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The Total Synthesis of Radermachol

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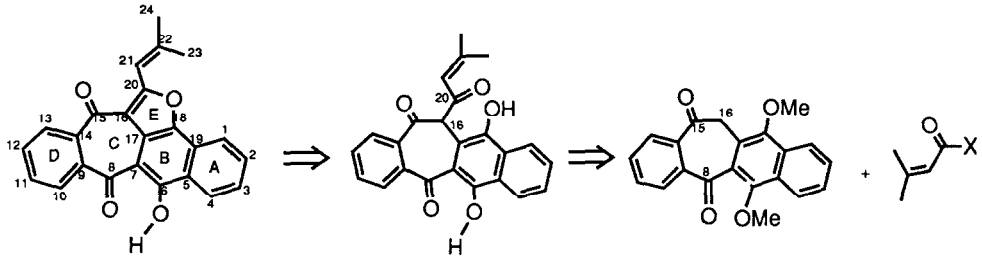
Abstract The red pigment, *radermachol (1), has been synthesized from 1,4-dimethoxynaphthelene in thirteen steps.*

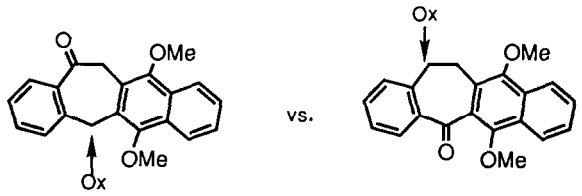
Radermachol (**1**),[1] a red pigment isolated from *Radermachera xylocarpa,* has a fused aromatic structure not encountered previously in any other natural product A retrosynthetic analysis (Scheme 1) indicated the preparation of **3** as a key intermediate for introduction of the dimethylacryloyl group and subsequent cyclization.



Radermachol **1** **2** **3** **4**

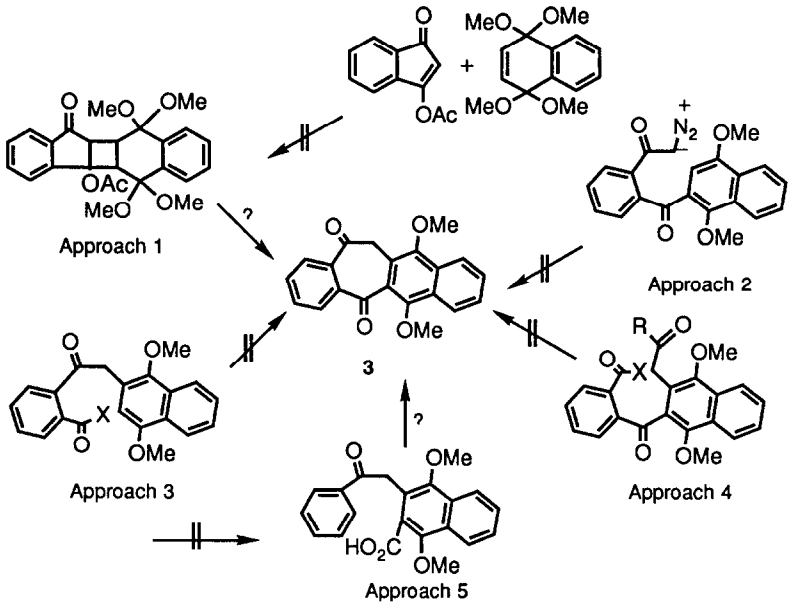
Scheme 1

Five synthetic routes for the preparation of **3** proved to be unsuccessful (Scheme 2) [2,3] We then considered the synthesis of a monoketone and introduction of the second carbonyl group by oxidation Between the two monoketones (**5**) and (**6**), we chose **5** as our synthetic target, since the two methylenes in **5** should have different properties and therefore could be manipulated separately, whereas in **6**, the methylenes have similar features



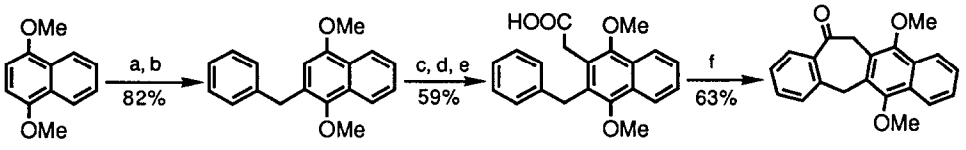
5 **6**

The synthesis of **5** (Scheme 3) commenced by the benzoylation of 1,4-dimethoxynaphthalene in the presence of TFAA to give 2-benzoyl-1,4-dimethoxynaphthalene, which by reduction with Et_3SiH in acidic medium afforded 2-benzyl-1,4-dimethoxynaphthalene (**7**), mp 61-62°C. Introduction of the acid chain in **7** was accomplished by bromomethylation, dis-



