Biomimetic Synthesis

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Total Synthesis of Coralloidolides A, B, C, and E**

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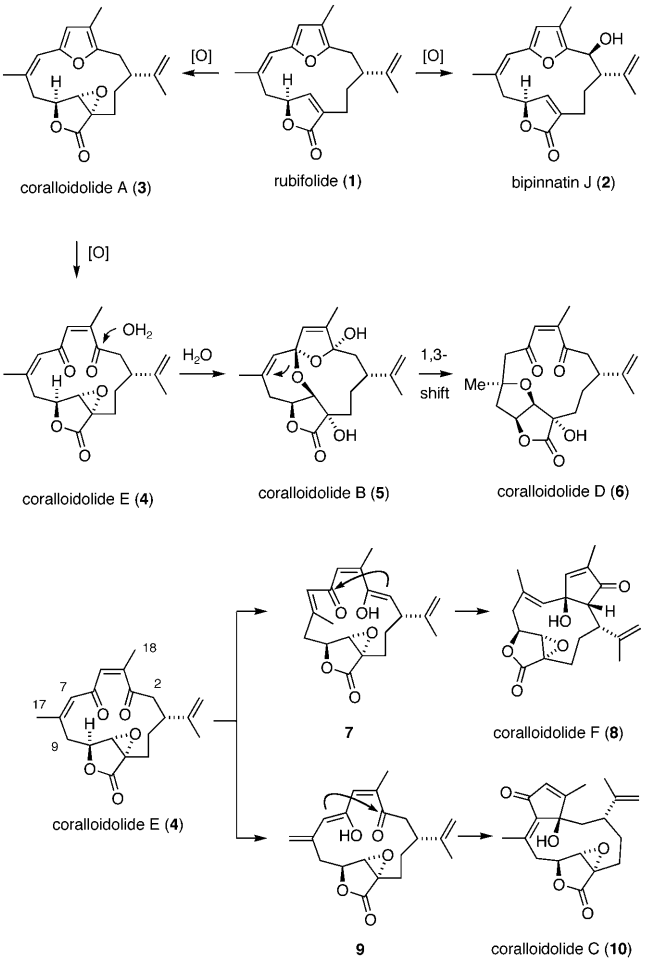
Dedicated to Klaus Römer on the occasion of his 70th birthday

The furanocembranoids are a steadily growing family of natural products that beautifully demonstrate how nature generates complexity and biological activity through oxidative diversification of low-oxidation-state precursors.[1] The biosynthesis of these diterpenoids involves the formation of a 14-membered cembrane ring from geranylgeranyl pyrophosphate, followed by oxidative transformations that initially install furan and the butenolide moieties. These heterocycles often engage in further oxidative processes, which underlie the remarkable skeletal and biological diversity of the furanocembranoids.

In previous publications, we[2] and others[3] have identified rubifolide (**1**) (Scheme 1) as a possible biosynthetic precursor of bipinnatin J (**2**) and numerous other complex diterpenoids, such as intricarene and bielschowskysin.[4] We have now expanded this proposed set of biosynthetically related molecules to include the coralloidolides, a family of diterpenoids isolated from the alcynoacean coral *Alcyonium coralloides* by Pietra et al.[5] As such, they were the first furanocembranoids to be found in a Mediterranean organism, in contrast to most other members of the family, which are of Caribbean origin.

It is intriguing to speculate that the coralloidolides are naturally derived from rubifolide (**1**). Rubifolide (**1**) has been found in other tropical corals, such as *Gersemia rubiformis*, as well as in a nudibranch, *Tochuina tetraquetra*, but it has not been isolated from *A. coralloides*.[6] In the biosynthesis presumably epoxidation of the electrophilic $\Delta^{11,12}$ double bond yields coralloidolide A (**3**). Oxidative cleavage of the furan ring of **3** then affords coralloidolide E (**4**), which features a prominent 2,5-diene-1,4-dione moiety (Scheme 1).

