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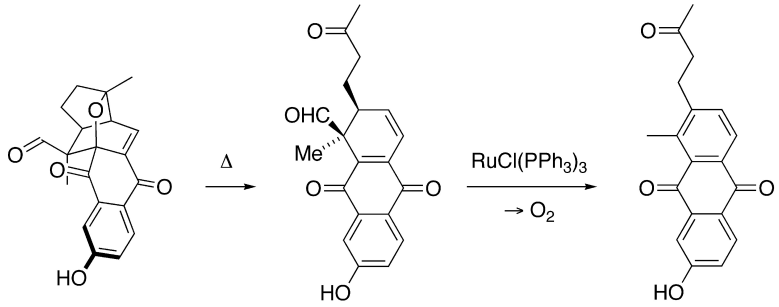

pinnatal — sterekunthal A — anthrakunthone

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Biomimetic Synthesis of Antimalarial Naphthoquinones

Jeremiah P. Malerich, Thomas J. Maimone, Gregory I. Elliott,† and Dirk Trauner*

Contribution from the Department of Chemistry, University of California−Berkeley, Berkeley, California 94720-1460

Received January 6, 2005; E-mail: trauner@cchem.berkeley.edu

Abstract: The total synthesis of naphthoquinone natural products isolated from the Bignoniaceae plant family is described. Pinnatal, isopinnatal, sterekunthals A and B, pyranokunthones A and B, and anthrakunthone have been prepared along the lines of a biosynthetic proposal involving pericyclic reactions as key steps. The first case of catalysis in oxa 6π electrocyclizations is reported.

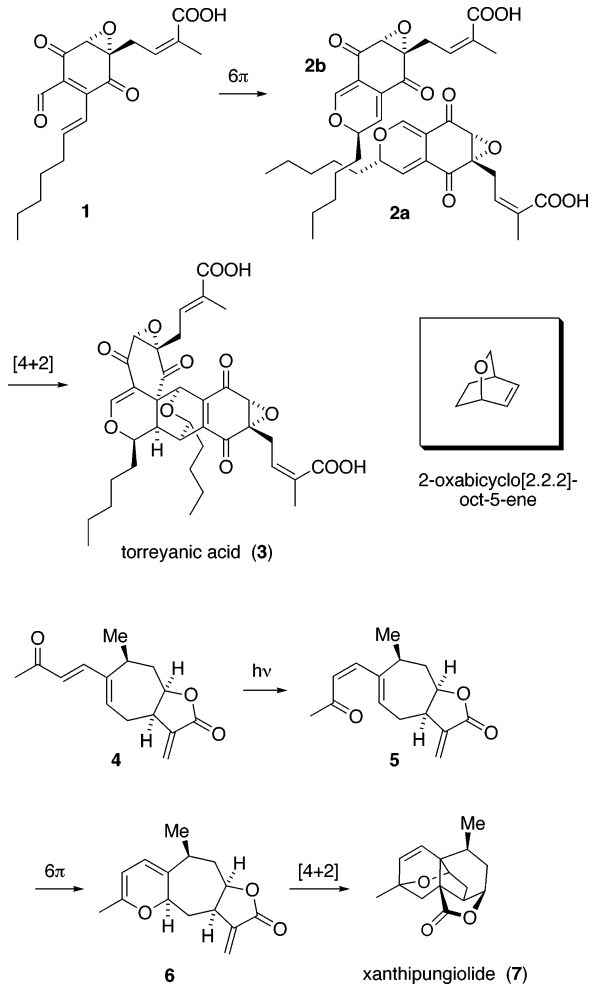
Introduction

Pericyclic reaction cascades are very effective in creating structurally complex molecules from simple precursors. Increasingly they have been recognized to play a role in the biosynthesis of natural products. Various combinations of electrocyclizations, sigmatropic rearrangements, and cycloadditions have been found, for instance 8π−6π electrocyclization cascades,[1] [3,3]-sigmatropic rearrangements followed by Diels−Alder reactions,[2] or combinations of electrocyclizations with cycloadditions.[1a,3]

Oxa 6π electrocyclization followed by [4+2] cycloadditions are a special case (Scheme 1). A recent example for such a sequence can be found in the biosynthesis of torreyanic acid (**3**).[4] As originally proposed by Clardy and subsequently demonstrated by Porco's total synthesis, aldehyde **1** undergoes reversible 6π electrocyclization to afford two diastereomeric pyrans, **2a** and **2b**, which subsequently dimerize via [4+2] cycloaddition to generate the natural product **3**.

A related oxa 6π electrocyclization/Diels−Alder cascade was proposed by Bohlmann to account for the formation of the complex sesquiterpene xanthipungolide (**7**) from xanthatin (**4**).[5] Photochemical isomerization of **4** sets the stage for subsequent oxa 6π electrocyclization (**5** → **6**). The resulting pyran **6** is then intercepted by Diels−Alder reaction involving the *exo*-methylene lactone moiety as dienophile to afford the pentacyclic natural product.

Scheme 1. Oxa 6π-Electrocyclization/Diels−Alder Cascades in Biosynthesis



The elegance and efficiency of these electrocyclization/Diels−Alder cascades prompted us to investigate how frequently they occur in nature. Searching for their retron, a 2-oxabicyclo[2.2.2]-oct-5-ene moiety, in electronic databases, we discovered pinnatal (**8**),[6] isopinnatal (**9**),[7] and sterekunthal B (**10**)[8] (Chart 1). These

† Current address: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Rd., La Jolla, CA 92037.

(1) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996. (b) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221−2224. (c) Moses, J. E.; Baldwin, J. E.; Bruckner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670−3684. (d) Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968−15969.
(2) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115. (b) Nicolaou, K. C.; Sasmal, P. K.; Xu, H. *J. Am. Chem. Soc.* **2004**, *126*, 5493−5501.
(3) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935−3938. (b) Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911−4913.
(4) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232−3233. (b) Li, C. M.; Johnson, R. P.; Porco, J., J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095−5106.
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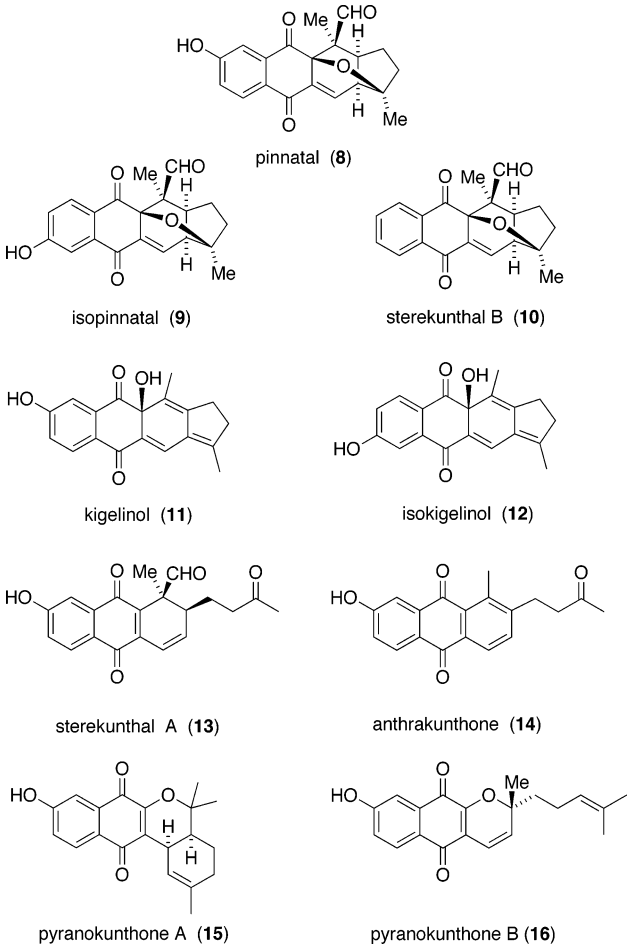
10.1021/ja050092y CCC: $30.25

