Syntheses of Natural Products Having an Epoxyquinone Structure

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1. Introduction

Natural products having an epoxyquinone structure are widely distributed in nature and have been attracting much attention because of their unique structures and interesting biological activities. As these natural products have a variety of biological activities such as antitumor, antibacterial, antifungal, enzyme-inhibitory, and other activities, they are of great interest as potent lead compounds from the viewpoint of medicinal chemistry. As the epoxyquinone structure is chemically reactive, it is suggested to play an important role in the biological activities. This role, however, is not clear, and its elucidation is of interest to bioorganic and organic chemists. Generally, these natural products have a relatively small molecular weight but are highly functionalized, mainly with oxygen. Consequently, they contain a number of sequential asymmetric carbon centers. Therefore, from the viewpoint of synthetic organic chemistry, these natural products are a challenging and interesting target to test novel synthetic strategies or to test the utility of a novel asymmetric reaction or a novel chiral reagent. For these reasons, we were also greatly interested in natural products having an epoxyquinone structure. Although some reviews dealing with cyclohexene epoxides had been published by the beginning of 2004,[1−3] no systematic review was published. When we started preparing this manuscript, Marco-Contelles and co-workers just published an interesting and comprehensive review dealing with the chemistry and biology of naturally occurring cyclohexene epoxides.[4] Although their review covered a wide range of this type of naturally occurring compounds, some natural products, such as a part of manumycin-type antibiotics and natural

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Kazuyuki Miyashita was born in Wakayama, Japan, in 1957. After graduating from Kyoto Pharmaceutical University in 1979, he entered the Graduate School of Pharmaceutical Sciences, Osaka University, as a graduate student, and studied organic chemistry. In 1983, he was promoted to a research associate of the Faculty of Pharmaceutical Sciences, Osaka University, and he obtained his Ph.D. degree in 1988. From 1994 to 1995, he carried out postdoctoral research with Professor Schahriar Mobashery at the Department of Chemistry, Wayne State University. Since 1998, he has been working as an associate professor at the Graduate School of Pharmaceutical Sciences, Osaka University. His current research interests are in the fields of organic and bioorganic chemistry, particularly focusing on total syntheses of biologically active natural products to reveal a mechanism of biological action.

Takeshi Imanishi was born in Osaka, Japan, in 1944. He studied organic synthetic chemistry at Osaka University (1963–1972) and obtained his doctoral degree in Pharmaceutical Chemistry from Osaka University in 1972, spent some years at the Faculty of Pharmaceutical Sciences, Osaka University, as Research Associate, and then moved to Kanazawa University as Associate Professor at the Faculty of Pharmaceutical Sciences in 1978. He returned to Osaka University in 1982 and was promoted to Professor of Organic Chemistry at the Faculty of Pharmaceutical Sciences in 1990. He received the Award for Young Scientists from the Pharmaceutical Society of Japan in 1983. Now he is Professor of Bioorganic Chemistry at the Graduate School of Pharmaceutical Sciences. His current research activities are in the areas of organic and bioorganic chemistry, focused on developing useful biofunctional or biorelated compounds, such as artificial analogues of nucleic acids, coenzymes, lipids, peptides, and amino acids. He is also engaged in synthetic studies on biologically active natural products.

products having an epoxynaphthoquinone or epoxyphenanthroquinone structure, were not included. In this article, we particularly focused on the syntheses of the relatively complex natural products that have an epoxyquinone structure and are not described in their review article. Therefore, although a number of natural products having an epoxybenzoquinone structure are known, only manumycin and related compounds are included in this review.

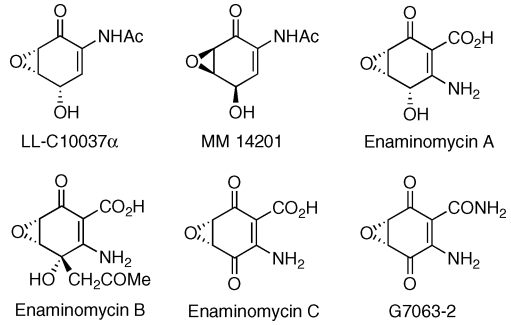


Figure 1. LL-C10037α and related natural products.

Natural products containing an epoxynaphthoquinone structure, such as preussomerins, palmarumycins, and spiroxins, and panepophenanthrin, which contains an epoxyphenathroquinone structure, are also included in this review, as these compounds contain a benzene-fused epoxybenzoquinone structure.

2. Epoxybenzoquinones: Manumycin and Related Compounds

Manumycin antibiotics mainly have an epoxyaminocyclohexanone structure as a common structural unit (mC$_7$N unit) and a variety of acyl side chains on the amino nitrogen (upper side chain) and at the C4 position (lower side chain), as shown in Figure 2. As an excellent review of manumycin family antibiotics was published by a German group in 1998,[5] the structural features and biological activities of manumycin antibiotics are introduced briefly. The most structurally simple analogues are LL-C10037α,[6,7] isolated from *Streptomyces* LL-C10037, and its related compounds, having an epoxybenzoquinone structure (Figure 1).

Differently from LL-C10037α, manumycins A−G have two unsaturated side chains at the upper and lower positions and, as is also easily noted, have a 2-amino-3-hydroxycyclopent-2-enone structure (C$_5$N unit) connected at the terminal position of the lower side chain with an amide bond. Manumycin A was first isolated as a main metabolite of *Streptomyces parvalus*,[8] and it is the most representative member of this family.[9,10] Related natural products such as asukamycin,[11,12] U-62162,[13] U-56407,[14] nisamycin,[15−17] alisamycin,[18−20] and colabomycin[21,22] also have been isolated from *Streptomyces* sp. As a general biological activity, most of the manumycin antibiotics are known to be antibacterial, particularly against Gram-positive bacteria, and also possess antifungal activity and cytotoxic activity. Interestingly, a screening study of ras farnesyl transferase inhibitors revealed three compounds, UCF1-A, -B and -C, which were found to be identical to manumycins B, C, and A, respectively.[23]As described above, almost all of these natural products have an epoxyaminocyclohexanone nucleus as a common structure and are called type I manumycins. In contrast, some manumycin antibiotics such as LL-C10037β,[7] TMC-1 A−D,[24] manumycin D (= TMC-1 E) and colabomycin D have a reduced form of the nucleus, a β-hydroxyaminocyclohexanone structure, and are called type II manumycins (Figure 3).[5] Strictly, these compounds do not have an epoxyquinone structure, but they are included in this

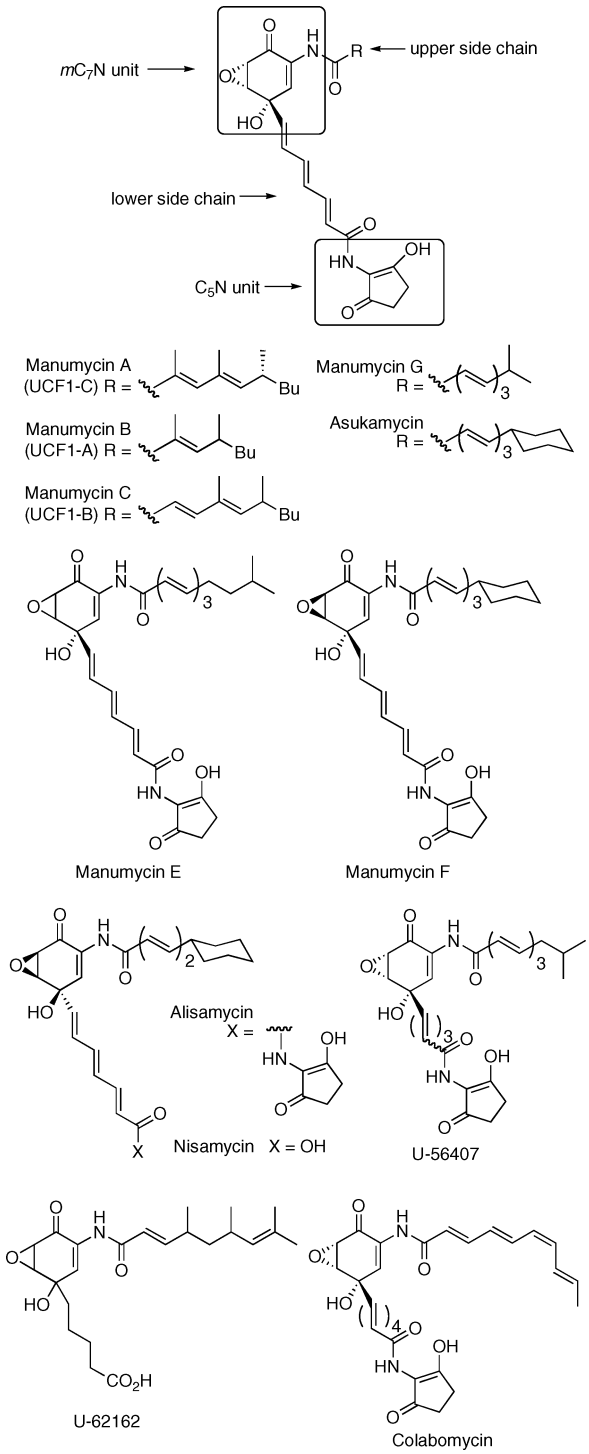


Figure 2. Structures of type I manumycins.

article. As, for example, TMC-1 A−D also show cytotoxic activity against various cell lines in vitro,[24] the structure−activity relationship between type I manumycins and type II manumycins is of great interest.

3. Epoxynaphthoquinones: Natural Products Having a Bisnaphthospiroketal Structure

These natural products having an epoxynaphthoquinone structure simultaneously possess a bisnaphthoquinone spiroketal structure as a common structural unit. These compounds have been attracting much attention not only because of their unique structures but also because of their interesting biological activities. From their structural features, these natural products are divided into three categories (types A, B, and C), as shown in Figure 4. The first type (type A) of the natural products is the most typical example and has a spiroketal structure composed of 1,8-dihydroxynaphthalene and naphthoquinone. In the second type (type B) compounds, two naphthyl structural units are connected with an ether linkage in addition to the basic bisnaphthoquinone spiroketal structure included in the compounds of type A. The last type (type C) compounds have a binaphthyl structure in place of the binaphthyl ether structure of type B compounds. As is easily assumed from these structures, these compounds appear to be biosynthetically related.

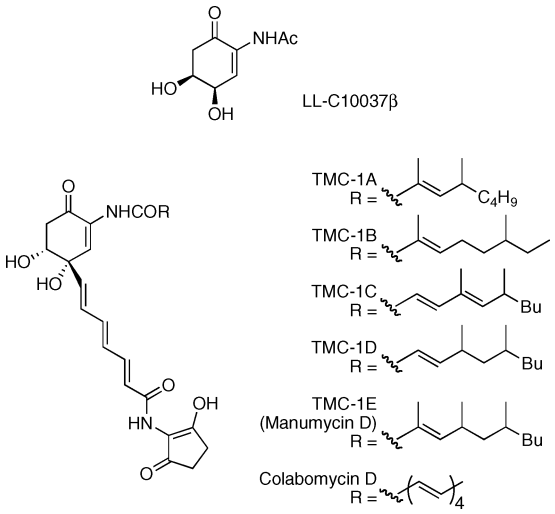


Figure 3. Structures of type II manumycins.

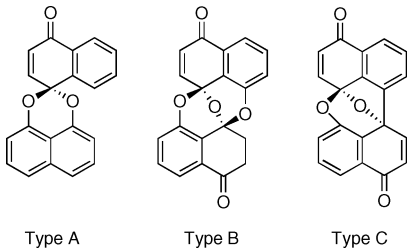


Figure 4. Basic structures of types A, B, and C.

3.1. Bisnaphthospiroketal (Type A)

Since MK3018 was first isolated by Ogishi et al. in 1989,[25] various compounds bearing a type A structure as a basic skeleton have been isolated from fungal metabolites by some groups. Many of these compounds are known to show antimicrobial activity. Due to the complex structural variation of the compounds and the fact that they were named arbitrarily, the relation between the structures and the compound names is sometimes confusing. In 1993, Schlingmann and co-workers isolated highly oxygenated bisnaphthospiroketals, diepoxins α, η, ζ, and σ, as antimicrobial compounds from a nonsporulating fungus, LL-07F275,[26] and determined their absolute stereochemistry by means of the exciton coupled CD technique in 1996.[27] Although they

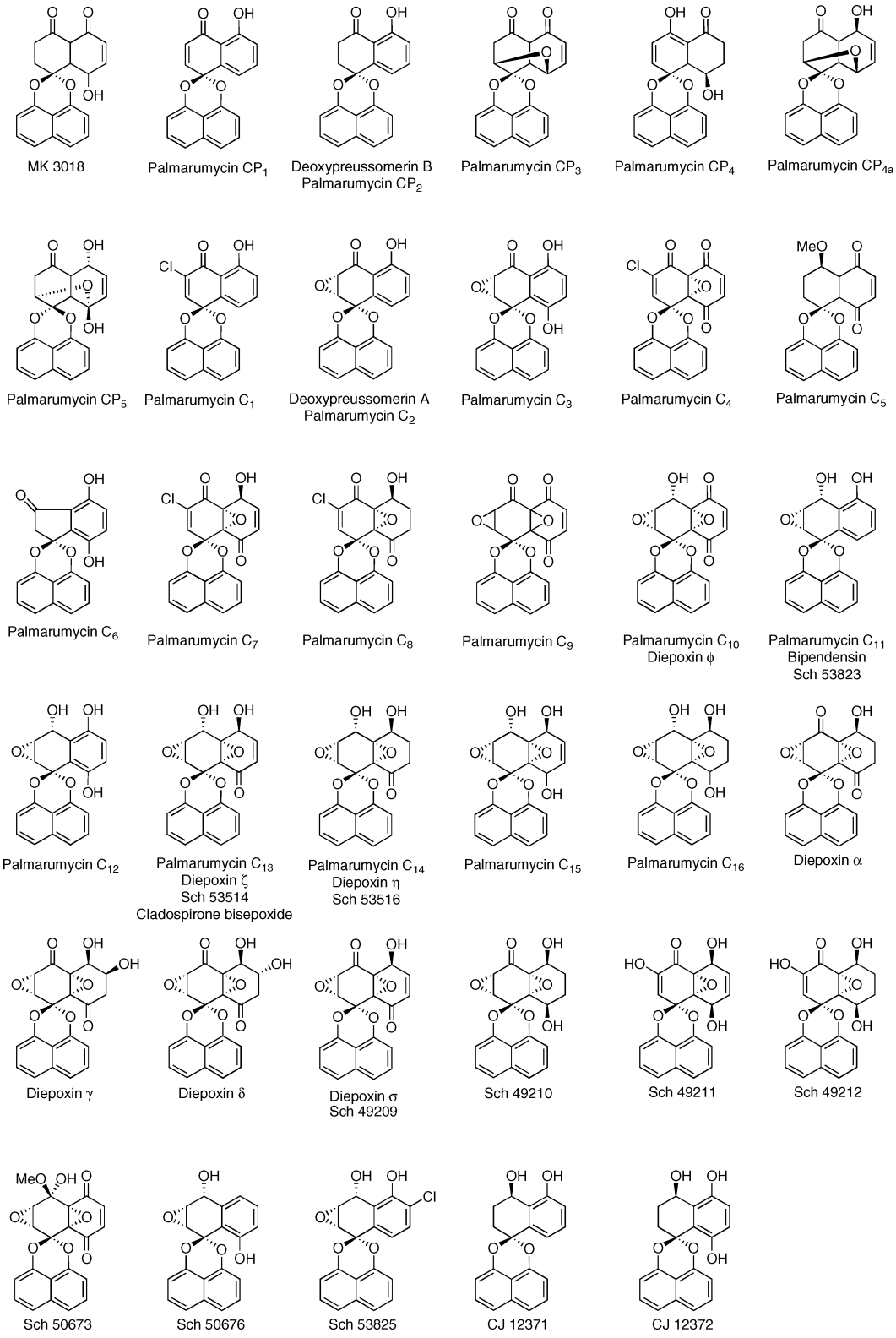


Figure 5. Structures of type B natural products.

