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Published on Web 12/17/2003

Total Synthesis of Hybocarpone and Analogues Thereof. A Facile Dimerization of Naphthazarins to Pentacyclic Systems

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Abstract: The total synthesis of the lichen-derived antitumor agent hybocarpone (**1**) and related compounds is described. The successful route to hybocarpone features a novel radical-based dimerization/hydration cascade which generates the bridging hindered carbon−carbon bond of the molecule in a stereocontrolled manner, setting the relative configurations of the four contiguous stereocenters in a single step. The conjecture is made that this process may not be so dissimilar to the biosynthetic pathway leading to the formation of hybocarpone in nature. The developed sequence to these molecular frameworks also features the first example of a synthetically useful Diels−Alder trapping of a photochemically generated hydroxy-*o*-quinodimethane species with a 1,1-disubstituted olefin to form a quaternary center, and includes an efficient route to hydroxynaphthoquinone-type structures represented by the monomeric subunit of the natural product.

Introduction

Hybocarpone (**1**; Figure 1) is a naturally occurring compound which was first described in 1999 by J. Elix and his team at the University of Canberra as part of their program of identifying lichen metabolites with important biochemical properties.[1] Hybocarpone is one of three identifiable compounds produced by the lichen species *Lecanora hybocarpa*, which grows in the Louisiana woodland. When spores are collected from these lichen and cultured in a specific way, **1** can be isolated from the mycobiont. This novel pentacyclic compound was shown to be cytotoxic against the murine mastocytoma P815 transplantable tumor cell line with an IC_{50} of 150 ng/mL.[1] At the present time, the mechanism by which this natural product effects cell death in cancer cells is unknown. The flat, aromatic character of the hybocarpone structure, coupled with its dense concentration of reactive functionalities such as the 1,2,4-triphenolic and diketone moieties, however, suggests a possible DNA intercalation/DNA damage pathway as a viable mode of action for this compound. A closely related class of natural products, the naphthazarins, have been studied in detail, leading some researchers to conclude that they interfere with the cellular DNA replication machinery (e.g., DNA topoisomerase I and/or II via formation of a cleavable complex).[2] The various mechanisms proposed to explain the biological activity of the naphthazarins rely on the quinone moiety as the key functionality

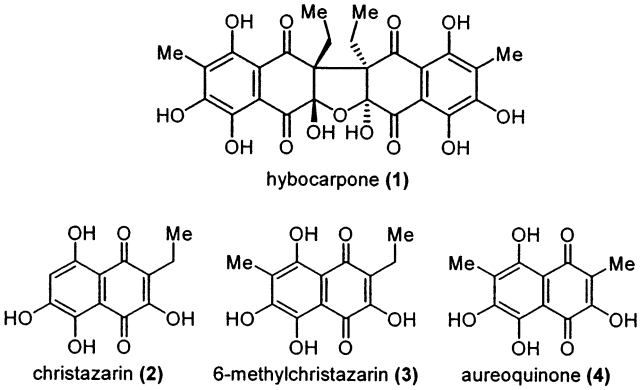

Figure 1. Molecular structures of **1** and related naphthazarin natural products (**2**−**4**).

reacting with biological nucleophiles or electron-transfer reagents as a means to induce the observed biological effects.[3] Structurally, **1** is composed of two naphthazarin units; however, it contains no quinone functionality, rendering any comparison between hybocarpone and the naphthazarins rather speculative in terms of their mode of action.

Several other lichen species are reported to produce naphthazarin monomers with structures related to that of **1**.[4−6]

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(2) (a) For a review of such naphthazarin natural products including alkannin and shikonin, see: Papageorgiou, V.; Assimopoulou, A.; Couladouros, E.; Hepworth, D.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 271−300. See also: (b) Song, G.-Y.; Kim, Y.; Zheng, X.-G.; You, Y.-J.; Cho, H.; Chung, J.-H.; Sok, D.-E.; Ahn, B.-Z. *Eur. J. Med. Chem.* **2000**, *35*, 291−298.
(3) (a) Ahn, B.-Z.; Sok, S.-E. *Curr. Pharm. Des.* **1996**, *2*, 247−262. (b) You, Y.-J.; Zheng, X.-G.; Yong, K.; Ahn, B.-Z. *Arch. Pharm. Res.* **1998**, *21*, 595−598.
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10.1021/ja030497n CCC: $27.50

Apparent from Figure 1 is the fact that the monomeric subunit of hybocarpone is itself a natural product (**3**). The red compounds christazarin (**2**) and 6-methylchristazarin (**3**) have been isolated from the cultured mycobiont of *Cladonia cristatella*.[4,5] Shortly after the disclosure of the hybocarpone structure, the Berg group isolated yet another naturally occurring hydroxynaphthoquinone possessing interesting biological activity, which they termed aureoquinone (**4**; Figure 1).[6]