Chart 1. Naphthoquinones from Bignoniaceae



complex natural products belong to a growing class of naphthoquinone derivatives isolated from trees of the Bignoniaceae family. Other members of this series are kigelinol (**11**) and isokigelinol (**12**),[7] sterekunthal A (**13**),[8] anthrakunthone (**14**),[8] and pyranokunthones A (**15**) and B (**16**).[8] All of them share a common naphthoquinone (or modified naphthoquinone) moiety, which is fused to heterocyclic or carbocyclic ring systems of varying complexity.

Biological Activity. The natural products shown in Chart 1 accumulate in the root bark of Bignoniaceae trees, whose extracts have been used extensively in African tribal medicine.[9] The activity of their components has been evaluated in a number of contexts.[10] Houghton and co-workers showed that isopinnatal has IC_{50} values of 0.76 and 1.55 μM against chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum*, respectively.[11] The kigelinols were 10 times less active than isopinnatal toward the strains tested. In a separate study by Jennett-Siems, the antiplasmodial activity of the natural products isolated from *S. kunthianum* was assessed.[8] Sterekunthal A proved to be the most potent against the poW and Dd2 strains of *P. falciparum* (IC_{50}: 3.8 and 1.2 μM, respectively), while related pinnatal and sterekunthal B were somewhat less active (IC_{50}: 16−97 μM). Isopinnatal was demonstrated to have activity against *Trypsonoma* parasites with IC_{50} values of 0.37 μM against *T. brucei brucei* and 0.73 μM against *T. brucei rhodesiense*.[12] Once again, the kigelinols were 10-fold less effective. In a study of anticancer activity by Houghton, isopinnatal was shown to have slightly lower IC_{50} values against melanoma cell lines (G361: 33 μM, StML11a: 15 μM) than nonmelanoma cells (C32: 48 μM, CHO: 176 μM).[13] The full evaluation of these compounds was somewhat hampered by their limited availability, increasing their attractiveness as targets of total synthesis.

Unified Biosynthetic Proposal. A detailed retrosynthetic and biosynthetic analysis of the compounds shown in Chart 1 led us to conclude that they are all linked by a common biosynthetic pathway featuring an oxa 6π electrocyclization/Diels−Alder cascade (Scheme 2). According to our proposal, prenylated hydroxynaphthoquinone **17** undergoes oxidation of the aromatic nucleus and in the most activated allylic position to yield hypothetical intermediate **18**. Hydroxynaphthoquinone **17**, the prenylated version of the widely distributed natural product lapachol, has been previously isolated from the roots of *Conospermum teretifolium*, an Australian plant only distantly related to the Bignoniaceae.[14] Its oxidation product **18** eliminates water and undergoes facile double-bond isomerization to yield **19**, whose cyclization via intramolecular hetero Diels−Alder reaction affords pyranokunthone A (**15**). Alternatively, dehydration of **18** to afford **20**, followed by oxa 6π electrocyclization, gives pyranokunthone B (**16**). Selective allylic oxidation of this natural product then affords unsaturated aldehyde **21**. This key intermediate undergoes intramolecular [4+2] cycloaddition to form the complex heterocyclic framework of pinnatal (**8**). Another pericyclic step, a retro hetero Diels−Alder reaction, converts pinnatal (**8**) into sterekunthal A (**13**). Finally, a Baeyer−Villiger type oxidation of **13**, followed by elimination of formic acid, affords fully aromatized anthrakunthone (**14**). Anthrakunthone could also arise from sterekunthal A via vinylogous retro Claisen condensation followed by oxidative aromatization of the resulting cyclohexadiene.

The kigelinols presumably stem from pinnatal and isopinnatal, respectively. Baeyer−Villiger type oxidation, possibly catalyzed by an enzyme of the aromatase class,[15] could furnish formate **22**. Elimination of formic acid with concomitant opening of the strained heterocycle, which is stereoelectronically set up for an E2 elimination, yields kigelinol (**11**). The isomeric natural products isopinnatal (**9**), sterekunthal B (**10**), and isokigelinol (**12**) would arise from an analogous pathway, differing only in the oxidation pattern of the aromatic ring.

Inspired by this biosynthetic hypothesis we have set out to synthesize the antimalarial naphthoquinones shown in Chart 1. We now wish to give a full account of our studies, which culminated in the total synthesis of pinnatal, isopinnatal, sterekunthal B, sterekunthal A, anthrakunthone, and the

