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Biomimetic Synthesis of (±)-Pinnatal and (±)-Stereokunthal A

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Pericyclic reactions such as cycloadditions, sigmatropic rearrangements, and electrocyclizations have been identified in many biosynthetic pathways.¹ In several cases, their occurrence has been corroborated by biomimetic total synthesis.² With the recent disclosure of the crystal structure of a Diels–Alderase, the enzymology of these reactions appears to have gained a firm footing as well.³

The plant family of *Bignoniaceae* has yielded a range of biologically active natural products whose biosynthesis might also involve pericyclic steps (Chart 1). Pinnatal (**1**) and isopinnatal (**2**) were isolated from the “sausage tree” *Kigelia pinnata*.⁴ The related naphthoquinones stereokunthal A (**4**) and B (**3**) have recently been found together with pinnatal in *Stereospermum kunthianum*.⁵ Pyranokunthones A (**5**) and B (**6**), as well as anthrakunthone (**7**), were also isolated from the root bark extract of *S. kunthianum*. Pinnatal, isopinnatal, and stereokunthal A are highly effective against *Plasmodium falciparum* representing interesting lead compounds for drugs against malaria.

Structurally, the natural products share a modified naphthoquinone core. In the case of compounds **1**–**3**, the remaining 10 carbons are incorporated in a complex heterocyclic ring system featuring three quaternary and two tertiary stereocenters. While the relative stereochemistry of the compounds has been elucidated by detailed NMR studies and an X-ray structure analysis,⁴ their absolute stereochemistry remains unknown.

It is interesting to speculate whether *all* the natural products shown in Chart 1 are derived from a common biosynthetic precursor, naphthoquinone **8**, through a series of oxidations and pericyclic reactions (Chart 2). Naphthoquinone **8**, the prenylated version of the widely distributed natural product lapachol (**9**), has been previously isolated from the roots of *Conospermum teretifolium*, a plant only distantly related to the *Bignoniaceae*.⁶

According to our biosynthetic hypothesis, oxidation of the aromatic nucleus and the benzylic/allylic position in the side chain of **8** affords intermediate **10** (Scheme 1). Subsequent β -elimination leads to triene **11** as a mixture of geometrical isomers, which cyclize in different ways. A [4 + 2] cycloaddition of (*E*)-**11** affords pyranokunthone A (**5**). By contrast, (*Z*)-**11** undergoes 6π electrocyclicization to yield pyranokunthone B (**6**). Stereoselective allylic oxidation of **6** then leads to another hypothetical intermediate **12**, which undergoes an intramolecular Diels–Alder reaction to afford pinnatal (**1**).⁷

Stereokunthal A (**4**) is formed from pinnatal (**1**) via retro hetero Diels–Alder reaction.⁸ Finally, a Baeyer–Villiger-type oxidation of the formyl group, followed by elimination of formic acid, could aromatize the cyclohexadiene ring to afford anthrakunthone (**7**).⁹ Analogous biosynthetic routes with different oxidation patterns in the aromatic ring lead to isopinnatal (**2**) and stereokunthal B (**3**).

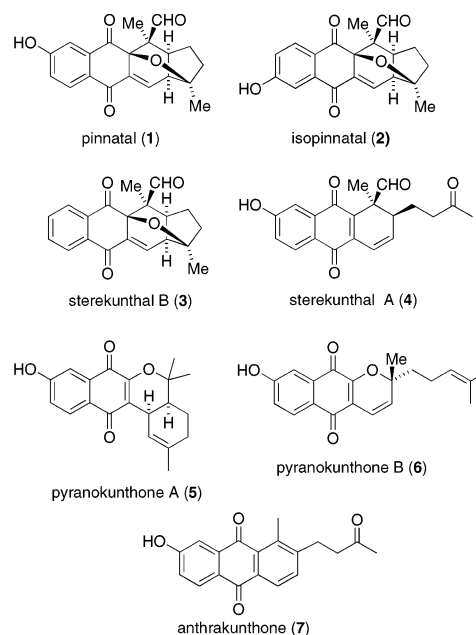
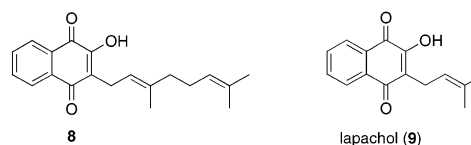
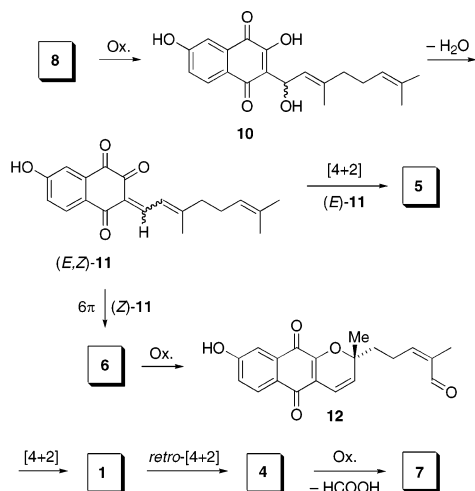
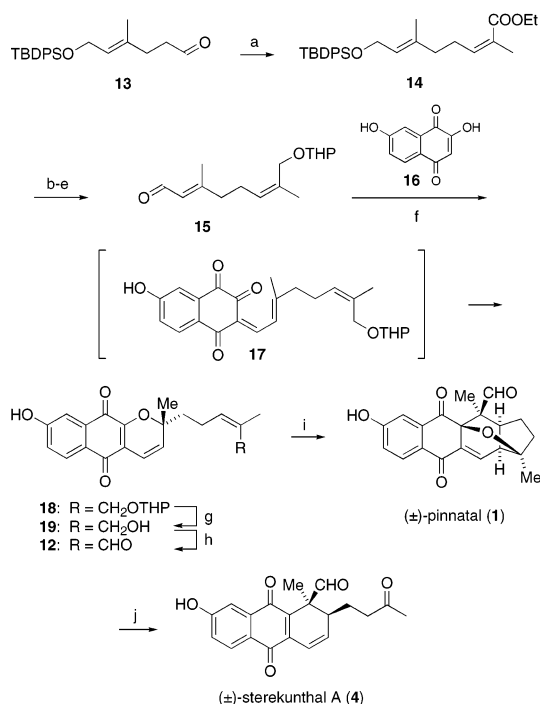
Chart 1. Bioactive Natural Products Isolated from *Bignoniaceae*

