Biosynthetic and Biomimetic Electrocyclizations

Christopher M. Beaudry, Jeremiah P. Malerich, and Dirk Trauner*

Department of Chemistry, University of California, Berkeley, Berkeley, California 94720-1460

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1. Introduction

Pericyclic reactions have long been considered a biosynthetic rarity. In contrast to their prominence in the laboratory, they seemed to play only minor roles in Nature. Over the past decades, however, enough examples have been amassed to demonstrate that pericyclic reactions occur quite frequently in biosynthetic pathways.

Pericyclic reactions include cycloadditions, sigmatropic rearrangements, and electrocyclizations. Biosynthetic cycloadditions have been recently featured in a comprehensive review by Williams.[1] The aim of the present article is to provide a counterpart highlighting electrocyclic reactions that have been found or suspected in the biosynthesis of natural products. In many cases, these biosynthetic considerations have inspired biomimetic syntheses, whose success in turn validates the proposal. We consider reactions as biosynthetic if they occur in a given organism or in its immediate environment. This definition includes reactions that occur spontaneously and do not require enzyme catalysis, which are very common among electrocyclizations.

Biosynthetic and biomimetic electrocyclizations have never been systematically reviewed. Since numerous examples have recently surfaced in the literature, we feel that the time has come to make such an attempt. For the sake of simplicity, we use the term "electrocyclizations" both for the forward reaction and electrocyclic ring openings.

This review is organized primarily along the number of electrons involved in a given π system that undergoes the electrocyclic reaction. Following electrocyclizations of 4π systems, electrocyclic reactions involving 6 and 8 π-electrons are discussed. Thermal and photochemical reactions are presented in that order. Systems including heteroatoms (usually oxygen but occasionally nitrogen), which are confined to 6 π-electrons, are presented separately. Finally, the question of whether biosynthetic electrocyclizations require enzyme catalysis is briefly addressed.

One of the most attractive features of biomimetic electrocyclizations is that they often participate in pericyclic reaction cascades.[2] In combination with cycloadditions, for instance, they are able to rapidly generate molecular complexity and diversity, an aspect that is given ample attention in this review. If the cascade involves several electrocyclizations, priority is given to the highest number of π-electrons. In some cases, the occurrence of electrocyclic reactions or reaction cascades in biosynthetic pathways is quite speculative. Nevertheless, these cases have been included provided they have inspired biomimetic syntheses.[2]

By contrast, total syntheses featuring electrocyclic reactions that have not been proposed or are unlikely to be biomimetic are generally not covered in this review. This means that many elegant synthetic applications of electrocyclizations, such as Woodward's celebrated porphyrin to chlorin conversion used in the synthesis of chlorophyll, will not be discussed.[3] The theory of electrocyclizations will not be recapitulated here either. The reader is referred to a series of reviews that have appeared on this subject.[4] As a reminder, the stereochemical course of electrocyclizations in the ground state and excited state is summarized below:

	thermal	photochemical
4π	conrotatory	disrotatory
6π	disrotatory	conrotatory
8π	conrotatory	disrotatory

Although this review aims to be comprehensive, it is possible that we have missed some examples of biosynthetic and biomimetic electrocyclizations. Due to the somewhat murky definition of "biomimetic" and the vast range of natural products covered, judgments have been occasionally unavoidable, especially in the oxa-6π section. Furthermore, not all material presented is discussed in equal depth. The emphasis of this review lies on biosynthetic and biomimetic pathways that have been published within

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Christopher Beaudry grew up near Milwaukee, WI. He received his B.S. in chemistry from the University of Wisconsin, Madison, in 2000. Subsequently, he began graduate research in the Trauner group at the University of California, Berkeley, earning his Ph.D. in 2005. Early in 2006 he will begin postdoctoral research under the direction of Prof. Larry Overman. His research interests include the synthesis of biologically active natural products.

Jeremiah Malerich was born and raised in northern New Jersey. He attended the University of Notre Dame and earned his B.S. in 2001. That year, he began his doctoral studies at the University of California, Berkeley, in the Trauner group. His graduate work has focused on the biomimetic synthesis of natural products.

Dirk Trauner was born and grew up in Linz, Austria. After studying biology and then biochemistry at the University of Vienna, he joined the research group of Professor Johann Mulzer. Having completed a formal total synthesis of (−)-morphine, he received his Ph.D. in 1997 from the University of Vienna. From 1998 to 2000, he was a postdoctoral fellow with Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center. During his New York years, he developed a total synthesis of (+)-halichlorine, a potent inhibitor of a cell adhesion molecule. Dirk is currently an assistant professor of chemistry at the University of California, Berkeley. His research interests range from synthetic methodology and natural products to molecular machines, ion channels, and neurons.

the past decade. By contrast, classic examples of electrocyclic reactions in biosynthesis, such as the endiandric acid or the vitamin D cascades, which have been covered in numerous reviews, will be treated relatively briefly here.

2. All-Carbon Systems

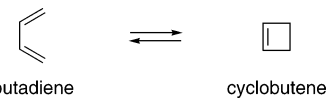
2.1. 4π Systems

Electrocyclizations of butadienes afford cyclobutenes (Scheme 1). Due to the highly strained nature of their products, these reactions are usually thermodynamically unfavorable. Accordingly, cyclobutenes will readily revert to butadienes unless constrained in polycyclic frameworks.

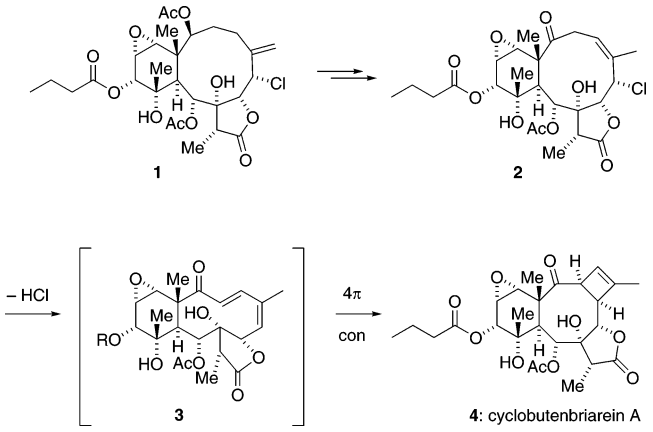
Examples of 4π electrocyclic reactions in the biosynthesis of natural products are relatively rare. In fact, the majority of the cyclobutenes found in Nature do not seem to be formed through electrocyclizations.

The recently described cyclobutenbriarein A (**4**), which was found along with unnamed natural product **1** in the gorgonian coral *Briareum asbestinum*,

Scheme 1



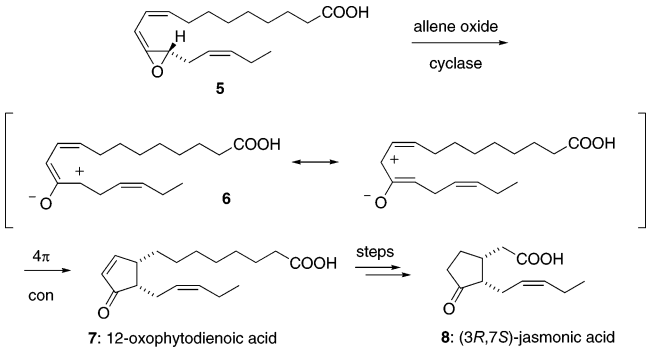
Scheme 2. Biosynthetic Origin of Cyclobutenbriarein A



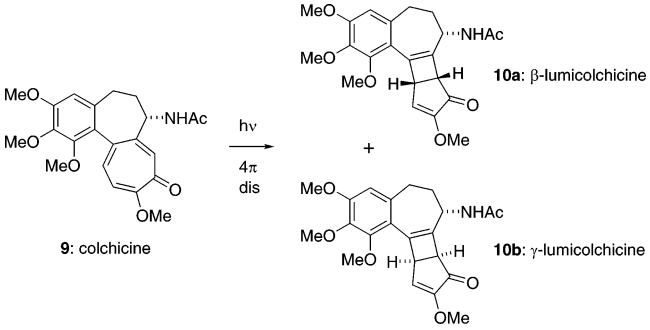
could be an exception (Scheme 2).[5] Biosynthetically, **4** possibly stems from **1**, via saponification, oxidation, and double bond isomerization to afford **2**. Subsequent elimination of hydrogen chloride then gives (*Z*,*E*)-cyclodecadiene **3**, whose conrotatory 4π electrocyclization yields cyclobutenbriarein A (**4**). In the isolation paper, however, Jiménez suggested an S_N2-type displacement of the secondary chloride in **2** to account for the formation of the cyclobutene.

Nazarov reactions, which involve conrotatory 4π electrocyclizations of pentadienyl cations,[6] have been proposed to occur biosynthetically. A reaction of this type has been invoked in the biosynthesis of jasmonic acid **8** (Scheme 3).[7] This compound has been shown to stem from the chiral allene epoxide **5**, which in itself is derived from α-linoleic acid. It was proposed that heterolytic cleavage of the epoxide ring, medi-

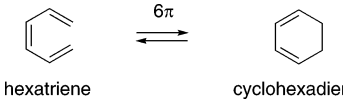
Scheme 3. Proposed Nazarov Cyclizations in Biosynthesis



Scheme 4. Formation of Lumicolchicines



Scheme 5



ated by the enzyme allene oxide cyclase, would afford the oxido pentadienyl cation **6**, whose conrotatory 4π electrocyclization directly affords the *cis*-disubstituted cyclopentenone 12-oxophytodienoic acid (**7**). Note that a proton-transfer step is not required in this mechanism, as opposed to the classical Nazarov reaction. Oxidative degradation and reduction of **7** then gives (3*R*,7*S*)-jasmonic acid (**8**). A similar biosynthetic pathway has been proposed to occur in the biosynthesis of certain racemic marine prostaglandins. A biomimetic approach toward allene oxides and cyclopentenones has been reported by Corey.[8]

Irradiation of colchicine (**9**) affords β- and γ-lumicolchicine (**10a**,**b**) via disrotatory 4π electrocyclization involving the tropolone ring (Scheme 4).[9] Lumicolchicines have been isolated from the leaves and bulbs of numerous *Colchicum* species.

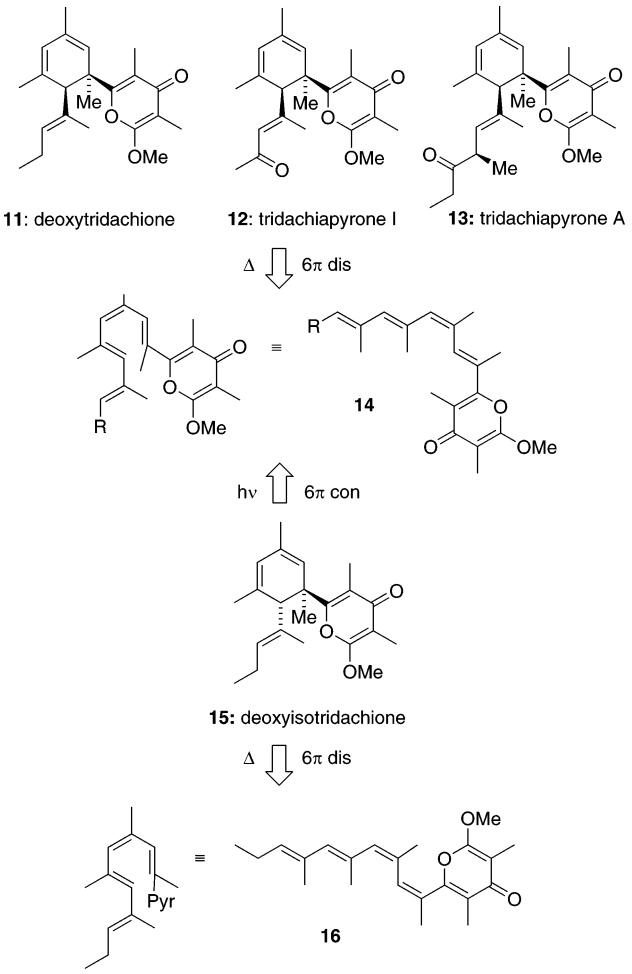
2.2. 6π Systems

Electrocyclizations of hexatrienes afford cyclohexadienes (Scheme 5). Typically, these reactions require relatively high temperatures to occur. Thermodynamically, they are driven by the formation of a σ-bond at the expense of a π-bond, a feature they share with all electrocyclizations.

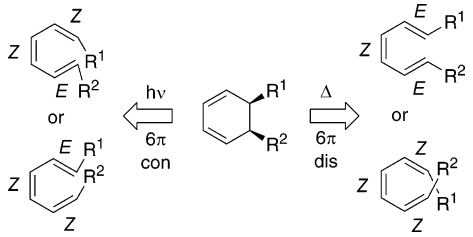
Natural products displaying the cyclohexadiene motif are quite common. In some cases, an electrocyclic origin from a triene can be suspected and has been corroborated by biomimetic synthesis.

Certain saccoglossan molluscs produce polyketides whose biosynthesis presumably entails a 6π electro-

Scheme 6. Cyclohexadienes Isolated from Saccoglossan Molluscs



Scheme 7. The Electrocyclization Manifold

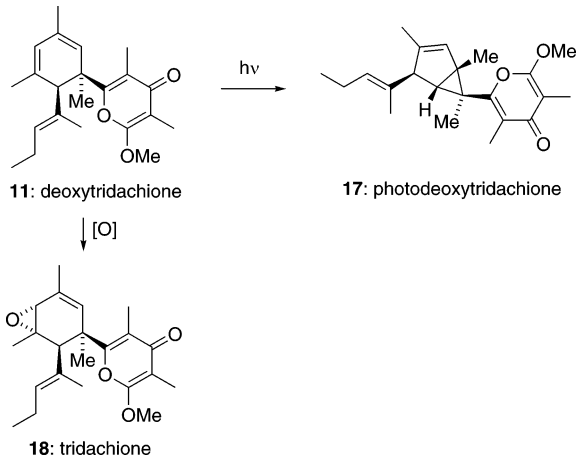


cyclization (Scheme 6). Retrosynthetically, the cyclohexadienes deoxytridachione (**11**),[10] tridachiapyrone I (**12**),[11] and tridachiapyrone A (**13**)[12] can be readily traced to tetraenes of type **14** via thermal 6π electrocyclic ring opening. Deoxyisotridachione (**15**)[13] could be formed from **14** (with R = Me) through photochemical, conrotatory electrocyclization or from isomeric tetraene **16** by way of a thermal reaction.

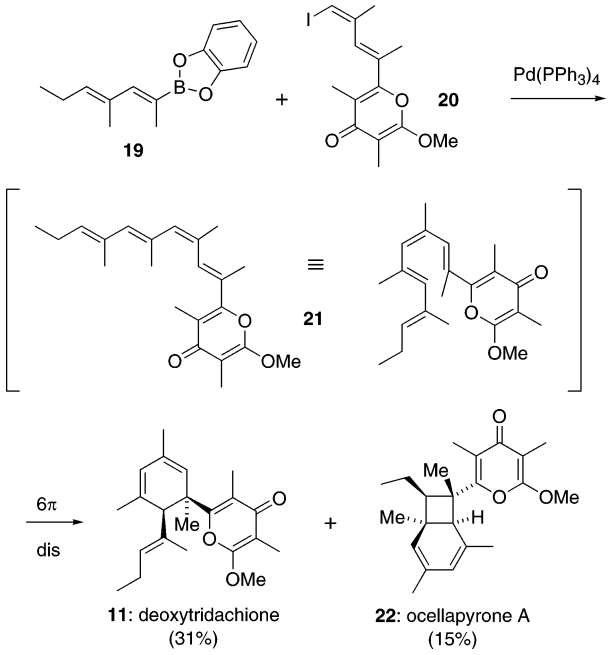
Generally, a simple unsymmetrical cyclohexadiene can be traced to four different geometrical triene isomers, depending on the conditions (thermal vs photochemical) and the torquoselectivity of the ring opening (Scheme 7). Similar concerns apply to unsymmetrical cyclobutenes, cyclooctatrienes, and even (2*H*)-pyrans. To simplify the discussion, not all of these possibilities are considered here.