This functional group lends itself to several alternative reaction pathways, resulting in the formation of other members of the coralloidolide family. In the first of these, hydration of the dienedione functionality and transannular opening of the epoxide in **4** would give the tetracyclic coralloidolide B (**5**). It is conceivable that this intricate bis-



Scheme 1. Rubifolide and its proposed biosynthetic relations with bipinnatin J and the coralloidolides.

acetal could rearrange to yield coralloidolide D (**6**). Alternatively, selective tautomerization of **4** and double-bond isomerization could afford dienone enol **7**, which could undergo transannular aldol addition to the C6 carbonyl to afford coralloidolide F (**8**). Finally, a second mode of tautomerization and aldol addition (via **9**), followed by shifting of the double bond to the thermodynamically more stable position, would afford coralloidolide C (**10**).[7]

We have recently described a short synthesis of racemic bipinnatin J (**2**)[2a] and its near-quantitative transformation to rubifolide (**1**) (Scheme 2).[2b] Our efficient synthetic approach puts us in a position to test the proposed biosynthetic relationships in the laboratory in depth and identify conditions for the selective interconversion of the coralloidolides.

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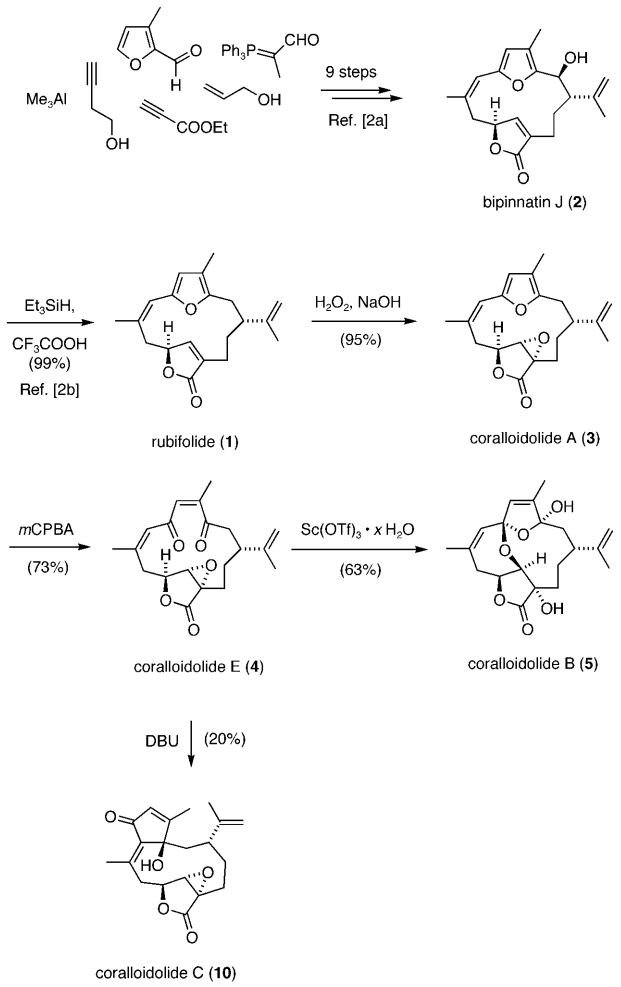
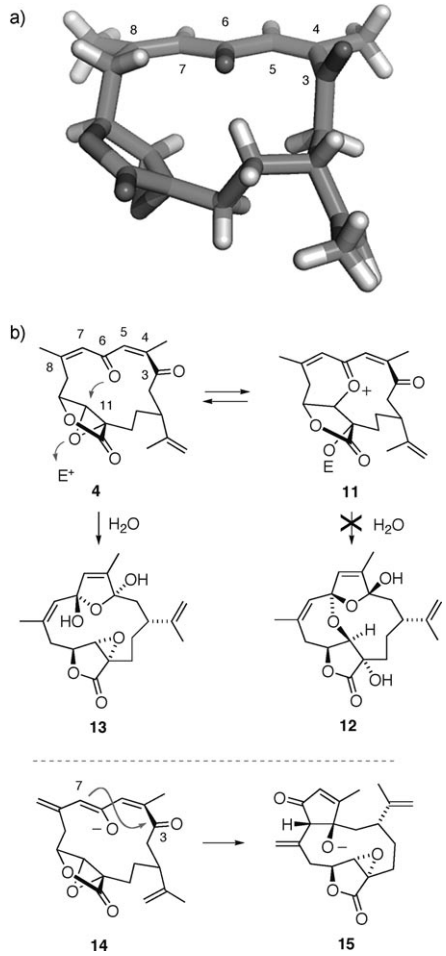


