The Synthesis of Radermachol

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Five different approaches to the preparation of 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (**3**), an intermediate needed for the synthesis of radermachol (**1**), the red pigment from the roots of *Radermachera xylocarpa*, are described. The synthesis of radermachol (**1**) has been accomplished from 1,4-naphthoquinone in 14 steps.

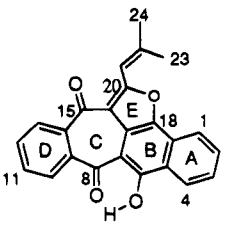
Introduction

Radermachol, a red pigment isolated from *Rademachera xylocarpa* K. Schum., was assigned structure **1** by a single-crystal X-ray analysis.[1] The fused ring system of radermachol contains one five-, three six-, and one seven-membered rings. The two six-membered rings (B and D) fused to the seven-membered ring C are slightly nonplanar; the six-membered ring A and the five-membered ring E are perfectly planar. The seven-membered ring C has a boat conformation, the atoms C(9), C(14), C(16), and C(17) forming the basal plane with the atom C(15) at the prow and C(7) and C(8) at the stern. The conformation of the fused ring system can be described by the dihedral angles formed by planes through the different rings (A–B = 0.6°, B–C = 10.0°, B–E = 5.6°, C–D = 17.6°, C–E = 9.7°). Although radermachol is nonplanar, the molecule is probably not rigid. Flipping of the carbonyl groups would make it achiral and hence no optical activity is observed. A number of furano- and dihydrofuranonaphthoquinones have been isolated from *R. sinica* Hemsl.[2] However, the fused ring system of radermachol is unique, has not been encountered so far in any other natural product, and is biogenetically interesting.[3] Fascinated by the unusual skeleton of radermachol, we undertook the synthesis of **1**, which was reported in a preliminary communication.[4]

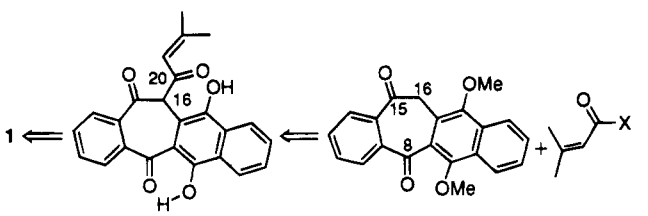
Results and Discussion

Retrosynthetic Analysis. A close scrutiny of the construction of radermachol (**1**) leads to the retrosynthetic strategy presented in Scheme 1, based on the disconnection of the bond between C(20) and the furano oxygen. Formation of the furan ring can be accomplished by treatment of **2** with acid or base followed by dehydration, *via* a nucleophilic attack of phenoxide on the C(20)-carbonyl group. Introduction of the 3,3-dimethylacryloyl group (**4**) on C(16) can be achieved by an intermolecular Claisen condensation to give **2**. The major synthetic challenge posed by this molecule is synthesis of the key intermediate cycloheptanedione **3**. It is necessary to protect the hydroxyl groups to prevent the dihydroxynaphthalene from oxidation. A concern is the choice of the protecting group which could be removed at a late stage of the synthesis followed by cyclization. In the final retrosynthetic analysis, a methyl ether was chosen since it would be resistant to a wide variety of reagents and could be easily removed using mild conditions.[5]

Scheme 1



Radermachol **1**



2 **3** **4**

Attempted Approaches to the Formation of Cycloheptanedione 3. Although synthesis of seven-membered diketones is well established, there is no precedent for synthesis of the diketo system contained in radermachol. The conformation of **3** can be described as two "intersected" planes formed through two different aromatic rings, which share atoms C(8) and C(16) and have the dihedral angle of nearly 100°. Study of a Dreiding model suggests that the seven-membered ring moiety in **3** is much more strained than a normal seven-membered diketone. The high strain of the cycloheptanedione ring explains several unexpected reactions involved in the construction of **3**. The present study discusses several synthetic routes attempted for the preparation of **3**.