The cyclohexadiene moiety of the molluscan natural products is occasionally masked by further trans-

Scheme 8. Transformations of Deoxytridachione



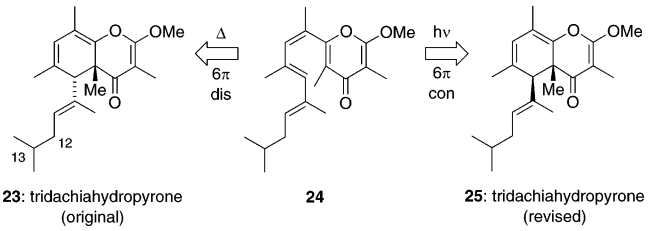
Scheme 9. Baldwin's Synthesis of Deoxytridachione



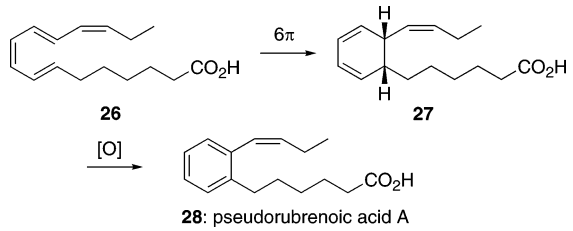
formations (Scheme 8). Biosynthetic studies by Ireland and Scheuer have shown that deoxytridachione (**11**) can be converted in vitro and in vivo into the isomeric photodeoxytridachione **(17**) by exposure to light.[10] This reaction was proposed to proceed through a photochemical [$_{\sigma}2_a + {}_{\pi}2_a$] rearrangement, but it could also occur through a biradical triplet mechanism.[14] Epoxidation of **11** gives tridachione (**18**),[15] the parent of the series.

Baldwin[16] and Trauner[17] independently reported biomimetic syntheses of deoxytridachione (**11**). In both cases, a convergent cross-coupling-electrocyclization strategy was chosen to assemble the polyene precursor **21** (Scheme 9). In Baldwin's synthesis, Suzuki coupling of vinyl boronate **19** with vinyl iodide **20** gave **21**. Upon heating in benzene solution, **21** underwent 6π electrocyclization to afford **11**. This intended target was accompanied by varying amounts of bicyclo[4.2.0]octadiene **22**, which was later isolated as a natural product. The formation of this compound, named ocellapyrone A, is further discussed in the 8π electrocyclization section (see below).

Scheme 10. Biosynthetic Origin of Tridachiahydropyrone



Scheme 11. Proposed Biosynthesis of Pseudorubrenoic Acid A



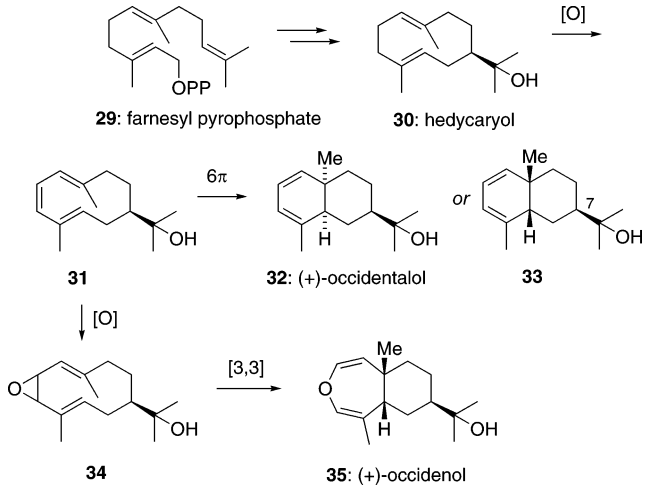
Tridachiahydropyrone is a unique member of the tridachiapyrone family (Scheme 10).[11] Unlike its congener tridachiapyrone A (**13**), tridachiahydropyrone has a rearranged polypropionate skeleton with the C-12 methyl group shifted to C-13. Moreover, tridachiahydropyrone apparently results from 6π electrocyclization of a linear polyene with participation of the γ-pyrone moiety. To date, no biomimetic studies have been reported. However, a total synthesis effort has cast doubt on the originally proposed structure **23** and suggested **25** as the true structure of tridachiahydropyrone.[18] This compound could stem from **24** via photochemical, conrotatory 6π electrocyclization or from a geometrical isomer of **24**.

Pseudorubrenoic acid A (**28**) is an antimicrobial carboxylic acid isolated from the soil bacterium *Pseudomonas fluorescens*. Due to the lack of oxygen functionality, Rickards postulated that this compound is constructed by a pathway distinct from the common biosynthesis of aromatic polyketides.[19] Instead, pseudorubrenoic acid could arise from tetraene **26** (Scheme 11). Disrotatory 6π electrocyclization would give cyclohexadiene **27**, whose oxidation affords the natural product. This biosynthetic proposal was supported by synthetic studies.

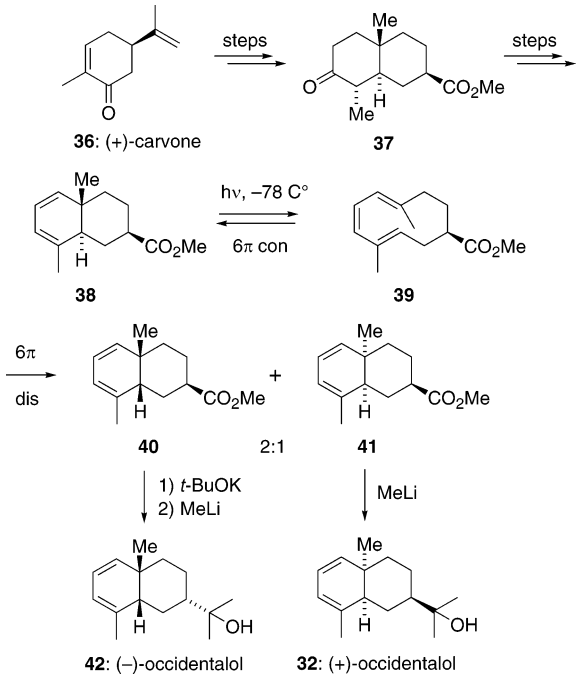
A range of bi- and tricyclic sesqui- and diterpenes have been proposed to arise via 6π electrocyclizations. The eudesmane-type sesquiterpene (+)-occidentalol (**32**) was isolated from the wood of *Thuja occidentalis*,[20] but its exact structure remained in question until verified by Hortmann's biomimetic total synthesis (see below).

The proposed biosynthesis starts with enzymatic cyclization of farnesol pyrophosphate (**29**) to afford hedycaryol (**30**) (Scheme 12).[21] Dehydrogenation of this natural product would afford (*E*,*Z*,*E*)-cyclodecatriene **31**, whose disrotatory 6π electrocyclization yields **32**. Although predicted by Hortmann, the possible diastereomer of this cyclization, 7-*epi*-occidentalol (**33**), was never isolated from natural sources. Triene **31** also plays a role in the hypothetical biosynthesis of (+)-occidenol (**35**), which was found along with **32**.[22] Selective epoxidation of this material

Scheme 12. Biosynthesis of Occidentalol and Occidenol



Scheme 13. Hortmann's Synthesis of (+)- and (−)-Occidentalol



would provide divinyl epoxide **34**, which undergoes a [3,3]-sigmatropic rearrangement to generate the dihydrooxepine moiety of **35**.

Following the above proposal, Hortmann accomplished a biomimetic synthesis of both enantiomers of occidentalol (Scheme 13).[22] In an elegant strategy, a sequence of electrocyclic reactions was exploited to access *cis*-decalin structures from the corresponding *trans*-compounds. To this end, enantiomerically pure *trans*-decalin **37** was prepared from (+)-carvone (**36**) in several steps. This material was further elaborated to bicyclic diene **38**. When irradiated with UV light at −78 °C, the *trans*-fused decalin **38** underwent conrotatory 6π electrocyclic ring opening to give a 1:2 mixture of **38** and triene **39** at the photostationary state. After raising the temperature to −20 °C, disrotatory 6π electrocyclization of **39** proceeded to give a 2:1 mixture of diastereomers **40** and **41**. Treatment of ester **41** with methyllithium gave (+)-occidentalol (**32**). The diastereomer **40** was converted to (−)-occidentalol (**42**) by equilibration under basic conditions followed by conversion of the ester functionality to the tertiary alcohol.

Scheme 14. Biosynthesis of Dictyolene and Dictyoxepin

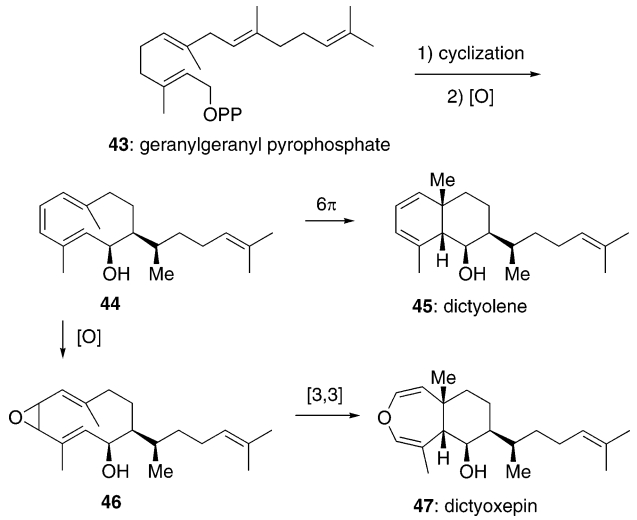
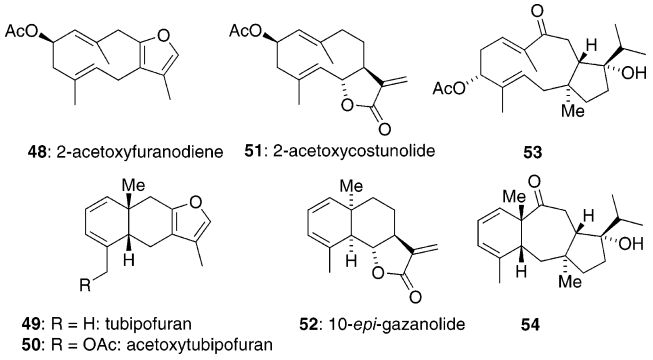


Chart 1. Pairwise Occurrence of Cyclohexadiene Terpenoids and Their 1,5-Diene Congeners

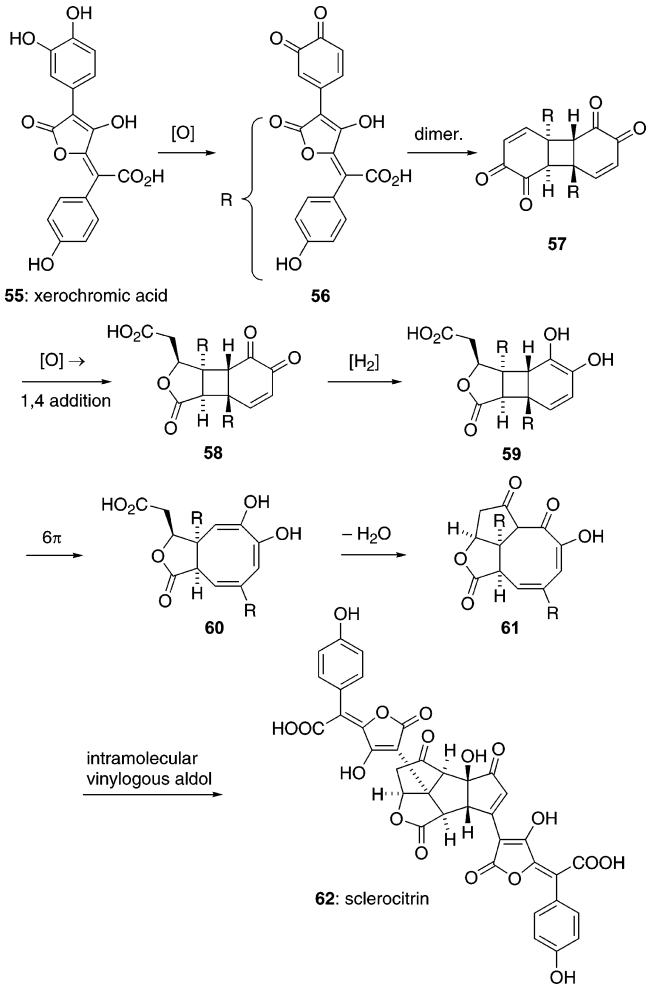


The diterpenes dictyolene (**45**) and dictyoxepin (**47**), obtained from the extracts of the brown algae *Dictyota acutiloba*, bear a similar structural relationship to the sesquiterpenes **32** and **35** (cf. Scheme 12).[23] Consequently, an analogous biosynthesis was proposed (Scheme 14). Cyclization and oxidation of geranylgeranyl pyrophosphate (**43**) would lead to the hypothetical germacryl intermediate **44**. Disrotatory 6π electrocyclization then affords dictyolene (**45**). Alternatively, epoxidation of **44** is followed by a [3,3]-sigmatropic rearrangement, releasing the ring strain of the epoxide **46**, to give dictyoxepin (**47**).

Analogous oxidations of terpenoid 1,5-dienes, followed by electrocyclizations, can be suspected in the biosynthesis of several other cyclohexadienes (Chart 1). For instance, 2-acetoxyfuranodiene (**48**)[24] is clearly related to tubipofuran (**49**) and acetoxytubipofuran (**50**),[25] whereas 2-acetoxycostunolide (**51**) relates to 10-*epi*-gazanolide (**52**).[26] The dolabelldienone **53** corresponds to the tricyclic diterpene **54**.[27] In all three cases, elimination of acetic acid would establish the triene system, whose 6π electrocyclization affords the cyclohexadiene natural products.

Steglich proposed a thermal 6π electrocyclic ring opening in the biosynthesis of the complex pigment

Scheme 15. Steglich's Proposed Biosynthesis of Sclerocitrin



sclerocitrin (**62**) (Scheme 15).[28] This intriguing compound was isolated in large quantities from the fungus *Scleroderma citrinum* (the common earthball). It is clearly a dimer of xerochromic acid (**55**), also present in the fungal extracts. Biosynthetic oxidation of **55** to *ortho*-quinone **56**, followed by a formal [2 + 2] dimerization, which presumably proceeds in a stepwise fashion, would afford compound **57**. Oxidative cleavage of one of the 1,2-dione moieties and intramolecular conjugate addition of the resultant carboxylate then gives γ-lactone **58**. The remaining 1,2-dione is reduced to enediol **59**. This compound then undergoes disrotatory 6π electrocyclic ring opening, releasing the ring strain of the central cyclobutane, to yield **60**. Dieckmann-type condensation (**60** → **61**), followed by intramolecular vinylogous aldol addition, completes the biosynthesis of sclerocitrin (**62**).

The biosynthesis of natural products featuring oxepine moieties presumably proceeds through thermal 6π electrocyclic ring opening of arene oxides (Scheme 16).[29] These reactive intermediates can also rearrange to afford phenolic compounds in a process known as "NIH shift". Note that naturally occurring dihydrooxepines can stem from transformations of oxepins (see below) or from epoxidation of a triene, followed by [3,3]-sigmatropic rearrangement (cf. Scheme 12).