isolated additional diepoxins γ, δ, ϕ, ι, and κ, from the same fungal culture, they described that the occurrence of some of these compounds depended on fermentation conditions and isolation method.[27] In 1994, Peter and co-workers also isolated a highly oxygenated bisnaphthospiroketal, cladospirone bisepoxide, from the saprophytic fungus *Cladosporium chlorocephalum* strain.[28] In the next year, they revised its structure and elucidated its absolute stereostructure by X-ray crystallographic analysis.[29] In 1994, Krohn and co-workers isolated four kinds of type A natural products as antibacterial compounds from endophytic fungus, *Coniothyrium palmarum*, determined their structures by means of X-ray crystallographic and spectral analyses, and named them palmarumycins CP_1-CP_4.[30] They also

showed that palmarumycin CP_3 was particularly active against fungi.[30] Palmarumycins CP_{4a} and CP_5 having an additional ether bridge structure were also isolated from the same fungus.[31] Alternatively, they isolated a series of type A compounds from unidentified *Coniothyrium* sp. as well and named them palmarumycins C_1-C_{16}.[32] Interestingly, palmarumycin C_{11} was found to be identical with bipendensin which had been isolated by Connolly[33] in a very small amount from the African tree *Afzeria bipendensis*. Although bipendensin also appeared to be produced by a concomitant fungus, the real origin of the compound isolated by Connolly was not clear. It was also found that palmarumycins C_{13} and C_{14} were identical with diepoxines ζ and η, respectively. Chu and coworkers at Schering-Plough extensively screened a novel antitumor compound from a fungal culture of *Nattrassia mangiferae* and identified a number of type A compounds such as Sch 49210, Sch 53514, Sch 53516,[34] Sch 49209,[35] Sch49211, Sch 49212,[36] Sch 50673, Sch 50676,[37] Sch 53823, and Sch 53825.[38] Most of these compounds were shown to have phospholipase D inhibitory activity. The Merck group isolated two type A compounds, deoxypreussomerins A and B, which are identical with palmarumycins C_2 and CP_2, respectively, accompanied with type B compounds (Figure 5), preussomerins, from unidentified coelomycetes and showed that these compounds have ras farnesyl transferase inhibitory activity.[39] As some manumycin analogues were also reported to have ras farnesyl transferase inhibitory activity,[11,12] the structural relation between these compounds is of interest. The fact that type A and type B compounds were isolated together from the same fungus strongly suggests a biosynthetic relationship between these two types of compounds. It is also interesting that CJ 12371 and CJ 12372 isolated from an unidentified fungus by the Pfizer group exhibit DNA gyrase inhibitory activity.[40]

3.2. Bisnaphthospiroketal and Binaphthyl Ether (Type B)

Preussomerins isolated to date are shown in Figures 6 according to subtypes I, II, and III proposed by Taylor.[41] Compounds of subtype I have a conjugated ketone or allyl alcohol moiety at the lower naphthalene (CD ring) unit and include preussomerins A, D, E, and G. 3′-*O*-Desmethyl-1-epipreussomerin C and preussomerins C and I−L belong to subtype II and have a β-oxyketone moiety at the lower naphthalene unit at the same position. Compounds belonging to the last type, subtype III, have a saturated ketone or alcohol moiety and include preussomerins B, F, and H. As a common biological agent, preussomerins are known to show antibacterial and antifungal activity.

Gloer and co-workers first discovered preussomerin A as an antifungal metabolite produced by coprophilous fungus, *Preussia isomera,* in 1990.[42] Since then, a series of preussomerins have been isolated as a fungal metabolite as follows. Preussomerins B−F were also isolated by them from the same fungus in 1991 and were shown to have antibacterial activity.[43] Polishook and co-workers at Merck also isolated

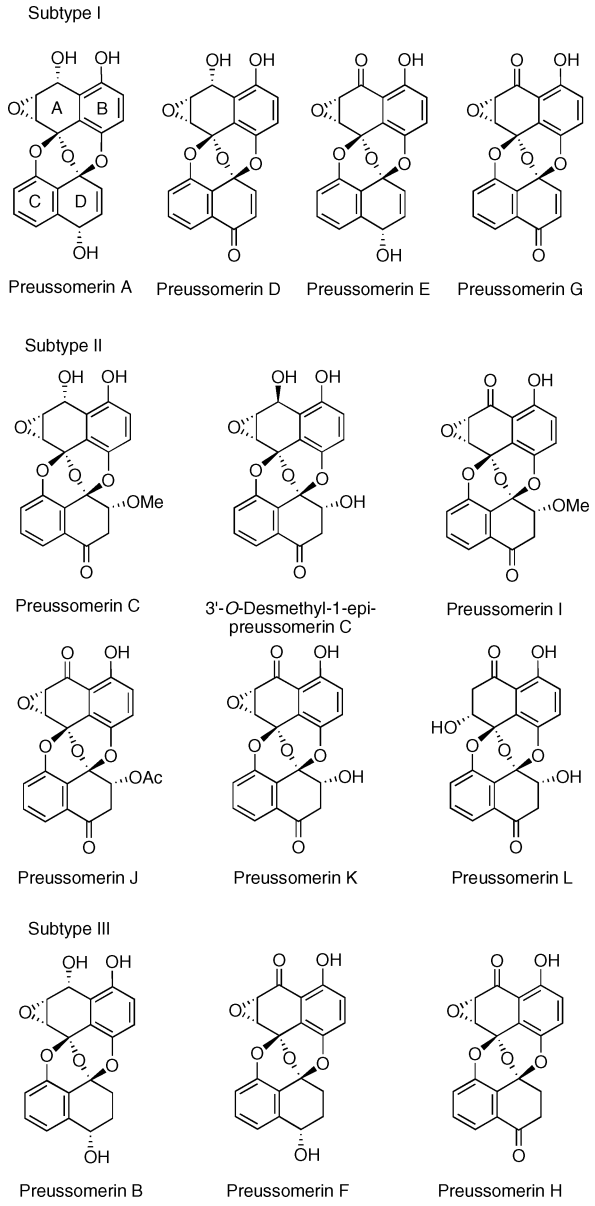


Figure 6. Structures of preussomerins.

preussomerin D as an antimicrobial compound from an endophytic fungus, *Hormonema dematioides*.[44] As described above, preussomerins A and B and novel preussomerins G, H, and I were isolated by the Merck group as ras farnesyl transferase inhibitors accompanied by the type A compounds deoxypreussomerins A and B. Therefore, preussomerins were strongly suggested to be biosynthesized from the type A compound as a precursor.[39] In 1999, Gloer's group isolated 3′-*O*-desmethyl-1-epipreussomerin C as an antibacterial and antifungal metabolite from a coprophilous fungus, *Sporormiella vexans* (JS 306).[45] Preussomerins J, K, and L were isolated from an endophytic fungus, *Mycelia sterile*, and their absolute stereochemistry was determined by means of CD calculations by Krohn and co-workers.[46] 3′-*O*-Desmethylpreussomerin I was also isolated accompanied by known preussomerins E−I, deoxypreussomerin A, and bipendensin from a lichenicolous fungus, *Microsphaerosis* sp. BCC 3050, by a group from Thailand in 2002.[47]

3.3. Bisnaphthospiroketal and Binaphthyl (Type C)

So far, spiroxins A−E (Figure 7), which were isolated from marine-derived fungal strain LL-37H248 in 1999,[48] are the only compounds belonging to type C natural products. The absolute stereochemistry was determined by means of the exciton coupled CD technique in 2001.[49] Spiroxin A, isolated as a major component, was reported to show antibacterial activity against Gram-positive bacteria and antitumor activity against ovarian cancer in nude mice by McDonald's group.[48] In the same paper, they reported that spiroxin A can show single-strand cleavage of double-strand DNA in the presence of thiols, which could cause the antitumor activity. However, the biological activity of the other spiroxins and the mechanistic details of DNA cleavage induced by spiroxin A are unknown.

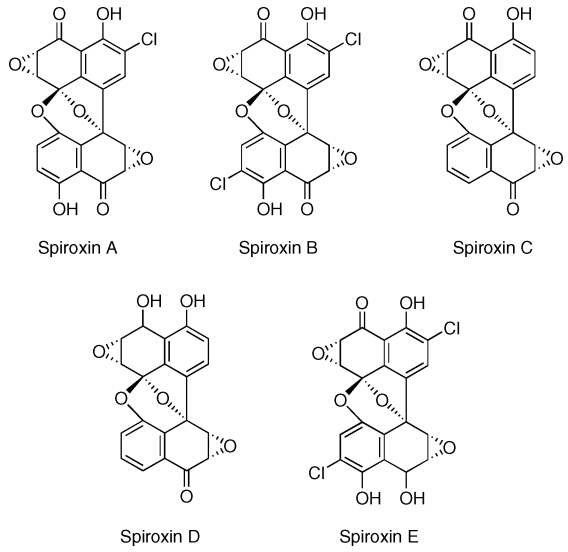


Figure 7. Structures of spiroxins A−E.

4. Epoxyphenathroquinone: Panepophenanthrin

Panepophenanthrin (Figure 8) was isolated from the fermented broth of a mushroom strain, *Panus rudus* IFO8994, by Sekizawa and co-workers in 2002 and is characterized by its unique molecular structure, having a tetracyclic epoxyphenathroquinone skeleton, which has been elucidated by spectroscopic and X-ray crystallographic analyses.[50] It is also noteworthy that panepophenanthrin is the first inhibitor for the ubiquitin-activating enzyme. Therefore, it is of great use as a biological tool and could provide further information about ubiquitin functions that are related to disease.

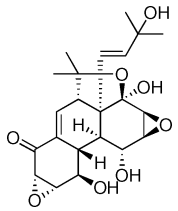


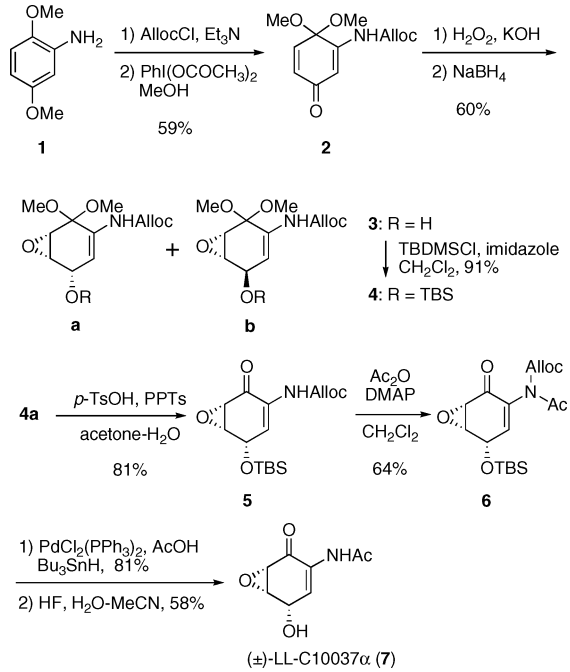
Figure 8. Structure of panepophenanthrin.

5. Syntheses of Manumycin and Related Compounds

5.1. Wipf's Total Synthesis of LL-C10037α

The total synthesis of racemic LL-C10037α (**7**) was reported in 1994 by Wipf and Kim.[51] In the next year, they reported details of the synthesis and the first total synthesis of optically active LL-C10037α (**7**).[52] At first, they synthesized racemic LL-C10037α (**7**) as follows. Aniline **1** was protected with an alloc group and then oxidized with a hypervalent iodine reagent in methanol to give quinone monoacetal **2**. Epoxidation and $NaBH_4$ reduction afforded *cis*-epoxyalcohol **3a** as a major product. The major isomer **3a** was transformed into (±)-LL-C10037α (**7**) by changing the alloc group to an acetyl group as shown in Scheme 1. As is easily expected, if the acetyl group was employed from the beginning of the synthesis in place of the alloc group, the synthetic steps can be shortened. However, they described that, through this synthetic procedure, the acetyl group could not be employed as a protecting group; when an acetyl group was employed, 1,2-reduction with $NaBH_4$ failed, and deacetylation was also observed on epoxidation. (±)-Epi-LL-C10037α was also synthesized from the minor isomer **4b**.

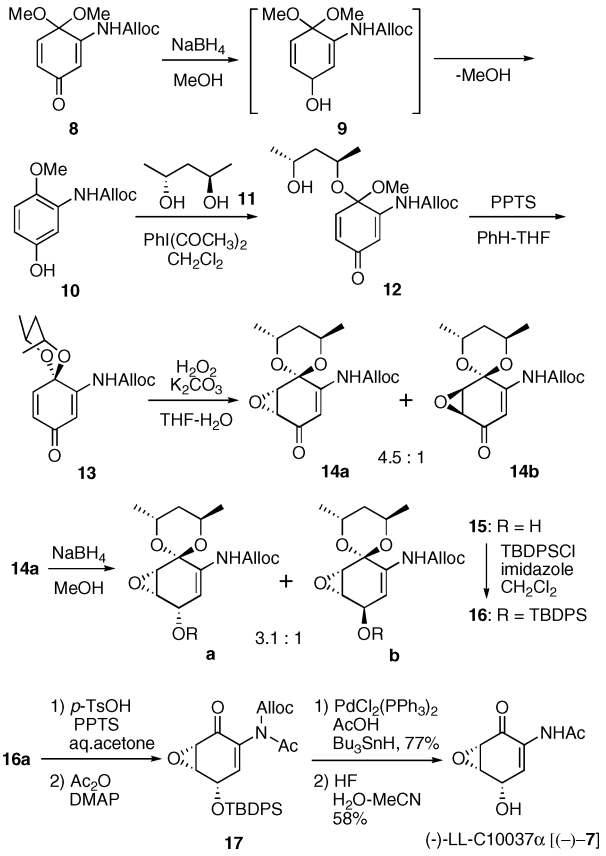
Scheme 1. Wipf's Total Synthesis of (±)-LL-C10037α (7) (Reprinted with Permission from Ref 51. Copyright 1994 American Chemical Society)



Optically active LL-C10037α (**7**) was also synthesized according to a similar procedure using (2*R*,4*R*)-pentane-2,4-diol (**11**) for acetal protection as shown in Scheme 2.[52] As acetal exchange reaction between dimethylacetal **8** and diol **11** resulted in failure, phenol **10** was reoxidized with a hypervalent iodine reagent in the presence of diol **11** to give acetal **13** after PPTS treatment. Epoxidation of **13** afforded α-epoxide **14a** as a major product, which was ex-

plained by consideration of a favorable conformation of **13** confirmed by NOE experiment. Epoxide **14a** was transformed into optically active LL-C10037α (**7**) by the same procedure as that for racemic compound **7**. The ee value of the final product (**7**) determined by comparison of $[\alpha]_D$ values was reported to be 94%.