The molecular structure of **1** was proposed using a combination of spectroscopic and molecular modeling data and later confirmed by single-crystal X-ray crystallographic analysis. It is characterized by a novel and unprecedented molecular architecture containing a dinaphtho[2,3-*b*:2,3-*d*]furantetraone skeleton. The hydration of the two carbonyl functionalities, while not surprising, raises questions of molecular and isomeric stability. Hybocarpone is actually a hydrated dimer, possessing a C_2 element of symmetry. This structural property is vividly illustrated by the molecule's simple ^{13}C NMR spectrum, which exhibits only 13 carbon signals.[1] While examples of the monomeric hydroxynaphthoquinones abound, it is the dimeric nature of hybocarpone which makes this naturally occurring substance especially intriguing. It is reasonable and tempting to speculate that nature is able to successfully dimerize **3** in a diastereo- and enantioselective fashion to produce **1**.

Prompted by the striking molecular structure and biological activity of **1**, we initiated a program directed toward its total synthesis, with the specific initial goal of identifying an efficient means of chemically constructing the unusual central carbon−carbon bond. In this paper, we describe in detail our results in this area, which culminated in the total synthesis[7] of **1** and a number of designed analogues (vide infra).

Results and Discussion

As noted above, disconnection of the central carbon−carbon bond and hemiketals that adjoin the monomeric units of **1** leads to the known lichen metabolite **3** (Figure 1). This retrosynthetic disconnection is productive only if one can successfully identify a synthetic process for constructing this bond in a selective fashion. At the time this work began, there was no known method for the direct formation of such a bond. Thus, initial efforts focused on a dimerization strategy which had a more solid literature precedent. Thus, oxidative dimerization of ketone enolates held promise, as it has been shown to be capable of forging highly congested carbon−carbon bonds to produce 1,4-diketones.[8,9] Mindful of the biological activity exhibited by the naphthazarins, our initial synthetic designs had, as a secondary goal, the development of methodology for the construction of compound libraries with varying substitutions attached to the rings, including naphthazarins of type **7** (Figure 2) and pentacycles of type **6** (Figure 2). It seemed reasonable that tetralones **5** (Figure 2) would be a good platform from which to launch such an expedition.

Initial Approach to the Hybocarpone Framework. While searching for a methodology suitable for the construction of the required tetralone monomeric units, we came across reports on the photochemical generation of reactive hydroxy-*o*-quinodimethanes **9** (Figure 3) from *o*-alkylbenzaldehydes **8** and their subsequent trapping in Diels−Alder reactions to afford benzannulated bicycles in varying yields.[10−12] We thus reasoned that if appropriately developed into a synthetically useful process, such technology could serve as the cornerstone for a general and flexible tetralone synthesis as projected in Figure 3.

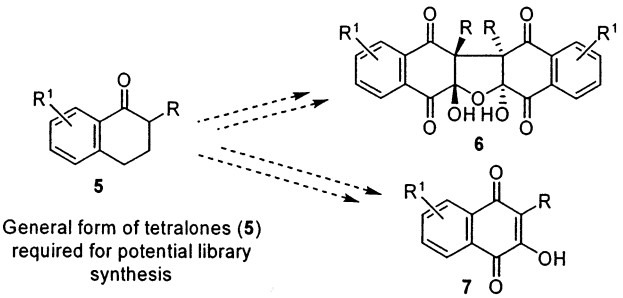

Figure 2. Potential hybocarpone **6** and hydroxynaphthoquinone **7** libraries from tetralones **5**.

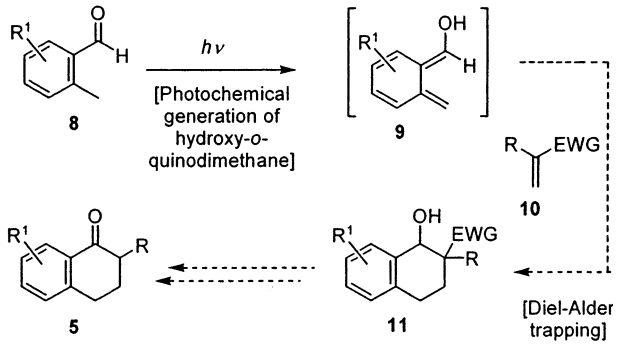

Figure 3. Proposed general synthesis of varied tetralones **5** via photochemically induced benzannulation of *o*-methylbenzaldehydes **8**. EWG = electron-withdrawing group.

