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A Four-Step Total Synthesis of Radermachol

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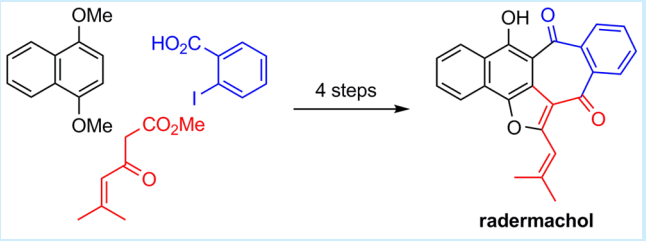
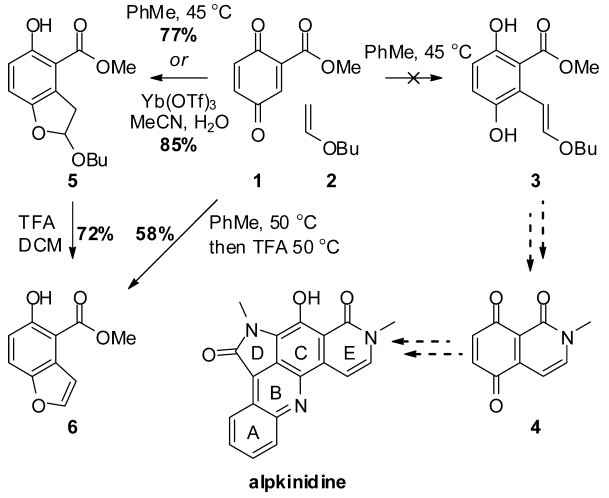
Supporting Information

ABSTRACT: Radermachol has been synthesized in four steps and an overall yield of 22% via key ytterbium triflate catalyzed furannulation and intramolecular nucleophilic acylation reactions.



As part of investigations into the total synthesis of the marine pyrroloacridine alpkinidine,[1] we attempted to generate its CE ring system by beginning with a Michael-type addition of butyl vinyl ether (**2**) to the very electrophilic ("activated") quinone **1**,[2] with the view that the adduct **3**, or some related species, could be elaborated to isoquinolinetrione **4**, and then on to the natural product (Scheme 1). In practice, the reaction of **1** and **2** cleanly produced the dihydrobenzofuran **5**, resulting from intramolecular interception of the initial Michael adduct by the (formerly) quinonoid oxygen atom, a formal [3 + 2] cycloaddition. A survey of the literature revealed that similar reactions have been known for some time.[3]

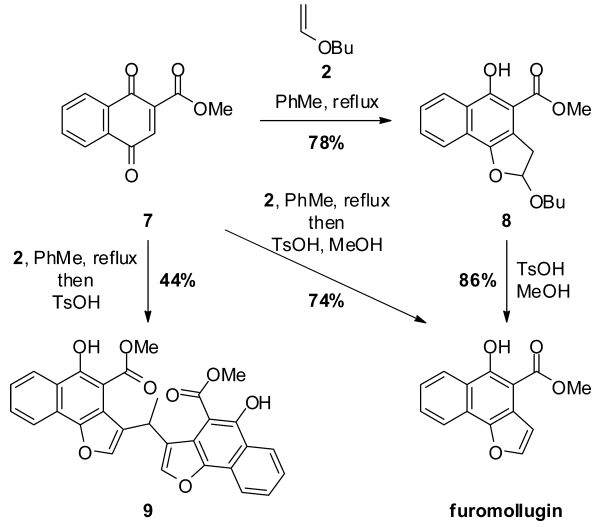
Scheme 1. Unexpected Formal [3 + 2] Cycloaddition of Electron-Deficient Quinone 1 with Butyl Vinyl Ether (2), and Subsequent Aromatization: A Net Furannulation



It was apparent that a simple acid-catalyzed elimination of BuOH from **5** would generate the benzofuran **6**, and indeed the expected outcome was achieved in good yield, either on isolated acetal **5** or in one pot over the two steps. Such "furannulations" have not been extensively exploited in natural product synthesis.[4] Several 5-hydroxybenzo[2,3-*b*]furan natural products bearing an electron-withdrawing group at the 4-position are known, and the methodology exemplified in Scheme 1 provides a very rapid, regiospecific route to this substructure. Thus, we set out to prove its utility in the total synthesis arena.