Scheme 2. Wipf's Total Synthesis of (−)-LL-C10037α [(−)-7] (Reprinted with Permission from Ref 52. Copyright 1995 Thieme)

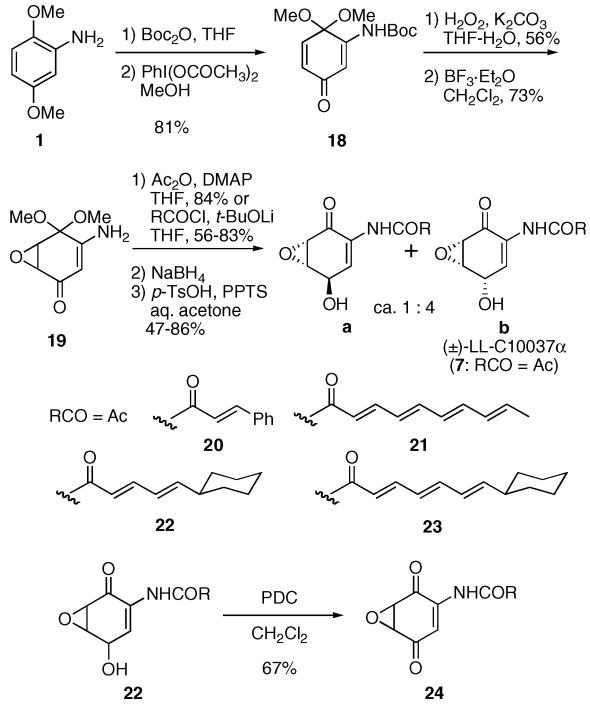


Although Wipf and Coish reported the preparation of a triene moiety corresponding to the upper side chain and the lower side chain of manumycin A employing hydrozirconation of acetylene as a key reaction,[53] they have not reported synthesis of the natural products.

5.2. Taylor's Total Synthesis of (±)-LL-C10037α

In 1996, Taylor and co-workers reported the total synthesis of racemic LL-C10037α (**7**).[54] They also employed hypervalent iodine oxidation to obtain quinone monoacetal **18**. Although they protected an amino group with a Boc group, it was selectively removed without affecting the acetal and epoxy moieties by treatment with BF_3 etherate to give amine **19**. After acetylation, **19** was transformed into (±)-LL-C10037α (**7**). Not only the acetyl group but also other acyl groups, which were found in manumycin family antibiotics, were introduced to the amino group, and alisamycin degradation product **24** was also synthesized after PDC oxidation as shown in Scheme 3.

Scheme 3. Taylor's Total Synthesis of (±)-LL-C10037α (7) (Reprinted with Permission from Ref 54. Copyright 1996 Elsevier)



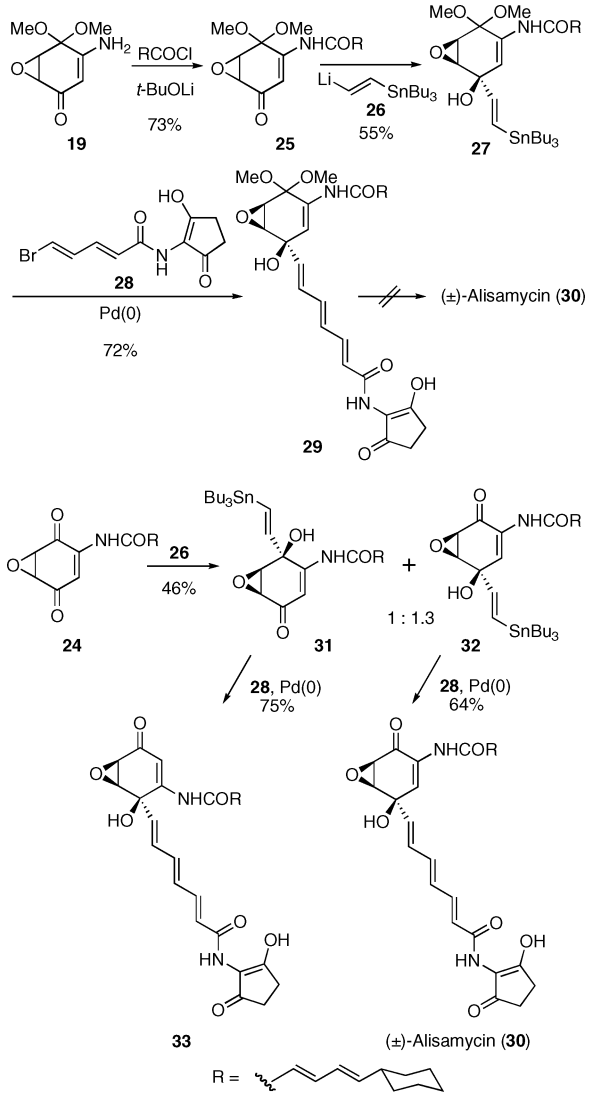
5.3. Taylor's Total Synthesis of (±)-Alisamycin

In 1996, Taylor and co-workers reported the first synthesis of the manumycin family antibiotic alisamycin (**30**) in a racemic form as shown in Scheme 4.[55] Starting from epoxyquinone monoacetal **19** reported before,[54] an acyl side chain was introduced at first to give amide **25**. To construct the lower side chain, they treated amide **25** with stannylvinyllithium **26**, giving *cis*-epoxyalcohol **27**, stereoselectively. Stille coupling of stannane **27** with vinyl bromide **28** afforded **29** in good yield. The last step was deprotection of the acetal moiety of **29** but was reported to fail under various reaction conditions. Therefore, they focused on epoxydiketone **24**, treatment of which with an organolithium reagent **26** afforded regioisomeric 1,2-adducts, **31** and **32**, in a ratio of 1:1.3. Major isomer **32** was derived into (±)-alisamycin (**30**) via Stille coupling reaction. The regioisomer of alisamycin, **33**, was also obtained from **31** similarly.

5.4. Taylor's Total Synthesis of (+)-MT 35214

In 1998, Taylor and co-workers reported asymmetric synthesis of (+)-MT 35214 (**36**), an enantiomer of LL-C10037α (**7**),[56] employing Wynberg's phase transfer epoxidation procedure as shown in Scheme 5.[57−60] They examined epoxidation of the quinone monoacetal **18** described above under various conditions and found that the reaction with *N*-benzylcinchonidinium chloride (**34**) afforded the best result (71% chemical yield, 89% ee). Although they reported asymmetric epoxidation of **18** with various sugar hydroperoxides in 2000,[61] the enantioselectivity of the reaction was less than that of the present reaction. Epoxide **35** was transformed into (+)-MT 35214 (**36**)

Scheme 4. Taylor's Total Synthesis of (±)-Alisamycin (30) (Reprinted with Permission from Ref 55. Copyright 1996 Elsevier)

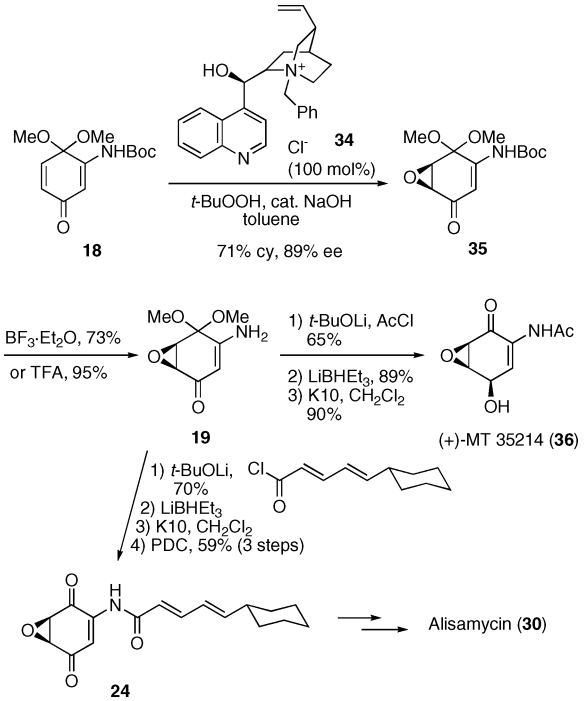


and optically active diketone **24** similarly to that for the racemic compounds described above.[54] As Taylor's group had already synthesized (±)-alisamycin (**30**) from racemic **24** as described above,[55] formal total synthesis of optically active alisamycin (**30**) was simultaneously achieved.

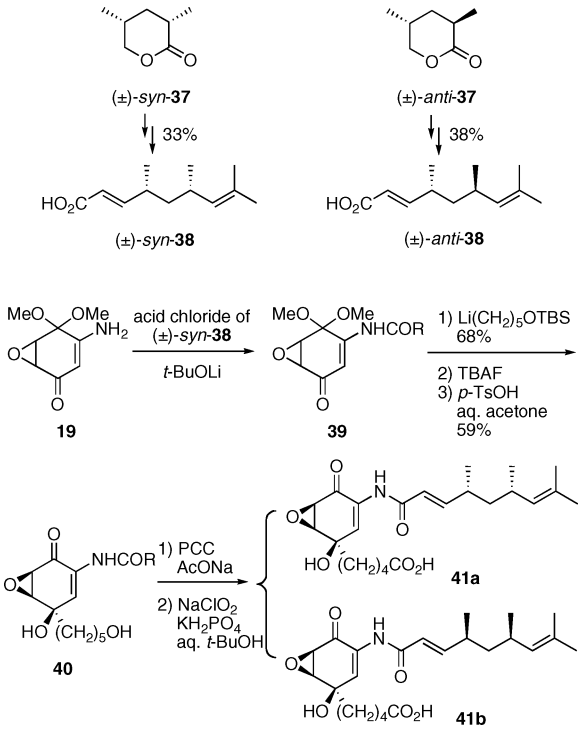
5.5. Taylor's Total Synthesis of (±)-U-62162

In 1998, the first synthesis of racemic U-62162 (**41**) was also reported by Taylor and Alcaraz (Scheme 6).[62] At first, two stereoisomers of side chain carboxylic acids, *syn*-**38** and *anti*-**38**, were prepared from *syn*- and *anti*-lactones **37**, respectively, according to a sequence of DIBAL-H reduction, Swern oxidation, and Wittig reaction. These two carboxylic acids, *syn*-**38** and *anti*-**38**, were coupled with epoxyquinone monoacetal **19** to afford a couple of diastereomeric mixtures. Reaction of *syn*-**39** with an organolithium reagent stereoselectively afforded *cis*-epoxyalcohol **40** after deprotection. In their synthesis of alisamycin (**30**) described above,[55] deprotection of the acetal failed, but in this case, deprotection of the acetal took place after desilylation, giving epoxyketone **40**. Eventually, the primary hydroxyl group of **40** was oxidized to give a pair of diastereomers, **41a** and **41b**, one of which was reportedly identical with U-62162 (**41**) by comparison of NMR data. Although the stereochemistry of U-62162 was unknown, *cis*-epoxyalcohol arrangement and *syn*-orientation of the side chain were established through this total synthesis.

Scheme 5. Taylor's Total Synthesis of (+)-MT 35214 (36) (Reprinted with Permission from Ref 56. Copyright 1998 Elsevier)



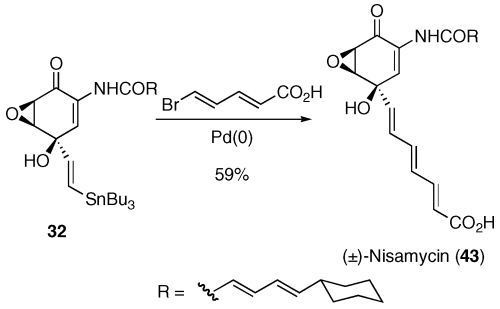
Scheme 6. Taylor's Total Synthesis of (±)-U-62162 (41) (Reprinted with Permission from Ref 62. Copyright 1998 The Royal Society of Chemistry)



5.6. Taylor's Total Synthesis of (±)-Nisamycin and (+)-Manumycin A

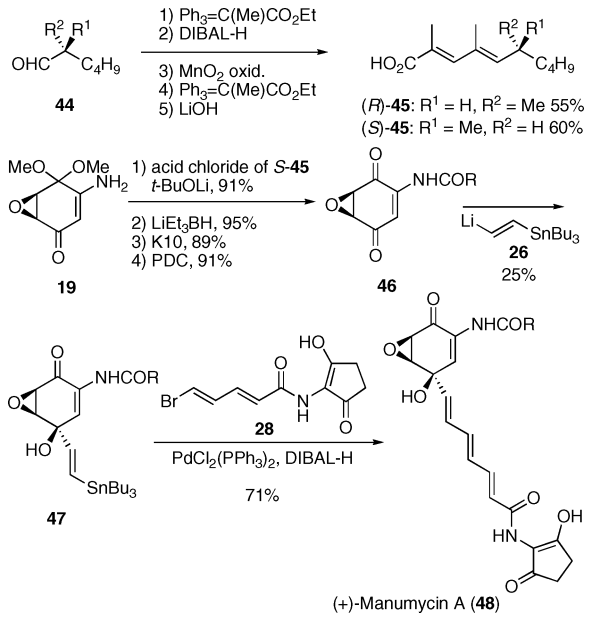
In the same year, 1998, Taylor and co-workers reported synthesis of manumycin A (**48**)[63] and nisamycin (**43**) as well as details of the synthesis of LL-C10037α (**7**) and alisamycin (**30**)[64] communicated before.[54,55] As described above, their key steps for the construction of the lower side chain are a combination of 1,2-addition of stannylvinyllithium to epoxyquinones and Stille-type coupling of the resultant vinylstannane with vinyl halides. This methodology was utilized for the synthesis of nisamycin (**43**) as well (Scheme 7).

Scheme 7. Taylor's Total Synthesis of (±)-Nisamycin (43) (Reprinted with Permission from Ref 63. Copyright 1998 Thieme)



Manumycin A, manumycin B, and EI-1625-2 were originally assigned to have an *anti*-epoxyalcohol structure, which was rather surprising and strange from the fact that all other manumycin members have a *syn*-relationship and from the biosynthetic mechanism proposed by Floss and co-workers.[65,66] Taylor and co-workers synthesized enantiomeric (+)-manumycin A (**48**), having a *syn*-epoxyalcohol structure, by employing their method as shown in Scheme 8, and they successfully showed that manumycin A

Scheme 8. Taylor's Total Synthesis of (+)-Manumycin A (48) (Reprinted with Permission from Ref 64. Copyright 1998 American Chemical Society)



has a revised structure as indicated by **48**. They have synthesized both enantiomers of the acyl side chain, (*R*)- and (*S*)-**45**, of manumycin A and coupled them with optically active epoxyquinone acetal **19**. Construction of the lower side chain was achieved as described above to give (+)-manumycin A, having a *syn*-relationship. Chromatographic and spectral data clearly indicated that the product was an enantiomer of natural (−)-manumycin A. Therefore, the structure of manumycin A was shown to have a *syn*-epoxyalcohol structure, which is in accord with the biosynthetic mechanism proposed by Floss' group.[65,66] They reported that the structures of manumycin B and EI 1625-2 would also need to be revised as shown in Figure 9. These results described above clearly proved that their methodology is highly effective as a general synthetic route not only for natural manumycin family antibiotics but also for their analogues.