Absent as reaction partners among the literature examples of photoenolization/Diels−Alder (PEDA) dienophiles were 1,1-disubstituted olefins, which would lead to the formation of quaternary carbon centers. Given the quaternary centers present in our targeted structure, we set out to test whether such partners could be induced to react in the desired manner. Aldehyde **12** (Scheme 1) is accessible without column chromatography through a few simple operations starting from the inexpensive 2,6-dimethylphenol by following the procedures of Liebeskind and Fieser[13−15] (with a few significant modifications; see the Experimental Section in the Supporting Information). For the initial PEDA reaction attempt, this aldehyde (**12**) was dissolved in benzene with 2 equiv of methyl α-ethacrylate (**13**)[16] and irradiated for 8 h according to the most common procedure used for such reactions.[17] Gratifyingly, the expected union did occur, delivering the targeted annulation product **14** in ca. 30% yield as a 2:1 mixture of *syn*- and *anti*-diastereoisomers (subsequent optimization increased the yield of this reaction to 81%).[18]

(7) For a preliminary comunication, see: Nicoalou, K. C.; Gray, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 761−763.
(8) Frazier, R.; Harlow, R. *J. Org. Chem.* **1980**, *45*, 5408−5411.
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(11) Charlton, J.; Alauddin, M. *Tetrahedron* **1987**, *43*, 2873−2889 and references therein.
(12) Sammes, P. *Tetrahedron* **1976**, *32*, 405 and references therein.
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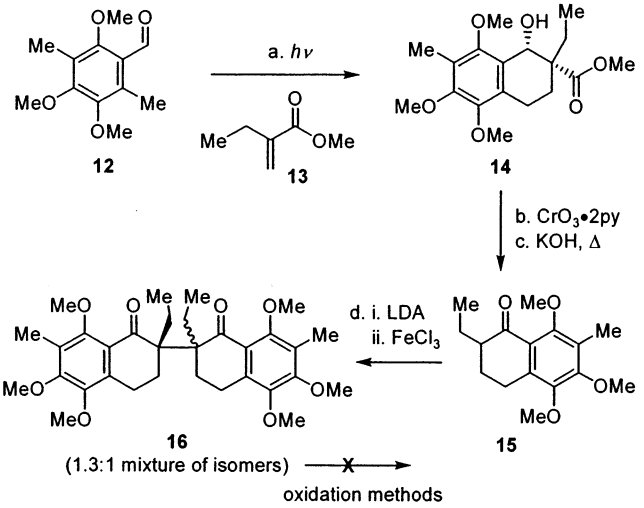
(16) Stetter, H.; Kuhlmann, H. *Synthesis* **1979**, *1*, 29−30.
(17) Charlton, J.; Plourde, G.; Koh, K. *Can. J. Chem.* **1989**, *67*, 574−579.

Scheme 1. Construction of Dimer **16** and Unsuccessful Attempts To Elaborate It to **1**[a]



[a] Reagents and conditions: (a) **13** (6.0 equiv), *hν*, toluene, 4 h, 81% (2:1 ratio of diastereoisomers, major isomer shown); (b) CrO_3·2py (6.0 equiv), CH_2Cl_2, 0−25 °C, 1 h, 86%; (c) 1 M aqueous KOH, EtOH, 90 °C, 6 h, 80%; (d) (i) LDA (1.1 equiv), THF, −78 °C, 1 h; (ii) then $FeCl_3$ (1.1 equiv) in DMF, −78 to 0 °C, 4 h, 52%. LDA = lithium diisopropylamide.

Benzylic oxidation was accomplished through the use of the Collins reagent (CrO_3·2py) to give a β-keto ester (86% yield), which was decarboxylated with KOH in refluxing EtOH to access the targeted tetralone **15** in 80% yield (Scheme 1).

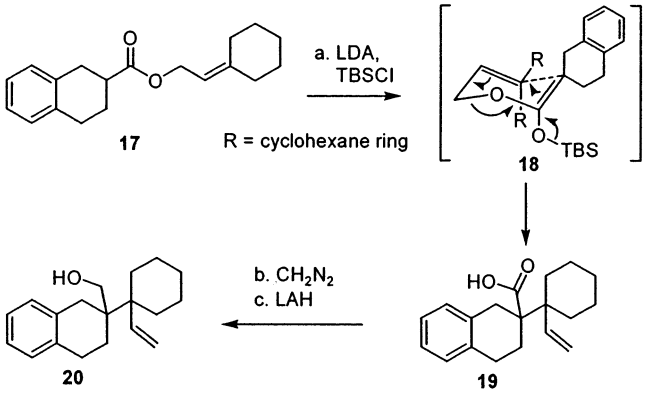
Among several dimerization protocols which were investigated, the most successful was the Harlow procedure, which employs anhydrous $FeCl_3$ as the oxidant on the pregenerated lithium enolate of the ketone substrate.[8] Thus, exposure of the enolate of **15** (generated by the action of LDA) to a solution of $FeCl_3$ in DMF using techniques for the rigorous exclusion of oxygen allowed for the production of reasonable quantities of the easily separable *meso*- and *d*,*l*-isomers of dimer **16** (Scheme 1). Unfortunately, this fully substituted tetralone dimer (**16**) proved recalcitrant to oxidation, decomposing rapidly upon exposure to several reagents, and preventing further advancement toward the targeted system.[19]