Scheme 2. Total synthesis of coralloidolides A, B, C, and E.

Given the multitude of electrophilic positions in 2,5-diene-1,4-diones and the range of possible enol forms they can form, these investigations proved to be a challenging exercise in chemoselective synthesis.

We now report the synthesis of coralloidolides A, B, C, and E by means of selective oxidations and transannular cyclizations. Our sequence starts with a chemoselective nucleophilic epoxidation of rubifolide (**1**), which provided coralloidolide A (**3**) as a single diastereomer (Scheme 2). Oxidative cleavage of the furan ring in **3** with *m*CPBA proceeded with a similar degree of chemoselectivity and afforded coralloidolide E (**4**). This key compound was then subjected to numerous reaction conditions to explore its transformations into other members of the family. In most cases, this led to the consumption of starting material and formation of a large number of intractable products. After extensive experimentation, however, we found that treatment of **4** with scandium triflate in its hydrated form in dioxane led to its clean conversion into coralloidolide B (**5**).[8] Interestingly, this reaction proceeds well in only dioxane as solvent; attempts to carry out the reaction in acetone, DMF, or a mixture of dioxane and water reduced the reaction rates and gave significantly diminished yields.

We were able to obtain an X-ray crystal structure of **4**, which provided useful insights into the mechanism and diastereoselectivity of this transformation. As can be seen in Scheme 3 a, the molecule adopts a conformation, wherein the



Scheme 3. X-ray crystal structure of **4** (a) and diastereoselectivity of the transannular cyclizations (b).

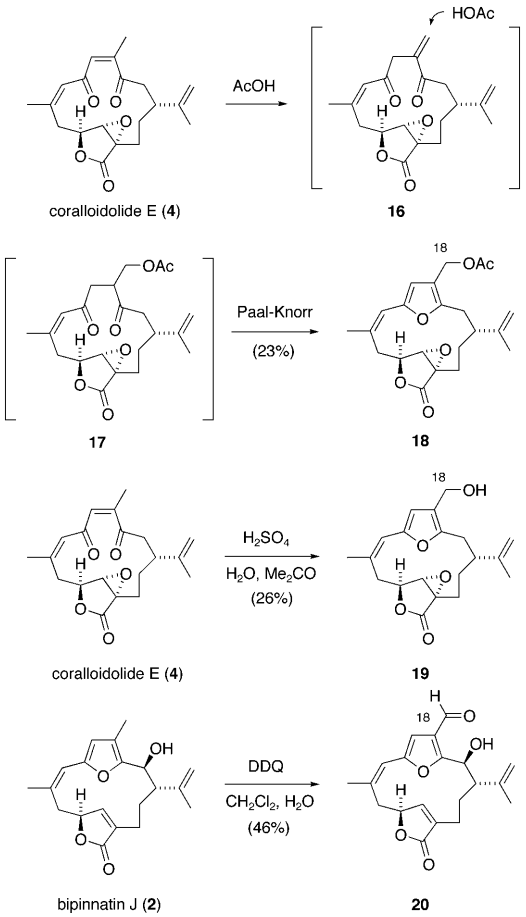
C4–C8 segment of the dienedione moiety of **4** is fully planar. The remaining C3 carbonyl group resides in an almost perpendicular orientation. (The dihedral angle C5-C4-C3-O is −106°.) Although this places the oxygen of the C6 carbonyl group in close proximity (within 3.2 Å) to the electrophilic C11 of the epoxide, the oxocarbenium ion **11** resulting from direct nucleophilic attack would afford an exceedingly strained isomer **12** upon hydration. Therefore, it appears more likely that the transannular epoxide opening proceeds in a stepwise fashion via the hydrate **13**, as originally suggested by Pietra et al.[5a] It is plausible that scandium triflate plays a twofold role in this process, catalyzing both the initial hydration of the dienedione and the subsequent intramolecular nucleophilic attack of the resulting diol **13** to afford coralloidolide B (**5**).