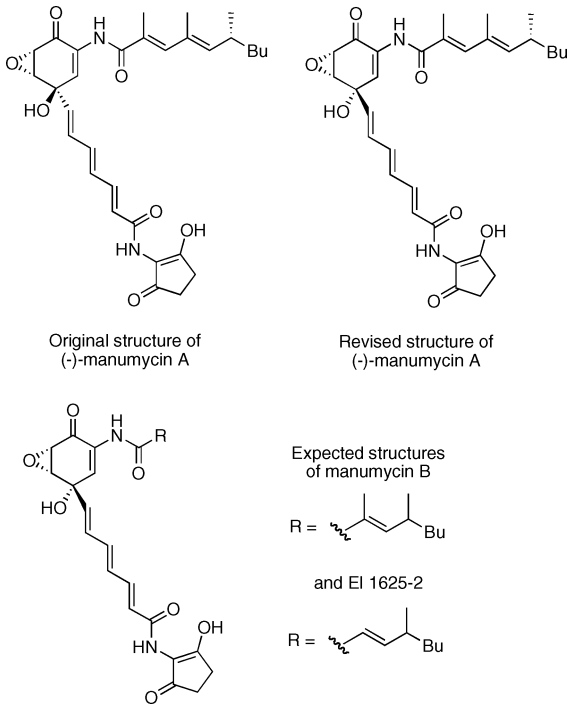


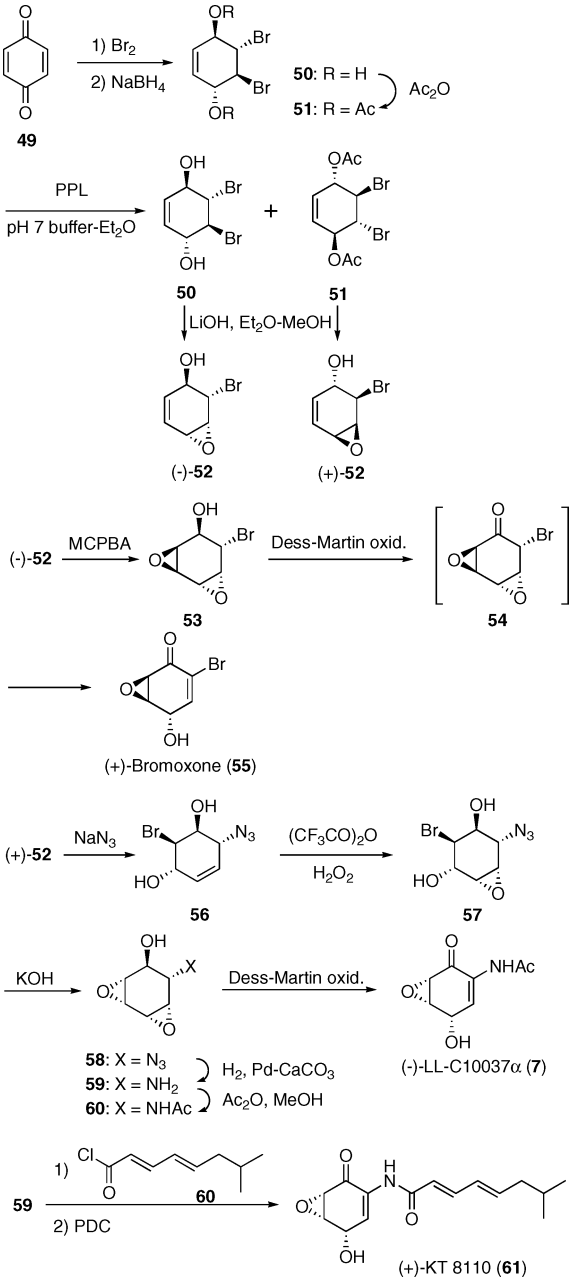
Figure 9. Structures of (−)-manumycins A, B, and EI 1625-2. (Reprinted with permission from ref 64. Copyright 1998 American Chemical Society.)

5.7. Altenbach's Total Synthesis of (−)-LL-C10037α

In 2000, Altenbach and co-workers reported the total synthesis of (−)-LL-C10037α (**7**) and the related natural products (+)-bromoxone (**55**) and (+)-KT 8110 (**61**) employing enzymatic resolution as a key step (Scheme 9).[67] They applied their resolution method[68] to C_2-symmetrical diacetate **51** prepared from benzoquinone and obtained optically active diol **50** and diacetate **51** both in 38% yields and >99% ee after recrystallization. Treatment of diol **50** with LiOH as a weak base selectively afforded monoepoxide (−)-**52**, not a bisepoxide. Under the same conditions, diacetate **51** also gave enantiomeric epoxide (+)-**52** accompanying hydrolysis of acetate. The optically active epoxide (−)-**52** was transformed into (+)-bromoxone (**55**). Introduction of an amino group

to (+)-**52** was successfully achieved by nucleophilic cleavage of the epoxide with the azide anion and subsequent reduction, and (−)-LL-C10037α (**7**) and (+)-KT 8110 (**61**) were synthesized after introduction of acyl side chains, an acetyl group and **60**, respectively.

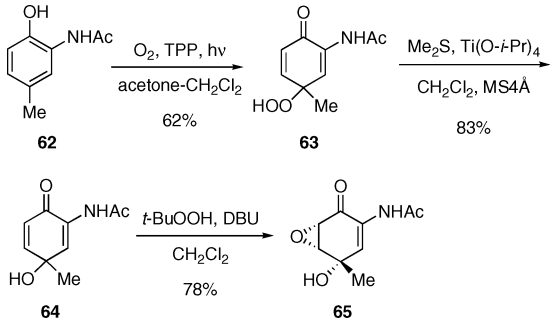
Scheme 9. Altenbach's Total Synthesis of (−)-LL-C10037α (7) and Natural Products (Reprinted with Permission from Ref 67. Copyright 2000 American Chemical Society)



5.8. Kilic's Synthesis of an LL-C10037α Analogue

Although, for the purpose of construction of the quinone structure, oxidation of hydroquinone with hypervalent iodine reagents has been widely employed, Kilic and co-workers reported an alternative method employing photooxygenation, in 2002 (Scheme 10).[69] Aminophenol **62** was photooxygenated in the presence of TPP as a photosensitizer to give hydroperoxide **63**, reduction of which with dimethyl sulfide in the presence of titanium tetraisopropoxide afforded alcohol **64**. Weitz−Scheffer epoxidation of **64** was reported to take place in a completely diastereoselective manner due to participation of the hydroxyl group to give LL-C10037α analogue **65**.

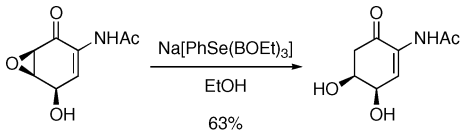
Scheme 10. Kilic's Synthesis of LL-C10037α Analogue 65 (Reprinted with Permission from Ref 69. Copyright 2002 Thieme)



5.9. Taylor's Total Syntheses of Type II Manumycin Antibiotics

In 1999, Taylor and co-workers utilized their method for the synthesis of type II manumycin antibiotics, (−)-LL-C10037β (**66**), (+)-TMC-1A (**68**), and (±)-colabomycin D (**72**), which have a β-hydroxyketone structure in place of the epoxyketone structure.[70,71] Employing (+)-MT 35214 (**36**), which is an enantiomer of (−)-LL-C10037α (**7**) and has already been synthesized by their group, they examined reductive cleavage of epoxyketone to β-hydroxyketone and found that $Na[PhSeB(OEt)_3]$ prepared in situ by $NaBH_4$ reduction of PhSeSePh[72] was effective for the purpose (Scheme 11). The (−)-LL-C10037β (**66**) obtained was reported to be extremely sensitive to acid but to be entirely identical with natural (−)-LL-C10037β (**66**) by comparison of spectral properties.

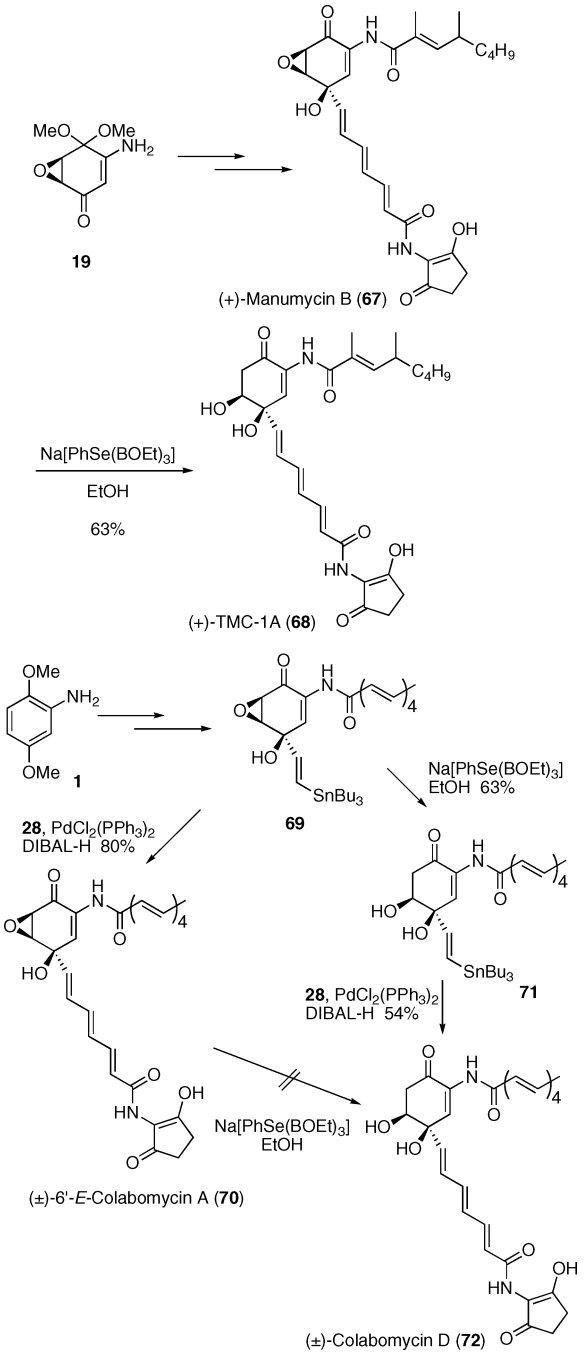
Scheme 11. Taylor's Synthesis of (−)-LL-C10037β (66) (Reprinted with Permission from Ref 70. Copyright 1999 The Royal Society of Chemistry)



They synthesized optically active TMC-1A (**68**) and racemic colabomycin D (**72**) by a combination of the present reduction of epoxyketone and their own synthetic method for manumycin analogues having an epoxyketone structure described above (Scheme 12). (+)-TMC-1A (**68**) was synthesized from (+)-manumycin B (**67**) which was prepared according to their own method employing asymmetric epoxidation. In the synthesis of (±)-colabomycin D (**72**), they described that the reduction of (±)-6′-*E*-colabomycin A (**70**) was examined at first, but the result was unsatisfactory due to the problem of insolubility of **70**. They overcame this problem by reduction of the epoxyketone **69** prior to Stille coupling. The former synthesis of (+)-TMC-1A (**68**) revised the structure

of manumycin B (**67**) to have a *syn*-epoxyalcohol unit not an *anti*-epoxyalcohol unit as originally reported, and the latter synthesis of (±)-colabomycin D (**70**) confirmed that the acyl side chain of natural colabomycin A has the unusual 6′-*Z*-geometry as originally reportred.

Scheme 12. Taylor's Total Synthesis of (+)-TMC-1A (68) and (±)-Colabomycin D (72) (Reprinted with Permission from Refs 70 and 71. Copyright 1999 The Royal Society of Chemistry)



6. Syntheses of Epoxynaphthoquinone Natural Products Having a Type A Structure

In 1997, Wipf and Jung reported the first synthetic study toward diepoxin σ (**73**), which is a typical example of this type of natural products.[73] In this paper, they analyzed retrosynthesis of diepoxin σ as shown in Figure 10 and studied a long-range stereochemical induction of chiral acetals having a trifluoromethyl group as a model experiment. As a consequence, they found that 1,2-addition to naphthoquinone acetal **75** took place in a dipole-controlled diastereoselective manner (Scheme 13).

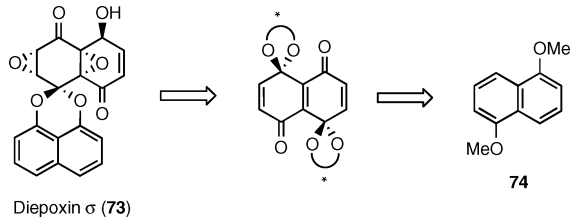
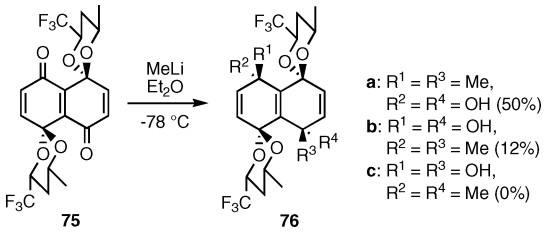


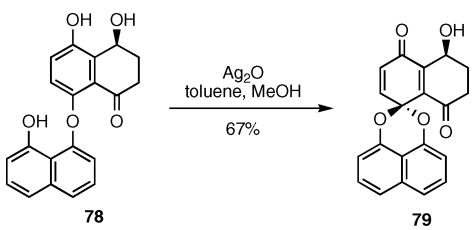
Figure 10. Wipf's retrosynthesis of diepoxin σ (**73**). (Reprinted with permission from ref 73. Copyright 1997 Wiley-VCH Verlag.)

Scheme 13. Diastereoselective 1,2-Addition to Chiral Acetal 75 (Reprinted with Permission from Ref 73. Copyright 1997 Wiley-VCH Verlag)



In the same year, Krohn and co-workers also reported the construction of the basic skeleton of palmarumycin by the use of oxidative cyclization.[74] They isolated biaryl ether **78** from the fungus, *Coniothyrium palmatum*, from which they had already isolated palmarumycins.[30,32] This fact strongly suggested that the biaryl ether **78** would be an open-chain precursor in biosynthesis of palmarumycins. To prove this hypothesis chemically, they treated **78** under various oxidative conditions and found that spiroacetal **79** was obtained in 67% yield by treatment with Ag_2O in toluene, as was reported by Merlini and Zanarotti in their synthesis of (+)-eusiderin (Scheme 14).[75] They also showed that the absolute configuration of **79** was identical with that of natural palmarumycins by means of CD measurement, strongly suggesting that palmarumycins are biosynthesized via an open-chain precursor **78**.

Scheme 14. Krohn's Biomimetic Oxidation of Binaphthyl Ether 78 (Reprinted with Permission from Ref 74. Copyright 1997 Elsevier)



Total syntheses of this type of natural products were extensively studied mainly by three groups, Wipf's, Taylor's, and Barrett's groups.