Scheme 16. Formation of Oxepines through Electrocyclic Ring Opening

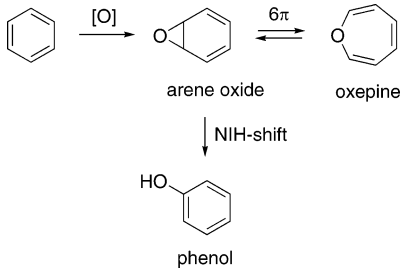
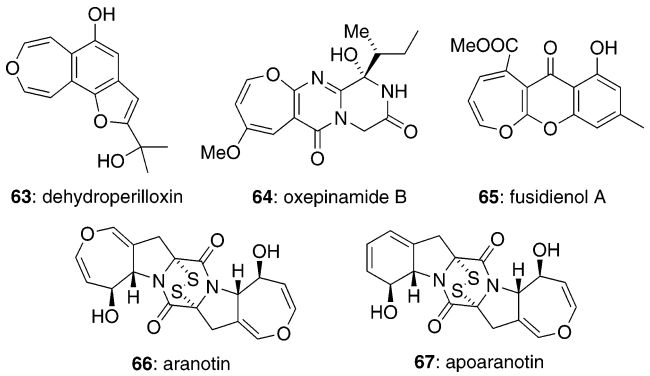
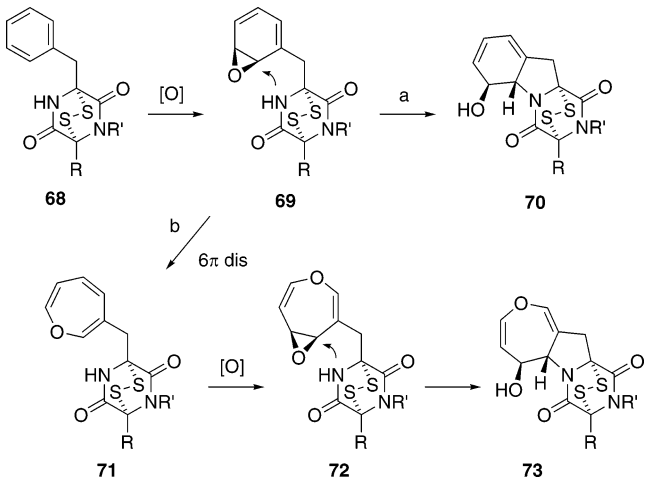


Chart 2. Naturally Occurring Oxepine and Dihydrooxepine Derivatives



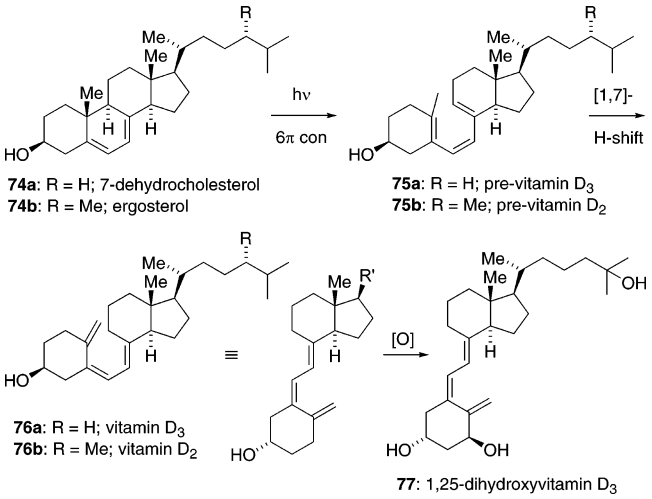
Scheme 17. Proposed Biosynthesis of Aranotin and Related Molecules



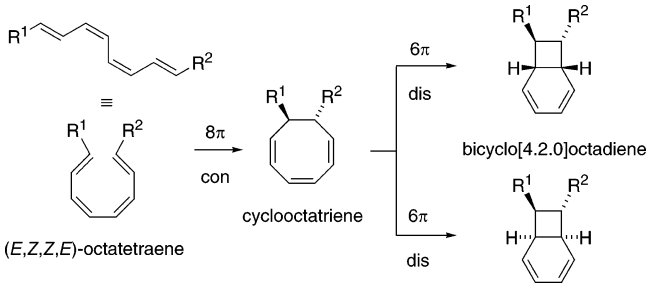
A sample of natural products featuring the oxepine motif, which have been proposed to stem from arene oxides, is shown in Chart 2. Aranotin (**66**)[30] and its congener apoaranotin (**67**),[31] as well as oxepinamide B (**64**)[32] and fusidienol A (**65**),[33] have been isolated from fungi (*Arachniotus aureus*, *Acremonium sp.,* and *Fusidium griseum*, respectively), whereas dehydroperilloxin (**63**)[34] is plant-derived (from *Perilla frutescens*, the wild basil).

Neuss proposed a biogenesis of the aranotins from phenylalanine-derived diketopiperazine **68** (Scheme 17).[31] Enzymatic epoxidation of **68** would give arene oxide **69**. Intramolecular nucleophilic attack by the proximal nitrogen then affords indolyl ring structure **70** (path a). Alternatively, 6π electrocyclic ring opening of **69** produces oxepine **71** (path b). A second epoxidation yields **72**, which cyclizes to generate the ring system **73** found in both **66** and **67**.

Scheme 18. Biosynthesis of the D-Vitamins



Scheme 19. 8π Electrocyclizations and the 8π−6π Cascade



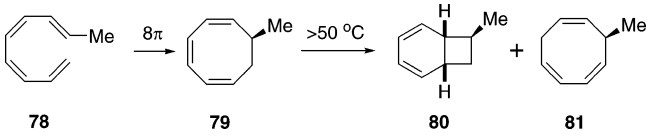
The biosyntheses of vitamin D_3 (**76a**) and vitamin D_2 (**76b**) are arguably the best-known examples of electrocyclic reactions in Nature (Scheme 18). The transformations of 7-dehydrocholesterol (**74a**) and ergosterol (**74b**) into vitamin D_3 (**76a**) and vitamin D_2 (**76b**), respectively, have been extensively reviewed, and they are therefore only briefly summarized here.[35] Photochemical conrotatory ring opening of **74a** leads to pre-vitamin D_3 (**75a**). A [1,7]-hydrogen shift then gives vitamin D_3 (**76a**). Vitamin D_2 (**76b**) is generated analogously in plants from ergosterol (**74b**). Oxidation of vitamin D_3 (**76a**) in the liver and kidney provides the active form of vitamin D, 1,25-dihydroxyvitamin D_3 (**77**).

2.3. 8π Systems

Octatetraenes undergo 8π electrocyclizations to afford cyclooctatrienes. These reactions normally have low activation barriers and occur at room temperature or below. In many cases, the 8π step is followed by a 6π electrocyclization of the resulting cyclooctatriene, which overall leads to bicyclo[4.2.0]-octadiene systems (Scheme 19).[36] Note that, unless the tetraene is symmetrical ($R^1 = R^2$), two diastereomers can be formed in the 6π step.

Accordingly, simple cyclooctatrienes are practically unknown as natural products. The only genuine example appears to be 7-methylcycloocta-1,3,5-triene (**79**), which is present at trace levels in the hydrocarbon blend from the brown algae *Cutleria multifida* (Scheme 20).[37] Boland concluded that this compound arises from the 8π electrocyclization of (1*Z*,5*Z*,7*E*)-

Scheme 20. Biosynthetic Origin and Transformations of 7-Methylcyclooctatriene



nonatetraene (**78**) and confirmed this proposal by total synthesis. The half-life of **78** was found to be on the order of minutes at room temperature. Interestingly, synthetic **79** does not readily undergo 6π electrocyclization at room temperature to afford a bicyclo[4.2.0]octadiene. However, if heated above 50 °C, **79** isomerizes to **80** and **81**, the products of disrotatory 6π electrocyclization and [1,5]-hydrogen shift, respectively. Both compounds were subsequently found in natural sources.[38]

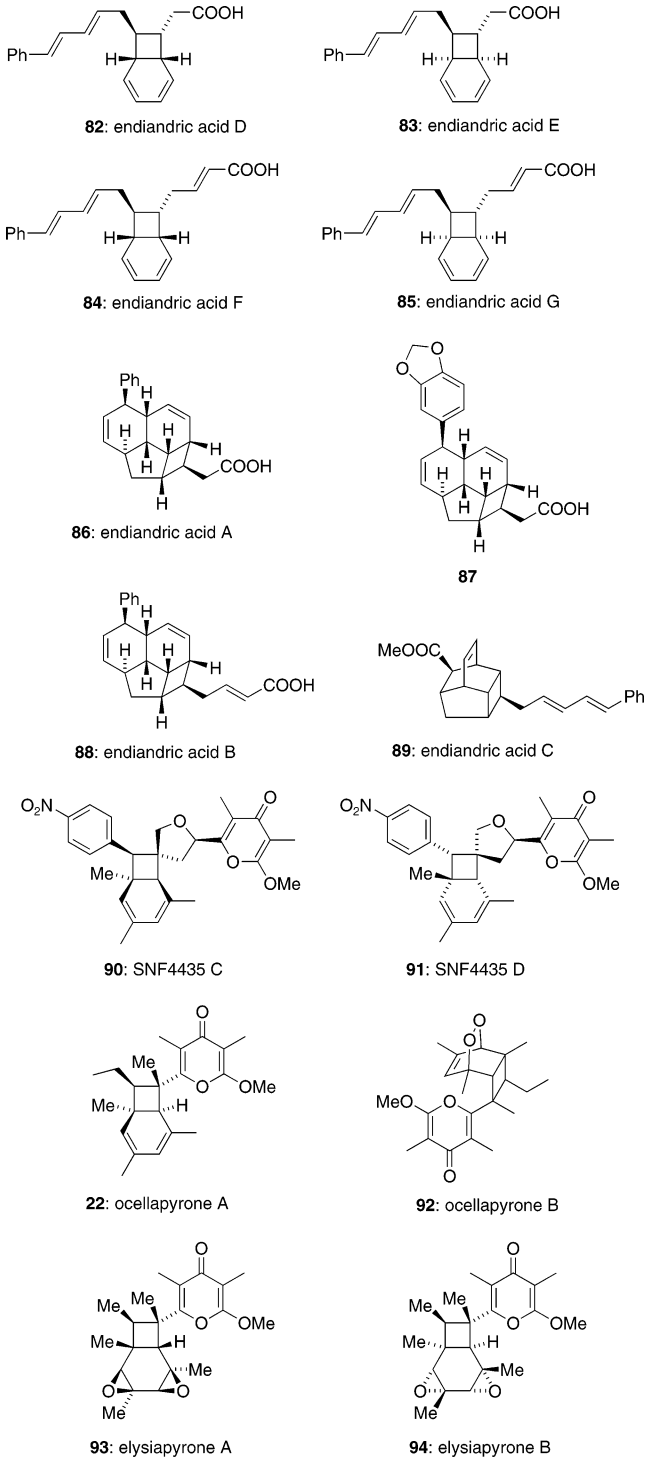
Until recently, natural products containing, or derived from, the bicyclo[4.2.0]octadiene skeleton were quite rare, with the notable exception of the endiandric acids. Within the last few years, however, the collection of natural products whose biosynthesis involves an 8π−6π electrocyclization cascade has grown considerably (Chart 3).

In the early 1980s Black disclosed the structures of endiandric acids A−C and E−G (**83**−**86**, **88**−**89**), isolated from leaves of the Australian laurel *Endiandra introrsa*.[39] Subsequently, methylenedioxy endiandric acid A (**87**) was reported.[40] Remarkably, the endiandric acids, which feature up to eight stereocenters, were isolated as racemates. To explain this observation, Black proposed that the endiandric acids E−G are formed spontaneously, i.e., without the assistance of enzymes, from achiral precursors through 8π−6π electrocyclization cascades. Additional Diels−Alder reactions would then lead to the more complex members of the family, e.g. endiandric acids A, B, and C.

The feasibility of biomimetic 8π−6π electrocyclization cascades was first demonstrated by Nicolaou (Schemes 21 and 22) with a series of biomimetic syntheses of the endiandric acids.[41] In the course of these elegant experiments, the "missing" endiandric acid D (**82**), which had not been found in Nature, was established as a legitimate member of the family.

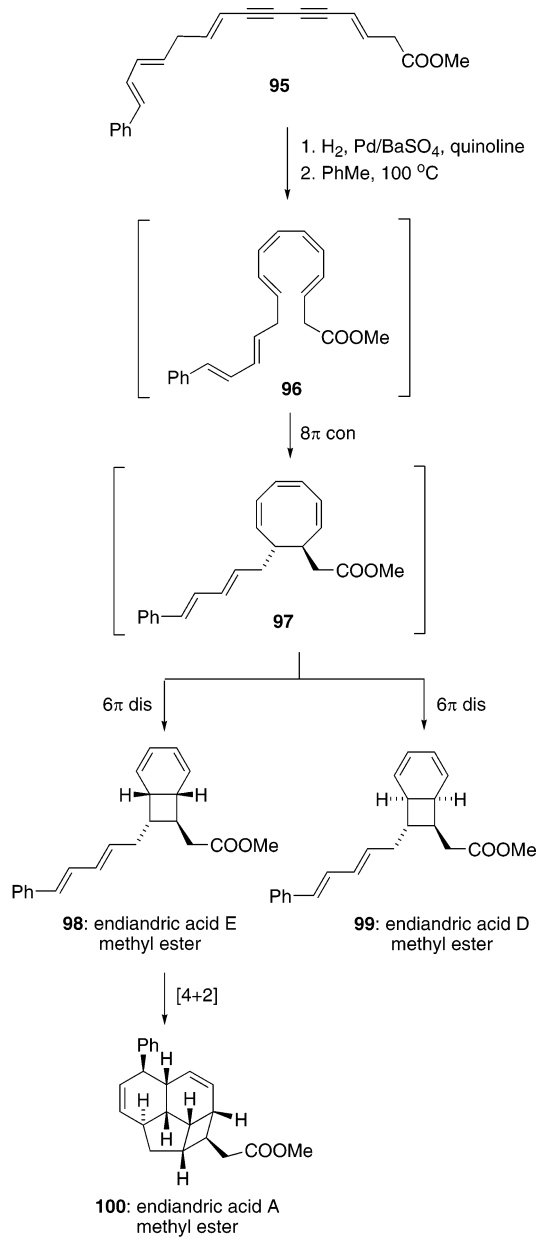
In Nicolaou's study aimed at endiandric acids A, D, and E, diene diyne **95** was quickly assembled through alkyne cross-coupling and olefination chemistry. Twofold Lindlar hydrogenation gave octatetraene **96**, which underwent spontaneous 8π conrotatory electrocyclization to form cyclooctatriene **97** as a racemate. This compound could not be isolated, since it underwent subsequent 6π disrotatory electrocyclization to give endiandric esters D (**99**) and E (**98**). Heating **98** to 100 °C in toluene resulted in intramolecular Diels−Alder reaction yielding endiandric ester A (**100**). Note that **99** cannot undergo such a cycloaddition but can equilibrate with **98**. Indeed, it was shown that this entire cascade could be achieved in one operation by Lindlar hydrogenation of diyne **95** and subsequent heating of the resulting material to give endiandric ester A (**100**) in 30% overall yield.

Chart 3. Natural Products Stemming from 8π−6π Electrocyclization Cascades



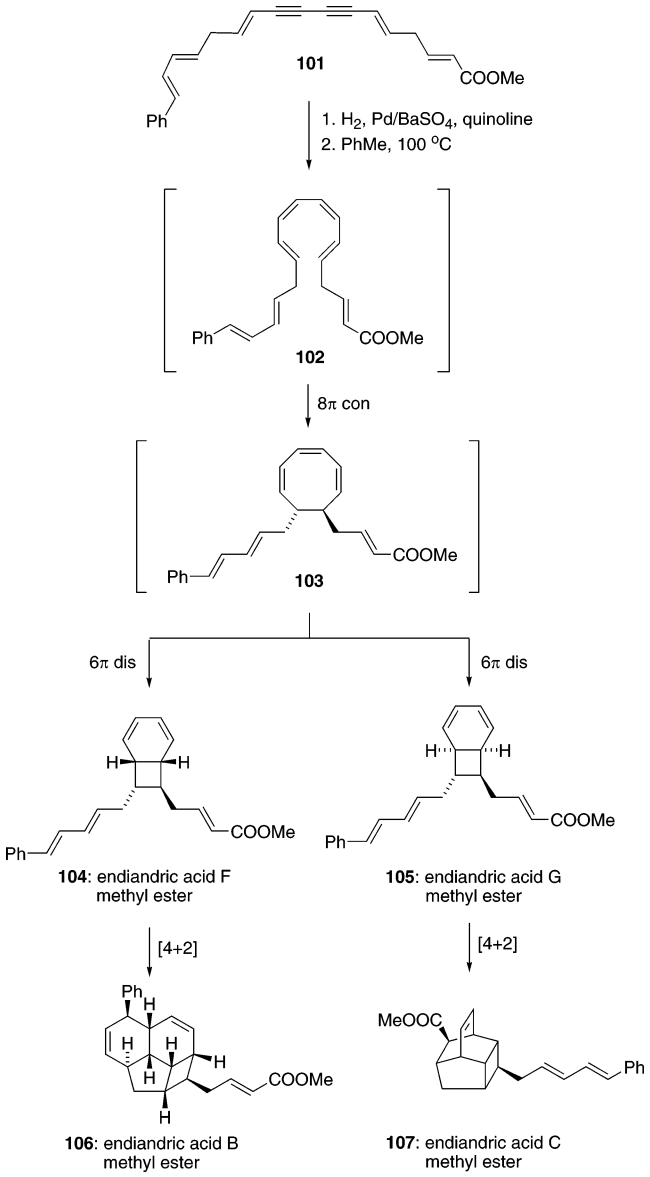
Other members of the endiandric acid family were available starting from pentaene-diyne **101**. As above, Lindlar hydrogenation of **101** gave a polyene (**102**), which underwent conrotatory 8π electrocyclization to give cyclooctatriene **103** as a racemate. Subsequent disrotatory 6π electrocyclization afforded endiandric ester F (**104**) and G (**105**). Heating endiandric ester F (**104**) to 100 °C in toluene again resulted in intramolecular Diels−Alder reaction to form endiandric ester B (**106**). Endiandric acid ester G (**105**) contains a dieneophile in close proximity to the cyclohexadiene functionality and undergoes intramolecular Diels−Alder reaction at 100 °C in toluene yielding endiandric ester C (**107**). As above, the entire transformation could be achieved in a single operation. Hydrogenation of diyne **101**, followed by heating to 100 °C in toluene, gave a 4.5:1 mixture of the methyl esters of endiandric acids B (**106**) and C (**107**) in 28% combined yield.