Our first efforts focused on furomollugin (Scheme 2), which was originally isolated[5] from the rhizomes of *Galium mollugo L.*, a European herbaceous annual from the Rubiaceae family, commonly known as false baby's breath. Furomullogin has since been found in several *Rubia* species[6] and has been shown to exhibit activity against the hepatitis B virus[6c] and weak cytotoxicity to a human colon carcinoma cell line (HT-29), possibility mediated through topoisomerase inhibition.[6e]

Scheme 2. A Rapid, Regiospecific Synthesis of Furomollugin



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The original isolators synthesized furomollugin in two steps and 2% overall yield by cyclocondensation of glyoxal with 1,4-dihydroxy-2-naphthoic acid, followed by selective esterification with diazomethane.[5] Furomollugin was produced as a minor byproduct in Trauner's elegant biomimetic synthesis of the complex 5-hydroxybenzo[2,3-*b*]furan natural product rubicordifolin.[7] The same group reported a second synthesis from the related benzochromene natural product mollugin, via an efficient sequence of oxidation, and base-induced rearrangement and retro-Friedel–Crafts hydroxyalkylation, en route to a total synthesis of rubioncolin B.[8] A similar ring contraction of mollugin was later reported by De Kimpe and co-workers.[9]

Our synthesis of furomollugin is outlined in Scheme 2. The required quinone **7**[10] was prepared by Fischer esterification of 1,4-dihydroxynaphthoic acid,[11] followed by oxidative demethylation. The reaction of **7** with butyl vinyl ether (**2**) gave acetal **8** in good yield. Acid-catalyzed aromatization then afforded furomollugin. The one-pot procedure in toluene was complicated by a cascading Friedel–Crafts alkylation of the initial product with excess butyl vinyl ether, providing the dimer **9** in moderate yield. Switching solvent to MeOH before acidification avoided the problem and gave furomollugin in a slightly better yield than the two-pot process.

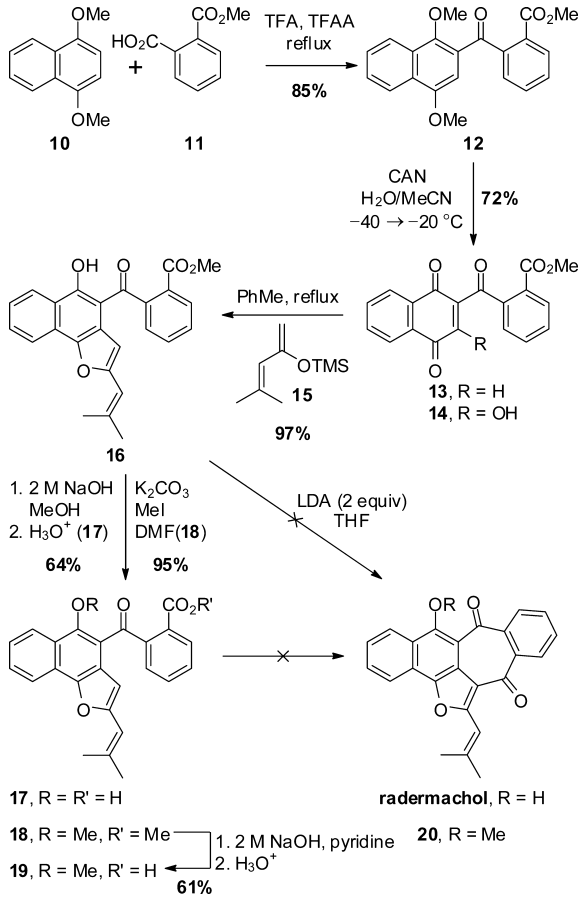
During the course of our work, Lee and Xia reported a synthesis of furomollugin by a very similar method, using ceric ammonium nitrate as a Lewis acid catalyst for the cyclization reaction of **1** with ethyl vinyl ether, and tosic acid-catalyzed elimination of EtOH to provide the natural product in excellent yield over two steps.[12] They have since used this methodology to synthesize diverse furomollugin analogues and assess them for antioxidant and antibacterial activities.[13]