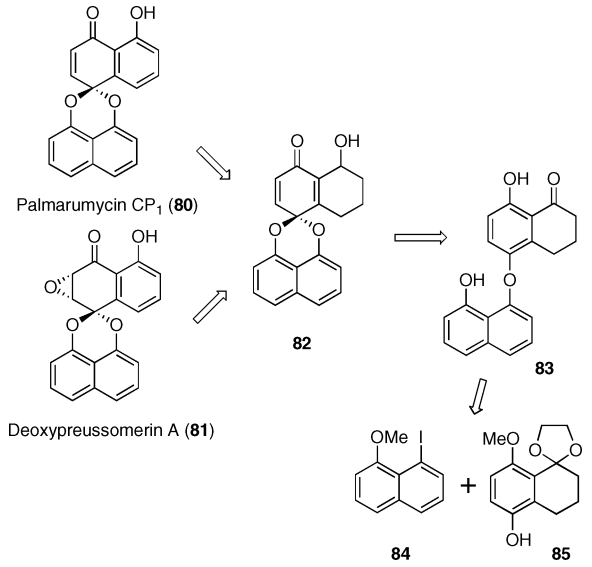
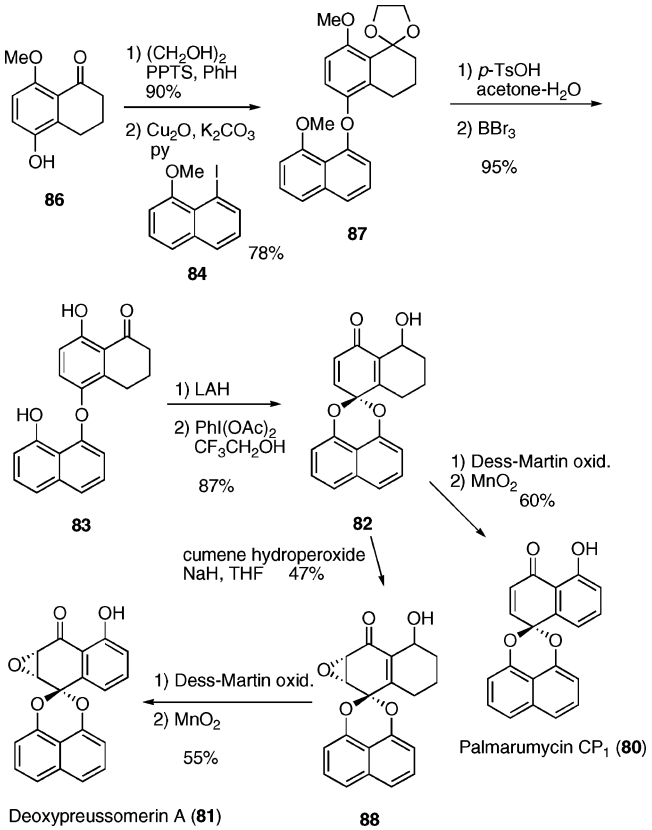


Figure 11. Wipf's retrosynthesis of palmarumycin CP_1 and deoxypreussomerin A. (Reprinted with permission from ref 76. Copyright 1998 American Chemical Society)

6.1. Wipf's Total Synthesis of Palmarumycin CP_1 and Deoxypreussomerin A

Wipf and Jung reported the total synthesis of palmarumycin CP_1 (**80**) and deoxypreussomerin A (**81**) according to a biomimetic approach, as shown in Figure 11, in which open-chain precursor **83** was cyclized under oxidative conditions.[76] The open-chain precursor **83** was synthesized in good yield by an Ullmann ether coupling reaction[77] between phenol **85** and iodide **84**. In this reaction, protection of the ketone moiety of **86** as an ethylene acetal was reported to be essential. After several steps, oxidative cyclization with iodobenzene diacetate in 2,2,2-trifluoroethanol smoothly took place to afford spiroacetal **82** in good yield. Aromatization of **82** afforded palmarumycin CP_1 (**80**), while nucleophilic epoxidation and subsequent aromatization afforded deoxypreussomerin A (**81**), as shown in Scheme 15.

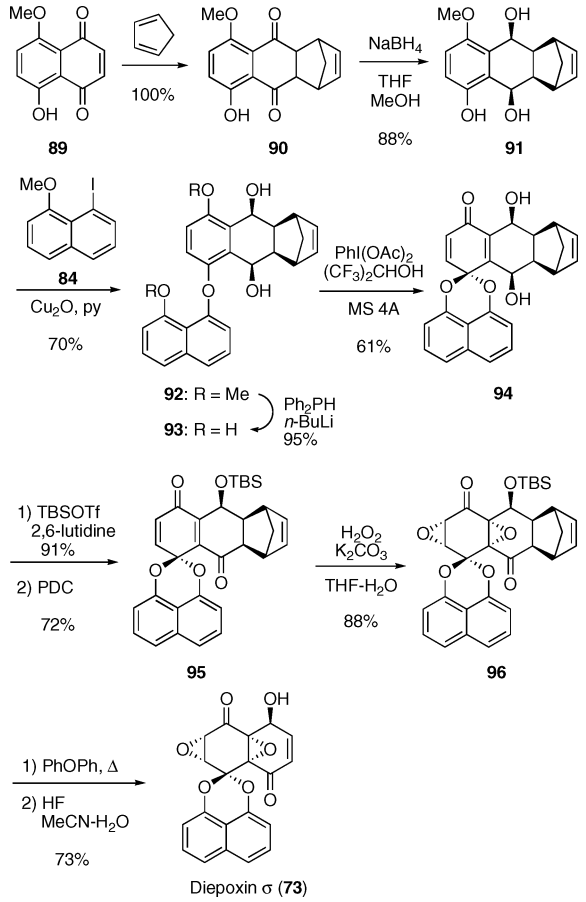
Scheme 15. Wipf's Total Synthesis of Palmarumycin CP_1 (80) and (±)-Deoxypreussomerin A (81) (Reprinted with Permission from Ref 76. Copyright 1998 American Chemical Society)



6.2. Wipf's Total Synthesis of Diepoxin σ

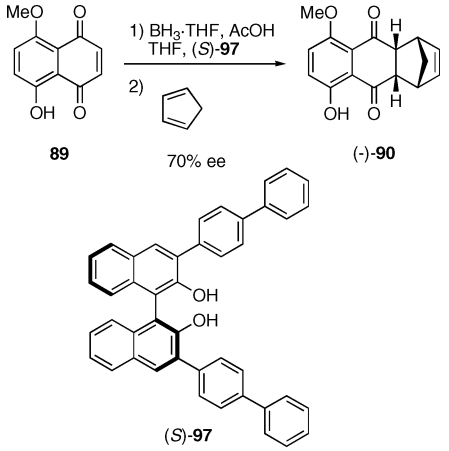
In 1999, Wipf and Jung successfully achieved the first total synthesis of diepoxin σ (**73**), a highly oxygenated derivative of the type A compound, according to a similar biomimetic pathway to that described above,[76] as shown in Scheme 16.[78] A characteristic feature of their synthesis is that a reactive enone alkene moiety was protected as a Diels–Alder adduct with cyclopentadiene to construct an epoxyketone moiety regioselectively. Although retro-Diels–Alder reaction of **96** required high temperature, it was successfully conducted without affecting the epoxyketone moiety to give diepoxin σ (**73**) after removal of a TBS group. As they obtained optically active (−)-**90** (70% ee) by asymmetric Diels–

Scheme 16. Wipf's Total Synthesis of (±)-Diepoxin σ (73) (Reprinted with Permission from Ref 78. Copyright 1998 American Chemical Society)



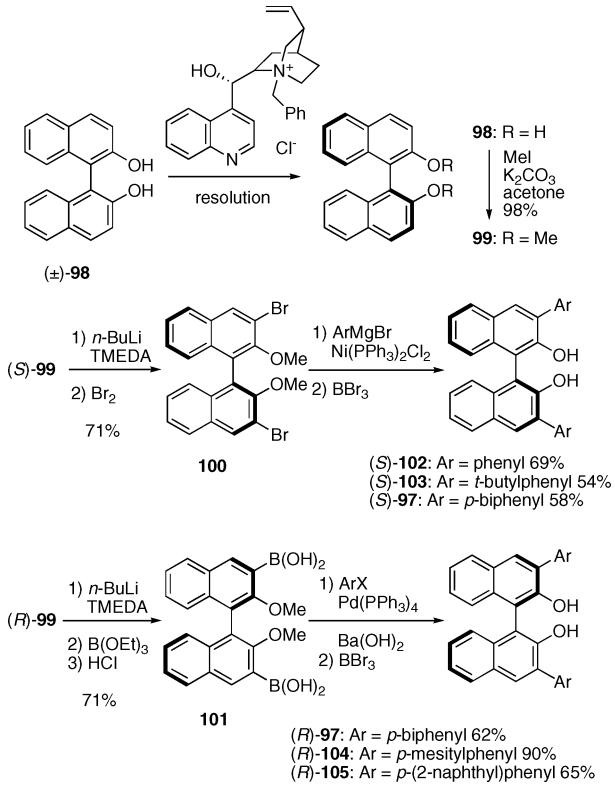
Alder reaction employing optically active binaphthol (*S*)-**97** as a chiral ligand (Scheme 17), they reported that this synthetic route would lead to asymmetric synthesis of this type of natural products.

Scheme 17. Wipf's Asymmetric Diels–Alder Reaction (Reprinted with Permission from Ref 78. Copyright 1998 American Chemical Society)



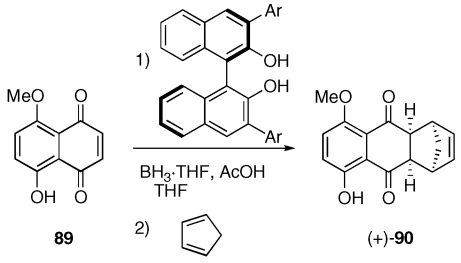
In 2000, they reported details of the synthesis of (±)-diepoxin σ (**73**) described above[78] and an asymmetric Diels–Alder reaction.[79] On the basis of the asymmetric Diels–Alder reaction reported by Kelly's[80] and Yamamoto's[81] groups, boranes modified with chiral binaphthol derivatives were employed as a catalyst. In this paper, they prepared various aryl-substituted binaphthols **97** and **102**–**105** by means of a Pd(0)- or Ni(0)-catalyzed cross-coupling reaction as a key reaction, as shown in Scheme 18, and

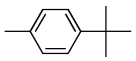
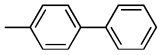
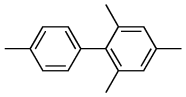
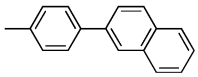
Scheme 18. Wipf's Synthesis of Chiral Binaphthols (Reprinted with Permission from Ref 79. Copyright 2000 American Chemical Society)



studied borane-catalyzed asymmetric Diels–Alder reaction of naphthoquinone **89** and cyclopentadiene employing the binaphthols **97** and **102**–**105** as a chiral ligand (Table 1). As a consequence, the bulkier the substituent (Ar) on the chiral ligand, the higher the enantioselectivity of the Diels–Alder reaction, and the maximum 94% ee was obtained when **105** was employed as a chiral ligand. They have not achieved the synthesis of the optically active natural product employing the asymmetric Diels–Alder adduct **90**. However, as they have successfully synthesized (±)-diepoxin σ (**73**) from racemic adduct **90** in the same paper, this result means the formal asymmetric total synthesis of (+)-diepoxin σ (**73**).

Table 1. Wipf's Asymmetric Diels–Alder Reaction (Reprinted with Permission from Ref 79. Copyright 2000 American Chemical Society)



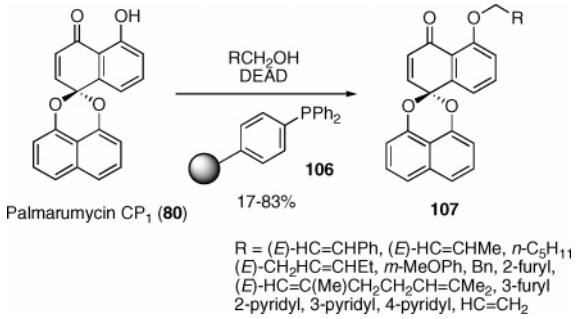
Chiral ligand	Ar	ee (%) 0 °C	ee (%) -78 °C	Sign of $[\alpha]_D$ for **90**
(*S*)-**102**		<30	–	(–)
(*S*)-**103**		37	42	(–)
(*R*)-**97**		–	88	(+)
(*R*)-**104**		52	54	(–)
(*S*)-**105**		–	94	(–)

6.3. Wipf's Application of Their Syntheses to Palmarumycin Analogues

Utilizing their syntheses, Wipf and co-workers synthesized several analogues as well as natural products, deoxypreussomerin A (**81**) and palmarumycin CP_1 (**80**), and studied their biological activity in 2001.[82,83] They successfully constructed a small library of palmarumycin analogues **107** having a variety of substituents at the phenolic hydroxyl group, which were introduced by Mitsunobu reaction with polymer-supported triphenylphosphine **106** as shown in Scheme 19. These analogues **107** were subjected to study of their cytotoxic activity against human breast cancer cells, MCF-7 and MDA-MB-231 cells, and were revealed to be low-micromolar growth

inhibitors. At the same time, these compounds **107** were reported to work as a novel inhibitor against thioredoxin−thioredoxin reductase.[84]

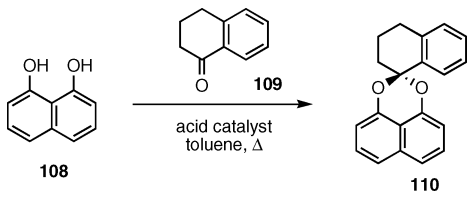
Scheme 19. Wipf's Synthesis of *O*-Substituted Palmarumycin CP_1 Derivatives 107 (Reprinted with Permission from Ref 83. Copyright 2001 Elsevier)



6.4. Taylor's Total Syntheses of Palmarumycins CP_1, CP_2, and CJ 12371

Taylor and co-workers also reported total syntheses of palmarumycins CP_1 (**80**), CP_2 (**114**), and CJ 12371 (**115**) and some analogues in 1998.[85] In this paper, they described that as a biomimetic approach was unsuccessful in their case, they focused on direct acetalization reaction. As a model study, they studied acetalization of tetralone **109** with 1,8-naphthalenediol (**108**) under acidic conditions, as summarized in Table 2, and found that trifluoromethanesulfonic acid

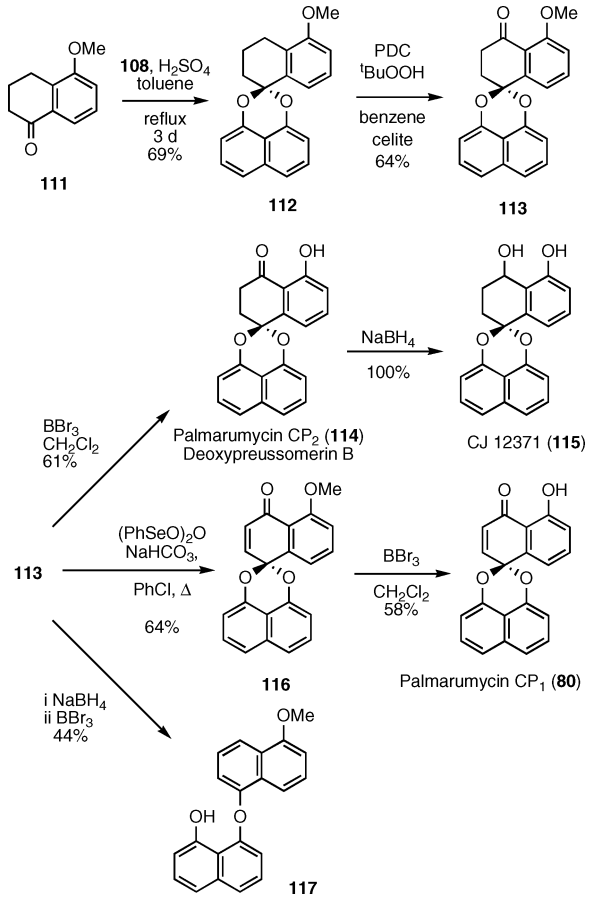
Table 2. Taylor's Acetalization of Tetralone 109 (Adapted with Permission from Ref 85. Copyright 1998 Elsevier)



acid catalyst	yield (%)
Amberlite 15	22
p-TsOH	40
Montmorillonite K10	44
H_2SO_4	64
TfOH	74

or sulfuric acid in refluxing toluene afforded the best result. Utilizing this method, they successfully synthesized spiroacetal **112**, which was then oxidized to a key intermediate **113** for the synthesis of palmarumycins and related compounds as shown in Scheme 20. It was also reported that, in the synthesis of CJ 12371 (**115**), demethylation should be achieved before reduction of a ketone group of **113**, as, after reduction, aromatization of a tetrahydronaphthalene ring was reported to take place under conditions of the demethylation reaction as shown in Scheme 20. After demethylation, palmarumycin CP_2 (**114**) was reduced to give CJ 12371 (**115**).