Scheme 21. Nicolaou's Studies on Endiandric Acids A, D, and E



About 20 years after the first synthesis of endiandric acids, the optically active polyketides SNF4435 C (**90**) and SNF4435 D (**91**) were isolated from a culture broth of *Streptomyces spectabilis*.[42] Biosynthetically, these compounds can be traced back to a common precursor, tetraene **109**, through an 8π−6π electrocyclization cascade (Scheme 23).[43] Interestingly, the SNF4435 compounds were found as a 3:1 mixture, which reflects the expected diastereoselectivity in the 8π electrocyclization step. By contrast, the 6π electrocyclizations appear to be highly diastereoselective, since the other two possible diastereomers were never found in Nature nor in the

Scheme 22. Nicolaou's Studies on Endiandric Acids B, C, F, and G

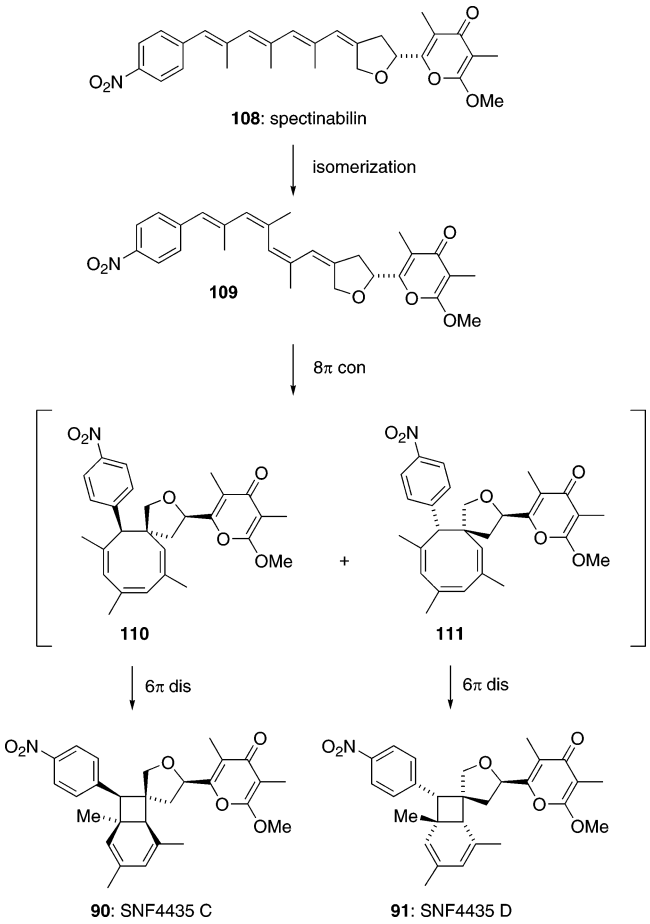


course of synthetic studies (see below). Note that **109** is a stereoisomer of spectinabilin (**108**), another natural product previously isolated from *S. spectabilis*.[44] Accordingly, it has been proposed that the SNF compounds could stem from spectinabilin through spontaneous or enzyme-catalyzed isomerization, followed by electrocyclization.[45]

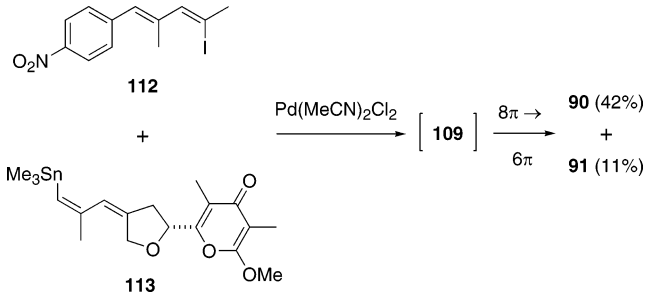
The proposed biosynthetic origin of the SNF compounds has been synthetically verified by several total syntheses. In Parker's synthesis, vinyl iodide **112** underwent cross-coupling with vinyl stannane **113** to yield tetraene **109**, which then underwent the electrocyclization cascade (Scheme 24).[46] Beaudry and Trauner used an "umpoled" approach involving stannane **114** and enantiomerically pure iodide **115** to achieve the key cross-coupling in high yield (Scheme 25).[47] Baldwin reported a total synthesis of spectinabilin (**108**), which subsequently underwent thermal isomerization followed by electrocyclization to afford the SNF compounds (Scheme 26).[48]

The facile isomerization of polyenes triggering electrocyclization cascades was also exploited by

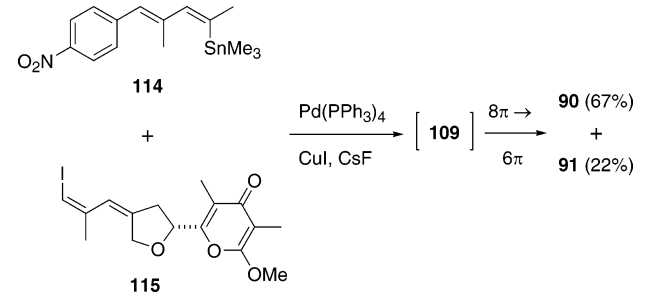
Scheme 23. Biosynthetic Origin of the SNF4435 Compounds



Scheme 24. Parker's Total Synthesis of SNF4435 C and D



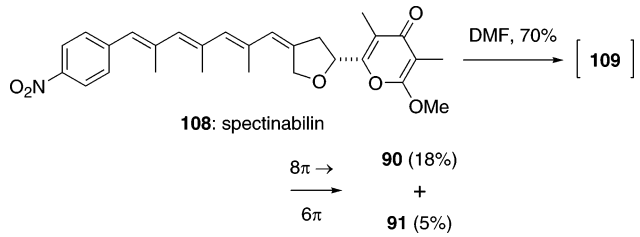
Scheme 25. Trauner's Total Synthesis of SNF4435 C and D



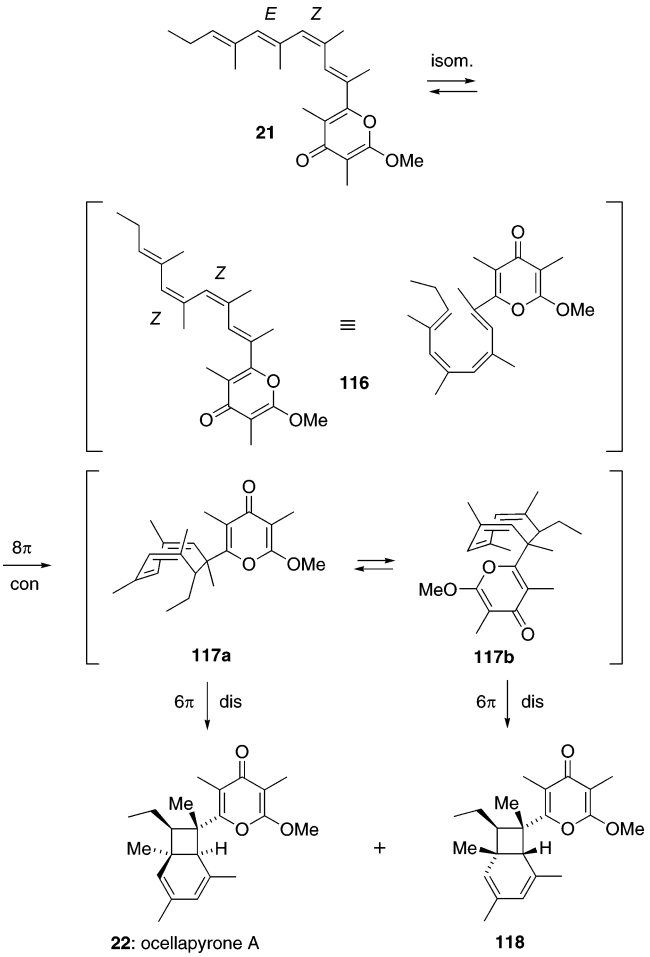
Baldwin[49] and Trauner[50] in their respective syntheses of the molluscan polypropionate ocellapyrone A (**22**; Scheme 27).[51]

In the course of synthetic studies directed at deoxytridachione (**11**; cf. Scheme 9), both groups

Scheme 26. Baldwin's Total Synthesis of SNF4435 C and D



Scheme 27. Serendipitous Synthesis of Ocellapyrone A

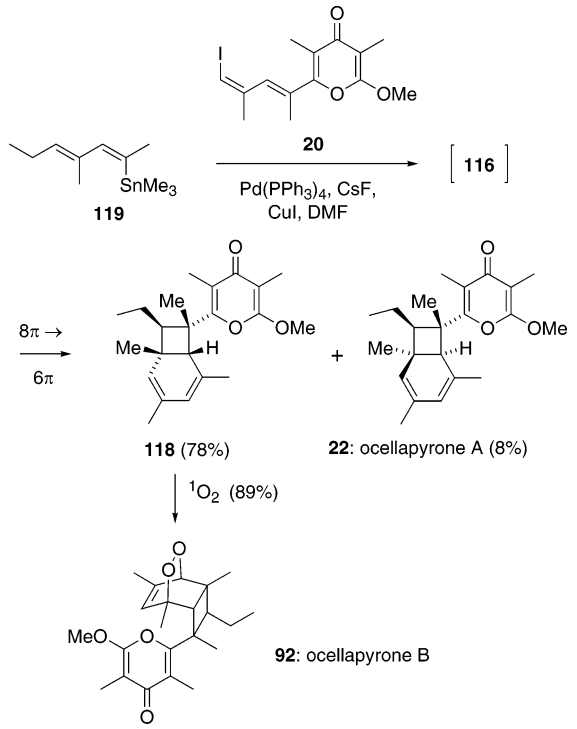


arrived at tetraene **21**. This compound was found to slowly undergo isomerization at room temperature, followed by 8π−6π electrocyclization, to give ocellapyrone A (**22**) and its isomer **118** in varying amounts. Note that under different conditions **21** underwent 6π electrocyclization to give deoxytridachione (**11**) as the major product (cf. Scheme 9).

In a more rational approach to the ocellapyrones, vinyl stannane **119** was coupled to iodide **20** to enter the electrocyclization cascade directly and afford ocellapyrone A (**22**) and its isomer **118** (Scheme 28).[50] Diels−Alder reaction of the latter with singlet oxygen then gave racemic ocellapyrone B (**92**).

The elysiapyrones (**93**, **94**), which were isolated from the mollusc *Elysia diomedea*,[52] bear a close structural similarity to the ocellapyrones. Darias proposed that these optically active compounds could be formed through an enzymatically assisted elec-

Scheme 28. Rational Synthesis of Ocellapyrones A and B



trocyclization cascade, followed by [4 + 2] cycloaddition of singlet oxygen and rearrangement of the resultant endoperoxide moiety.

The elysiapyrones were synthesized in racemic form by closely following this proposed pathway (Scheme 29).[53] Stille cross-coupling of **120** with **20**, gave transient tetraene **122**, which underwent the electrocyclization cascade to afford the diastereomers **121** and **123**. Subsequent cycloaddition of singlet oxygen and ruthenium catalyzed isomerization of the resultant endoperoxides **124** and **125** gave the structurally intriguing natural products **93** and **94**.

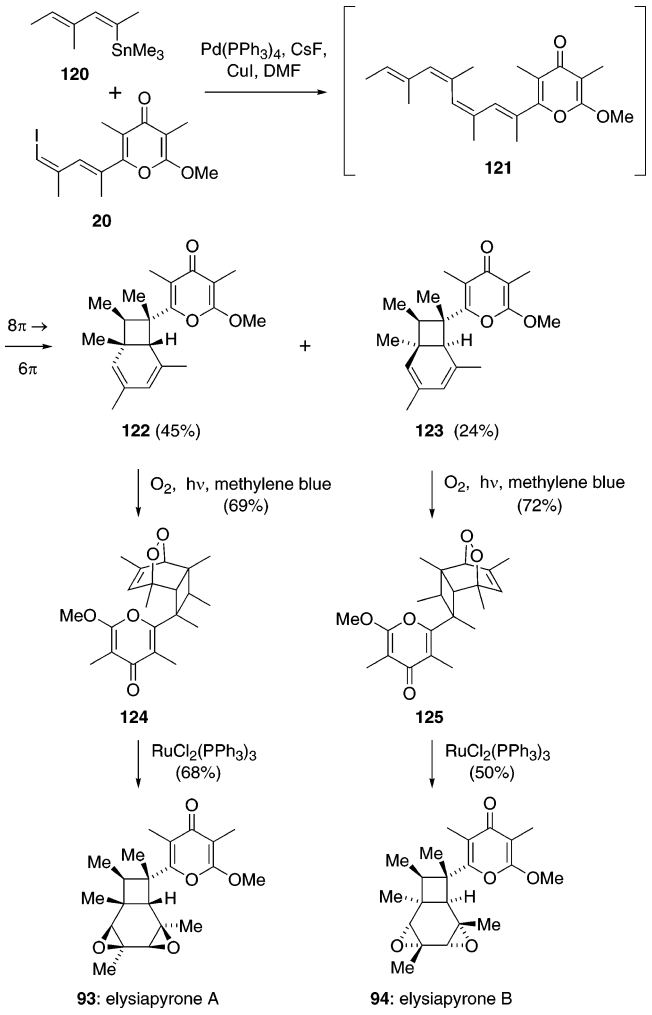
3. Heteroatom-Containing Systems

3.1. Oxa-6π Systems

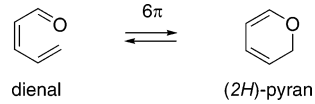
Oxa-6π electrocyclizations are essentially thermoneutral reactions and have low activation energies, which renders them highly reversible (Scheme 30). The equilibrium between the dienal (or dienone) and (*2H*)-pyran isomer is a function of the electronic nature of the system, with electron-withdrawing substituents in the 2-position favoring the closed (*2H*)-pyran form.[4a,54]

Although electrocyclizations of this type are common in Nature, simple (*2H*)-pyrans that are not masked by further transformations or fused to aromatic systems are relatively rare. Briareolate ester G (**127**), whose $\Delta^{7,8}$ stereochemistry could not be fully established, appears to be correlated with briareolate ester B (**126**) through transannular oxa-6π electrocyclization, with a possible intermediate *E*,*Z*-isomerization (Scheme 31).[55] Note the close relationship of these compounds with cyclobutenbriarein A (**4**), another natural product from *B. asbestinum* that could be formed through electrocyclization (cf. Scheme 2).