A second approach, which looked to the powerful Ireland−Claisen rearrangement to forge the sterically encumbered bond at the junction joining the two monomeric units, also suffered from difficulties encountered in bringing even simple model systems to the desired oxidation state (Scheme 2). It is, however, interesting to note the success of this approach, generating the bond at the quaternary center of polycyclic structures **19** and **20** (Scheme 2).[20]

With these two approaches failing to deliver the desired hybocarpone framework, it was finally concluded that a modified strategy involving the coupling of a highly oxidized monomer might be more successful, on the basis of the minimization of both the number and the difficulty of post-dimerization transformations.

A Second-Generation Approach toward Hybocarpone Relying on the Dimerization of Highly Oxidized Intermediates. In a redesigned approach toward **1**, we aimed to follow a synthetic strategy which was conceptually much simpler than the initial attempt discussed above, and perhaps one that was related to its biosynthesis. The symmetrical structure of **1** and the existence of the monomeric subunit in nature led to a conceptual identification of naphthazarin **24** (Figure 4) as a potential precursor. Requirements for a successful implementation of this concept include (a) the identification of methodology suitable for the construction of the extremely hindered carbon−carbon bond that adjoins the two halves of the dimer and (b) the successful control of the relative stereochemistry of the four stereogenic centers of **1** during the assembly process. We proposed that oxidation of a protected form (**24**) of **3** via a single-electron-transfer (SET) process could lead to the highly reactive radical cation **23**, which might have a sufficient lifetime to undergo intermolecular coupling, leading to intermediate **22**

Scheme 2. Construction of a Hindered Carbon−Carbon Bond via Claisen Rearrangement on a Model System[a]



[a] Reagents and conditions: (a) LDA (1.2 equiv), (TBS)Cl (1.5 equiv), HMPA, THF, −78 °C, 2 h; then warm to 60 °C, 1 h; (b) CH_2N_2, ether, 5 min; (c) LAH (6.0 equiv), THF, 4 h, 48% for three steps.

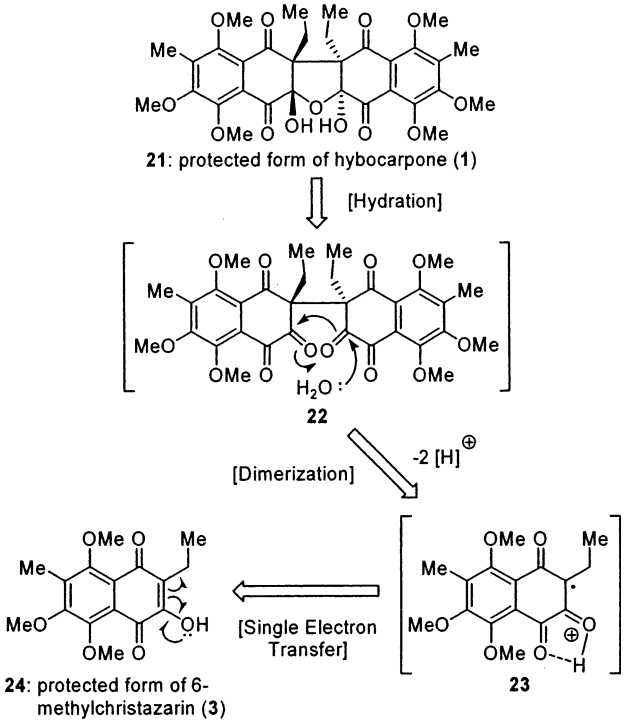


Figure 4. Second-generation retrosynthesis of hybocarpone hexamethyl ether (**21**) bases on the oxidative dimerization of hydroxynaphthoquinone **24**.

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(19) Jacob, P. Callery, P. Shulgin, A. Castagnoli N. *J. Org. Chem.* **1976**, *41*, 3627−3629.
(20) For the first report of a Claisen rearrangement which creates vicinal quaternary centers, see: Denmark, S.; Harmata, M. *Tetrahedron Lett.* **1984**, *25*, 1543−1546.