Diels–Alder Approach. A retrosynthetic analysis for the preparation of **3** is shown in Scheme 2. The Diels–Alder adduct **5** was prepared in 72% yield by reaction of 1,4-naphthoquinone with 1,3-butadiene in acetic acid.[6] Isomerization of **5** to **6** (R = H) was unsuccessful by the literature procedure.[7] Treatment of

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(1) Joshi, B. S.; Gawad, D. H.; Pelletier, S. W.; Kartha, G.; Bhandary, K. *Tetrahedron Lett.* **1984**, *25*, 5847.

(2) Inoue, K.; Chen, C. C.; Inouye, H.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. I* **1981**, 2764.

(3) Simpson, T. J. *Nat. Prod. Rep.* **1987**, *4*, 639.

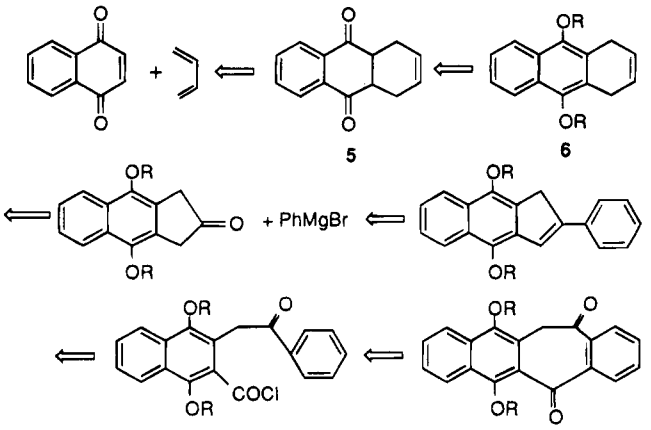
(4) Jiang, Q. P.; Joshi, B. S.; Pelletier, S. W. *Tetrahedron Lett.* **1991**, *32*, 5283.

(5) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; pp 88–92.

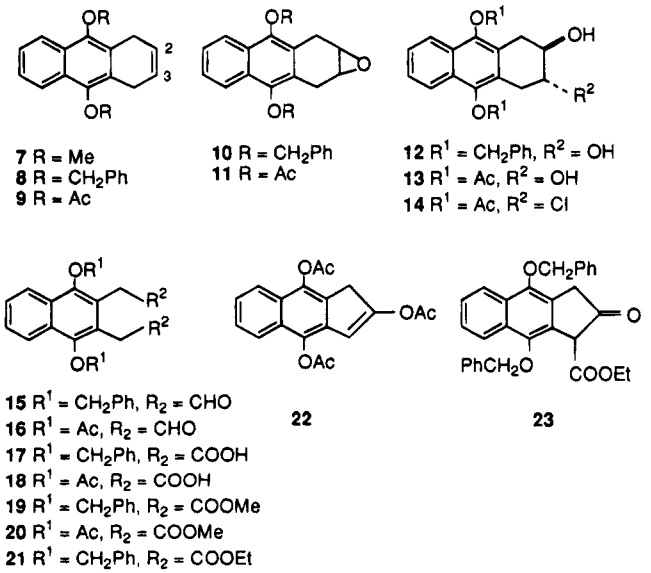
(6) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98.