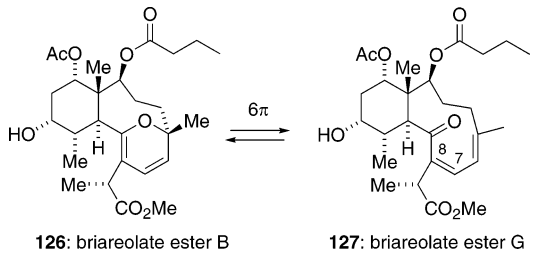
Scheme 29. Trauner's Synthesis of the Elysiapyrones



Scheme 30



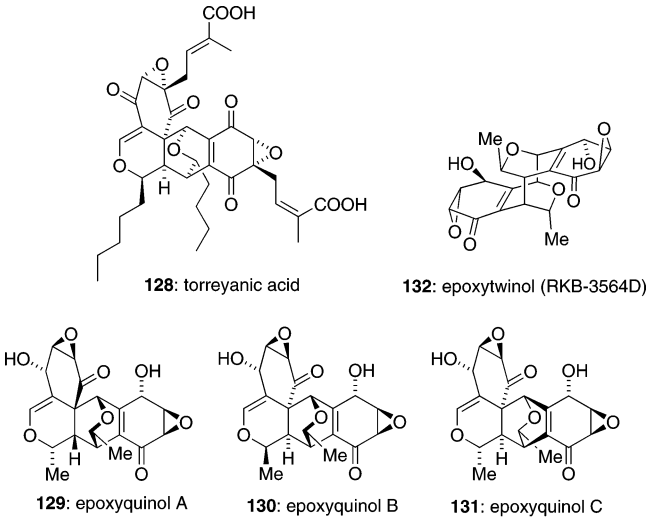
Scheme 31. Interconversion of Briareolates



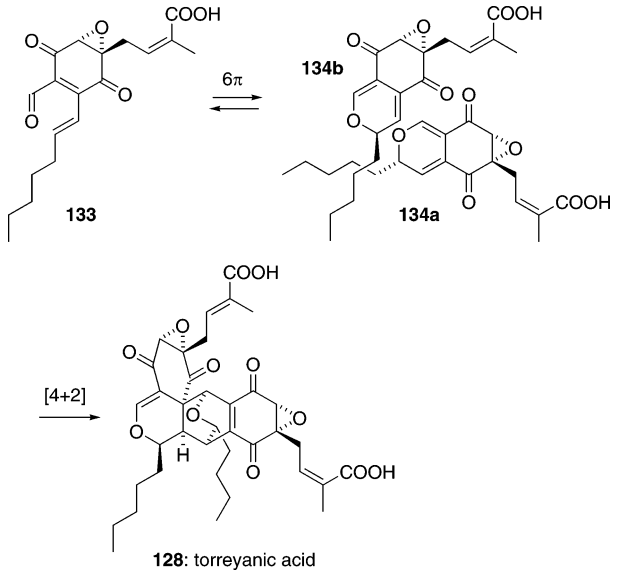
(2*H*)-Pyrans are quite reactive, showing a tendency to undergo subsequent cycloadditions, often with dimerization. Indeed, several dimeric natural products that stem form (2*H*)-pyrans have been discovered (Chart 4).

Clardy isolated torreyanic acid (**128**) from the endophytic fungus *Pestalotiopsis microspora*.[56] This complex natural product was proposed to arise from Diels–Alder dimerization of two diastereomeric (2*H*)-pyrans, compounds **134a**,**b**, which are in equilibrium with each other via dienal **133** (Scheme 32). A

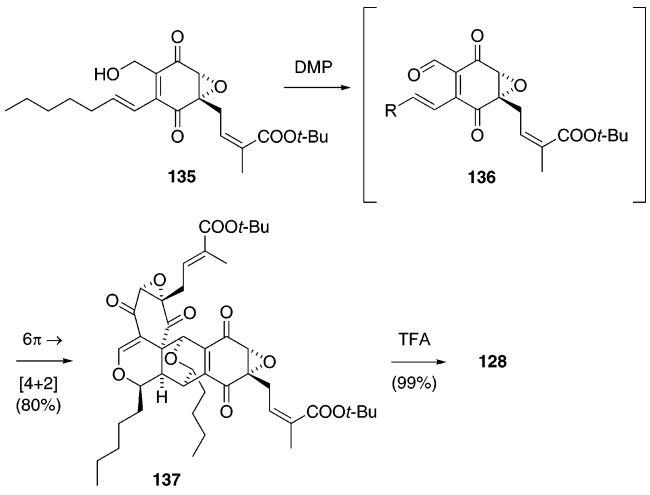
Chart 4. (2*H*)-Pyran Dimers



Scheme 32. The Torreyanic Acid Cascade

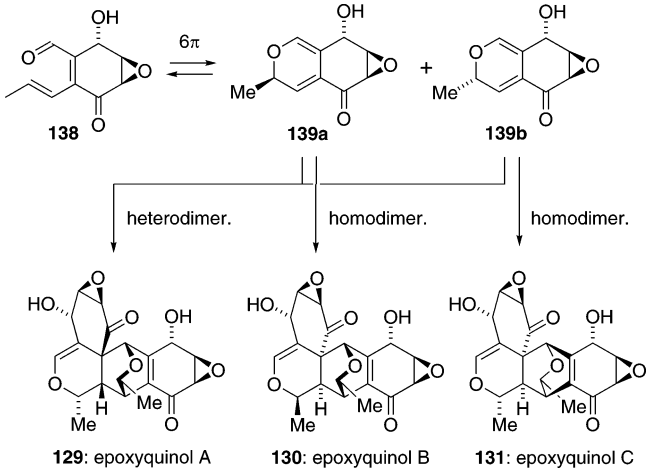


Scheme 33. Porco's Synthesis of Torreyanic Acid

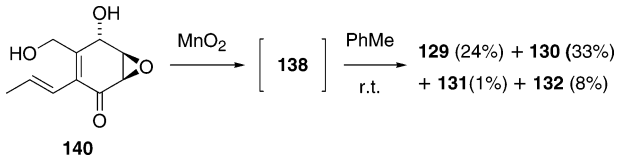


synthetic study by Porco verified this proposal and provided detailed insight into the thermodynamics of the electrocyclization (Scheme 33).[57] Treatment of enantiomerically pure quinone epoxide **135** with

Scheme 34. Biosynthetic Origin of Epoxyquinols A−C



Scheme 35. Hayashi's Epoxyquinol Synthesis



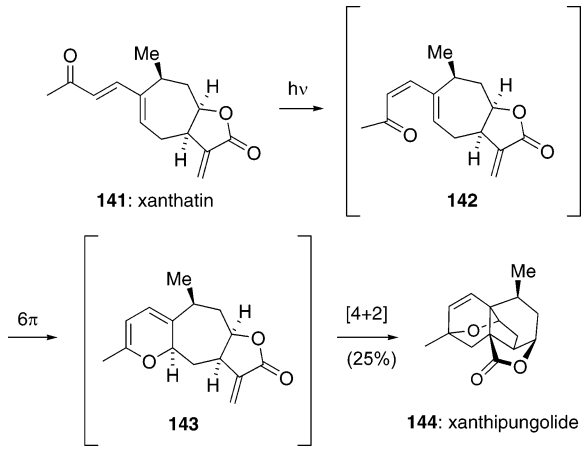
Dess−Martin periodinane (DMP) led to formation of aldehyde **136**, which underwent electrocyclization−dimerization to yield **137** as a single diastereomer. Deprotection of the carboxylic acid functions then gave torreyanic acid (**128**).

A similar dimerization accounts for the formation of the fungal metabolites epoxyquinols A−C (**129**−**131**; Scheme 34).[58] Osada proposed that these natural products stem from dienal **138**. Oxa-6π electrocyclization gives diastereomeric pyrans **139a**,**b**. Heterodimerization of these affords epoxyquinol A (**129**), whereas homodimerization of **139a** and **139b** gives epoxyquinols B (**130**) and C (**131**), respectively, via *exo* cycloaddition. A formal [4 + 4] cycloaddition of **139a** produces epoxytwinol (RKB-3564D; **132**).[59]

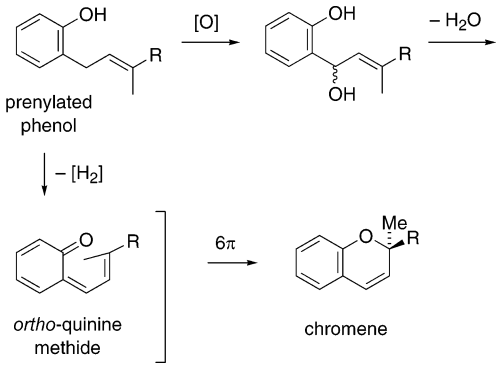
Hayashi,[58c] Porco,[60] Kuwahara,[61] and Mehta[62] have published asymmetric syntheses of the epoxyquinols using different routes to the biosynthetic precursor **138**. In Hayashi's approach (Scheme 35), the primary allylic alcohol **140** underwent manganese dioxide mediated oxidation to afford **138**. As predicted, oxa-6π electrocyclization provided (*2H*)-pyran epimers **139a**,**b**, which underwent different modes of Diels−Alder dimerization to afford **129**, **130**, and **131**, along with [4 + 4]-dimer **132**.

The sesquiterpene lactone xanthipungolide (**144**) was isolated from the Egyptian weed *Xanthium pungens*, along with xanthatin (**141**).[63] Xanthipungolide was proposed to arise from xanthatin via *Z*,*E*-isomerization (→**142**) followed by oxa-6π electrocyclization to afford (*2H*)-pyran **143**, which then undergoes intramolecular Diels−Alder reaction (Scheme 36). Indeed, irradiation of **141** afforded **144** in 25% yield. Presumably, the oxa-6π electrocyclization step is not highly diastereoselective, yet it is reversible. As the two possible diastereomers rapidly interconvert, only **143** can effectively undergo the intramolecular cycloaddition. Synthetic approaches toward xanthatin (**141**) have been reported.[64]

Scheme 36. Biosynthetic Origin of Xanthipungolide



Scheme 37. Biosynthetic Origin of Chromenes from *ortho*-Prenylated Phenols



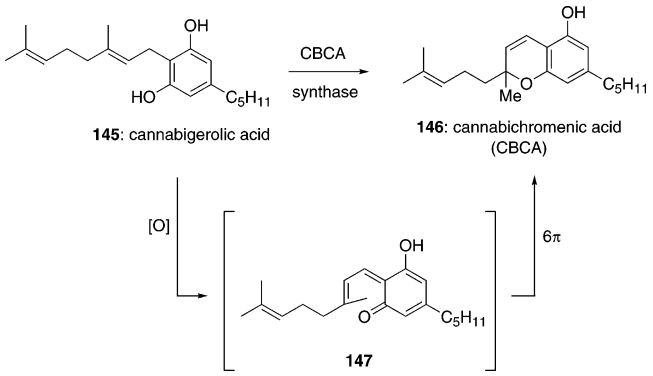
The chromene motif occurs very frequently among natural products. More than 1500 chromenes have been isolated from natural sources. Biosynthetically, most of these appear to stem from *ortho*-prenylated phenols or (hydro-)quinones.

Several mechanisms can be envisioned for the conversion of a prenylated phenol to a chromene, some of which involve an oxa-6π electrocyclization (Scheme 37). For instance, hydroxylation of the benzylic position, followed by 1,4-elimination of water, could afford a vinyl *ortho*-quinone methide, whose oxa-6π electrocyclization leads to the chromene core. Alternatively, direct enzymatic dehydrogenation could lead to the vinyl *ortho*-quinone methide.

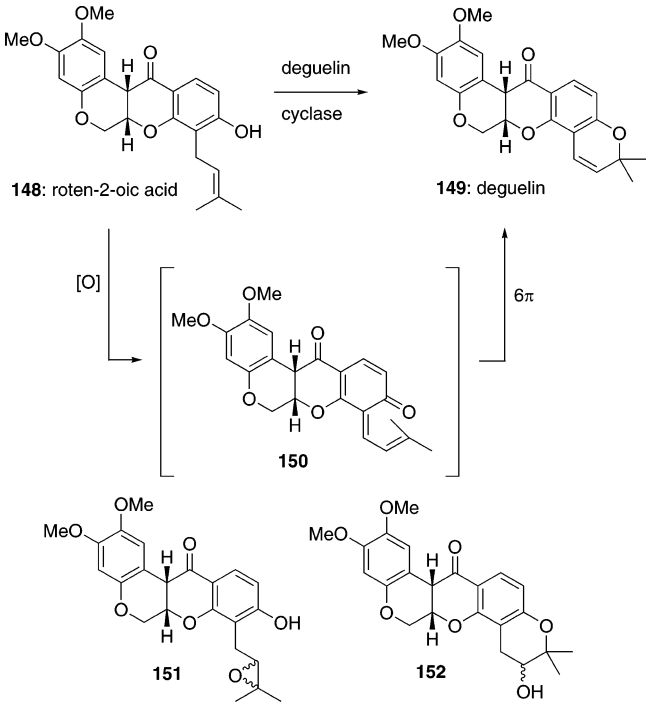
Enzymes that mediate chromene formation from prenylated phenols have been identified. For instance, cannabichromenic acid synthase (CBCA synthase) from *Cannabis sativa* catalyzes the conversion of cannabigerolic acid (**145**) to (+)-cannabichromenic acid (**146**), whose absolute stereochemistry is unknown (Scheme 38).[65] It appears that this enzyme is not a cytochrome P-450-type monooxygenase but achieves dehydrogenation of the substrate to yield **146** via **147**. However, the typical coenzymes (NAD, FAD, FMN) of dehydrogenases seem to be absent.

Deguelin cyclase catalyzes the conversion of roten-2-oic acid (**148**) to deguelin (**149**) in the plant *Tephrosia vogellii* (Scheme 39).[66] Again, this reaction presumably involves a vinyl-*ortho*-quinone methide intermediate (**150**). Like CBCA synthase, the enzyme does not seem to belong to the cytochrome P-450

Scheme 38. Cannabichromenic Acid Synthase



Scheme 39. Deguelin Cyclase



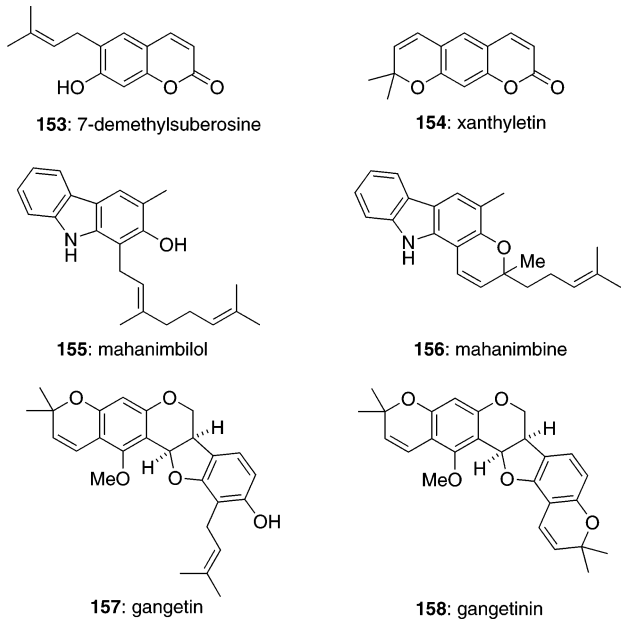
group and resembles more closely the non-heme iron protein isopenicillin N synthase. No conversion to deguelin (**149**) was observed when epoxide **151** or hydroxychromane **152** was added to germinating seeds of *T. vogellii*. This suggests that the formation of the chromene moiety does not proceed via epoxidation of the prenyl side chain, followed by intramolecular epoxide opening and dehydration, which is another conceivable mechanism for the biosynthetic formation of chromenes.

Similar enzymes can be suspected in the biosynthesis of many other chromenes, such as the ones shown in Chart 5, which have been isolated together with their uncyclized putative precursors.[67]

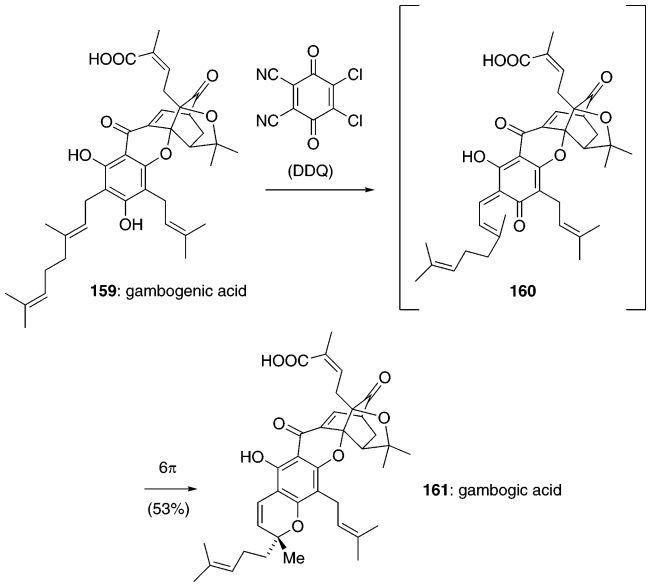
The conversion of a prenylated phenol to a chromene has been achieved in a biomimetic fashion. For instance, DDQ oxidation of gambogenic acid (**159**) gave gambogic acid (**161**) via **160**.[68] Both natural products were isolated from the tropical tree *Garcinia hanburyi* (Scheme 40).