The successful synthesis of furomollugin inspired us to tackle a more challenging target, radermachol (Scheme 3). This bright red pigment was first isolated[14] from *Radermachera xylocarpa* K. Schum, a plant from the Western Ghats of India. Its unique, fused pentacyclic structure was established by spectroscopic analysis and X-ray crystallography.[14] It has since been found in *Tecomella undulata*, another Indian plant from the *Bignoniaceae* family.[15] Although both plant sources are used as traditional medicines, it seems that the biological activity of radermachol has not been investigated. Two previous syntheses of radermachol exist. The first, from the Pelletier group, afforded the natural product in 14 steps and 7% overall yield.[16] The second, by Hauser and Yin,[17] intercepted an intermediate in the Pelletier's synthesis, providing radermachol in 11 steps.

Our first approach to radermachol is outlined in Scheme 3. Friedel–Crafts acylation of 1,4-dimethoxynaphthalene (**10**) with phthalic acid monomethyl ester (**11**) proceeded smoothly in refluxing TFAA/TFA,[16b,18] without the need for Lewis acid catalysis. CAN-mediated oxidative demethylation[19] of **12** was effective at low temperatures, giving quinone **13** in an acceptable yield; at higher temperatures the overoxidation product **14**, presumably arising from conjugate addition of water to **13** and reoxidation, predominated. To our delight, the key furannulation—reaction with silyl ether **15**,[20] derived in one step from mesityl oxide, followed by *in situ* treatment with TFA—gave the desired isobutenylbenzofuran **16** in excellent yield.

The first efforts to achieve ring closure to form the pentacyclic framework of radermachol began with treatment of **16** with 2 equiv of LDA. The rationale here was that the first equivalent would deprotonate the phenolic hydroxyl, deactivating the diarylketone to nucleophilic attack and, along with the

Scheme 3. Unsuccessful Approach to Radermachol



ester substituent, helping to direct lithiation of the proximal furan β-carbon by the second equivalent of LDA. The lithiated intermediate so formed could then attack the ester, giving radermachol in one operation. In practice, only the starting material was returned suggesting that there was no directed lithiation.

We then resorted to intramolecular Friedel–Crafts acylation of the activated furan β-position to effect the final ring closure. Although challenging in the presence of the sensitive isobutenyl substituent, we were encouraged by the already demonstrated stability of this group to TFA. Ester **16** was first saponified to give **17** (Scheme 3). Unfortunately, neither the in situ generated trifluoroacetic mixed anhydride nor acid chloride underwent the desired cyclization, despite many attempts and, in the latter case, with various Lewis acids. In all cases, intractable mixtures of products were formed. Based on the hypothesis that the free phenol may contribute to these failures, **16** was methylated and then saponified. However, when **19** was subjected to another raft of Friedel–Crafts acylation conditions, no radermachol methyl ether (**20**) could be isolated from the multitude of products formed.