(6) Joshi, K. C.; Singh, P.; Taneja, S.; Cox, P. J.; Howie, R. A.; Thomson, R. H. *Tetrahedron* **1982**, *38*, 2703−2708.
(7) Akunyili, D. N.; Houghton, P. J. *Phytochemistry* **1993**, *32*, 1015−1018.
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(9) Irvine, F. R. *Woody Plants of Ghana*; University Press: Oxford, 1961.
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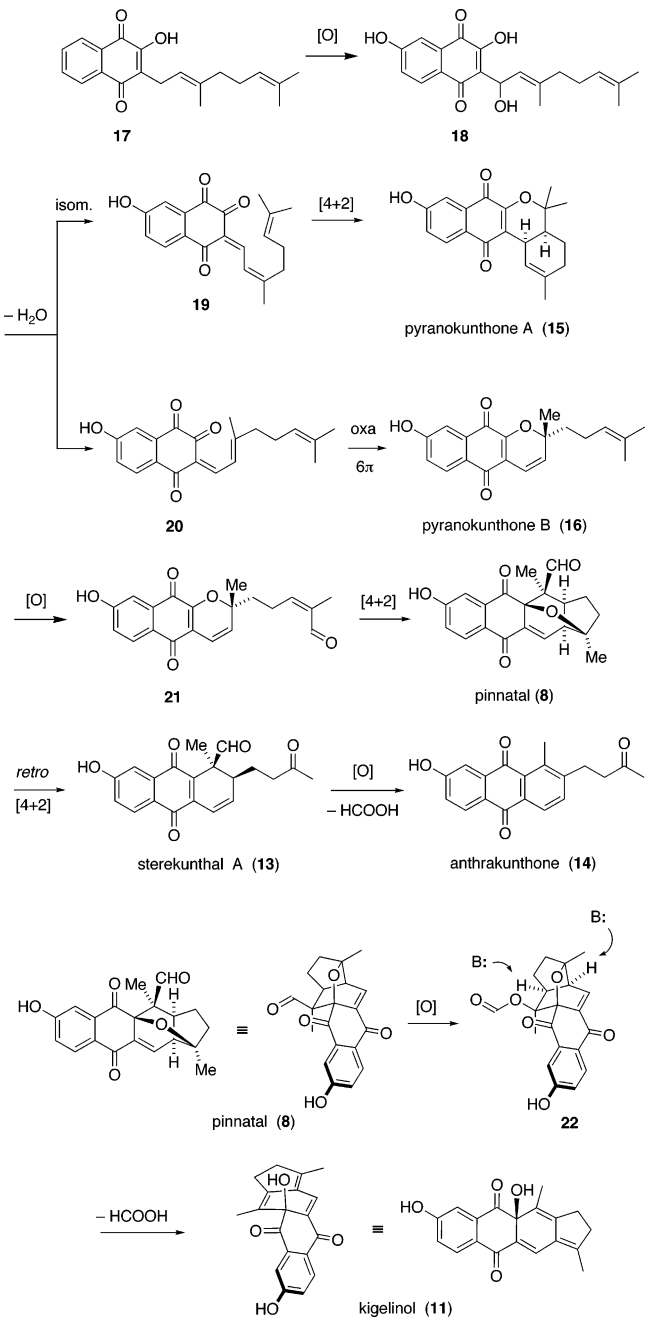
(13) Jackson, S. J.; Houghton, P. J.; Retsas, S.; Photiou, A. *Planta Med.* **2000**, *66*, 758−761.
(14) Cannon, J. R.; Joshi, K. R.; McDonald, I. A.; Retallack, R. W.; Sierakowski, A. F.; Wong, L. C. H. *Tetrahedron Lett.* **1975**, *32*, 2795−2798.
(15) Michal, G. *Biochemical Pathways*; Wiley: Berlin, 1999.

Scheme 2. Biosynthetic Proposal



pyranokunthones. Our investigations on the asymmetric synthesis of pinnatal and sterekunthal A, as well studies on the kinetics of the central oxa 6π electrocyclization, are described in detail as well.

Results and Discussion

Model Systems. Our initial attempts toward pinnatal and isopinnatal sought to rapidly explore the feasibility of a Knoevenagel condensation/electrocyclization/cycloaddition cascade to rapidly assemble the molecular skeleton of **8**, **9**, and **10** (Scheme 3). Thus, allylic alcohol **24**, which was obtained in three steps from geranyl acetate,[16] was oxidized with MnO_2 to give unsaturated aldehyde **25**. Heating **25** with commercially available 2-hydroxynaphthoquinone (**26**), catalytic amounts of β-alanine, and HOAc accomplished two-thirds of our desired sequence providing pyran **27**. Seeking more forceful conditions to promote the ensuing Diels–Alder reaction, **27** was heated to 160 °C in a sealed tube. Analysis of the sole product of this reaction discounted the anticipated pinnatal analogue **28**. Instead, the compound was identified as methyl ketone **29**. We quickly realized that we had performed the desired intramolecular Diels–Alder reaction, but it was followed by an unexpected hetero [4+2] cycloreversion. Literature searches at the time of this result resulted in no hits for natural products corresponding to **29**. Therefore, while we were excited by this result, our next goal was to prevent the unforeseen retro Diels–Alder reaction. Only after we completed the synthesis of pinnatal (see below) did we realize that **29** corresponds to sterekunthal A (**13**).

To more closely model the pinnatal and isopinnatal systems, we sought to prepare analogues containing the phenolic hydroxyl group in protected form (Scheme 4). Reported procedures to obtain 2,6- and 2,7-dihydroxynaphthoquinone by oxidation of naphthalene diols were unsuccessful in our hands.[17] Therefore, we considered methoxy naphthoquinones **31**, assuming the phenol could be deprotected at a later stage in our efforts toward the natural products. These compounds were readily prepared by autoxidation of commercially available methoxy tetralones **30**.[18] Condensation/electrocyclization reactions of **31** with aldehyde **24** produced corresponding oxygenated pyrans **32**. In a fashion similar to **27**, compounds **32** were converted to methyl ketones **33** when subjected to elevated temperatures.

Attempts to promote the intramolecular Diels–Alder reaction of esters **32** with various Lewis acids gave mixed results. While we were never able to obtain the corresponding cycloadducts, we often isolated the products of Lewis-acid-promoted electrocyclic ring opening (see below). This allowed us to eventually investigate the kinetics of the oxa 6π electrocyclization in detail and led to the discovery of acid catalysis in these reactions.

Still hoping to catalyze the desired Diels–Alder reaction, we turned to organocatalysis (Scheme 5).[19] This seemed to be a prudent strategy, given that transformation of the ester function in **32** to an aldehyde was necessary to complete the synthesis of pinnatal. However, reduction of this ester proved problematic in the presence of other reactive carbonyls and proceeded in very low yield. This was our first indication that a successful synthetic strategy would have to circumvent hydride reduction at a late stage. Nevertheless, sufficient amounts of allylic alcohol **34** were procured through DIBAL reduction of **32b**. Subsequent Swern oxidation gave unsaturated aldehyde **35**. Unfortunately, none of our attempts with several organocatalysts (e.g., with aminoester **36**) were successful. It is likely that the α-branching of the unsaturated aldehyde **35** rendered our substrate incompatible with this methodology.

Next, we explored the viability of a transannular Diels–Alder strategy (Scheme 6).[20] We reasoned that addition of the allylic alcohol function in **34** to the more electrophilic carbonyl group would form a macrocyclic acetal **38** (R = H, Me), setting the stage for a potentially biomimetic intramolecular cycloaddition.

(16) Marshall, J. A.; Lebreton, J.; Dehoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883–3889.