Although hardly biomimetic, a popular methodology for the installment of the ubiquitous 2,2-dimethylchromene moiety involves a related oxa-6π electrocyclization. In Theodorakis' recent synthesis of

Chart 5. Chromene Natural Products and Their Precursors



Scheme 40. Chromenes through Unsaturation

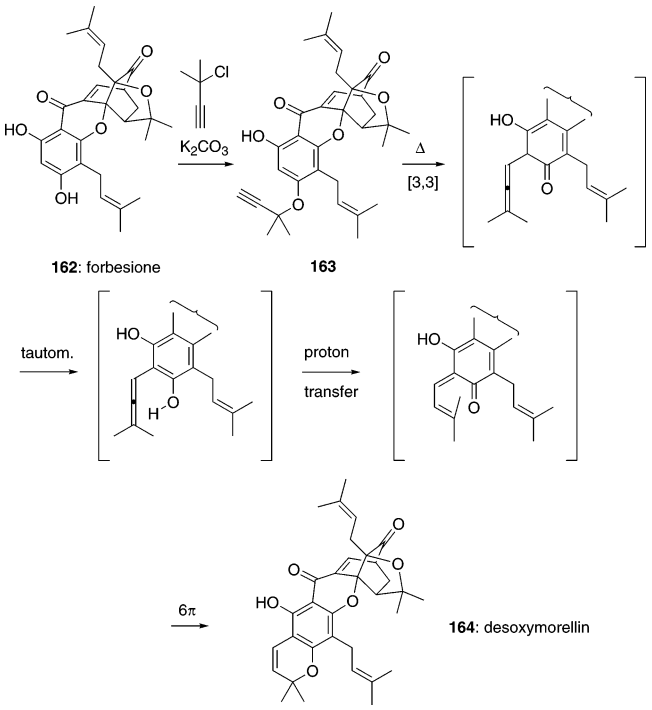


desoxymorellin (**164**), for instance, synthetic forbesione (**162**) was converted into propargyl ether **163** (Scheme 41).[69] Upon heating, this compound underwent aromatic Claisen rearrangement, followed by tautomerization, intramolecular proton transfer, and oxa-6π electrocyclization to afford **164**.

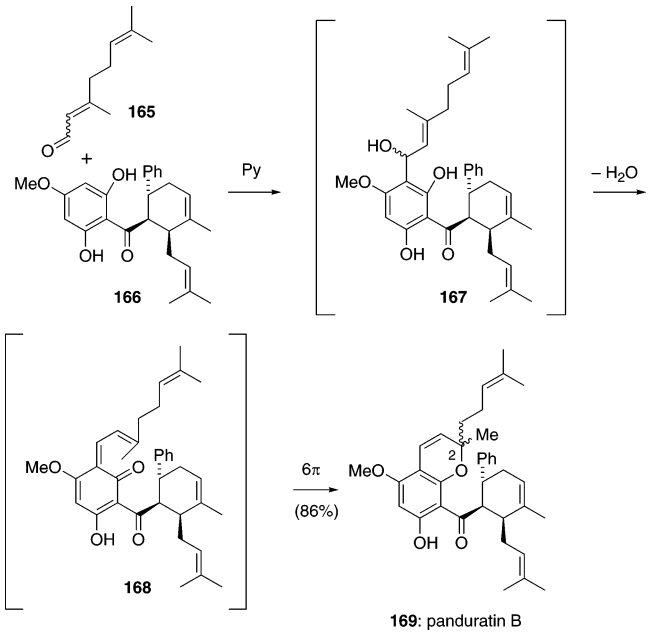
The vinyl *ortho*-quinone methide intermediate can also be accessed through condensation chemistry. In an example of this strategy, heating of resorcinol **166** with citral (**165**) gave panduratin B (**169**), a mixture of diastereomers at C2, presumably via benzylic alcohol **167** and vinyl *ortho*-quinone methide **168** (Scheme 42).[70]

An intramolecular condensation of this type has been used in a biomimetic total synthesis of smenochromene D (**173**), which appears to be the enantiomer of likonide B (**175**). The smenochromenes and likonides are a family of unusual natural products

Scheme 41. Chromenes through Claisen Rearrangement



Scheme 42. Chromenes through Condensation−Elimination

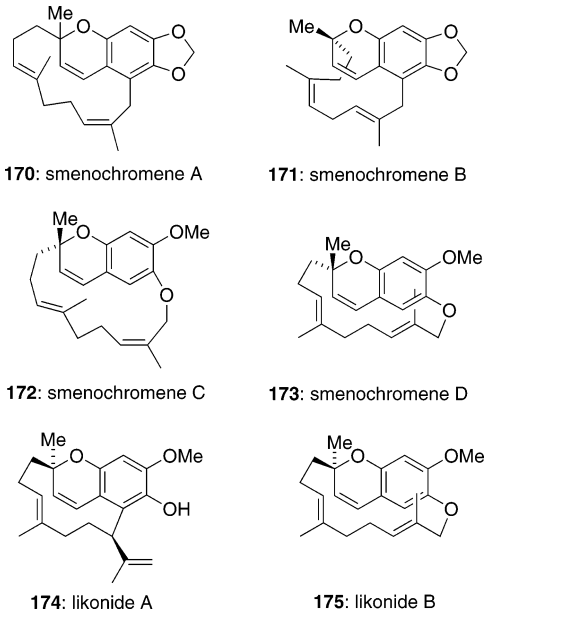


isolated from the sponges *Smenospongia sp.* and *Hyatella sp.*, respectively, whose chromene moiety is integrated in a macrocyclic ring system (Chart 6).[71]

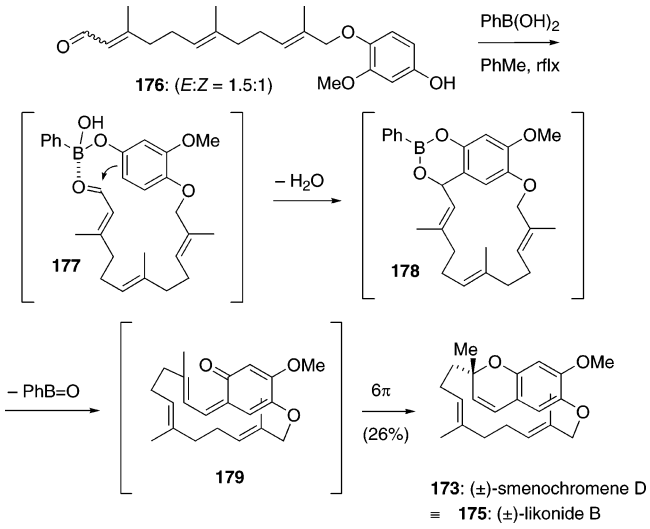
A biomimetic total synthesis of smenochromene D (**173**) was recently reported by Trauner (Scheme 43).[72] Heating of aldehyde **176** with phenylboronic acid affected macrocyclization to afford the natural product. This reaction presumably proceeds through the intermediacy of cyclic borate **178** and vinyl *ortho*-quinone methide **179**, whose oxa-6π electrocyclization installs the chromene system.

Chromenes frequently undergo further pericyclic transformations such as [2 + 2] cycloadditions or

Chart 6. The Smenochromenes and Likonides



Scheme 43. Synthesis of Smenochromene D

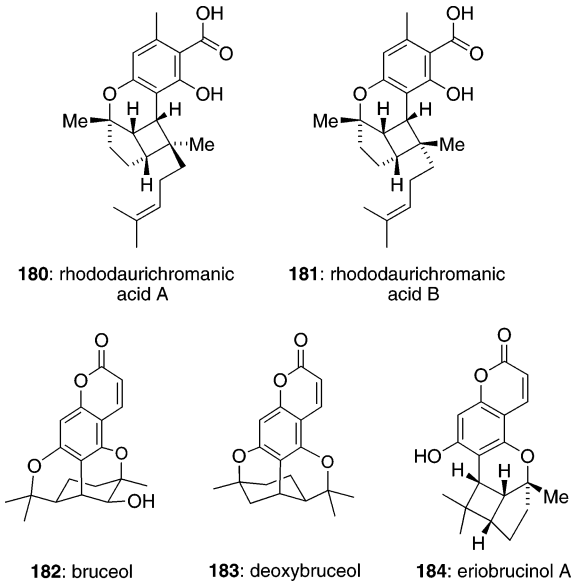


oxidations followed by [4 + 2] cycloadditions. A sample of natural products whose chromene moiety is masked in such a fashion is shown in Chart 7.

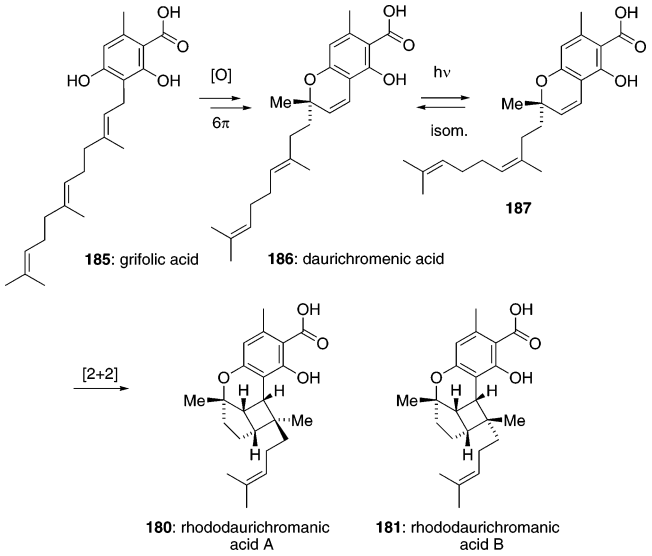
Rhododaurichromanic acids A (**180**) and B (**181**) were isolated from the Asian shrub *Rhododendron dauricum*.[73] Their biosynthesis can be envisioned to start from the prenylated resorcinol grifolic acid (**185**) or a related precursor (Scheme 44). Oxidation of **185** followed by oxa-6π electrocyclization would yield daurichromenic acid (**186**), which was also isolated from *R. dauricum*.[74] As experimentally verified by Kashiwada, **186** equilibrates with (*Z*)-configured **187** upon irradiation. Intramolecular [2 + 2] cycloaddition of the two isomers then produces the epimeric natural products rhododaurichromanic acids A and B (**180**, **181**).[73]

Hsung has achieved an expedient biomimetic synthesis of the rhododaurichromanic acids (Scheme 45).[75] Condensation of dione **188** with farnesal (**189**) and concomitant oxa-6π electrocyclization gave (*2H*)-pyran **190**. Acylation and oxidation provided **191**, the methyl ester of daurichromenic acid. Irradiation of

Chart 7. Chromenes Masked by Cycloadditions (and Oxidations)



Scheme 44. Biosynthesis of Rhododaurichromanic Acid

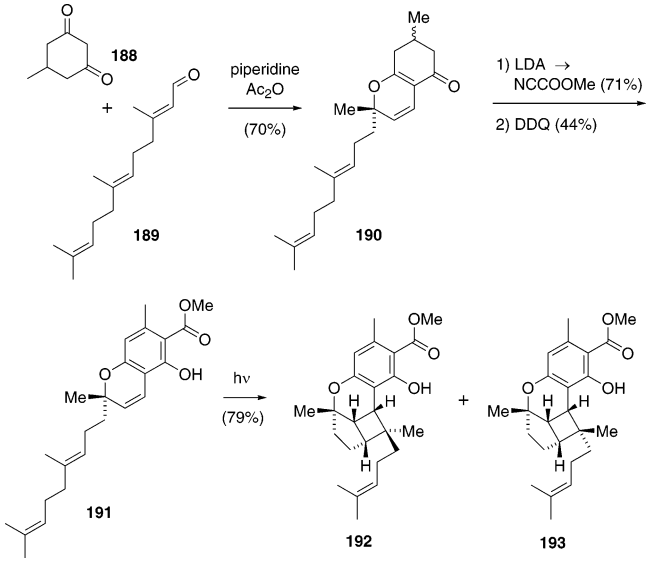


this material provided rhododaurichromanic methyl esters **192** and **193** as a 1:1 mixture, whose saponification gave the natural products. Wilson applied a similar strategy toward the synthesis of the rhododaurichromanic acids and analogues.[76]

Jin provided the first synthesis of daurichromenic acid (**186**; Scheme 46).[77] Under carefully optimized conditions, reaction of **194** and **189** under microwave irradiation gave 2-trimethylsilylethyl ester **195**. Subsequent liberation of the carboxylate function with fluoride afforded daurichromenic acid (**186**), whose photolysis again gave the rhododaurichromanic acids.

Interestingly, different cyclization modes of grifolic acid-type precursors could lead to molecules such as bisabosqual A (**196**)[78] and stachybotrydial (**197**; Chart 8).[79] These natural products isolated from fungi are presumably formed through a Diels−Alder reaction involving an *ortho*-quinone methide and polyolefin cyclization, respectively.

Scheme 45. Hsung's Total Synthesis of Rhododaurichromanic Acids A and B



Scheme 46. Jin's Total Synthesis of Daurichromenic Acid

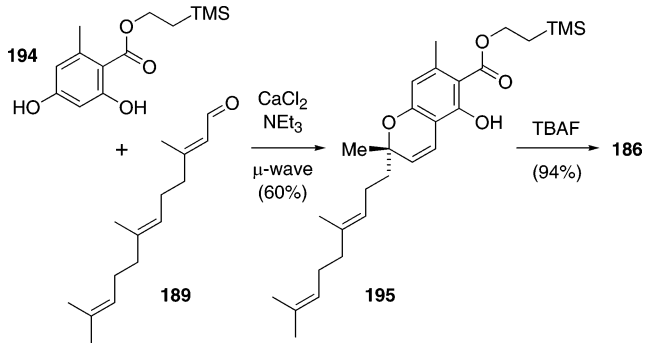
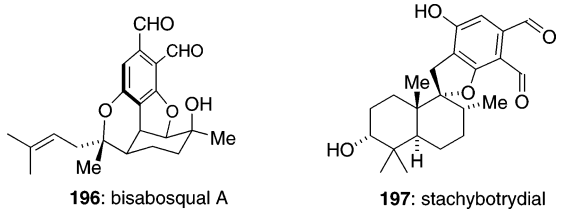


Chart 8

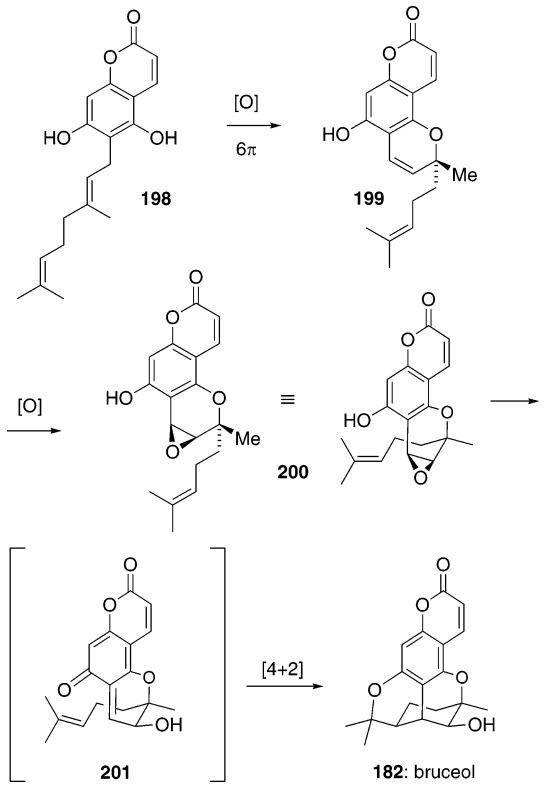


Diels−Alder reactions involving *ortho*-quinone methides and a [2 + 2] cycloaddition also mask the chromene moiety of bruceol (**182**),[80] deoxybruceol (**183**),[81] and eriobrucinol (**184**),[82] respectively (cf. Chart 7). These three natural products were isolated from the Australian plant *Eriostemon brucei*. Note that deoxybruceol is not simply the deoxygenated enantiomer of bruceol but features an isomeric coumarin moiety.