Chart 2. Prenylated Hydroxynaphthoquinones



With this biosynthetic hypothesis in mind, we have launched a program aimed at the total synthesis of the natural products shown in Chart 1. We now report a synthesis of racemic pinnatal and stereokunthal A featuring many of the proposed biosynthetic reactions as key steps.

Our syntheses started with the known aldehyde **13**,¹⁰ which was obtained from geraniol in a series of straightforward steps (Scheme 2). A highly stereoselective Still–Gennari olefination¹¹ afforded (*Z*)-ester **14** (*Z:E* > 20:1). Reduction of this material, followed by protection as the tetrahydropyranyl ether, removal of the silyl protecting group, and subsequent oxidation, furnished the α,β -unsaturated aldehyde **15**. Knoevenagel condensation of **15** with the known hydroxynaphthoquinone **16**¹² afforded triene **17**, which immediately underwent 6π electrocyclicization to yield pyran **18**.¹³ Acidic cleavage of the THP protecting group then gave allylic alcohol **19**, whose oxidation under Swern conditions afforded the hypothetical biosynthetic intermediate **12**. Upon standing neat at room temperature, this aldehyde underwent spontaneous cyclization to yield (±)-pinnatal (**1**). As predicted, heating of **1** in benzene solution resulted in retro hetero Diels–Alder reaction to afford (±)-

Scheme 1. Proposed Biosynthetic Relations**Scheme 2.** Total Synthesis of (±)-Pinnatal and (±)-Stereokunthal A^a

^a Reagents and conditions: (a) (TFEO)₂P(O)CH₂COOEt, KHMDS, 18-C-6 (76%); (b) DIBAL (94%); (c) DHP, PPTS (99%); (d) TBAF (90%); (e) MnO₂ (81%); (f) **16**, β-alanine, AcOH, PhH, 90 °C (54%); (g) pTsOH, MeOH (97%); (h) Swern reagent (87%); (i) rt, neat (91%); (j) PhH, 160 °C (92%).

stereokunthal A (**4**). The ¹H NMR, ¹³C NMR, IR, and MS spectra of our synthetic material were in full agreement with data published for the natural products (see Supporting Information).

The remarkably mild conditions of the Diels–Alder reaction leading to **1** suggest that this step is indeed biomimetic. We believe that the reaction is catalyzed by the phenolic hydroxy group of **12**.

Methylated versions of **12** failed to undergo the cycloaddition at ambient temperature. In principle, stereokunthal (**4**) could be an isolation artifact. However, since the retro hetero Diels–Alder reaction requires relatively high temperatures and anthrakunthone (**7**) is probably biosynthetically derived from **4**, it appears likely that **4** is truly a natural product.¹⁴

In summary, a concise synthesis of racemic pinnatal and stereokunthal A has been achieved, which probably reflects the biosynthesis of the natural products. Studies toward their asymmetric synthesis via Lewis acid-catalyzed intramolecular dynamic kinetic resolution are well underway. Total syntheses of other antimalarial naphthoquinones shown in Chart 1 have been achieved and will be reported in due course.

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Supporting Information Available: Full experimental details and spectra for compounds **12**–**19** and synthetic **1** and **4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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