0022-3263/94/1959-8220$04.50/0

Scheme 2



5 with Me_2SO_4 and NaH under N_2 gave the dimethyl ether **7**. The corresponding bis(benzyloxy) compound **8** was prepared similarly. 9,10-Diacetoxy-1,4-dihydroanthracene (**9**) was prepared by heating **5** with acetic anhydride. The next step is to cleave the C-2, C-3 double bond to give the dialdehyde and the diacid. Several attempts at the ozonolysis of **9** were unsuccessful. Treatment of **8** and **9** with OsO_4 gave the corresponding epoxides **10** and **11** which were cleaved with acid to give the corresponding *trans* diols **12** and **13**, respectively. The epoxide **11** when treated with HCl gave the chlorohydrin **14**. Periodic oxidation of the diols **12** and **13** afforded the dialdehydes **15** and **16** which upon oxidation with Kiliani reagent gave the carboxylic acids **17** and **18**, respectively. The carboxylic acids were esterified with CH_2N_2 to give the methyl esters **19** and **20**, and treatment of **17** with EtOH and H_2SO_4 gave the ethyl ester **21**. Dieckmann condensation of the diester **20** failed to give the expected cyclic ketone. Pyrolysis of the diacid **18** with Ac_2O (Blanc reaction) gave an enol acetate (**22**). A base-catalyzed Dieckmann reaction of **21** afforded the keto ester **23.** This route was abandoned because of the many steps involved in the preparation of **23**.



7 R = Me
8 R = CH_2Ph
9 R = Ac

10 R = CH_2Ph
11 R = Ac

12 R^1 = CH_2Ph, R^2 = OH
13 R^1 = Ac, R^2 = OH
14 R^1 = Ac, R^2 = Cl

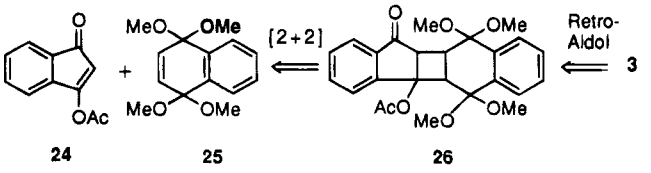
15 R^1 = CH_2Ph, R_2 = CHO
16 R^1 = Ac, R_2 = CHO
17 R^1 = CH_2Ph, R_2 = COOH
18 R^1 = Ac, R_2 = COOH
19 R^1 = CH_2Ph, R_2 = COOMe
20 R^1 = Ac, R_2 = COOMe
21 R^1 = CH_2Ph, R_2 = COOEt

22

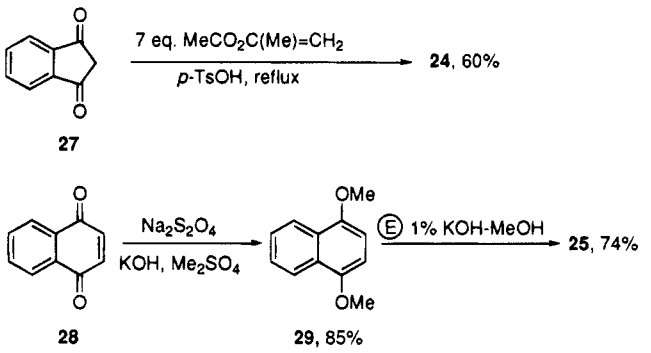
23

[2 + 2] Photoaddition and Retro-Aldol Condensation Approach. In this approach for the construction of **3** (Scheme 3), we intended to synthesize the cyclobutane intermediate **26** by photoaddition of **24** and **25**. Subsequent treatment of **26** with a base would open the strained cyclobutane ring *via* a retro-Aldol fragmentation to form **3**.

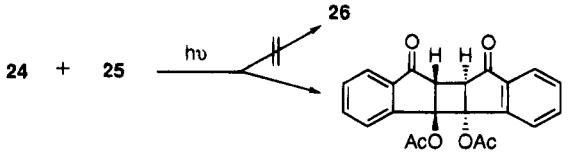
Scheme 3



Scheme 4



Scheme 5



30a, 63%

3-Acetoxyindenone (**24**) was prepared by refluxing 1,3-indandione (**27**) with 7-fold of isopropenyl acetate in the presence of a catalytic amount of *p*-TsOH.[8] A tandem reductive-methylation of 1,4-naphthoquinone (**28**) was effected by a phase transfer reagent.[9] Thus, treatment of **28** with $Na_2S_2O_4$ in aqueous THF in the presence of *n*-tetrabutylammonium bromide, followed by addition of KOH and Me_2SO_4, yielded 1,4-dimethoxynaphthalene (**29**) which on anodic oxidation in 1% KOH–MeOH gave 1,1,4,4-tetramethoxy-1,4-dihydronaphthalene (**25**)[10,11] (Scheme 4).