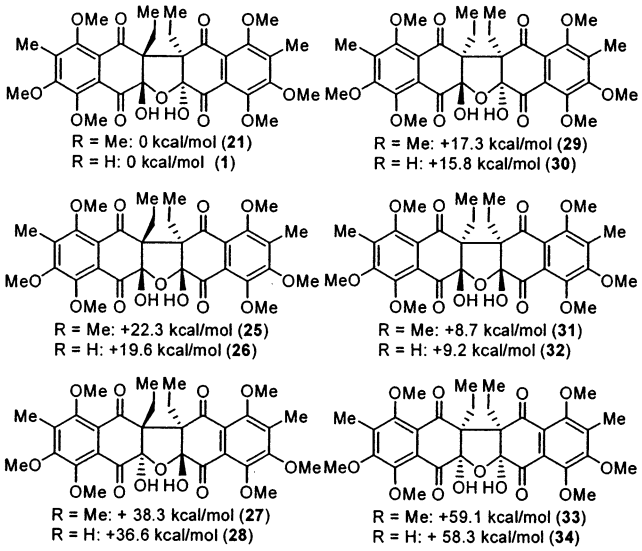
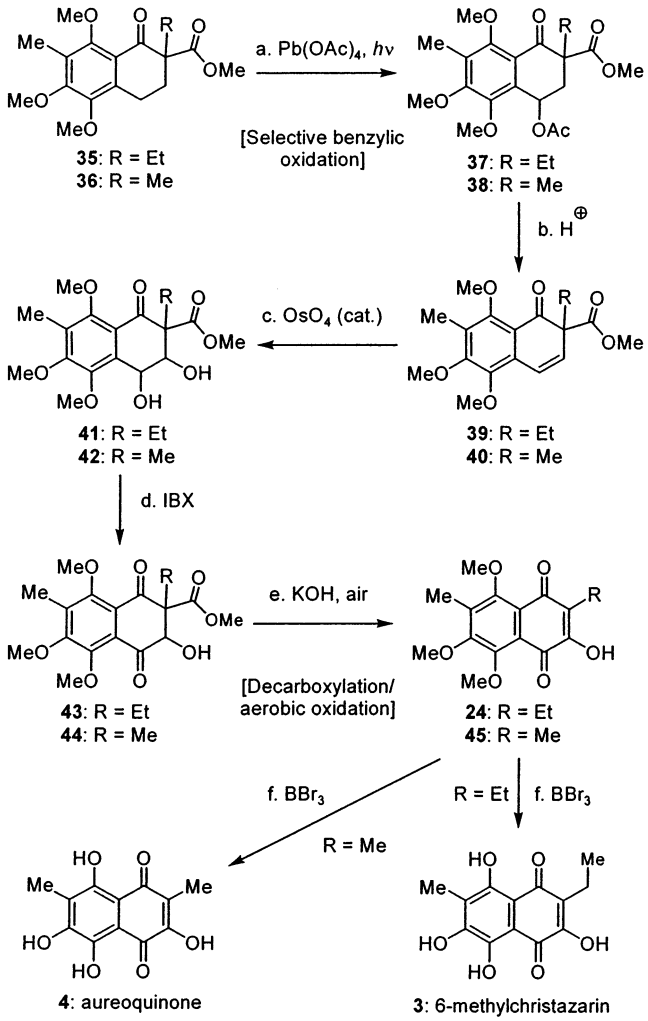


Figure 5. Calculated relative strain energies of the six possible hybocarpone diastereoisomers (R = H) and their corresponding hexamethyl ethers (R = Me) (see ref 21 for computational parameters).

after loss of two protons. It was anticipated that, at this stage, a hydration/ketalization event on the hexaketone intermediate **22** would furnish the desired hybocarpone framework **21**. This hydration/cyclization sequence would potentially lead to the formation of up to six diastereomeric furan systems by reaction of diketone **22** (Figure 4). Molecular modeling and computational studies indicated that, among these diastereoisomeric compounds (see the structures in Figure 5), the natural isomer **21** appeared to be clearly favored in terms of strain energy.[21] Since the central dihydroxyfuran systems of these diastereoisomeric compounds can exist in equilibrium with their open-chain counterparts, and because the calculated energy differences among them are large (>5 kcal/mol), it seemed reasonable to rely on thermodynamics to set the correct stereochemistry in this proposed hydration process. Only demethylation separates compound **21** from **1**. Due to the compelling attractiveness of this simple and straightforward strategy, we proceeded to attempt its laboratory execution, although there was no literature precedent for the key coupling reaction.

The new synthetic journey commenced from β-keto ester **35** (Scheme 3), which was already in hand from the previous attempt as described above (Scheme 1). To progress from this intermediate, conditions for the selective oxidation of the secondary benzylic position in the presence of a benzylic methyl group needed to be identified. Common protocols (e.g., NBS, DDQ, PDC) were found to be nonselective, attacking indiscriminately both potential oxidation sites within **35**. However, photochemically activated $Pb(OAc)_4$ was observed to favorably discriminate among the two positions (ratio ca. 25:1), making

Scheme 3. Synthesis of Naturally Occurring Naphthazarins **3** and **4** via a Series of Selective Oxidation Reactions[a]