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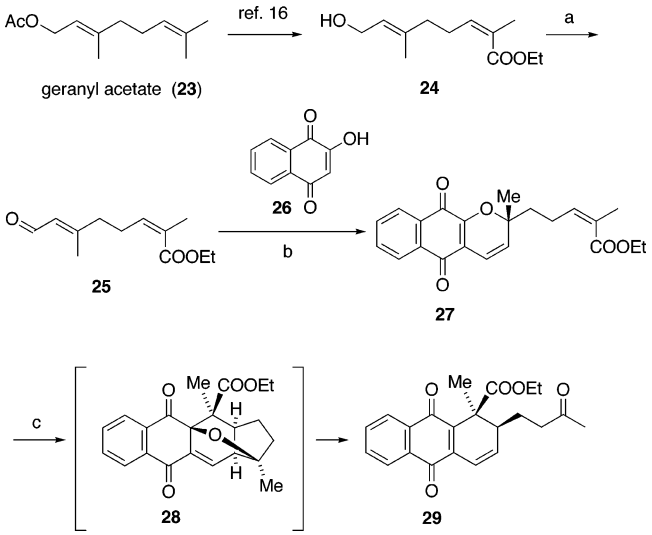
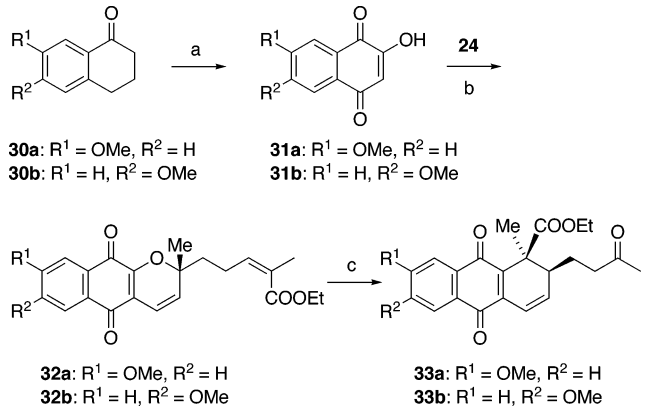
(20) Soucy, P.; L'Heureux, A.; Toro, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 9983–9987, and references therein.

Scheme 3. Initial Model Studies[a]



[a] Reagents and conditions: (a) MnO_2, 90%; (b) **26**, β-alanine, HOAc, 51%; (c) PhH, 160 °C, 82%.

Scheme 4. Oxidized Models[a]



[a] Reagents and conditions: (a) KO*t*Bu, O_2, **31a**: 68%, **31b**: 62%; (b) **24**, β-alanine, HOAc, **32a**: 50%, **32b**: 52%; (c) PhH, 160 °C, **33a**: 81%, **33b**: 82%.

Unfortunately, we were never able to reduce this attractive idea to practice despite exploring a variety of acetalization conditions.

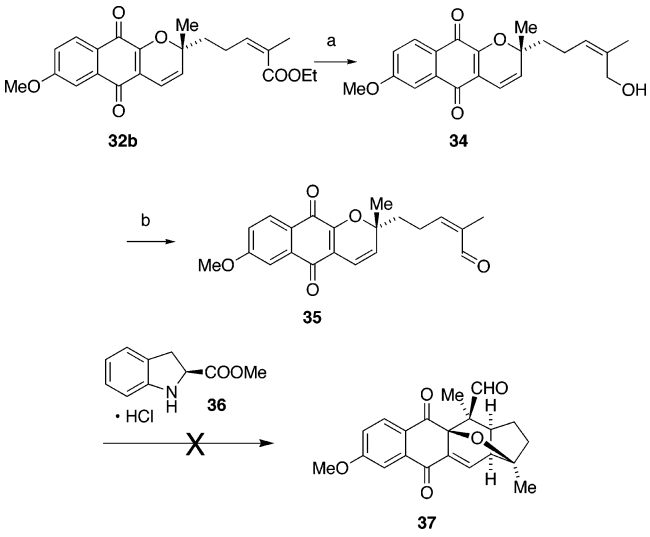
With our attempts at catalysis at ambient temperature unsuccessful, we turned to changing the thermodynamics of the system. Since cycloadditions typically have negative activation and reaction volumes, we reasoned that running the reaction at high pressure could provide a solution.[21] To our delight, pressurizing **32b** to 14 kbar (13800 atm) in CH_2Cl_2 for 50 h provided isopinnatal analogue **40** in 52% yield together with a 25% yield of recovered **32b** (Scheme 7). No product of cycloreversion was observed under these conditions.

Total Syntheses. With the results of these model studies in mind we streamlined our synthetic strategy to avoid an endgame deprotection of the phenol and oxidation state adjustment of the ester. Our revised plan sought to synthesize aldehyde **21**, a proposed biosynthetic intermediate (cf. Scheme 2), through oxidation of the corresponding alcohol.

To this end, naphthoquinone **31a** had to be demethylated (Scheme 8). Milder conditions (BBr_3, pyridine·HCl, NaSEt)

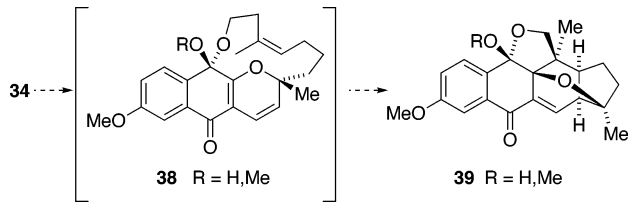
(21) Fringuelli, F.; Taticchi, A. In *The Diels−Alder Reaction*; Fringuelli, F., Taticchi, A., Eds.; Wiley: New York, 2002; pp 206−249.

Scheme 5. Attempted Organocatalysis[a]

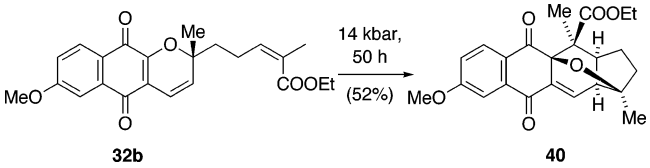


[a] Reagents and conditions: (a) DIBAL, 17%. (b) Swern reagent, 57%.