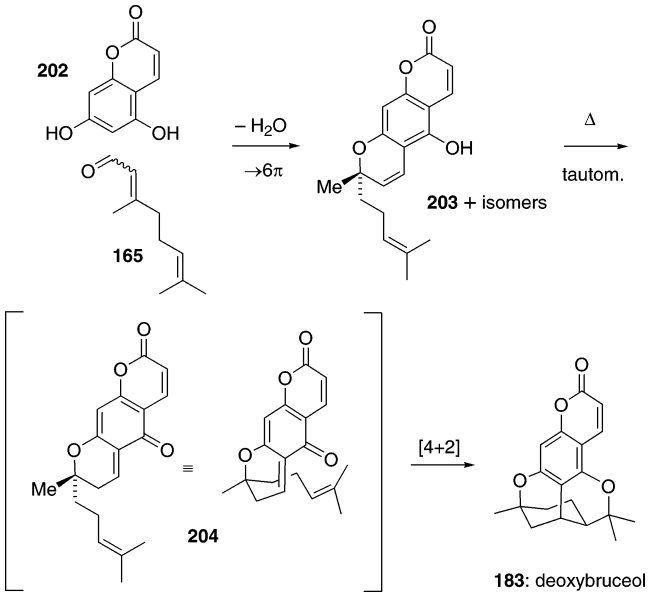
A proposed biosynthesis of bruceol starts with the oxidation of geranylated dihydroxycoumarin **198**, followed by oxa-6π electrocyclization to afford chromene **199** (Scheme 47). Epoxidation of this material (→**200**) sets the stage for *ortho*-quinone methide formation (→**201**) and cycloaddition leading to the natural product.

Deoxybruceol (**183**) has attracted some attention from the synthetic community. Crombie and Whiting

Scheme 47. Proposed Biosynthesis of Bruceol



Scheme 48. Crombie and Whiting's Biomimetic Synthesis of Deoxybruceol



showed that the so-called citran skeleton of deoxybruceol can be formed via condensation of dihydroxycoumarin **202** and citral (**165**), which initially affords chromene **203** along with several isomers (Scheme 48).[82] Under forcing conditions, **203** could be tautomerized to *ortho*-quinone methide **204**, which underwent intramolecular Diels–Alder reaction. Racemic deoxybruceol (**183**) was thus obtained in low yield along with a range of byproducts that arose from alternative cycloaddition modes. Some of these, e.g., eriobrucinol A (**184**), were later found to be natural products as well.

Scheme 49. Biosynthetic Origin of 6-Hydroxychromenes

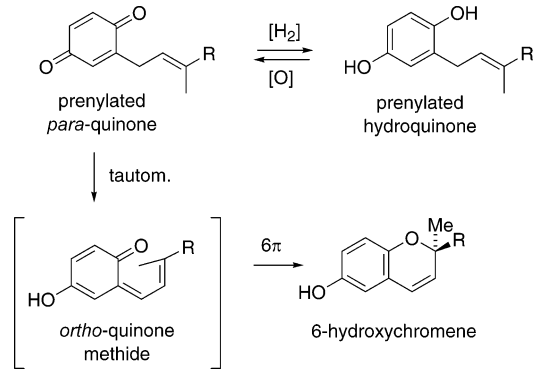
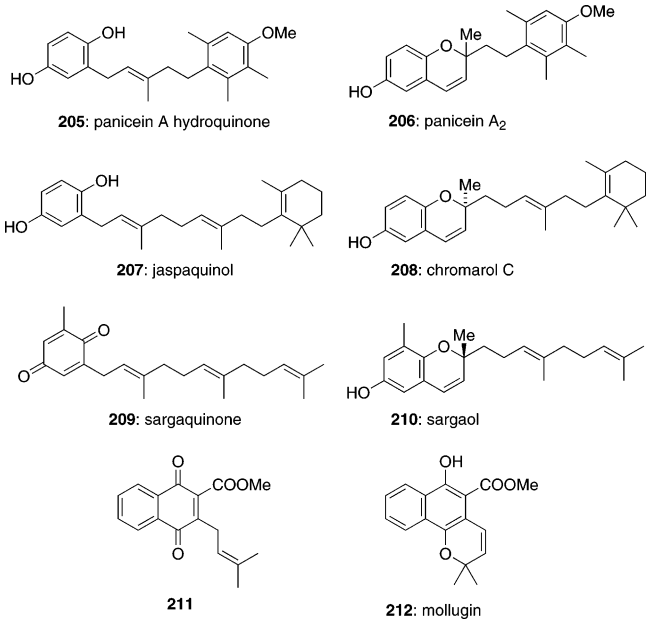


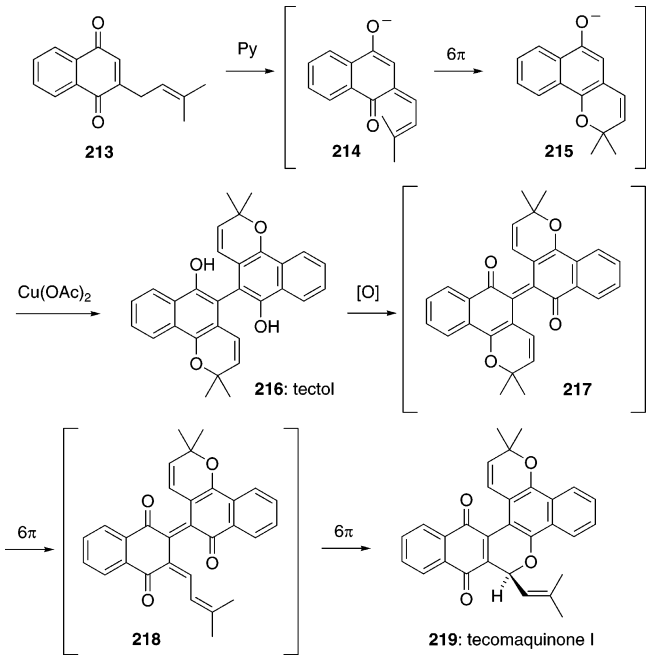
Chart 9. 6-Hydroxychromenes and Their Precursors



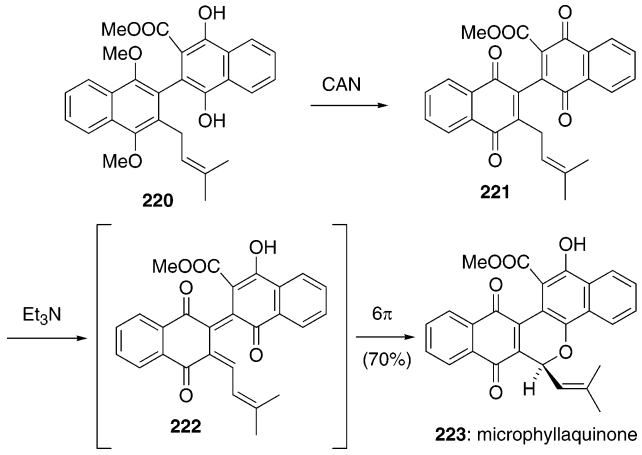
The tautomerization of prenylated *para*-quinones affords vinyl *ortho*-quinone methides that undergo oxa-6π electrocyclization to yield 6-hydroxychormenes (Scheme 49). Natural products of this type are widely found, often together with their putative quinone (or hydroquinone) precursors (Chart 9).[83] This facile conversion of prenylated quinones has been demonstrated in the laboratory, for instance for **209** → **210**[84] or **211** → **212**.[85]

An elegant example for exploiting this reactivity can be found in Thomson's synthesis of tecomaquinone I (**219**),[86] a natural product isolated from Teak wood (*Tectona grandis*).[87] Dissolution of deoxylapachol (**213**) in pyridine triggered oxa-6π electrocyclization via **214** to afford phenolate **215** (Scheme 50). Upon addition of copper(II) acetate, this compound underwent oxidative phenolic coupling to afford the natural product tectol (**216**). Further oxidation of tectol with either copper(II) acetate or DDQ gave tecomaquinone I (**219**). This reaction could proceed through intermediate **217**, which, incidentally, was the originally proposed structure of tecomaquinone I. Electrocyclic ring opening (**217** → **218**), followed by ring closure involving a different carbonyl group, would afford **219**.

Scheme 50. Thomson's Synthesis of Tecomaquinone I



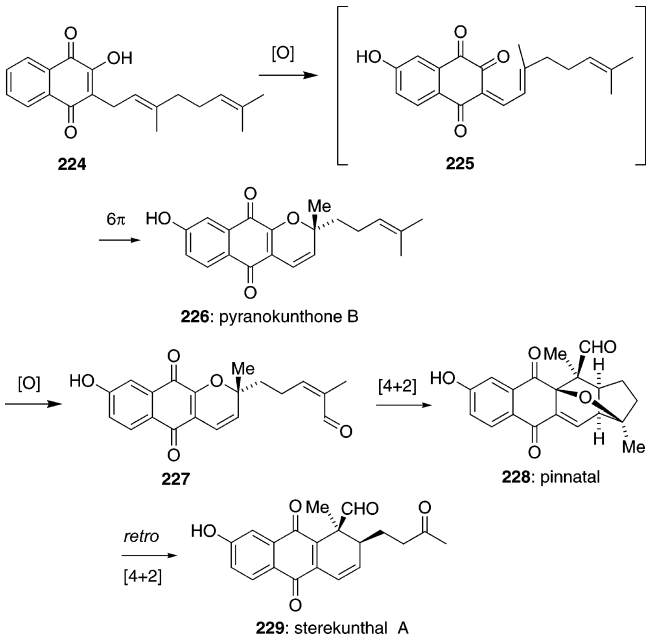
Scheme 51. Synthesis of Microphyllaquinone



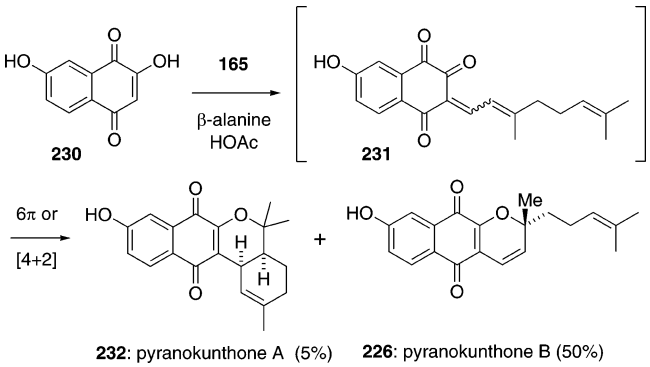
Lumb and Trauner achieved a synthesis of the related natural product microphyllaquinone (**223**),[88] which was isolated together with **219** from the shrub *Lippia microphylla* (Scheme 51).[89] Oxidation of the unsymmetrical naphthohydroquinone dimer **220** gave naphthoquinone dimer **221**. Upon heating in methanol, this compound underwent tautomerization (→**222**), followed by oxa-6π electrocyclization to afford microphyllaquinone (**223**).

Pyranokunthone B (**226**)[90] as well as pinnatal (**228**)[91] and sterekunthal A (**229**)[90] are antimalarial naphthoquinone derivatives that were isolated from certain trees of the *Bignoniaceae* family. Biosynthetic analysis suggests that these compounds are linked by a common pathway featuring an oxa-6π electrocyclization followed by cycloadditions (Scheme 52). According to a biosynthetic proposal by Trauner, geranylated hydroxynaphthoquinone **224** would undergo aromatic oxidation and dehydrogenation to yield **225**, whose oxa-6π electrocyclization gives pyranokunthone B (**226**). Hydroxynaphthoquinone **224**, the prenylated version of the widely distributed

Scheme 52. Proposed Biosynthesis of Antimalarial Naphthoquinones



Scheme 53. Biomimetic Synthesis of the Pyranokunthones

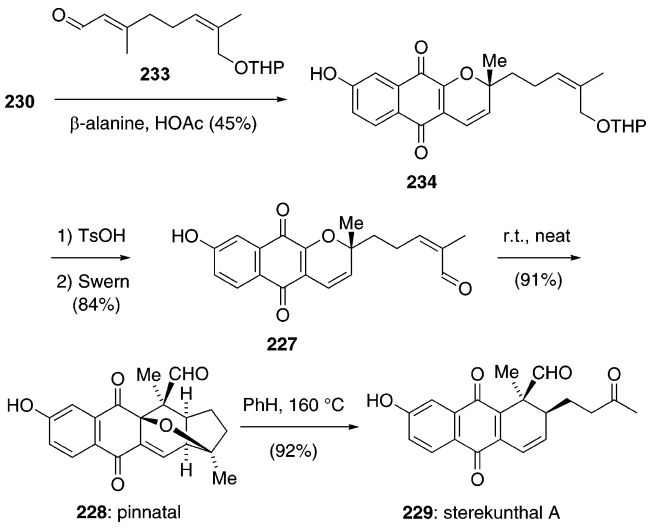


natural product lapachol, has been previously isolated from the roots of *Conospermum teretifolium*, an Australian plant distantly related to the *Bignoniaceae*.[92] Selective allylic oxidation of pyranokunthone B affords unsaturated aldehyde **227**, which undergoes intramolecular [4 + 2] cycloaddition to form the complex heterocyclic framework of pinnatal (**228**). Another pericyclic step, a *retro*-hetero-Diels–Alder reaction, converts pinnatal into sterekunthal A (**229**).

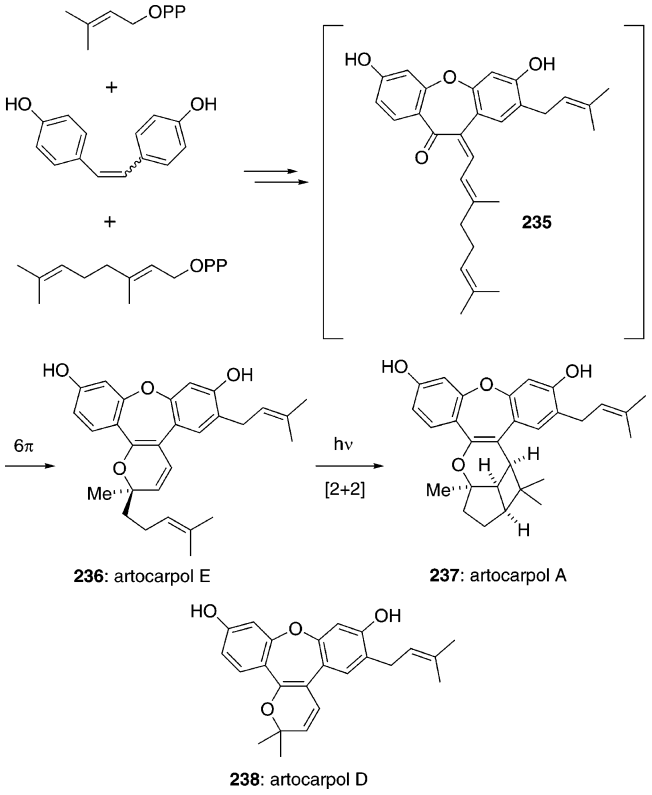
Malerich and Trauner achieved a biomimetic synthesis of **226**, **228**, and **229** along these lines (Schemes 53 and 54).[93] Knoevenagel condensation of dihydroxy naphthoquinone **230** with citral (**165**) gave a mixture of pyranokunthones A (**232**) and B (**226**) (Scheme 53). The former presumably arises from intramolecular cycloaddition of one of the geometrical isomers of intermediate **231**. Another isomer, namely **225**, undergoes the electrocyclization to afford **226**.

A similar condensation of **230** with unsaturated aldehyde **233** gave (*2H*)-pyran **234** (Scheme 54). Deprotection, followed by oxidation, then afforded the suspected biosynthetic intermediate **227**, which underwent intramolecular Diels–Alder reaction at room temperature to yield pinnatal (**228**). Heating of

Scheme 54. Biomimetic Synthesis of Pinnatal and Sterekunthal A



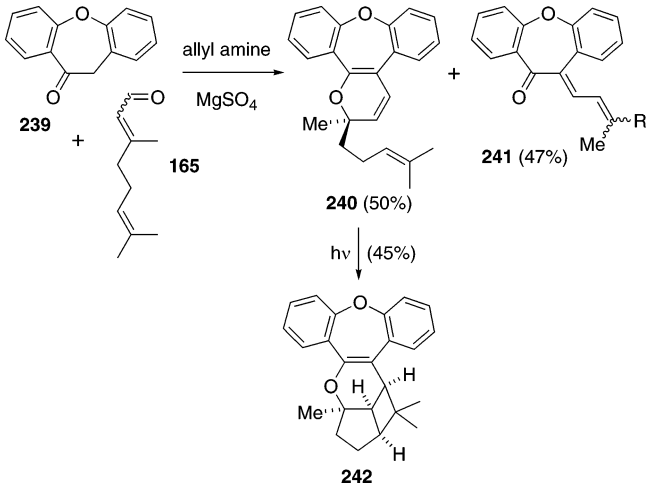
Scheme 55. Biosynthetic Origin of the Artocarpols



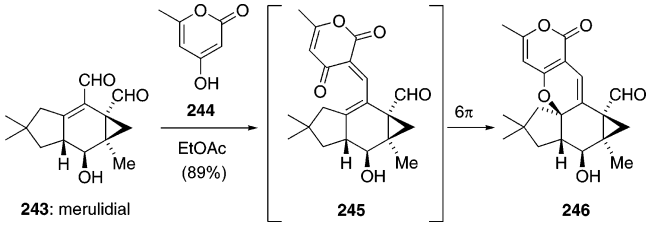
pinnatal in benzene solution effected retro-Diels–Alder reaction to give sterekunthal A (**229**).