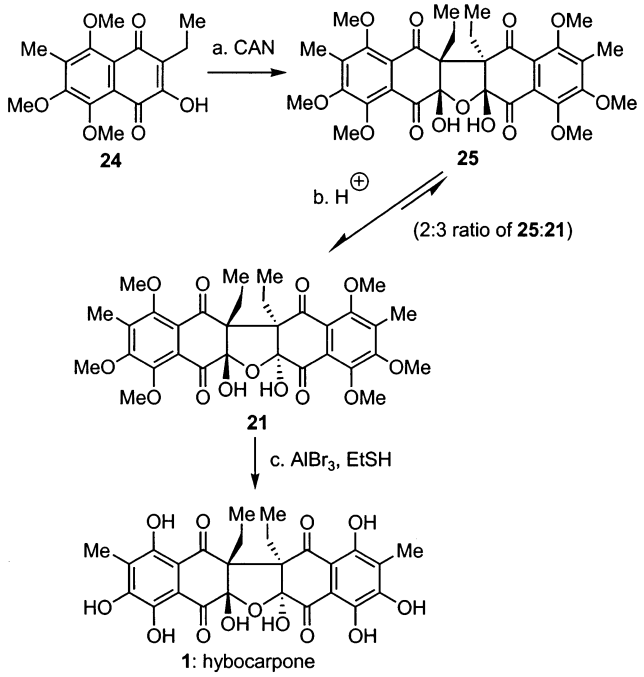
[a] Reagents and conditions: (a) $Pb(OAc)_4$ (1.4 equiv), *hν*, AcOH, 2 h, 71% (3:1 ratio of diastereoisomers); (b) HCl, AcOH, 90 °C, 4 h, 72%; (c) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF−*t*BuOH−H_2O−py (20:20:4:1), 12 h, 92%; (d) IBX (3.0 equiv), DMSO, 25 °C, 0.5 h, 92%; (e) 1.5 M aqueous KOH−THF (1:3.5), air, 1 h, 83%; (f) BBr_3 (10.0 equiv), CH_2Cl_2, −78 to +25 °C, 3 h, 40−50%. NMO = *N*-methylmorpholine *N*-oxide, and IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

this a highly useful transformation.[22] The precise origin of the observed selectivity and the generality and scope of this transformation leading to acetate **37** in 71% yield (3:1 mixture of acetate diastereoisomers) remain to be explored. Exposure of this oxidation product to HCl in AcOH at 90 °C gave the olefin **39** (72% yield), which was subjected to dihydroxylation with NMO−OsO_4(cat.) to afford vicinal diol **41** (92% yield, ca. 10:1 ratio of diastereoisomers, stereochemistry not determined). While a number of common oxidation protocols failed to yield the next targeted intermediate, IBX oxidation of **41** was selective and high-yielding, leading to the corresponding hydroxyketone **43** (92% yield), which was directly dissolved in THF and treated with aqueous KOH in the presence of air to afford, via a decarboxylation/oxidation sequence, the desired naphthazarin **24** in 83% yield (two steps). The unusual rapidity of the latter decarboxylation and the temperature (ambient) at

(21) The hybocarpone diastereoisomeric structures were modeled with Accelrys Insight II, 1998. Molecular dynamics calculations were performed with Accelrys Discover v. 2.98 on a cluster of SGI Origin servers running Irix 6.5. The relative energies of the diastereoisomeric structures were computed with the class II pairwise force field cff91 v. 2.0 (see: Dinur, U., Hagler, A. In *Reviews in Computational Chemistry*; Lipkowitz, K., Boyd, D., Eds.; VCH: New York, 1991; Vol. 2, p 527), with library parameters for bond, valence, torsion, and out-of-plane terms. Typically, 500 structures were generated within 250 ps at 800 K. They were annealed to 300 K in 5 ps. The structures were further minimized to convergence using a conjugate gradient algorithm, and the lowest energy structure cluster was selected as the preferred structure. We thank Dr. I. Ioannou for performing these calculations.

(22) We are aware of one other report of benzylic oxidation employing photochemically activated $Pb(OAc)_4$; see: Geiwiz, J.; Haslinger, E. *Helv. Chim. Acta* **1995**, *78*, 818−832.

Scheme 4. Synthesis of **1** via Successful Application of the Oxidative Quinone Coupling Strategy[a]



[a] Reagents and conditions: (a) **24** in MeCN; then add CAN (1.0 equiv) in degassed MeCN, −35 to 0 °C, sonication, 2 min; then 5 M aqueous KOH, 0−25 °C, 10 min, 19% plus 60% recovered starting material, **21**:**25** ratio ca. 3:2; (b) AcOH, $CHCl_3$, 5 min, >95%; (c) $AlBr_3$ (1 M in CH_2Br_2, 25 equiv), EtSH−$CHCl_2$ (1:2), 0 °C, 1 h, 60%. CAN = cerium ammonium nitrate.

which it proceeds suggest that the neighboring hydroxyl group plays a facilitating role in this conversion (**43** → **24**, Scheme 3). Indeed, a similar substrate which bore a protecting group on that hydroxyl group required elevated temperatures and prolonged reaction times to effect decarboxylation.