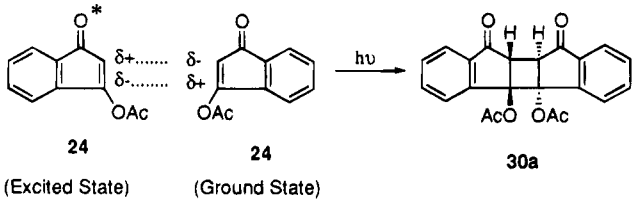
Subjecting compounds **24** and **25** to [2 + 2] photoaddition, by irradiation of the solution with a medium-pressure mercury lamp, did not afford the desired photoadduct **26**. Instead, a photodimer (**30a**) was obtained (Scheme 5). Various conditions were investigated in order to form **26**, e.g. use of C_6H_6 and hexane as solvents having widely different properties for absorption of UV light and use of a large excess of **25**. However, in each case only the diketone **30a** was obtained.

The dimer $C_{22}H_{16}O_6$ has four possible isomeric structures of the truxenone derivatives, namely **30a** (*syn-trans*), **30b** (*syn-cis*), **30c** (*anti-trans*), and **30d** (*anti-cis*). It is difficult to make a choice among the four isomers only on the basis of ^1H and ^{13}C NMR and mass spectral evidences since each molecule contains a certain symmetric element. As a matter of fact, the ^1H and ^{13}C NMR

(7) Grinev, A. N.; Ternet'ev, A. P. *J. Gen. Chem. USSR* **1958**, *28*, 77.

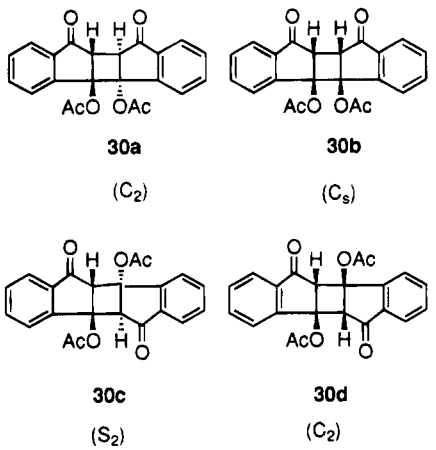
(8) Sraga, J.; Hrnciar, P. *Chem. Pap.* **1986**, *40*, 807.
(9) Kraus, G. A.; Man, T. O. *Synth. Commun.* **1986**, *16*, 1037.
(10) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.
(11) We thank Mr. Tse-Yuan Ou for his assistance in setting up the anodic oxidation experiment.

Scheme 6



24 (Excited State) 24 (Ground State) 30a

spectra of this dimer show the structural information corresponding only to half of the molecule. The correct structure was therefore determined by an X-ray diffraction study and was shown to be **30a**, in which two indanone rings are joined head-to-head, but trans-oriented to each other with respect to the cyclobutane ring.[12]

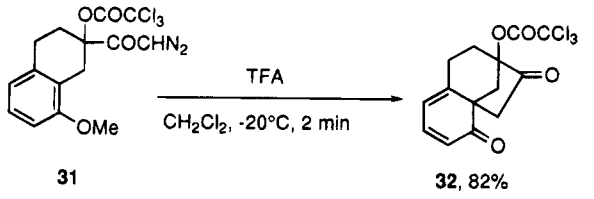


30a (C_2) **30b** (C_s) **30c** (S_2) **30d** (C_2)