Scheme 6. Proposed Transannular Cycloaddition



Scheme 7. High-Pressure Diels−Alder Reaction

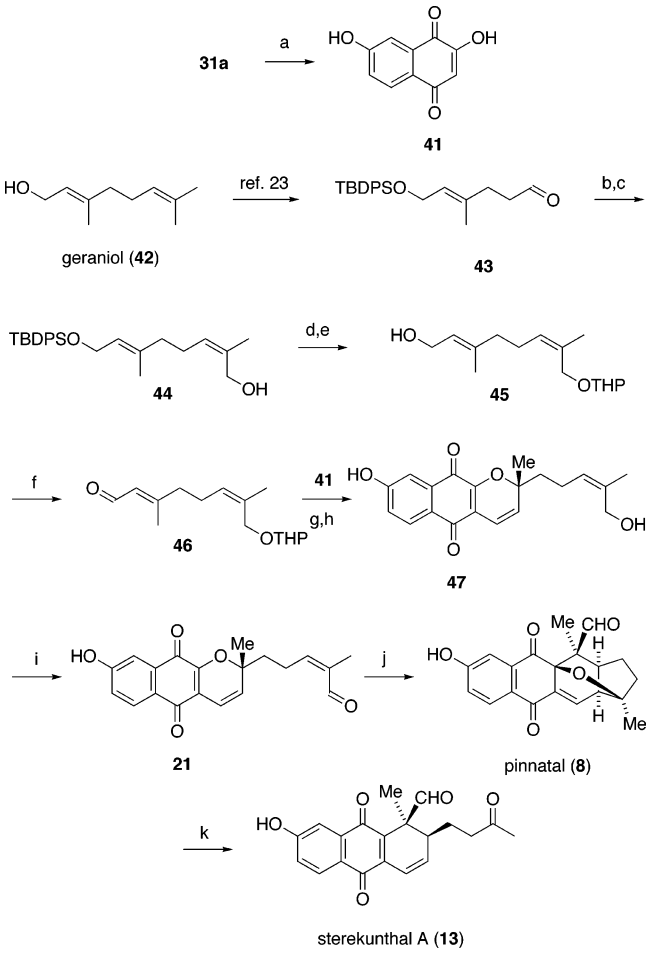


failed, and as a result **31a** was subjected to brief treatment with molten $AlCl_3$, followed by careful aqueous workup, to provide phenol **41**.[22] On the other hand, aldehyde **46** was synthesized in straightforward fashion in eight steps from geraniol, as previously described.[23,24] A Knoevenagel condensation/electrocyclization sequence involving **41** and **46**, followed by deprotection of the resulting THP ether under acidic conditions, provided allylic alcohol **47**. Subsequent Swern oxidation gave aldehyde **21**, a constitutional isomer of pinnatal. Given our previous experience dealing with the analogous Diels−Alder reaction model systems, we were prepared to subject this compound to high-pressure conditions. To our surprise however, cycloaddition of **21** proceeded at ambient temperature and pressure to provide pinnatal (**8**) in very good yield. The mildness of these conditions suggests that this intramolecular cycloaddition is indeed biomimetic. Finally, as predicted by our biosynthetic proposal, heating of pinnatal to elevated temperatures gave sterekunthal A (**13**) via retro hetero Diels−Alder reaction.[24]

Encouraged by this success, we hoped that the kigelinols and anthrakunthone could be procured along the lines of our

(22) Davies, J. E.; Roberts, J. C. *J. Chem. Soc.* **1956**, 2173−2176.
(23) Muto, S.; Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, *14*, 2159−2165.
(24) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554−9555.

Scheme 8. Synthesis of (±)-Pinnatal and (±)-Sterekunthal A[a]

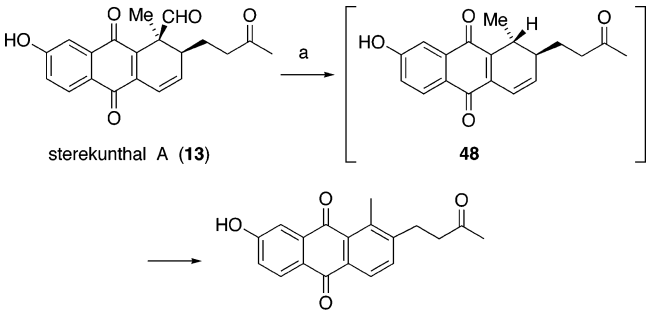


[a] Reagents and conditions: (a) $AlCl_3$, 53%; (b) $(TFEO)_2P(O)CH_2COOEt$, KHMDS, 18-crown-6 (76%); (c) DIBAL, 94%; (d) DHP, PPTS, 99%; (e) TBAF, 90%; (f) MnO_2, 81%; (g) β-alanine, HOAc, 54%; (h) TsOH, MeOH, 97%; (i) Swern reagent, 87%; (j) neat, rt, 91%; (k) PhH, 160 °C, 92%.

proposed biosynthesis as readily as their precursors. Unfortunately, attempts to elicit selective Baeyer−Villiger oxidation of pinnatal and sterekunthal A were unsuccessful, presumably due to the steric hindrance of the formyl group. This largely ruled out syntheses of the kigelinols; however, while the elimination of formic acid was not possible, we hoped that transition metal mediated deformylation of sterekunthal A, followed by spontaneous oxidative aromatization of the resulting cyclohexadiene, would be more fruitful. Indeed, treatment of sterekunthal A (**13**) with Wilkinson's catalyst followed by aerobic workup yielded anthrakunthone (**14**) (Scheme 9).

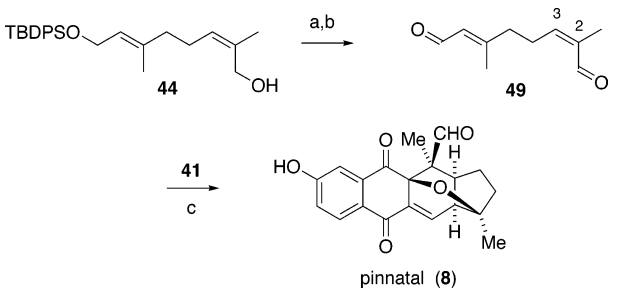
To further shorten our synthesis of pinnatal and minimize protective group manipulations, we attempted a one-pot Knoevenagel condensation/electrocyclization/cycloaddition cascade. To this end, bisaldehyde **49** was prepared by deprotection and Swern oxidation of **44**. We reasoned that the regiochemistry of the condensation would be biased toward the desired formyl group based on steric grounds. In the event, heating naphthoquinone **41** with **49** in the presence of ethylenediamine diacetate (EDDA) did give pinnatal in 10% yield. Unfortunately, this low yield could not be increased, although a variety of conditions were explored. Isomerization of the C2−C3 double bond appeared to be a major side reaction. A one-pot synthesis of sterekunthal A (**13**) involving a tandem Knoevenagel condensation/electrocyclization/cycloaddition/cycloreversion sequence was attempted as well, but none of the desired natural product could be isolated.

Scheme 9. Synthesis of Anthrakunthone[a]



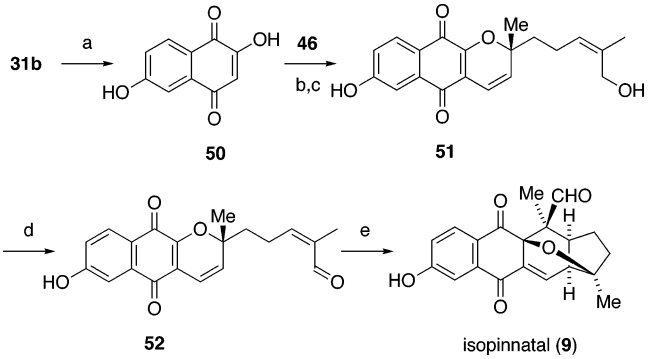
[a] Reagents and conditions: (a) $RhCl(PPh_3)_3$, then air, 47%.