The efficient arrival at **24** represented an important milestone in the synthetic effort toward hybocarpone. Cleavage of the three aryl ethers was accomplished in modest yield by exposure of this intermediate (**24**; Scheme 3) to BBr_3 (−78 to +25 °C) for several hours. Thus, upon workup of the reaction mixture, the deep-red-colored **3** was obtained in 49% yield. The advancement of the latter compound (**3**) toward **1** was attempted under various conditions, albeit without success. In a second foray and with an eye on **4**, the aforementioned synthetic sequence leading to **24** (Scheme 3) was revisited, beginning with methyl methacrylate in the initial PEDA reaction to afford the new starting material **36**. This sequence led from the latter compound (**36**) to the trimethyl ether-protected **45**, which was deprotected to afford **4** in yields similar to those for **3**. Although the synthetic sequences to **24** and **45** involved several steps, they are operationally simple and generally rapid. Furthermore, the entire route requires only a few chromatographic separations. Thus, this synthetic strategy may provide practical access to a number of substituted naphthazarins and tetralones such as **15**, **3**, and **4** (Schemes 1 and 3).

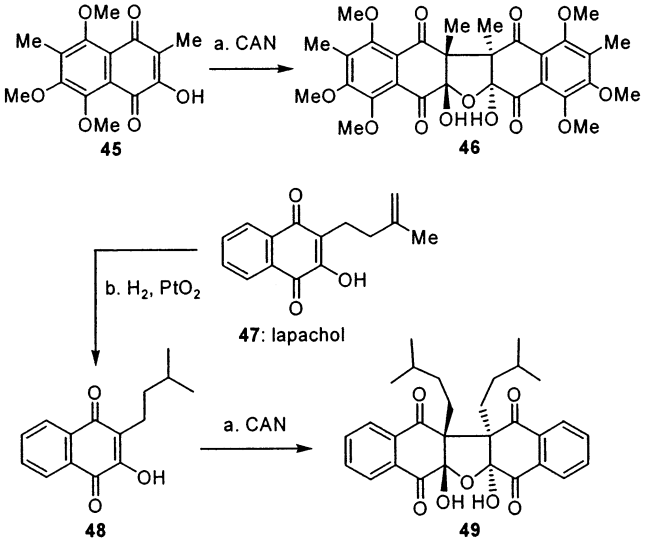
With quantities of naphthazarin **24** at hand, we proceeded to investigate its dimerization via the proposed (Figure 4) radical-based pathway to **1**. Upon screening a number of reagents, success was finally found in the use of cerium ammonium nitrate (CAN) as an oxidant, which proved equal to the task of initiating the crucial coupling reaction (Scheme 4). Thus, in a remarkably brief event, exposure of **24** to 1 equiv of CAN in MeCN at −35 °C under sonication conditions led to the isolation of two isomeric hybocarpone derivatives, **21** and **25** (**21**:**25** ratio ca. 3:2), which were separated on deactivated silica gel and spectroscopically characterized. A key to success in this transformation was the quench, which must be strongly basic or no product is isolated. Although the yield of the pentacycles **25** and **21** was rather low (combined 19% in the best run), the majority of the starting monomer **24** was recovered unchanged, and in high purity, by acid/base extraction. This recovered material (**24**) could be resubjected to dimerization without additional purification. After three such reiterations, **25** and **21** were obtained in a combined 36% yield.

To our delight, the more complex ^1H NMR spectrum ($CDCl_3$, 500 MHz) of **25** (Scheme 4) was observed to undergo simplification as this, apparently unfavorable, isomer was transformed to the thermodynamically most stable hybocarpone isomer (**21**). This acid-catalyzed transformation was strong evidence that both of the isolated pentacycles bear the *trans* relationship of the two ethyl groups at the junction joining the two monomeric units of both isomers. This selectivity might be predictable on the basis of severe steric congestion within the *cis* isomer (see Figure 5). The generation of **1** from its hexamethylated derivative (**21**) was effected by exposure to $AlBr_3$–EtSH in methylene chloride at 0 °C (60% yield). Synthetic **1** was purified by reversed-phase (RP)-HPLC and fully characterized by spectroscopic means. It exhibited spectral data (^1H and ^{13}C NMR, mass spectrometry) identical to those reported for natural hybocarpone.[1,23]

