. *Heterocycles* **2002**, *56*, 553.
(129) Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885.
(130) (a) Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651. (b) Izuhara, T.; Katoh, T. *Org. Lett.* **2001**, *3*, 1653.
(131) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825.
(132) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768.
(133) Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363.
(134) Bugni, T. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Van Wagoner, R. M.; Ireland, C. M. *J. Org. Chem*. **2000**, *65*, 7195.
(135) Anderson, M. G.; Jarman, T. B.; Rickards, R. W. *J. Antibiot*. **1995**, *48*, 391.
(136) (a) Sassa, T.; Nukina, M. *Agric. Biol. Chem*. **1984**, *48*, 1923. (b) Sassa, T.; Yoshikoshi, H. *Agric. Biol. Chem*. **1983**, *47*, 187. (c) Ayer, W. A.; Van Altena, I.; Browne, L. M. *Phytochemistry* **1990**, *29*, 1661. (d) Fujimoto, H.; Nakamura, E.; Kim, Y.-P.; Okuyama, E.; Ishibashi, M.; Sassa, T. *J. Nat. Prod*. **2001**, *64*, 1234.
(137) (a) Hara, M.; Han, M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3333. (b) Nagase, T.; Kawata, S.; Yamazaki, E.; Ishiguro, H.; Matuzawa, Y. *Hepathology* **1993**, *18*, 190.
(138) Box, S. J.; Gilpin, M. L.; Gwynn, M.; Hanscomb, G.; Spear, S. R.; Brown, A. G. *J. Antibiot.* **1983**, *36*, 1631.
(139) (a) Lee, M. D.; Fantini, A. A.; Morton, G. O.; James, J. C.; Borders, D. B.; Testa, R. T. *J. Antibiot.* **1984**, *37*, 1149. (b) Shen, B.; Whittle, Y. G.; Gould, S. J.; Keszler, D. A. *J. Org. Chem*. **1990**, *55*, 4422. (c) Whittle, Y. G.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5043.
(140) (a) Wipf, P.; Kim, Y. *J. Org. Chem*. **1994**, *59*, 3518. (b) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis* **1995**, 1549.
(141) Kapfer, I.; Lewis, N. J.; Macdonald, G.; Taylor, R. J. K. *Tetrahedron Lett*. **1996**, *37*, 2101.
(142) Murphy, S. T.; Bencsik, J. R.; Johnson, C. R. *Org. Lett.* **1999**, *1*, 1483.
(143) Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433.
(144) Wynberg, H.; Marman, B. *J. Org. Chem*. **1980**, *45*, 158.
(145) (a) Noble, M.; Noble, D.; Sykes, R. B. *J. Antiobiot.* **1977**, *30*, 455. (b) Orezzi, G. P.; Arlandini, E.; Ballabio, M.; Cassinelli, G.; Di Matteo, E.; Garofano, M. L.; Inventi-Solari, A.; Arcamone, E. *Kangshengsu* **1986**, *11*, 474; *Chem. Abstr.* **1987**, *106*, 210630.
(146) (a) Uosaki, Y.; Agatsuma, T.; Tanaka, T.; Saitoh, Y. *J. Antibiot.* **1996**, *49*, 1079. (b) Tanaka, T.; Tsukuda, E.; Uosaki, Y.; Matsuda, Y. *J. Antibiot*. **1996**, *49*, 1085.
(147) (a) Matsumoto, N.; Tsuchida, T.; Umekita, M.; Kinoshita, N.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 900. (b) Matsumoto, N.; Tsuchida, T.; Sawa, R.; Iinuma, H.; Nakamura, H.; Naganawa, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1997**, *50*, 912.
(148) (a) Matsumoto, N.; Iinuma, H.; Sawa, T.; Takeuchi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2945. (b) Matsumoto, N.; Ariga, A.; To-e, S.; Nakamura, H.; Agata, N.; Hirano, S.-i.; Inoue, J.-i.; Umezawa, K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 865.
(149) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2221.
(150) Gao, X.; Yang, Q.; Minami, C.; Matsuura, H.; Kimura, A.; Yoshihara, T. *Plant Sci.* **2003**, *165*, 993.
(151) Tachihara, T.; Kitahara, T. *Tetrahedron* **2003**, *59*, 1773.
(152) Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2003**, *59*, 10159.
(153) Barros, M. T.; Matias, P. M.; Maycock, C. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321.
(154) Shotwell, J. B.; Koh, B.; Choi, H. W.; Wood, J. L.; Crews, C. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3463.
(155) Umezawa, K.; Ariga, A.; Matsumoto, N. *Anti-Cancer Drug Des.* **2000**, *15*, 239.
(156) Eatock, M. M.; Schätzlein, A.; Kaye, S. B. *Cancer Treatment Rev.* **2000**, *26*, 191.
(157) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.
(158) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192.
(159) Shoji, M.; Kishida, S.; Takeda, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 9155.
(160) (a) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 7205. (b) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem*. **2004**, *69*, 1548.
(161) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A. *Org. Lett.* **2002**, *4*, 3267.
(162) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 3569.
(163) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem Soc.* **2003**, *125*, 5095.
(164) Harper, J. K.; Barich, D. H.; Hu, J. Z.; Strobel, G. A.; Grant, D. M. *J. Org. Chem*. **2003**, *68*, 4609.
(165) Liang, M.-C.; Bardhan, S.; Li, C.; Pace, E. A.; Porco, J. A.; Gilmore, T. D. *Mol. Pharmacol.* **2003**, *64*, 123.
(166) Lei, X.; Johnson, R. P.; Porco, J. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 3913.
(167) Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod*. **2002**, *65*, 1491.
(168) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987.
(169) Pitsinos, E. N.; Vidali, V. P.; Couladouros, E. A. *Arkivoc* **2002**, *13*, 105.
(170) Czarny, M.; Liu, J.; Oh, P.; Schnitzer, J. E. *J. Biol. Chem*. **2003**, *278*, 4424.
(171) Brann, A. B.; Tcherpakov, M.; Williams, I. M.; Futerman, A. H.; Fainzilber, M. *J. Biol. Chem*. **2002**, *277*, 9812.
(172) Hanada, K.; Palacpac, N. M. Q.; Magistrado, P. A.; Kurokawa, K.; Rai, G.; Sakata, D.; Hara, T.; Horii, T.; Nishijima, M.; Mitamura, T. *J. Exp. Med*. **2002**, *195*, 23.
(173) Takagi, R.; Miyanaga, W.; Tamura, Y.; Ohkata, K. *Chem. Commun*. **2002**, 2096.
(174) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943.
(175) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166.
(176) Li, X.; Choi, H. D.; Kang, J. S.; Lee, C.; Son, B. W. *J. Nat. Prod.* **2003**, *66*, 1499.
(177) Whiteley, C. G. *Bioorg. Med. Chem*. **2002**, *10*, 1221.
(178) Chaicharoenpong, C.; Kato, K.; Umezawa, K. *Drug Exp. Clin. Res.* **2003**, *29*, 1.
(179) Miyajima, A.; Kosaka, T.; Seta, K.; Asano, T.; Umezawa, K.; Hayakawa, M. *J. Urology* **2003**, *169*, 1559.
(180) Chaicharoenpong, C.; Kato, K.; Umezawa, K. *Bioorg. Med. Chem*. **2002**, *10*, 3933.
(181) Schlörke, O.; Krastel, P.; Müller, I.; Usón, I.; Dettner, K.; Zeeck, A. *J. Antibiot.* **2002**, *55*, 635.

CR980013J