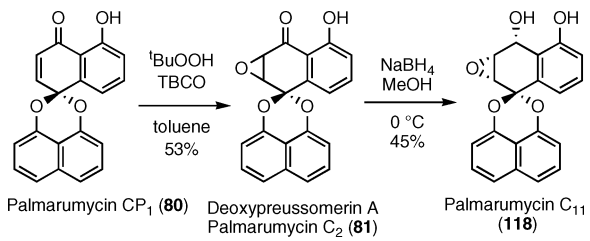
Scheme 20. Taylor's Total Synthesis of Palmarimycins CP_1 (80), CP_2 (114), and (±)-CJ 12371 (115) (Reprinted with Permission from Ref 85. Copyright 1998 Elsevier)



6.5. Taylor's Total Synthesis of Palmarumycin C_2 (Deoxypreussomerin A) and Palmarumycin C_{11}

In 1999, Taylor et al. reported application of their method[85] to the synthesis of epoxy analogues, deoxypreussomerin A (**81**, palmarumycin C_2) and palmarumycin C_{11} (**118**, bipendensin, Sch 53823), as well (Scheme 21).[86] They prepared deoxypreussomerin A (**81**) by epoxidation of palmarumycin CP_1 (**80**). Deoxypreussomerin A (**81**) was reduced by $NaBH_4$ to give **118** as a single diastereomer, the stereochemistry of which was assigned to be *syn* from their previous result.[87] It was described that the ^1H and ^{13}C NMR data of the product **118** were entirely consistent with those of palmarumycin C_{11} reported by Krohn et al.[30,32] but were different from those of bipendensin

Scheme 21. Taylor's Total Synthesis of (±)-Deoxypreussomerin A (81) and (±)-Palmarumycins C_{11} (118) (Reprinted with Permission from Ref 86. Copyright 1999 The Royal Society of Chemistry)

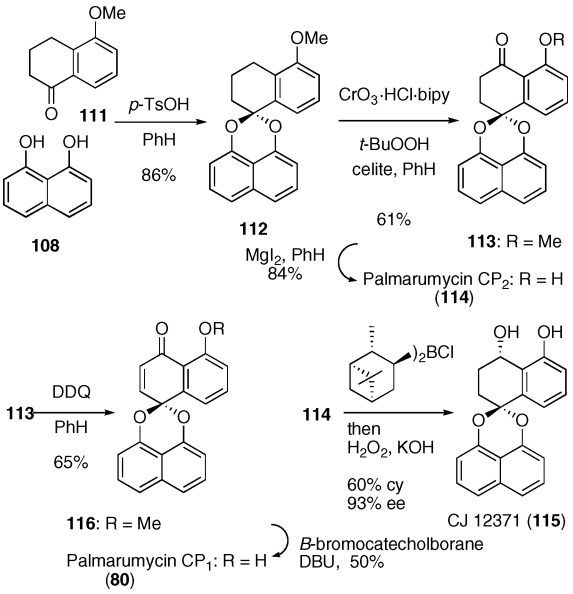


and Sch 53823 reported by Connolly et al.[33,88] and Chu et al.,[89] respectively. Although this result suggested that bipendensin and Sch 53823 have an *anti*-hydroxy-epoxide structure, Chu et al. reported that Sch 53825, a cometabolite of Sch 53823, has a *syn*-hydroxy-epoxide structure from a NOESY experiment.[89] Therefore, as Taylor and co-workers described in ref 99, the problem about the stereochemistry of these natural products still remains unresolved.

6.6. Barrett's Total Synthesis of Palmarumycins CP_1, CP_2, and CJ 12371

Barrett and co-workers also reported total syntheses of palmarumycins CP_1 (**80**), CP_2 (**114**), and CJ 12371 (**115**) in 1998.[90] They employed direct acetalization of tetralone **111** with 1,8-naphthalenediol **108** for the construction of the spiroacetal skeleton and obtained **112** under conventional conditions. Palmarumycins CP_1 (**80**) and CP_2 (**114**) were synthesized from **112** via oxidation procedures. Optically active CJ 12371 (**115**) was successfully obtained from palmarumycin CP_2 (**114**) in 60% chemical yield and 93% ee by asymmetric reduction, employing (+)-*B*-chlorodiisopinocampheylborane (Scheme 22).[91] To the best of our knowledge, this is the first example of asymmetric synthesis of this type of natural products. In 2002, Barrett and co-workers reported enantioselective synthesis of some other type A natural products employing asymmetric epoxidation under chiral phase transfer conditions. As they employ these type A natural products as an intermediate for the synthesis of a type B natural product, (−)-preussomerin G, this synthesis will be introduced in the synthesis of type B natural products (see section 7.3).

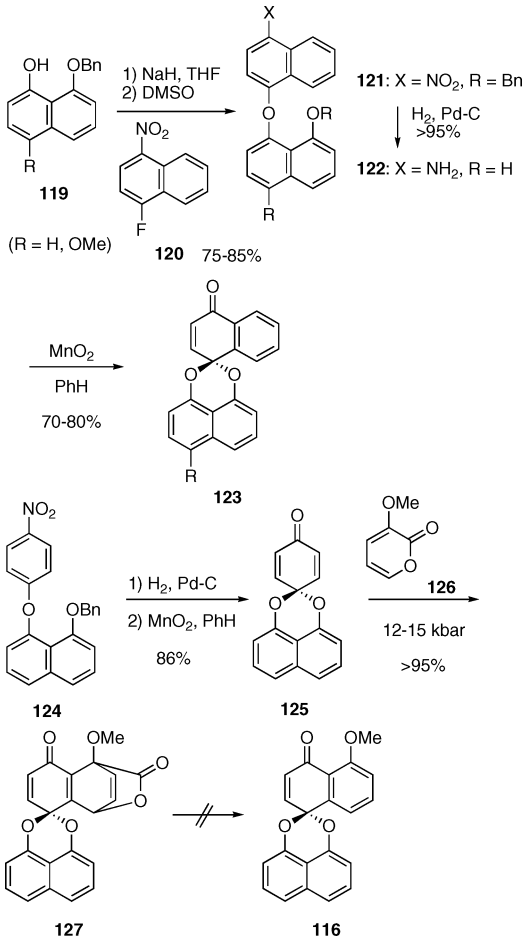
Scheme 22. Barrett's Total Synthesis of Palmarumycins CP_1 (80), CP_2 (114), and CJ 12371 (115) (Reprinted with Permission from Ref 90. Copyright 1998 The Royal Society of Chemistry)



6.7. Coutts' Synthetic Approach to a Palmarumycin Analogue

In 2000, Coutts and co-workers reported a novel way to construct a palmarumycin skeleton.[92] They employed a biomimetic procedure involving an aromatic nucleophilic substitution reaction and manganese dioxide oxidation as shown in Scheme 23. A characteristic feature of the reaction is that an aniline derivative, not phenol, was employed as a substrate for oxidation to construct the spiroketal skeleton. Not only naphthalene derivative **122** but also benzene derivative **124** was also applicable to this method, giving benzoquinone monoketal **125**. Diels−Alder reaction of **125** with pyrone **126** reportedly took place to give an adduct **127**. Although they have not yet obtained a decarboxylation product **116** from adduct **127**, they proposed that as aromatization was observed in its mass spectrum, the present approach would be a potent route for the construction of the palmarumycin skeleton.

Scheme 23. Coutts' Approach to Palmarumycin Analogues (Reprinted with Permission from Ref 92. Copyright 2000 Elsevier)



6.8. Hirama's Total Synthesis of CJ-12371

In 2003, Hirama's group also reported a quite different approach to the synthesis of the naphthospiroketal structure from those reported before, and they synthesized CJ 12372 (**135**) successfully.[93] The key reactions are the Suzuki−Miyaura cross-coupling reaction and Ag^+-mediated cationic cyclization of monothioortho ester **129** as shown in Figure 12. Monothioortho ester **129** was prepared from 1,8-naphthalenediol (**108**) employing thiophilic Grignard reaction, hydroboration, and the Suzuki−Miyaura

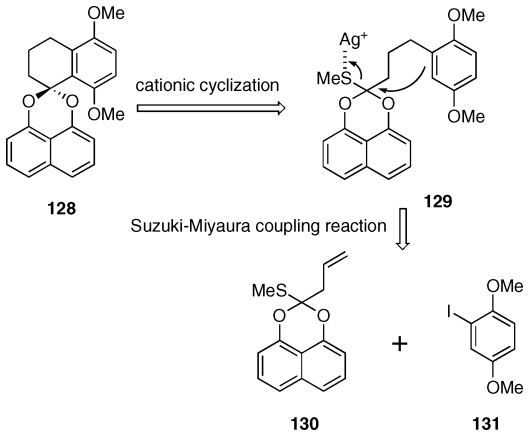
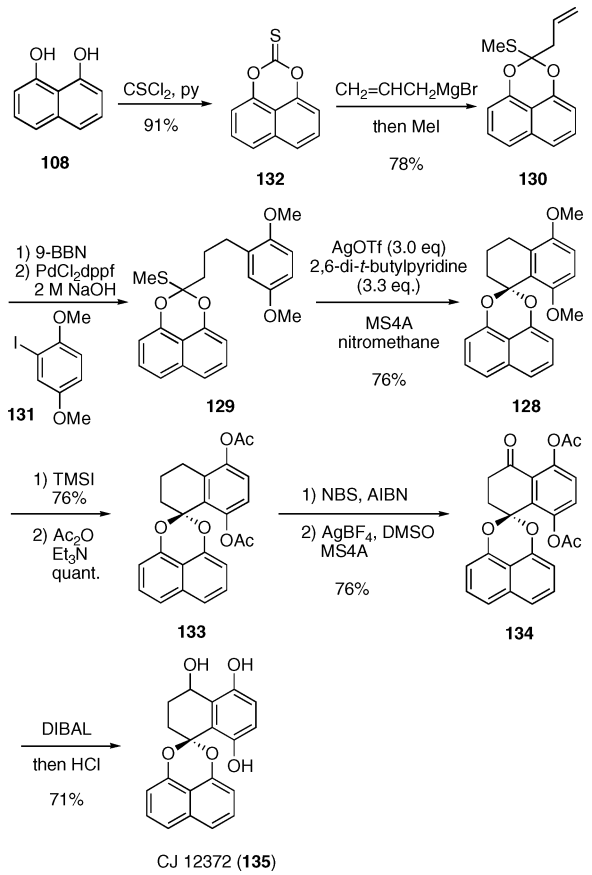


Figure 12. Hirama's synthetic plan for the type A skeleton. (Reprinted with permission from ref 93. Copyright 2003 The Japan Institute of Heterocyclic Chemistry.)

cross-coupling reaction with iodide **131**. They found that a combination of AgOTf and 2,6-di-*tert*-butylpyridine in nitromethane worked well to afford the desired product **128** in good yield. Compound **128** was transformed into CJ 12372 (**135**) via five steps as shown in Scheme 24. They proposed that compound **133** would serve as a common precursor not only for the present natural product, CJ 12372, but also for other types of natural products such as dieoxin σ, preussomerin G, and spiroxin A.

Scheme 24. Hirama's Total Synthesis of (±)-CJ 12372 (135) (Reprinted with Permission from Ref 93. Copyright 2003 The Japan Institute of Heterocyclic Chemistry)

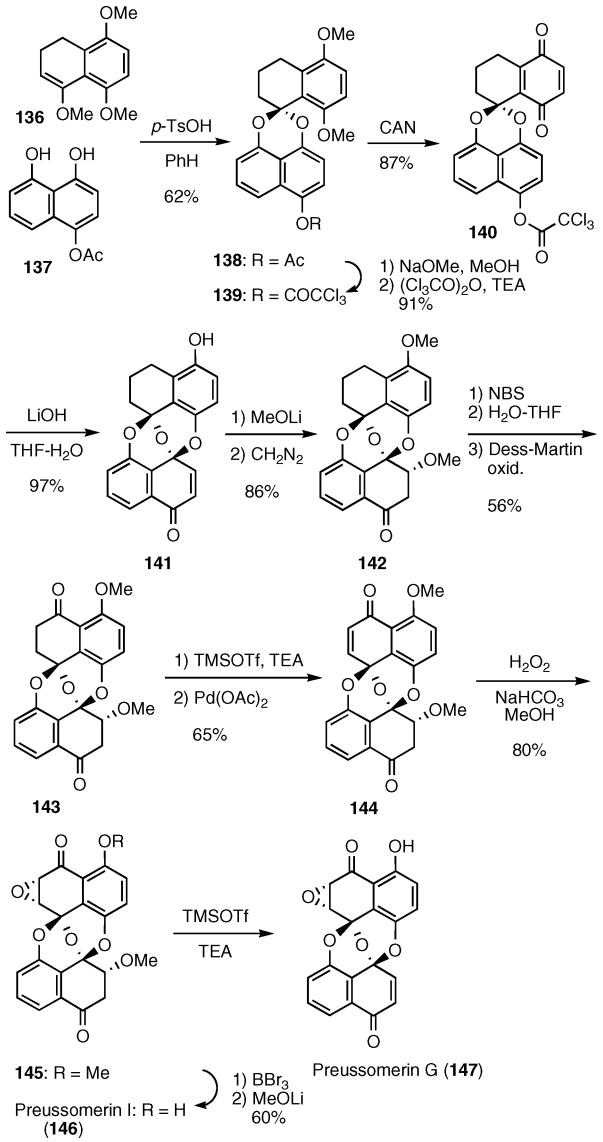


7. Syntheses of Epoxynaphthoquinone Natural Products Having a Type B Structure

7.1. Heathcock's Total Synthesis of Preussomerins G and I

In 1999, the opening page of the first issue of *Organic Letters* was adorned with the first total synthesis of type B natural products, preussomerins G (**147**) and I (**146**), which was reported by Chi and Heathcock.[94] They synthesized a palmarumycin skeleton by a direct acetalization method as the first step and then constructed a preussomerin skeleton via additional oxidation, which is a possible biomimetic route (Scheme 25).