Scheme 10. Condensation/Electrocyclization/Cycloaddition Cascade[a]



[a] Reagents and conditions: (a) TBAF, 92%; (b) Dess−Martin periodinane, 83%; (c) EDDA, 10%.

Scheme 11. Synthesis of (±)-Isopinnatal[a]

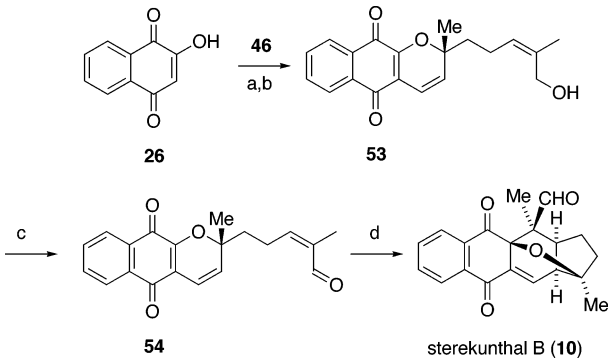


[a] Reagents and conditions: (a) $AlCl_3$, 61%; (b) EDDA, 82%; (c) TsOH, MeOH, 95%; (d) Dess−Martin periodinane, 85%; (e) neat, rt, 14 days, 81%.

The total synthesis of isopinnatal and sterekunthal B followed analogously that of pinnatal (Schemes 11 and 12). Pyrans **51** and **53** were prepared by condensation of naphthoquinones **50** and **26**, respectively, with aldehyde **46** under optimized conditions using EDDA in THF, followed by treatment with TsOH in MeOH. Oxidation with Dess−Martin and Swern reagents then gave aldehydes **52** and **54**, respectively. Cyclization of **52** to isopinnatal proceeded at a rate comparable to the pinnatal case, achieving full conversion over 10 days at room temperature. On the other hand, **10** was formed at a much slower rate, requiring 100 days to consume **54**. The X-ray structure of sterekunthal B is shown in Figure 1.

It is interesting to speculate on the differences in rates of the Diels−Alder reactions leading to model compound **40**, pinnatal (**8**), isopinnatal (**9**), and sterekunthal B (**10**). Both the electronic

Scheme 12. Synthesis of (±)-Sterekunthal B[a]



[a] Reagents and conditions: (a) **46**, EDDA, 86%; (b) TsOH, MeOH, 100%; (c) Swern reagent, 76%; (d) neat, rt, 100 days, 70%.

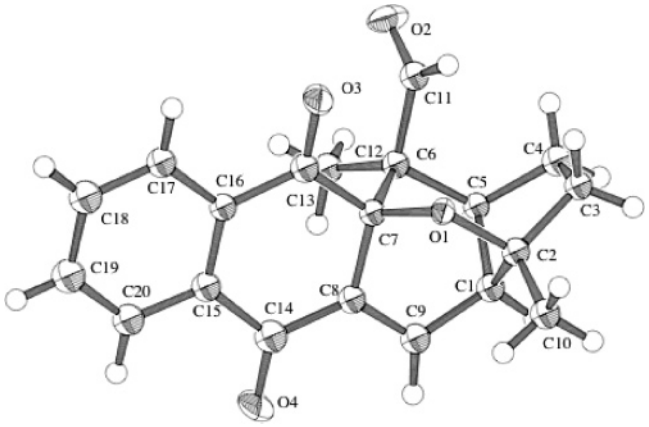


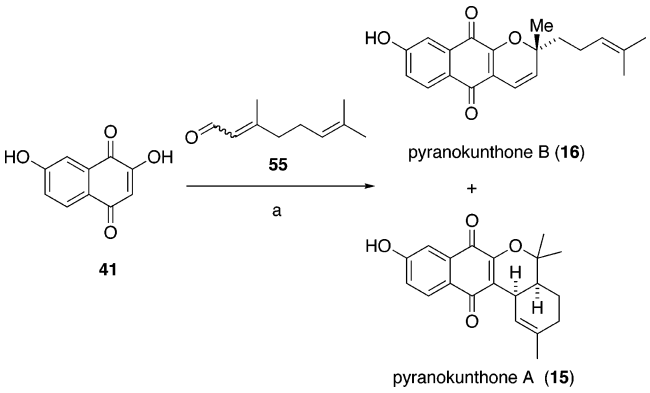
Figure 1. X-ray structure of sterekunthal B.

nature of the aromatic ring and the effects of a free phenol need to be considered. Whereas the slow rate of the cyclization of **54** could be explained based on electronic grounds, the fact that ester **32b** and aldehyde **37** failed to undergo appreciable cycloaddition at room temperature and ambient pressure suggests that the cyclization is catalyzed by the acidic phenol functionality.

Pyranokunthones A and B were obtained simultaneously by β-alanine-catalyzed reaction of **41** with citral (**55**), a commercially available 2:1 mixture of geranial and neral (Scheme 13). Under these conditions, the product of oxa 6π electrocyclization, pyranokunthone B (**16**), was formed as the major isomer (50%), whereas the hetero Diels−Alder product pyranokunthone A (**15**) was isolated only in very low yield (5%). This result is commensurate with previously reported pyran syntheses from 1,3-dicarbonyl compounds and citral.[25] Only in rare cases is the hetero Diels−Alder product observed.

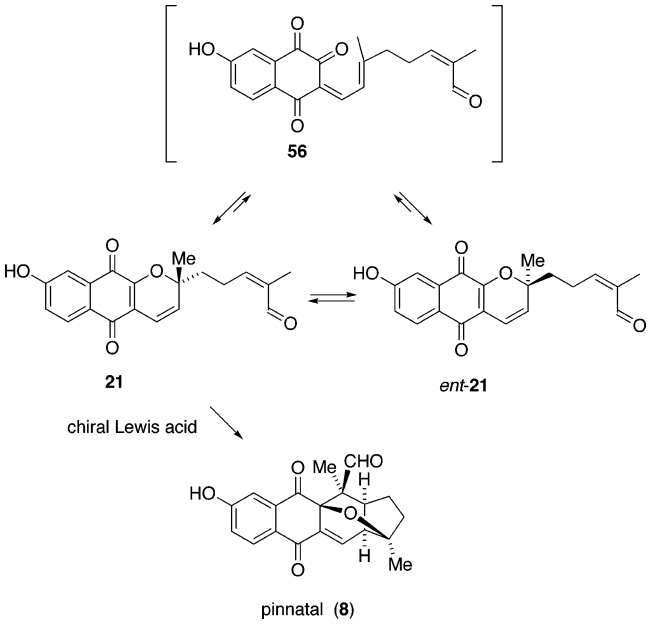
Enantioenriched Pinnatal. The first stereocenter in our synthetic pathway leading to pinnatal (and sterekunthal A) is set in the course of the oxa 6π electrocyclization. The resulting pyran **21**, however, is expected to undergo facile racemization via electrocyclic ring opening to give alkylidene trione **56**, followed by electrocyclic ring closure. In fact, **21** is an oxidized version of pyranokunthone B (**16**), which has been isolated only as a racemate from nature. Even though we did not observe **56** directly since the pyrone−dienone equilibrium lies overwhelmingly on the side of **21**, we believed it would be kinetically accessible at room temperature.