Our attempts to affect transannular aldol additions en route to coralloidolides F (**8**) and C (**10**) proved equally challenging. After considerable experimentation, we found that treatment of **4** with a large excess of 1,8-diazabicyclo-

[5.4.0]undec-7-ene (DBU) gave coralloidolide C (**10**) in modest yield. Since several intermediates were observed in the course of this reaction by thin-layer chromatography, and since all of them ultimately converged to coralloidolide C (**10**), it appears that **10** is the thermodynamic minimum of the series of natural products. Treatment with other bases, including LiHMDS, LDA, excess triethylamine, and pyridine, failed to give any aldol addition products.

Again, the conformation of **4** in the crystal can be used to explain the diastereoselectivity of the successful cyclization, provided the C3 carbonyl cannot reorient itself during the reaction owing to the constraints of the macrocyclic ring (Scheme 3b). Intramolecular nucleophilic attack of its enolate **14** occurs on the face of the C3 carbonyl that is oriented toward the macrocycle and affords intermediate **15**, protonation of which and subsequent double-bond isomerization then yields coralloidolide C (**10**).

Other attempts to convert **4** into **8** or **10** through transannular aldol additions and double-bond isomerizations have failed but have yielded additional interesting results (Scheme 4). For example, treatment of **4** with acetic acid gave 18-acetoxycoralloidolide A (**18**) as the only identifiable product. Similarly, when **4** was subjected to a mixture of aqueous sulfuric acid and acetone only the corresponding 18-hydroxycoralloidolide A (**19**) was isolated. Presumably, these transformations proceed through the intermediacy of double-bond isomer **16**, which undergoes conjugate addition of either acetate (→**17**) or water, followed by Paal–Knorr-type furan formation. The *exo*-methylene isomer **16** has been previously observed upon dissolution of coralloidolide E (**4**) in [D_5]pyridine and appears to be readily formed under a variety of acidic and basic conditions.[5c] Given its facile formation, it is likely that **16** exists in organisms that produce coralloidolides and thus qualifies as a genuine natural product. It is also interesting to speculate whether oxidation of the C18 methyl group in furanocembranoids can proceed through the mechanism depicted in Scheme 4 or requires enzymatic hydroxylation. It should be noted, however, that hydroxymethylene derivatives of type **19** are rarely, if ever, observed among furanocembranoids.



Scheme 4. Selective functionalizations at C18 of **4**.

The selective oxidation of the C18 methyl group could also be achieved by other chemical methods. For instance, treatment of bipinnatin J with excess DDQ gave aldehyde **20** in moderate yield. This provides another example of a highly selective oxidation of the fascinating furanocembranoid framework.

In summary, we have reported the first total synthesis of the furanocembranoids coralloidolides A, B, C, and E. Racemic coralloidolides B and C were synthesized without recourse to protecting-group chemistry, each in 13 steps, starting from the simple materials shown in Scheme 2. Several highly selective transformations have been discovered, which will undoubtedly find utility in synthetic approaches toward other members of the furanocembranoid class of natural products. Our synthetic work provides insight into the biogenetic relationships within this family and adds to the matrix of chemical and biosynthetic relations among furanocembranoids.

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