Scheme 2

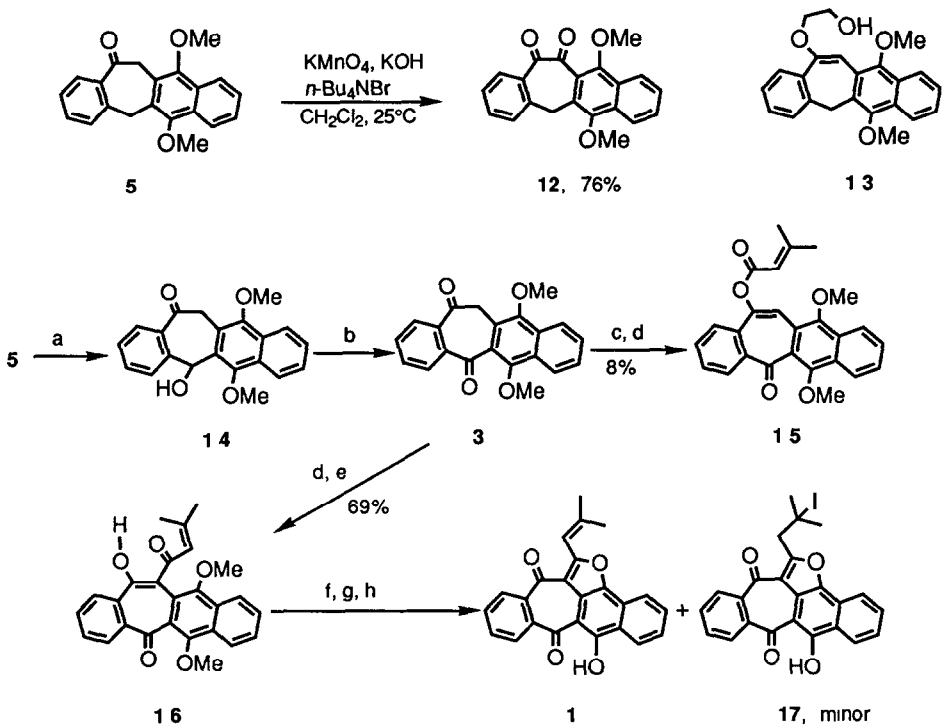
placement of the bromine by a cyano group and hydrolysis[4] to give **8** in a yield of 59%. Cyclization of the carboxylic acid (**8**) with PPA furnished 6,7-benzo-3,4(1,4-dimethoxy-2,3-naphtho)-1-oxosuberane (**5**), mp 134-136°C [5,6]



(a) $C_6H_5CO_2H$, CF_3CO_2H, $(CF_3CO)_2O$, Reflux, (b) Et_3SiH, CF_3CO_2H, 25°C; (c) $(CH_2O)_n$, HBr; (d) KCN, (e) OH^-, (f) PPA, 60-75°C

Scheme 3

Oxidation of **5** with $KMnO_4$–*n*-Bu_4NBr afforded the diketone (**12**) Similarly, oxidation of **5** with PCC or DDQ gave **12** as the only major product. An attempt to protect the keto group with ethylene glycol, resulted in the formation of the enol ether **13** Refluxing **5** with NBS in CCl_4 in the presence of dibenzoyl peroxide gave the bromo derivative, which was easily hydrolyzed by water during aqueous work-up or during purification on silica-gel to afford the alcohol (**14**) as an amorphous compound (Scheme 4) Oxidation of **14** with PCC gave the desired intermediate 6,7-benzo-3,4 (1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (**3**), mp 121 5-122.5°C, in 50% yield from **5** The structure of **3** was confirmed by an X-ray crystal structure determination [2b] The high strain of the cyclopentanedione ring can be clearly seen from the folded shape of the molecule in which the two planes formed by two different aromatic rings have a dihedral angle of nearly 100° The next step in our retro-synthetic analysis features the introduction of the side chain at the benzylic position in **3**