Scheme 25. Heathcock's Total Synthesis of (±)-Preussomerins G (147) and I (146) (Reprinted with Permission from Ref 94. Copyright 1999 American Chemical Society)



The most characteristic and interesting step in their synthesis is construction of the basic skeleton as follows. Expecting deactivation of the naphthalene ring toward oxidation conditions, they selected a trichloroacetyl group as a protecting group of a

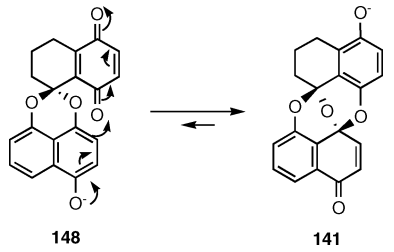


Figure 13. Equilibrium between quinone **148** and bisacetal **141**. (Reprinted with permission from ref 94. Copyright 1999 American Chemical Society.)

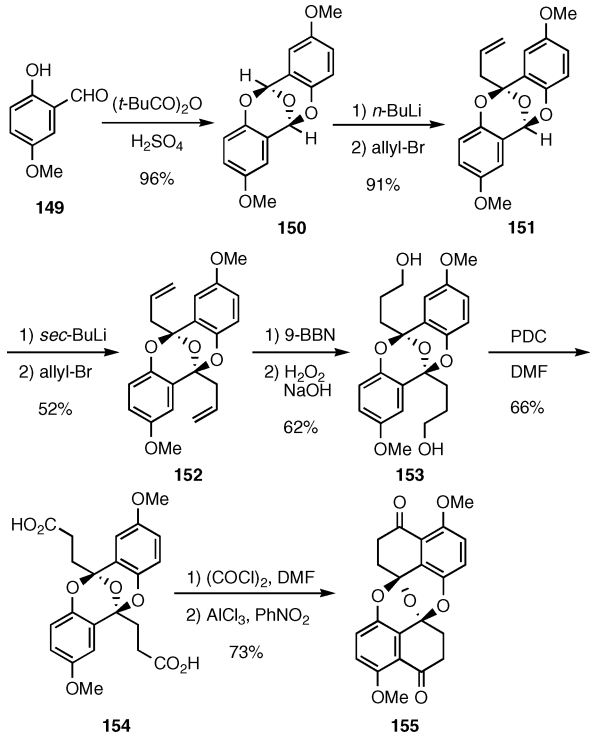
phenolic hydroxyl group on the naphthalene ring and successfully obtained quinone **140** in good yield. Interestingly, hydrolysis of the trichloroacetyl ester led to formation of the basic bisacetal skeleton. The driving force for the transformation was described to be resonance energy gained by formation of two isolated benzene rings in **141**. Ab initio calculations were also conducted and indicated that the energy difference between quinone **148** and the bisacetal **141** is about 7.9 kcal/mol in favor of **141** (Figure 13). This cyclization procedure would mimic the biosynthetic procedure well. Transformation of **141** into preussomerins I (**146**) and G (**147**) was achieved via sequential oxidation procedures including benzylic oxidation, dehydrogenation, and epoxidation. At first, the enone moiety of the lower ring system of **141** was protected from the sequential oxidation by 1,4-addition of methoxide, and then an epoxyketone structure of the upper ring was constructed to afford preussomerin I (**146**). Preussomerin G (**147**) was obtained by regeneration of the enone moiety.

7.2. Taylor's Total Syntheses of Preussomerins F, K, and L

In 2000, Taylor and co-workers reported a new route to construct a type B skeleton, which is unique and different from a biomimetic route.[95] They succeeded in condensing two salicylaldehyde molecules to obtain dimerized acetal **150**. One of two benzylic hydrogens was deprotonated by treatment with *n*-butyllithium, and allylation took place in good yield by treatment of the resultant benzylic acetal anion with allyl bromide to give **151**. Deprotonation of the second benzylic hydrogen was achieved by treatment with *sec*-butyllithium, and the resultant anion was trapped with allyl bromide again to give **152**. Transformation of **152** into dicarboxylic acid **154** via conventional procedures and subsequent Friedel–Crafts reaction afforded **155** having a type B skeleton as shown in Scheme 26.

In 2004, they reported application of the above method[95] to the synthesis of type B natural products, preussomerins K (**165**) and L (**163**) (Scheme 27).[96] In this paper, they employed oxetane in place of allyl bromide to trap the benzylic acetal anions, and they directly obtained dialkylated product **153** in one pot by sequential addition of *n*-butyllithium and *sec*-butyllithium. Construction of the type B skeleton was achieved via oxidation and Friedel–Crafts cyclization similarly to that described above to give a mixture of dimethoxy, monomethoxy, and desdimethyl de-

Scheme 26. Taylor's Synthesis of the Type B Skeleton (Reprinted with Permission from Ref 95. Copyright 2000 American Chemical Society)



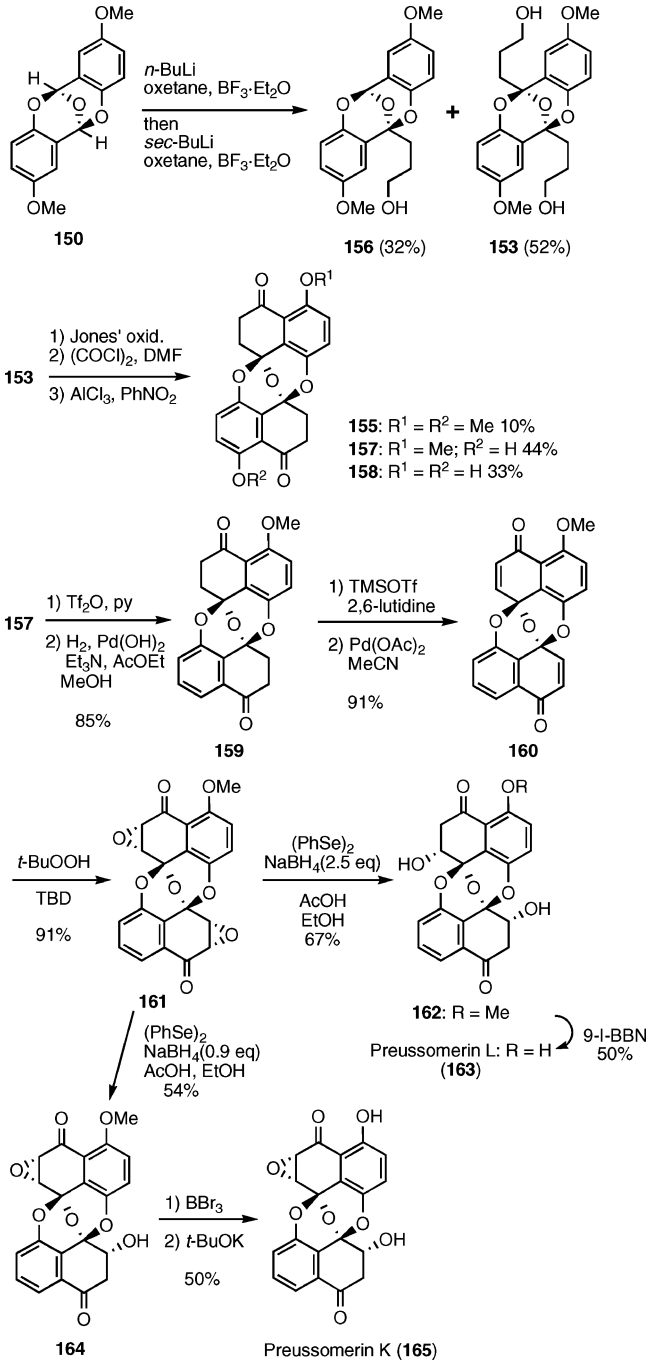
rivatives, **155**, **157**, and **158**. Employing monomethoxy derivative **157**, they removed the phenolic hydroxyl group by hydrogenolysis of the corresponding triflate employing $Pd(OH)_2$ in the presence of triethylamine, and they transformed it into bisepoxide **161** employing their epoxidation reaction.[97] Reduction of two epoxyketone moieties of **161** to β-hydroxyketones was achieved by an organoselenium-mediated procedure to afford preussomerin L (**163**).[72] In contrast, the epoxyketone having a *peri*-hydrogen, not a *peri*-methoxy group, was selectively reduced employing 0.9 equiv of $NaBH_4$ under the same conditions to give preussomerin K (**165**).

In their full article,[41] they have synthesized preussomerin F (**170**) as well as preussomerins K (**165**) and L (**163**) according to a similar procedure to that described above[96] (Scheme 28). In this case, they employed 5% Pd–C in place of $Pd(OH)_2$, and successfully reduced not only the phenolic triflate but also the benzylic ketone function of **157**. After protection of the benzylic hydroxyl group with the MOM group, the phenolic methoxy group of **167** was transformed into bismethoxymethoxy derivative **168**, which was dehydrogenated and epoxidized to afford **169**. Eventually, both methoxymethoxy groups of **169** were removed by acidic treatment to give preussomerin F (**170**). In this paper, they reported that it was important to change the phenolic methoxy group of **167** to a methoxymethoxy group to obtain preussomerin F (**170**). The epoxide moiety reportedly could not survive under demethylation conditions.

7.3. Barrett's Total Synthesis of Preussomerin G

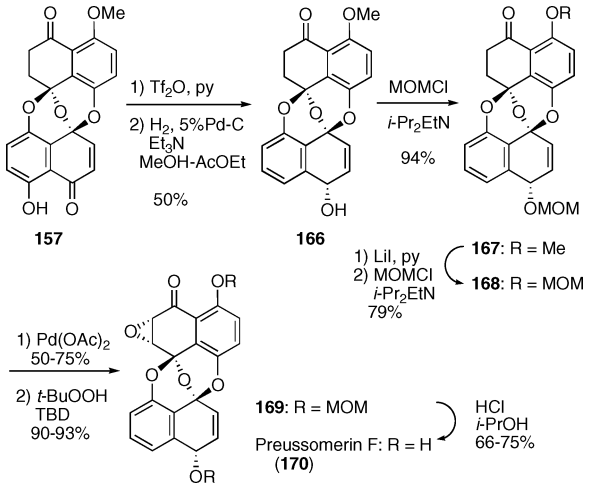
In 2002, Barrett and co-workers reported the first enantioselective total synthesis of this type of natural

Scheme 27. Taylor's Total Syntheses of (±)-Preussomerins K (165) and L (163) (Reprinted with Permission from Ref 96. Copyright 2004 Elsevier)

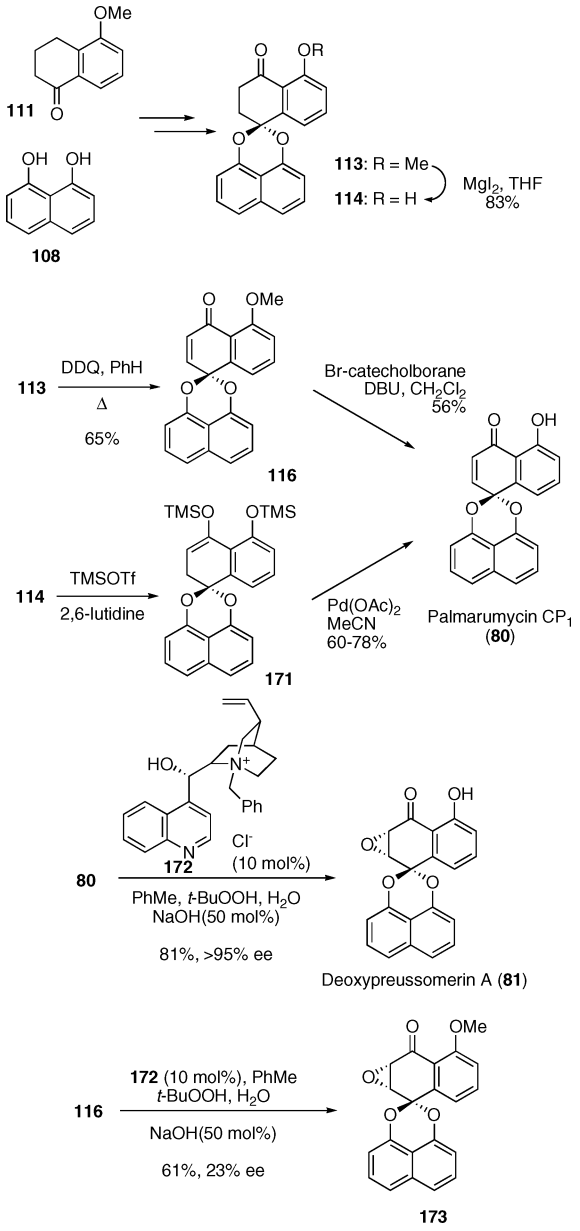


product, (−)-preussomerin G (**147**), employing a biomimetic route via (−)-deoxypreussomerin A (**81**).[98] At first, spiroacetal **113** was synthesized by direct acetalization of ketone **111** with 1,8-dihydroxynaphthalene (**108**), which they had already employed for the synthesis of type A natural products.[90] Although they have transformed **113** into palmarumycin CP_1 (**80**) via two routes, DDQ oxidation of **113** and Saegusa oxidation of **171**, the latter route was reportedly more effective, particularly in a large-scale reaction. Asymmetric epoxidation of **80** under chiral phase transfer conditions employing *N*-benzylcinchonium chloride (**172**) afforded (−)-deoxypreussomerin A (**81**) in good chemical and optical yields (Scheme 29). The

Scheme 28. Taylor's Total Synthesis of (±)-Preussomerin F (170) (Reprinted with Permission from Ref 41. Copyright 2004 The Royal Society of Chemistry)



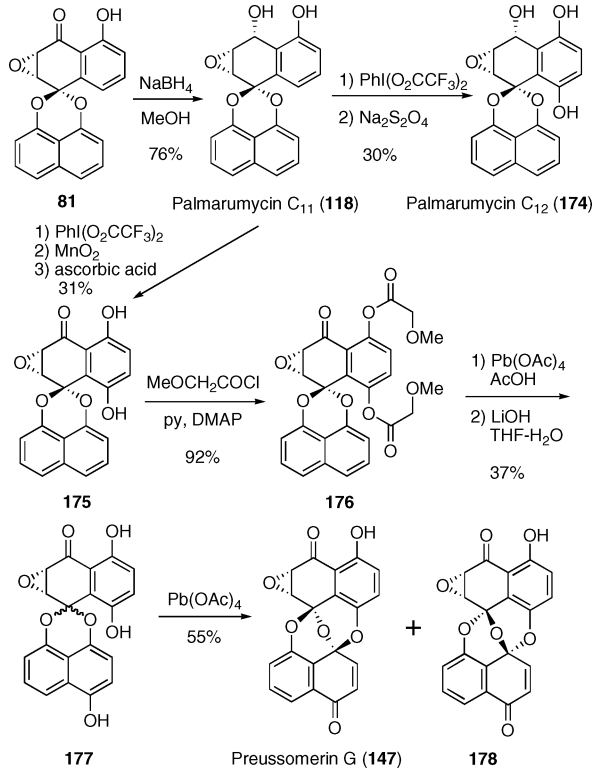
Scheme 29. Barrett's Synthesis of a Type A Intermediate (Reprinted with Permission from Ref 98. Copyright 2002 American Chemical Society)



absolute structure of **81** was determined by X-ray crystallographic analysis of the corresponding *N*-phenylsufonylproline ester. Interestingly, the same asymmetric epoxidation of the corresponding methyl ether **116** was reported to result in much slower and less efficient reaction, clearly indicating the important role of the phenolic hydroxyl group of **80** for the stereoselectivity. They calculated diastereomeric transition states composed of **80** and **172**, and they found that the transition state for **80** has a secondary interaction formed between the phenoxy-enone moiety and the positively charged ammonium residue of **172** and is consequently 3.9 kcal/mol more stable than that for a stereoisomer of **81**.