The artocarpol family of natural products was obtained from the root bark of *Artocarpus rigida*.[94] These dibenzooxepines share some biosynthetic patterns with the natural products discussed above. Lin proposed that the artocarpols arise from hydroxy stilbenes and terpenoid pyrophosphates (Scheme 55). Biosynthetic formation of dienone **235**, followed by oxa-6π electrocyclization, would yield artocarpol E (**236**). Artocarpol A (**237**) then results from an intramolecular [2 + 2] cycloaddition. Artocarpol D (**238**) would be produced analogously from a diprenylated stilbene.

Scheme 56. Wilson's Artocarpol Model Study



Scheme 57



Wilson reported the synthesis of analogues of artocarpols A and D along the lines of this biosynthetic hypothesis (Scheme 56).[95] Oxepinone **239** was reacted with citral (**165**) to give a mixture of (*2H*)-pyran **240** and isomeric dienones **241**, which cannot undergo electrocyclization. Irradiation of **240** gave [2 + 2] adduct **242** along with products of electrocyclic ring opening.

Hydroxypyrones stemming from the polypropionate pathway also engage in condensations followed by oxa-6π electrocyclization. The unnamed lactone **246**, isolated from *Merulius tremellosus*, was proposed to arise from condensation of merulidial (**243**) and triacetic acid lactone **244** (Scheme 57), also produced by the fungus.[96] Indeed, heating of **243** and **244** in EtOAc at reflux provided **246** in excellent yield, presumably via **245**.[97]

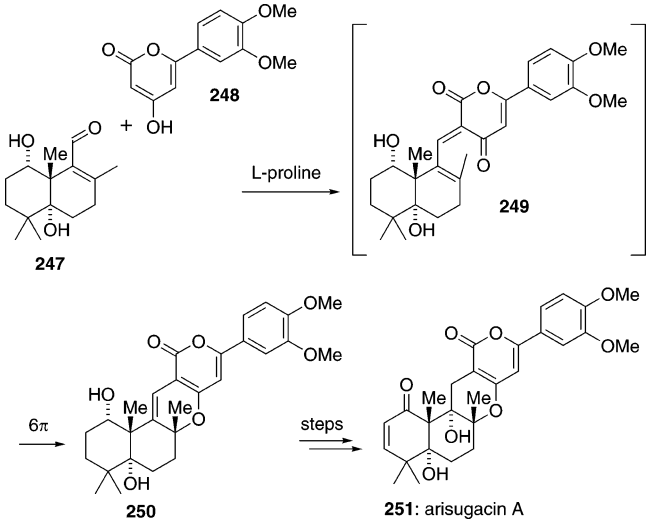
A related condensation–electrocyclization tandem was used by Omura[98] and Hsung in a total synthesis[99] of arisugacin A (**251**; Scheme 58).[100] In Omura's approach, Knoevenagel condensation of enal **247** with hydroxy pyrone **248** gave dienone **249**, which underwent stereoselective 6π electrocyclization to afford (*2H*)-pyran **250**. This material was elaborated to the natural product in a series of steps.

It is unlikely (and was not claimed), however, that these syntheses are truly biomimetic. This also applies to Barrero's approach[101] toward puupehedione (**257**),[102] which features an oxa-6π electrocyclization (**255** → **256**) as well (Scheme 59). It appears more likely that natural products of type **251** and **257** arise from polyolefin cyclizations terminated by (phenolic) hydroxy groups and subsequent oxidation.

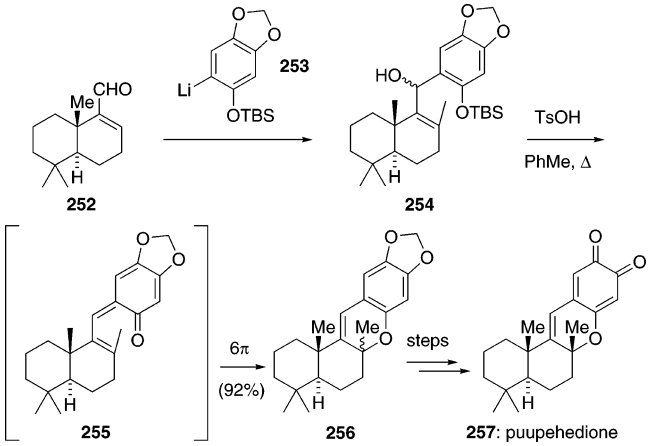
3.2. Aza-6π Systems

Azatrienes undergo aza-6π electrocyclization to afford dihydropyridines, which are easily oxidized to

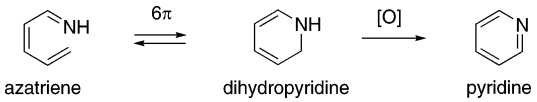
Scheme 58. Omura's Synthesis of Arisugacin A



Scheme 59. Barreo's Synthesis of Puupehedione



Scheme 60

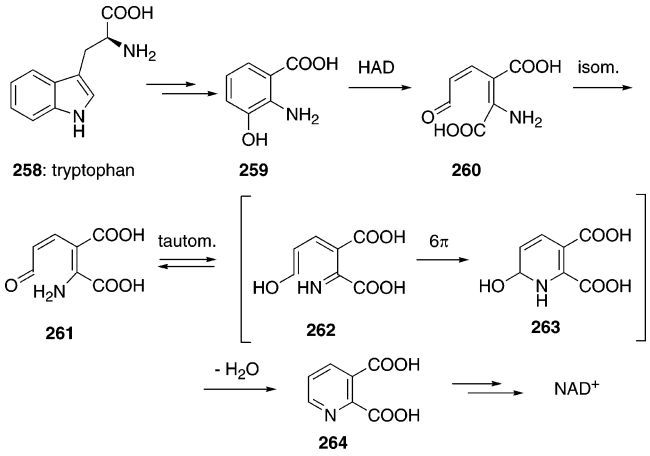


pyridines (Scheme 60). This sequence, which is fairly common in heterocylic chemistry, has been occasionally implied in the biosynthesis of pyridine natural products.

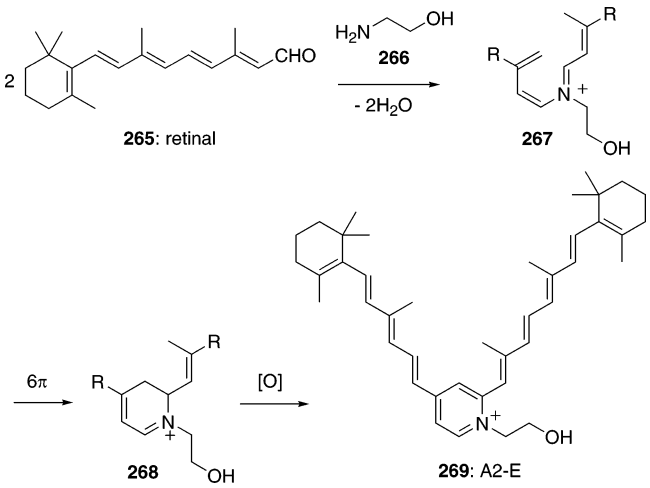
A nonenzymatic aza-6π electrocyclization has been proposed by Begley in the biosynthesis of nicotinamide adenine dinucleotide phosphate (NAD^+; Scheme 61).[103] The pathway involves degradation of tryptophan (**258**) to quinolinate (**264**), from which the pyridinium ring of NAD^+ is derived. Oxidative cleavage of 3-hydroxyanthanilate (**259**), catalyzed by 3-hydroxyanthanilate-3,4-dioxygenase (HAD), gives 2-amino-3-carboxymuconic semialdehyde (**260**), which undergoes isomerization to **261**. Begley provided evidence that the spontaneous conversion of **261** to **264** does not proceed through direct condensation but rather via tautomerization and aza-6π electrocyclization (**262** → **263**), followed by elimination of water.

Nakanishi proposed that an aza-6π electrocyclization plays a key role in the biosynthesis of the pyridinium bisretonoid A2-E (**269**), the major orange fluorophore of ocular age pigments (Scheme 62).[104]

Scheme 61. Proposed Biosynthesis of NAD^+



Scheme 62. Proposed Biosynthesis of Pigment A2-E



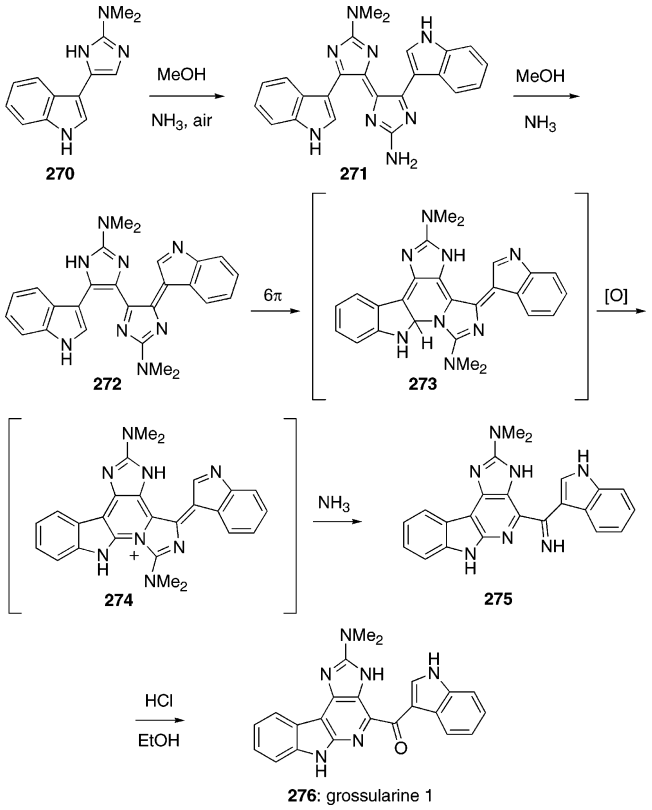
Twofold condensation of retinal (**265**) with ethanolamine (**266**) would give cationic azatriene **267**, whose 6π electrocyclization affords dihydropyridinium ion **268**. Oxidation of the latter yields pigment A2-E. To support this hypothesis, Nakanishi reported a one-step synthesis of pigment A2-E (**269**) along these lines. When **265** and **266** were treated with acetic acid in ethanol and an aerobic environment, **269** was obtained in 49% yield.[104] Katsumura has reported a similar approach to **269**, which hinges upon an aza-6π electrocyclization.[105]

Horne recently provided another elegant example of a biomimetic aza-6π electrocyclization with a synthesis[106] of grossularine 1 (**276**; Scheme 63).[107] Oxidative dimerization of indolyl aminoimidazole **270** gave **271**. Upon dissolution in methanolic ammonia, this material presumably underwent tautomerization to **272**, followed by aza-6π electrocyclization, to afford **273**. In the presence of air, **273** was oxidized to the pyridinium species **274**, which was cleaved by ammonia under the reaction conditions. Finally, alcoholysis of the resultant imine **275** gave grossularine 1 (**276**).

4. Enzymatic Catalysis in Biosynthetic Electrocyclizations

At first glance, there is little evidence electrocyclizations are enzymatically catalyzed. The role of

Scheme 63. Biomimetic Synthesis of Grossularine 1



enzymes in the biosynthesis of the molecules shown above appears to be largely confined to generating highly reactive intermediates, which then undergo electrocyclizations spontaneously. Of course, photochemical electrocyclic reactions do not require enzyme catalysis, since they proceed from high-energy excited states.

Nevertheless, some unsettling questions persist. For instance, the ocellapyrones (**22**, **92**) and elysiapyrones (**93**, **94**) have been isolated in optically active form although their putative precursors **116** and **121** are achiral polyenes. While it is possible, at least in principle, that racemic bicyclo[4.2.0]octadiene intermediates could undergo "kinetic resolution" by further enzymatic transformations, it is more likely that the stereochemical course of the $8\pi-6\pi$ electrocyclization cascade is guided by a protein. It is conceivable that the polyketide synthases (PKS) that generate the polyene precursors provide a chiral environment wherein the asymmetric electrocyclization occurs (Figure 1). The synthase may even accelerate the cyclization by conformationally preorganizing the precursor, thus functioning as a true catalyst. In this context, it is important to point out that, in the biosynthesis of aromatic polyketides, polycarbonyl intermediates undergo intramolecular condensations and aromatization while they are still covalently linked to the type II polyketide synthase.[108]

Similar considerations apply to the molluscan cyclohexadienes. Deoxytridachione (**11**) and tridachiahydropyrone (**25**), for instance, are optically active, although their presumed polyene precursors are achiral. In addition, the formation of cyclohexadienes, especially sterically crowded ones, through

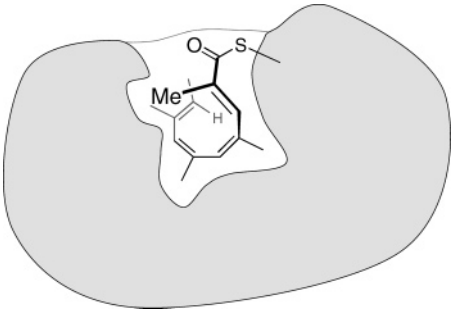


Figure 1. Asymmetric 8π electrocyclization of a PKS-bound tetraene.

thermal 6π electrocyclization has relatively high activation energies and is unlikely to occur at an appreciable rate at ambient temperature. Indeed, Baldwin's and Trauner's studies on deoxytridachione showed that elevated temperatures and microwave irradiation are needed to achieve the 6π electrocyclization and that alternative pathways exist at room temperature.

Other observations that point to a role of enzymes in biosynthetic electrocyclizations exist. Although many chromenes with only one stereocenter at C2 have been isolated as racemates, some, such as cannabichromenic acid (**146**), are optically active. Their biosynthesis could proceed through *ortho*-quinone methide intermediates, whose asymmetric electrocyclization could be guided by an enzyme. A similar role of an enzyme has been proposed in the biosynthesis of the optically active cyclopentenone **7**, which could proceed through 4π electrocyclization of the achiral oxido-pentadienyl cation **6**.

Furthermore, the naphthoquinone derivatives pinnatal (**209**) and sterekunthal A (**210**) are optically active although their putative precursor pyranokunthone B (**207**) was isolated as a racemate. It is possible that **207** is initially formed by an enzyme in enantiomerically pure form and slowly undergoes racemization, unless the (*2H*)-pyran moiety is trapped by an intramolecular Diels–Alder reaction.

5. Conclusion

In summary, we have shown that electrocyclic reactions occur regularly in the biosynthesis of natural products and are not confined to a few isolated examples. Most of the reactions reported to date appear to proceed spontaneously and do not require catalysis. While this makes them less attractive from an enzymologist's point of view, it provides great opportunities for biomimetic synthesis. After all, biomimetic synthesis is the attempt to follow biosynthetic pathways without the aid of enzymes. Indeed, biomimetic electrocyclizations have proven to be very effective in the construction of structurally highly complex natural products.

Nevertheless, the identification of enzymes that mediate asymmetric electrocyclizations, and the elucidation of their mechanisms of action (if they can be found), remains an important goal. Structural biology could shed light on the origin of asymmetric induction. In parallel, the development of catalytic asymmetric electrocyclizations will continue to cap-

tivate synthetic chemists.[109] To date, very little is known about catalysis in electrocyclizations, a situation that is hopefully bound to change over the coming years.[93]

6. Acknowledgments

This work was supported by National Institutes of Health Grant R01 GM067636 and a National Science Foundation CAREER Award. C.M.B. and J.P.M. thank Roche Biosciences and Bristol-Myers Squibb for predoctoral fellowships. Financial support by Glaxo Smith Kline, Eli Lilly, Astra Zeneca, Amgen, and Merck & Co. is also gratefully acknowledged.

7. Note Added in Proof

Since the submission of this review, the polyketide shimalactone A has been reported which displays a bicyclo[4.2.0]octadiene and is proposed to arise by an $8\pi-6\pi$ electrocyclization cascade process (cf. section 2.3): Wei, H.; Itoh, T.; Kinoshita, M.; Kotoku, N.; Aoki, S.; Kobayashi, M. *Tetrahedron* **2005**, *61*, 8054.

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