At this juncture, we wondered whether there was something unique about **1** which facilitates its synthesis via an oxidative dimerization approach. We pondered the notion that the developed dimerization protocol could be applied to other hydroxynaphthoquinones, leading to the corresponding pentacyclic products. To address this question, we prepared two related compounds for dimerization studies. The first such candidate was the hydroxynaphthoquinone **45**, which differs from **24** by the incorporation of a methyl, rather than an ethyl, group on the reacting carbon atom. The synthesis of this compound has already been mentioned above (Scheme 3). The second substrate (**48**; Scheme 5) was prepared by hydrogenation (PtO_2, H_2, EtOAc) of the naturally occurring (and commercially available) lapachol (**47**). This molecule (**48**) retains a high degree of steric bulk around the reacting carbon, but is unsubstituted on the aryl ring, changing the electronics of the hydroxynaphthoquinone. In each case, the expected pentacyclic compound (**46**, **49**) was isolated upon exposure of the monomeric unit to CAN in acetonitrile. For monomer **45**, the reactivity appeared to be similar to that of **24**, although it was noted that more starting material (70−80%) was recovered and a correspondingly lower amount of product **46** was formed (6−9%) in each of the several trials attempted. For the simpler precursor **48**, the dimerization process is noticeably less efficient (ca. 3% yield of **49**). However, in several runs, 93% of the starting material was recovered unchanged and at a high level of purity. Also of note is the different behavior of the dimeric pentacycles **46** and **49** as compared to **1**. The lapachol-derived compound **49** was isolated as a single isomer, and no other dimeric products were

(23) We thank Professor J. A. Elix, University of Canberra, for a generous gift of natural **1**.

Scheme 5. Oxidative Dimerization of Hydroxynaphthoquinones **45** and **48**[a]



[a] Reagents and conditions: (a) **45** or **48** in MeCN; then add CAN (1.0 equiv) in degassed MeCN, −35 to 0 °C, sonication, 2 min; then 5 M aqueous KOH, 0−25 °C, 10 min, 9% **46** plus 71% recovered starting material; 4% **49** plus 93% recovered starting material; (b) PtO_2(cat.), H_2 (1 atm), EtOAc, 4 h, filter catalyst, then bubble in air, 2 h, 83%.

evident. With the aureoquinone-derived dimer **46**, we were able to isolate two compounds in a ca. 1:1 ratio. The isomer we assigned structure **46** (Scheme 5) exhibited a simple ^{1}H NMR spectrum reminiscent of that of **1**. The other isomer exhibits the correct mass, by mass spectrometry, but its ^{1}H NMR spectrum supports a nonsymmetrical structure. However, unlike the hybocarpone isomer, it does not convert to the other isomer (i.e., **46**) under the conditions employed in the hybocarpone case (**25** → **21**). Furthermore, this second isomer appears to be prone to decomposition and has eluded full characterization.

The dimerization reaction itself is visually informative; a jet black color is formed when CAN is added to the hydroxynaphthoquinone. This color fades over several minutes at −35 °C or over 20 s at room temperature to a yellow hue very similar to that of the starting material. Allowing the reaction to proceed overnight did not increase the conversion. When the conditions were modified such that the black color was not observed (i.e., running the reaction in 4:1 MeCN−H_2O), no dimerization occurred. A number of highly polar and colored compounds were noticed as side products in these dimerization reactions in the hybocarpone series (although no individual side product was fully characterized) which appeared to arise from demethylation of the aryl ethers. This is not surprising, as CAN is known to cleave aryl methyl ethers at low temperature, particularly when they are made more labile by a carbonyl group located at the *ortho* position.[19] This hypothesis is further supported by the large percentage of starting material cleanly recovered in the reaction of the aryl-unsubstituted naphthoquinone **48** (Scheme 5), which does not suffer from such side reactions under the same reaction conditions.

Conclusion

With its novel and imposing structure, the naturally occurring hybocarpone molecule provided a unique opportunity for strategy and process development as well as analogue construction. Direct access to the hybocarpone skeleton was possible by oxidative dimerization of the corresponding naphthazarin monomer employing CAN as the oxidant. The success of this process may be taken as support of the notion that nature is also using this pathway in its biosynthesis of this bioactive molecule, although no direct evidence for such a mechanism exists at present. The synthetic technology developed en route to **1** was also applied for the construction of two novel hybocarpone analogues, namely, compounds **46** and **49**, as a demonstration of the potential power of this strategy to deliver libraries of this natural product for biological screening purposes. Among the novel synthetic objectives achieved in the described synthesis are the selective benzylic acetoxylation reaction, the first example of applying the photoenolization/Diels−Alder reaction protocol to construct quaternary centers, and a general method for the preparation of highly substituted tetralones and hydroxynaphthoquinones. The highlight of this study, however, must be the novel cascade sequence involving the oxidative dimerization/hydration process of the hydroxynaphthoquinones to the pentacyclic systems represented by **1**. The exploration of the generality and scope of the photoenolization/Diels−Alder reaction and its application to the synthesis of the hamigerans are described in the following paper in this issue.[18]

Acknowledgment. This work was financially supported by the National Institutes of Health, The Skaggs Institute for Chemical Biology, a Louis R. Jabinson fellowship (to D.L.F.G.), and grants from Amgen, Merck, and Pfizer.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JA030497N