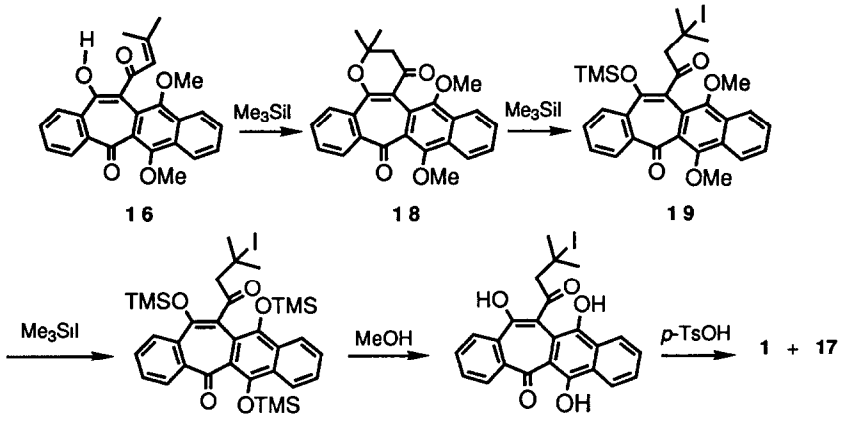


(a) NBS, CCl_4, $(PhCOO)_2$, Hydrolysis, (b) PCC, (c) Base, (d) Dimethylacryloyl chloride, (e) 2 eq $AlCl_3$, CH_2Cl_2, Reflux, (f) 5 eq Me_3SiI, $CDCl_3$, RT, 27 h; (g) MeOH, (h) p-TsOH, Benzene, Reflux, 5 h

Scheme 4

Theoretically, the acylation could be accomplished by an intermolecular Claisen condensation. However, treatment of **3** with a base, followed by addition of 3,3-dimethylacryloyl chloride gave the enol ester (**15**) in poor yield Varying conditions failed to give the required acylation product The formation of the enol ester **15** is due probably to the generation of a stable enolate, which upon formation of the ester extends the conjugation The final step of introduction of the 3,3-dimethylacryloyl moiety at the benzylic position was achieved by acylation under acidic condition

Heating diketone **3** with 3,3-dimethylacryloyl chloride **4** in the presence of $AlCl_3$ in CH_2Cl_2, afforded **16** as the major product The crude product was demethylated with Me_3SiI in $CDCl_3$ at rt and then treated with MeOH The resulting hydroquinone was subsequently heated with a catalytic amount of *p*-TsOH in refluxing benzene to afford radermachol (**1**) as red needles, mp 214 5-216 5°C, identical in all respects (co-tlc, mixture mp, ir, ms, ^1H nmr and ^{13}C nmr spectral comparison) with the natural product A minor compound obtained in the cyclyzation has been assigned structure **17** The last step of demethylation is not straightforward and probably proceeds by hydrolysis and cyclization as shown in Scheme 5 The demethylation reaction was followed by determining the ^1H nmr spectrum from time to time Addition of 5 equivalents of Me_3SiI immediately formed **18**, in which the two-proton AB pattern was observed at δ 2 90 and 3 28 ppm (J = 16 0 Hz), respectively, and the chelated hydroxyl proton and the vinyl proton in the starting material disappeared This AB system can be assigned to magnetically non-equivalent protons of the methylene group in **18** After one hour, the AB system disappeared, giving **19** in which two protons of the methylene group became equivalent



Scheme 5

The synthesis of radermachol (**1**) has been accomplished in thirteen steps from 1,4-dimethoxynaphthalene

References and Notes

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3 Ramasubbu, N , Bhandary, K K , Joshi, B S , Jiang, Q , Pelletier, S. W., *Acta Cryst.*, **1990**, *C46*, 1668; Ramasubbu, N , Bhandary, K. K., Joshi, B S , Jiang, Q.; Pelletier, S W *J. Cryst.Spectr.Res* **1991**, *21*, 0000

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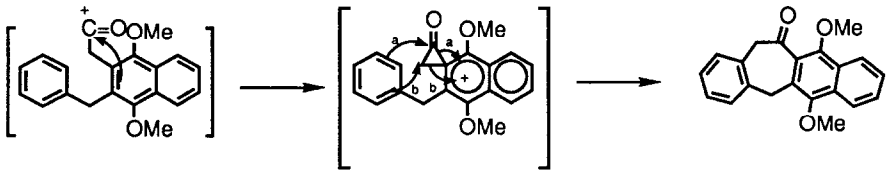
5. All new compounds gave spectral and analytical data consistent with their structures

6 The alternate cyclization product **9** via the cyclopropane intermediate **11** arising from the carbocation **10** was ruled out by an nOe experiment When the two methoxy groups at δ 3.93 and 3 09 were irradiated separately, two methylene singlets at δ 4.41 and 4.51, respectively, showed enhancements, demonstrating that both methylene groups in the product must be located at the positions benzylic to the 1,4 -dimethoxynaphthlene ring as in structure **5**



10 **11** **9**

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