Synthesis of (−)-preussomerin G (**147**) was achieved as follows (Scheme 30). Compound **81** was reduced with $NaBH_4$ to give palmarumycin C_{11} (**118**), which was also derivatized to palmarumycin C_{12} (**174**) by oxidation. On the other hand, palmarumycin C_{11} (**118**) was transformed into hydroquinone **175**, which was then protected with a methoxyacetyl group. After oxidation of **176** with $Pb(OAc)_4$, the methoxyacetyl groups were removed and oxidized again with $Pb(OAc)_4$ to give (−)-preussomerin G (**147**) and (+)-epipreussomerin G (**178**) as a 1:1 diastereomeric mixture.

Scheme 30. Barrett's Total Synthesis of Preussomerin G (147) (Reprinted with Permission from Ref 98. Copyright 2002 American Chemical Society)



8. Syntheses of Epoxynaphthoquinone Natural Products Having a Type C Structure

In 2003, racemic spiroxin C (**179**) was synthesized by Imanishi's group, which is, to the best of our knowledge, the only successful example of the synthesis of this type of natural products.[99] Judging from the biosynthetic pathways of the natural products belonging to types A and B,[39] the binaphthyl bond is assumed to be formed after formation of the spiroketal structure in the biosynthesis of spiroxins as well. However, as each reaction center of the bisnaphthospiroketal molecule appears to be too far apart to form a binaphthyl bond from a molecular model, the binaphthyl structure was planned to be constructed before formation of the bisnaphthospiroketal structure in our synthesis. Thereby, the first crucial step is preparation of the binaphthyl structure of **181** bearing two *peri*-substituents, which was expected to have large steric hindrance, and the next step is construction of the basic skeleton of spiroxins having a ring strain as shown in Figure 14.

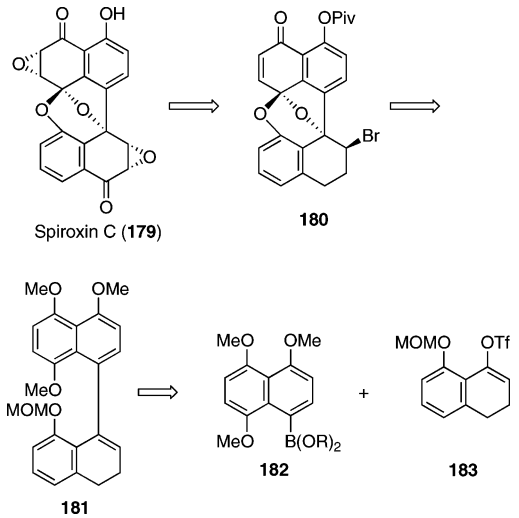
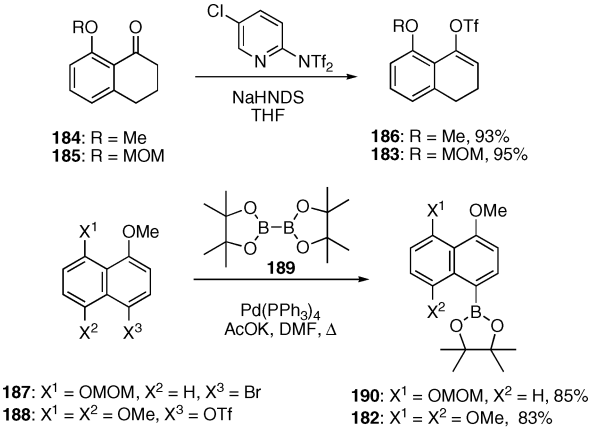


Figure 14. Imanishi's retrosynthesis of spiroxin C (**179**). (Reprinted with permission from ref 99. Copyright 2003 American Chemical Society.)

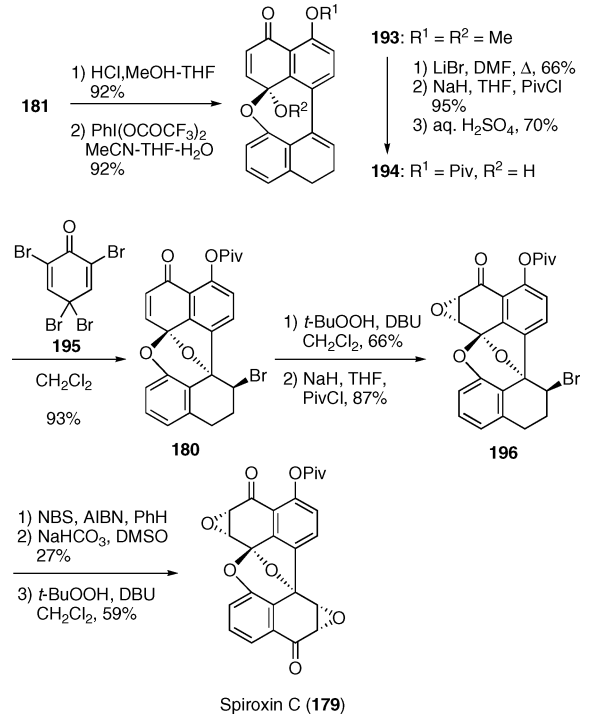
The first problem was overcome by a fluoride-assisted Suzuki−Miyaura coupling reaction as follows (Scheme 31). Enol triflates, **186** and **183**, were prepared according to conventional procedures,[100] while arylboranes, **190** and **182**, were prepared by Miyaura's method.[101] The coupling reaction of **186** with **190** was examined under usual conditions. However, nothing but homocoupling product **192** was unexpectedly obtained as an isolable product. As this result obviously suggested that arylborane **190** was inert and was not involved in the reaction, an activator for arylborane **190** was examined. After several attempts, n-Bu_4NF was found to be an effective additive to activate arylborane **190**, and the coupling product **191** was obtained in good yield. The coupling reaction between **182** and **183**, both of which have a *peri*-substituent, also took place smoothly under the same conditions to give **181** in good yield.

The next problem was construction of the basic skeleton of spiroxin C (**179**), which was resolved by an intramolecular bromoetherification reaction as follows (Scheme 32). Oxidation of the hydroquinone bismethyl ether moiety with a hypervalent iodine reagent and transformation of hydroxyl protecting groups afforded hemiacetal **194**. After several attempts, bromoetherification of **194** successfully took place by treatment with TBCO (**195**) as a Br^+ source to afford **180** having the basic skeleton of spiroxins. Compound **180** was transformed into spiroxin C (**179**)

Scheme 31. Imanishi's Synthesis of Binaphthyls Having *peri*-Substituents (Reprinted with Permission from Ref 99. Copyright 2003 American Chemical Society)



Scheme 32. Imanishi's Synthesis of (±)-Spiroxin C (179) (Reprinted with Permission from Ref 99. Copyright 2003 American Chemical Society)



via sequential procedures including epoxidation, benzylic oxidation, and epoxidation.

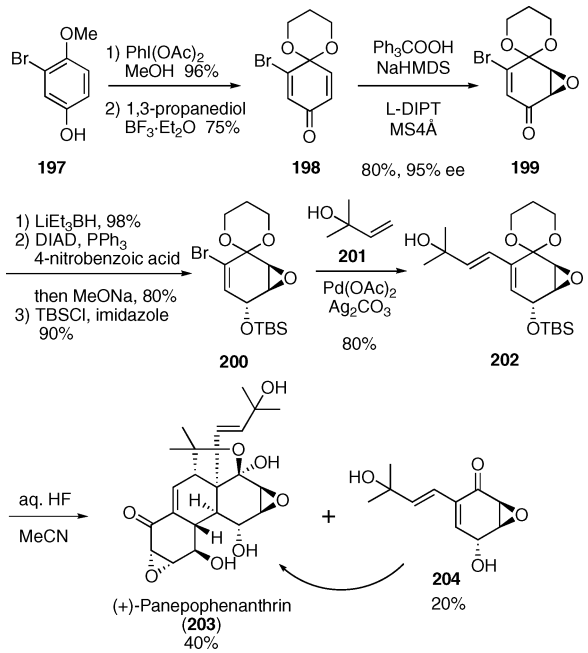
9. Syntheses of Panepophenanthrin

Because of its unique structure and interesting biological activity, namely inhibition of ubiquitine-activating enzyme, synthetic studies on the title compound have been extensively conducted since it was isolated in 2002.[50] Although three groups, Porco's, Baldwin's, and Mehta's groups, have achieved the total synthesis of this compound, a biomimetic approach which involves Diels–Alder type dimerization for construction of the basic skeleton was employed in every synthesis.

9.1. Porco's Total Synthesis of (+)-Panepophenanthrin

In 2003, Porco Jr. and co-workers reported the total synthesis of (+)-panepophenanthrin (**203**) (Scheme 33).[102] At first, they synthesized optically active

Scheme 33. Porco's Total Synthesis of (+)-Panepophenanthrin (203) (Reprinted with Permission from Ref 102. Copyright 2003 Wiley-VCH Verlag)



epoxide **199** from bromophenol **197** employing tartrate-mediated nucleophilic epoxidation as a key step, and they coupled *iso*-pentenyl side chain **201** under Heck-type reaction conditions. They had expected that tandem deprotection/Diels–Alder dimerization could proceed from **202** to give panepophenanthrin (**203**). As expected, deprotection of **202** by treatment with aqueous HF was reported to induce Diels–Alder dimerization, affording panepophenanthrin (**203**) and epoxyquinone **204**. It was also reported that epoxyquinone **204** spontaneously dimerized on standing at 25 °C without solvent to give panepophenanthrin (**203**). It is an interesting point which reaction, Diels–Alder reaction or hemiacetal formation, is the first step (Figure 15). They studied the timing of Diels–Alder dimerization and hemiacetal formation

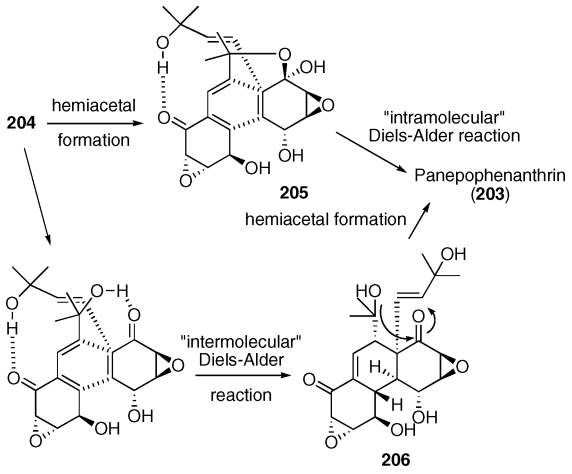


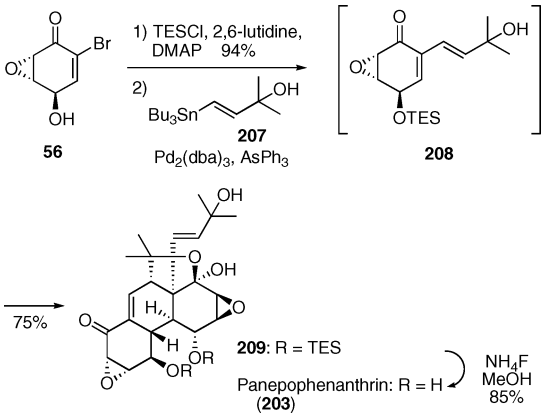
Figure 15. Possible routes from **204** to panepophenanthrin (**203**). (Reprinted with permission from ref 102. Copyright 2003 Wiley-VCH Verlag.)

by means of computational chemistry, which showed that the route involving intermolecular cycloaddition and subsequent hemiacetal formation is about 15 kcal/mol more favorable.

9.2. Baldwin's Total Synthesis of (±)-Panepophenanthrin

In the same year, 2003, Baldwin and co-workers successfully synthesized (±)-panepophenanthrin (**203**) via a similar biomimetic route as shown in Scheme 34.[103] Starting from (±)-bromoxone (**56**), they coupled an *iso*-pentenyl unit **207** under Stille coupling reaction conditions, which induced spontaneous Diels–Alder dimerization of **208** to give (±)-panepophenanthrin (**203**).

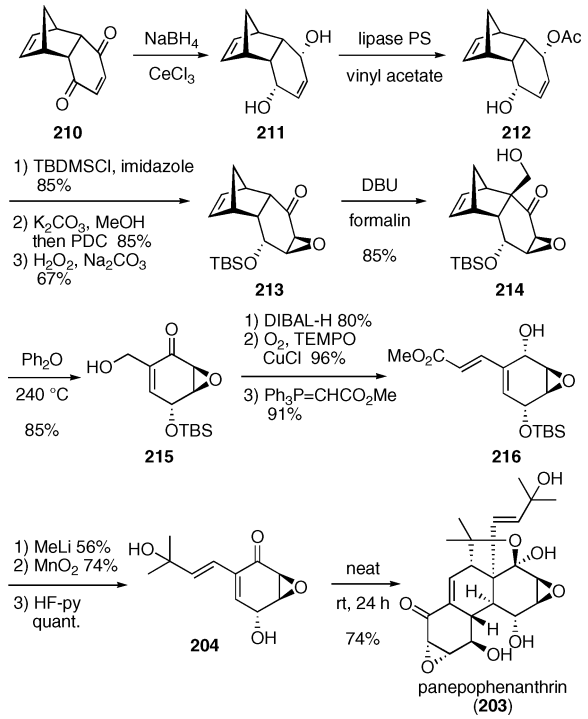
Scheme 34. Baldwin's Total Synthesis of (±)-Panepophenanthrin (203) (Reprinted with Permission from Ref 103. Copyright 2003 American Chemical Society)



9.3. Mehta's Total Synthesis of (+)-Panepophenanthrin

In 2004, Mehta's group also reported the total synthesis of (+)-panepophenanthrin (**203**) (Scheme 35).[104,105] They synthesized optically active epoxyketone **215** employing lipase-mediated desymmetrization of *meso*-diol **211** as a key reaction. In their synthesis, the *iso*-pentenyl side chain was constructed by Wittig reaction and methyllithium addition. Spontaneous Diels–Alder dimerization of **204** proceeded to give (+)-panepophenanthrin (**203**).

Scheme 35. Mehta's Total Synthesis of (+)-Panepophenanthrin (203) (Reprinted with Permission from Ref 104. Copyright 2004 Elsevier)



10. Acknowledgment

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