It was obvious at this juncture that electrophilic ring closure in this system was going to be very difficult. Accordingly, a nucleophilic ring-closure strategy was devised (Scheme 4). Acylation of 1,4-dimethoxynaphthalene (**10**) with 2-iodobenzoic acid (**21**) gave diarylketone **22**. With this substrate, oxidative demethylation proceeded cleanly, providing quinone **23** in excellent yield. Application of the furannulation protocol required an enol ether such as **24**, which presumably could be derived from β-ketoester **25**. However, it occurred to us that

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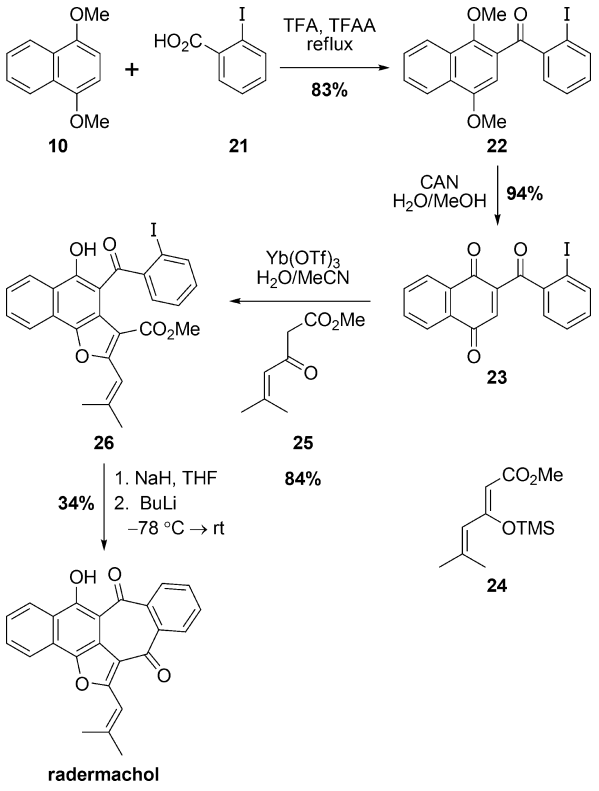
Scheme 4. Total Synthesis of Radermachol



the enol tautomer of **25** might itself be sufficiently nucleophilic for our requirements. These musings led us to the work of De Kimpe and co-workers, who showed that ytterbium triflate catalyzes the efficient one-pot furannulation of activated quinones with β-ketoesters.[21] A trial reaction of butyl vinyl ether (**2**) and quinone **1** (Scheme 1) with this catalyst gave the formal cycloaddition product **5** at room temperature, and more efficiently than the thermal procedure, giving us the confidence to apply this method to radermachol.

β-Ketoester **25** (Scheme 4) was prepared by Claisen-like condensation of mesityl oxide with Mander's reagent.[22] Pleasingly, in the presence of $Yb(OTf)_3$, **25** reacted with quinone **23** to give benzofuran **26** in good yield. In situ deprotonation of the phenol with NaH, followed by lithium−iodine exchange, allowed intramolecular nucleophilic acylation involving the methyl ester, providing radermachol in modest yield, accompanied by some starting material and the deiodinated product. The NMR spectroscopic data obtained for radermachol were essentially identical to those previously reported for the naturally derived material.[15] The ^{13}C NMR spectrum reported by Pelletier[16b] for synthetic radermachol is at slight variance with what we and Sing[15] observed; the resonance at 117.3 ppm is missing from Pelletier's data, and an additional (spurious) peak at 129.3 ppm was reported. All other data concur with our spectrum.

It is possible that the yield of the final cyclization could be improved by prior protection of the phenol in **26**. Then again, as mentioned previously, the corresponding phenoxide serves to deactivate the ketone carbonyl to nucleophilic attack, and no protecting group can achieve this. Moreover, given the brevity of the route in Scheme 4, and the good yields of the preceding steps, additional protection and deprotection steps did not seem warranted.

In conclusion, radermachol was prepared in four linear steps, from commercially available starting materials, and in an overall yield of 22%, a marked improvement over existing syntheses. This rapid and efficient synthesis provides a means to investigate the biological activity of radermachol and perhaps elucidate its ecological role.

■ ASSOCIATED CONTENT

Supporting Information

General experimental details and specific procedures, characterization of new compounds, including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The reference to Hauser and Yin was missing in the version published ASAP April 21, 2014; the new reference 17 was added and reposted April 22, 2014.