Scheme 13. Synthesis of (±)-Pyranokunthones A and B[a]



[a] Reagents and conditions: (a) **55**, β-alanine, HOAc, 50% **16** and 5% **15**.

Scheme 14. Intramolecular Dynamic Kinetic Resolution



Our hope was to selectively intercept *one* enantiomer of **21** via intramolecular Diels−Alder reaction using a chiral Lewis acid (Scheme 14). Provided the racemization (**21** ⇆ *ent*-**21**) proceeded at a much faster rate than the cycloaddition, an intramolecular dynamic kinetic resolution (intramolecular dynamic catalytic asymmetric transformation) could be achieved.[26] Unfortunately, this concept met with limited success. While the addition of chiral scandium triflate-pybox complexes,[27] e.g., **57**, to racemic **21** did provide enantioenriched pinnatal (ee's 20−55%), the yields of the natural product never surpassed 40% (Scheme 15). Note that these yields and enantiomeric excesses could be accounted for by a simple kinetic resolution of **21** lacking the dynamic component.[28] Extensive studies involving other chiral Lewis acids (e.g., Co-Salen, Ti-Binol, or Eu(hfc)$_3$ complexes) gave inferior results. In many cases, only isomerization to the *Z*-configured unsaturated aldehyde was observed.

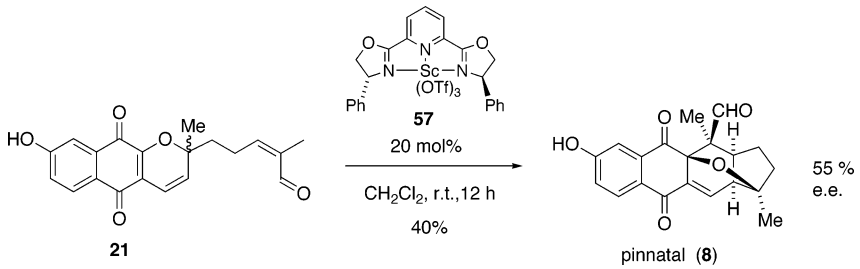
(25) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 1185−1194. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322. (c) Tapia, R. A.; Navarro, O.; Alegria, L.; Valderrama, J. A. *Heterocycl. Commun.* **1998**, *4*, 151−154.

(26) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 321−331.

(27) For a review of pybox complexes as ligands in asymmetric catalysis, see: Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154.

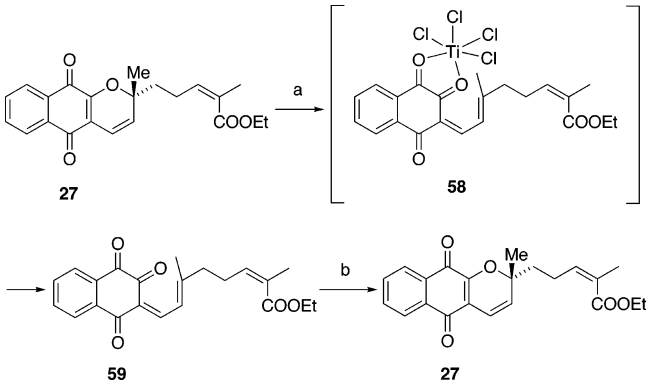
(28) However, no unreacted **21** could be recovered in these reactions.

Scheme 15. Synthesis of Enantioenriched Pinnatal[a]



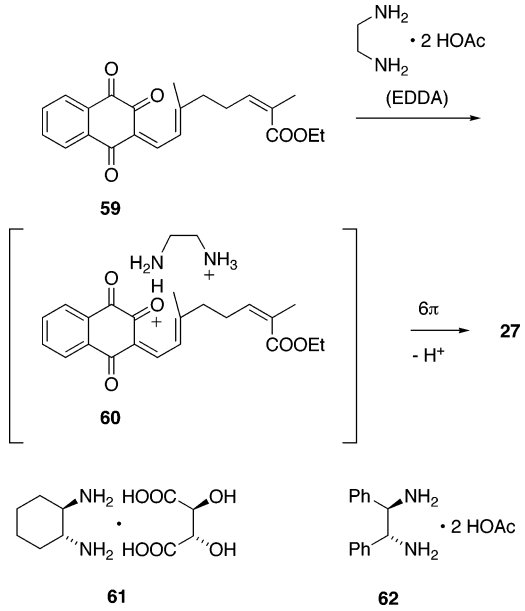
[a] The absolute configuration of pinnatal is arbitrary.

Scheme 16. Isolation and Electrocyclization of **59**[a]



[a] Reagents and conditions: (a) $TiCl_4$, then H_2O, 63% (78% BORSM); (b) rt, neat, 90 h, 99%.

Scheme 17. Catalysis of Oxa 6π Electrocyclizations



Kinetics of 6π-Electrocyclizations. As mentioned above, attempts to catalyze the intramolecular Diels−Alder reaction of model systems **27** and **32a**,**b** with Lewis acids occasionally resulted in the isolation of products of electrocyclic ring opening in varying amounts. Believing that a stoichiometric process was occurring, we added 1 equiv of $TiCl_4$ to **27**. Under these conditions, the surprisingly stable alkylidene trione **59** could be isolated after aqueous workup (Scheme 16). Presumably, the electrocyclic ring opening is driven by the formation of a stable titanium(IV) dione complex **58**, which is subsequently hydrolyzed.[29] To the best of our knowledge, this is the first time that a compound of type **59** has been isolated and characterized. As expected, alkylidene trione **59** underwent clean oxa 6π electrocyclization at room temperature to restore **27**.

Our strategy for the asymmetric synthesis of pinnatal was based on the presumption that the racemization of pyrans of type **27** would proceed rapidly at room temperature via electrocyclic ring opening/ring closure. With access to pure ring-opened product **59**, we had the unique opportunity to study the kinetics of the oxa 6π electrocyclization quantitatively.[30] To this end, **59** was heated to 90 °C in toluene-d_8. The concentrations of **59** and **27** were monitored by ^{1}H NMR (Figure 2). Surprisingly, the disappearance of **59** and the formation of **27** followed a second-order rate law, $-d[\mathbf{59}]/dt = k_2[\mathbf{59}]^2$, with a rate constant of $k_2 = 2.94 \times 10^{-3}$ ($\pm 0.15 \times 10^{-4}$) M^{-1} s^{-1}.

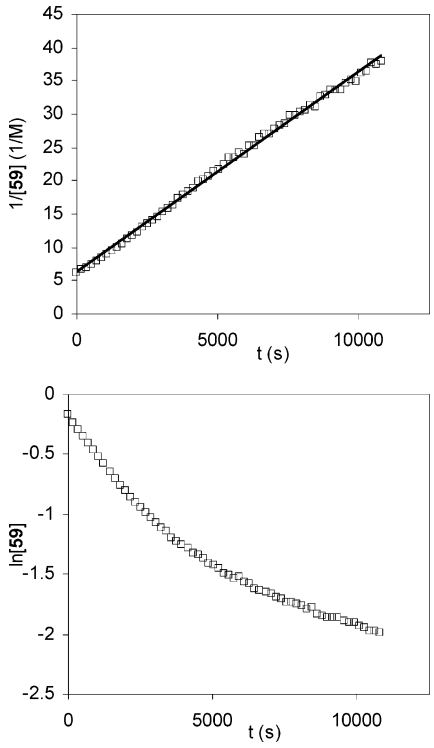


Figure 2. Second-order plot for **59** → **27** (90 °C, toluene). The first-order plot is shown for comparison.

While the reasons for its unexpected rate law remain to be determined,[31] this surprisingly slow cyclization led to the discovery of catalysis in oxa 6π electrocyclizations. Since the

(29) Titanium(IV) dione complexes are well precedented. See, for instance: Quinkert, G.; Becker, H.; Delgrosso, M.; Dambacher, G.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1993**, *34*, 6885−6888.

(30) For a discussion of the kinetics of electrocyclizations, see: Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; Vol. 43.

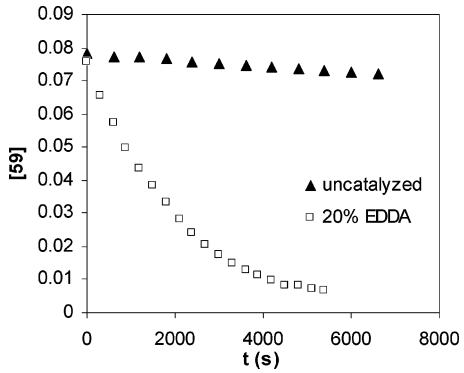
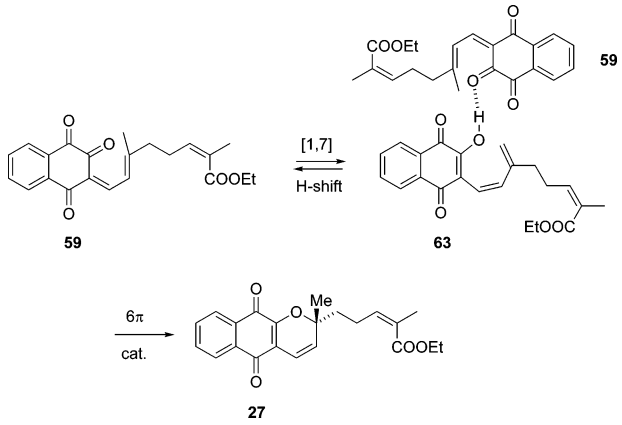


Figure 3. Effects of EDDA on oxa 6π electrocyclizations.

half-life for the conversion of **59** to **27** in toluene was determined to be 2.5 h for 0.2 M **59**, while our Knoevenagel condensation/electrocyclization tandems (e.g., **25** → **27**) are typically complete in 4 h, we suspected that EDDA was a catalyst not only for the condensation but also for the electrocyclization step. Accordingly, we repeated our kinetic studies in the presence of EDDA. Indeed, as shown in Figure 3, addition of 20 mol % EDDA led to a pronounced rate acceleration of the cyclization.

To our knowledge, this is the first clear-cut example of catalysis in an oxa 6π electrocyclization.[29,32] Presumably, it involves protonation of a carbonyl group to afford **61**, which then undergoes the electrocyclization at an increased rate. Dissolution of **59** in protic solvents, such as methanol, also resulted in faster electrocyclization. Attempts to catalyze the electrocyclization with chiral EDDA analogues such as **61** or **62**, or other chiral Broensted acids, afforded only racemic product. Although **27** could be resolved by analytical chiral HPLC, its racemization under these conditions is apparently fast enough to preclude catalytic asymmetric synthesis.

(31) A possible explanation invokes a reversible [1,7]-hydrogen shift generating vinylogous acid **63**. Compound **63** then acts as a catalyst to promote electrocyclization of **59**.



(32) For an example of catalysis in aza 4π-electrocyclic ring openings, see: Bongini, A.; Panunzio, M.; Tamanini, E.; Martelli, G.; Vicennati, P.; Monari, M. *Tetrahedron: Asymmetry* **2003**, *14*, 993−998.

Conclusion

In conclusion, the concise total synthesis of several biologically active natural products isolated from Bignoniaceae has been reported, lending credence to a unifying biosynthetic proposal.[33] Racemic pinnatal, isopinnatal, sterekunthals A and B, pyranokunthones A and B, and anthrakunthone have been prepared in quantities that allow for further exploration of their medicinal potential. Attempts toward the asymmetric synthesis of pinnatal and sterekunthal A have been met with limited success. In the course of these investigations, however, the kinetics of oxa 6π electrocyclizations have been elucidated and the first case of catalysis in these reactions was observed. Future investigations will be directed toward the generalization of catalysis in hetero 6π electrocyclizations, the study of its detailed kinetics, and the elucidations of its origin. The reasons for the unusual kinetic behavior of the uncatalyzed oxa 6π electrocyclization will be elucidated as well. In combination with detailed studies on the kinetics of the intramolecular Diels−Alder reaction, these investigations may lead to a satisfactory asymmetric synthesis of pinnatal and its congeners, such as sterekunthal A and kigelinol.

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Supporting Information Available: Complete experimental procedures and spectral data for previously unreported compounds, ^{1}H NMR spectra for selected compounds, X-ray crystal structure coordinates for sterekunthal B (**10**), and kinetics data for electrocyclizations. This information is available free of charge via the Internet at http://pubs.acs.org.

JA050092Y

(33) For a historical account of the development of this program, see: Malerich, J. P.; Trauner, D. In *Strategies and Tactics in Organic Synthesis*, Vol. 5; Harmata, M., Ed.; Elsevier: Amsterdam, 2004; pp 417−436.