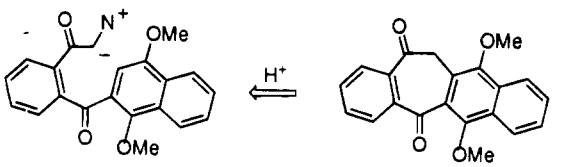
The ease of formation of the dimer is mainly due to the high reactivity of the enone **24** having five electrons delocalized over the five-membered ring and considered as a nonaromatic system according to the Huckel rule (Scheme 6). Indeed, **24** was not stable and slowly hydrolyzed back to 1,3-indandione (**27**) when stored in a N_2-filled container. In this particular case of photoreaction, the excited enone reacts rapidly with the very reactive ground-state enone to form the dimer, releasing the high energy embodied in the strained cyclopentadienone moiety. This mechanism also interprets the regiochemistry of the product.[13] Compound **30c**, one of the four possible isomers, should have a lower internal energy than **30a** but was not found in the reaction.

Intramolecular Friedel–Crafts Alkylation Approach. Mander and co-workers have developed an intramolecular Friedel–Crafts alkylation procedure for the construction of the bridged cyclopetanones from diazo keto compounds. An example is given in Scheme 7: treatment of **31** with TFA at −20 °C gave diketone **32**.[14] The utility of this methodology has been extended to the preparation of six-membered ketones, as demonstrated in the total syntheses of chelidonine,[15] as well as the construction of the ring systems of aphidicolin, stemodione, and stemodin.[16]

Scheme 7



31 32, 82%



33 3

Influenced by this chemistry, our next target molecule became the diazo ketone **33**. The approach was based on the premise that under Mander's conditions this reaction could overcome the deactivating effect of the carbonyl group toward the cyclization and generate **3**. This assumption, however, turned out to be incorrect.

2-Bromo-1,4-naphthoquinone (**35**) (Scheme 8), prepared by bromination of α-naphthol (**34**) with NBS,[17] on reductive-methylation gave 2-bromo-1,4-dimethoxynaphthalene (**36**). Treatment of **36** with *tert*-butyllithium, followed by addition of equimolar phthalic anhydride afforded **37.** The latter was treated with $EtCO_2Cl$, triethylamine, and CH_2N_2, followed by removal of the precipitated trimethylamine hydrochloride.[18] This step was assumed to generate the diazo ketone **33**; as a matter of fact the intermediate had a diazo keto group observed at 2080 cm^{-1} in the IR spectrum. Following the literature procedure,[14] the intermediate was treated with excess TFA. Instead of the anticipated **3**, an α,β-epoxy ketone (**38**) was obtained. This unexpected result prompted us to reexamine the structure of the intermediate obtained after treatment with CH_2N_2. The ^{13}C NMR spectrum revealed the presence of a carbonyl group at δ 186.8 and a quaternary carbon at δ 80.1, instead of two expected carbonyl groups for structure **33**. The former signal can be assigned to the keto part of the diazo keto group and the latter signal to an oxygen-attached carbon. The ^1H NMR spectrum showed the existence of a hydroxyl group at δ 4.87, which is exchangeable with D_2O. All these data allow us to assign structure **39** to this intermediate. The structure of **39** was confirmed by a single-crystal X-ray analysis.[19]

We believe that compound **33** is one of two possible intermediates leading to **39**, and the diazo group in the initially-formed **33** attacks the diaryl keto group, followed by a shift of the hydrogen in the diazo group to the resulting hydroxide anion. Treatment of **39** with TFA resulted in protonation of the methine carbon in the diazo keto moiety; subsequent nucleophilic attack of the hydroxyl group on this carbon leads to the formation of the α,β-epoxy keto moiety with the loss of nitrogen. The demethylation is believed to take place in a separate step.

Intramolecular Friedel–Crafts Acylation Approach. The strategy of ring closure of **40** to give **3** appeared promising since there are at least two factors

(12) Ramasubbu, N. K.; Bhandary, K.; Joshi, B. S.; Jiang, Q.; Pelletier, S. W. *Acta Crystallogr.* **1990**, *C46*, 1668.
(13) Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; pp 70–91.
(14) Blair, I. A.; Ellis, A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 405.
(15) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *Tetrahedron Lett.* **1980**, *21*, 3845.
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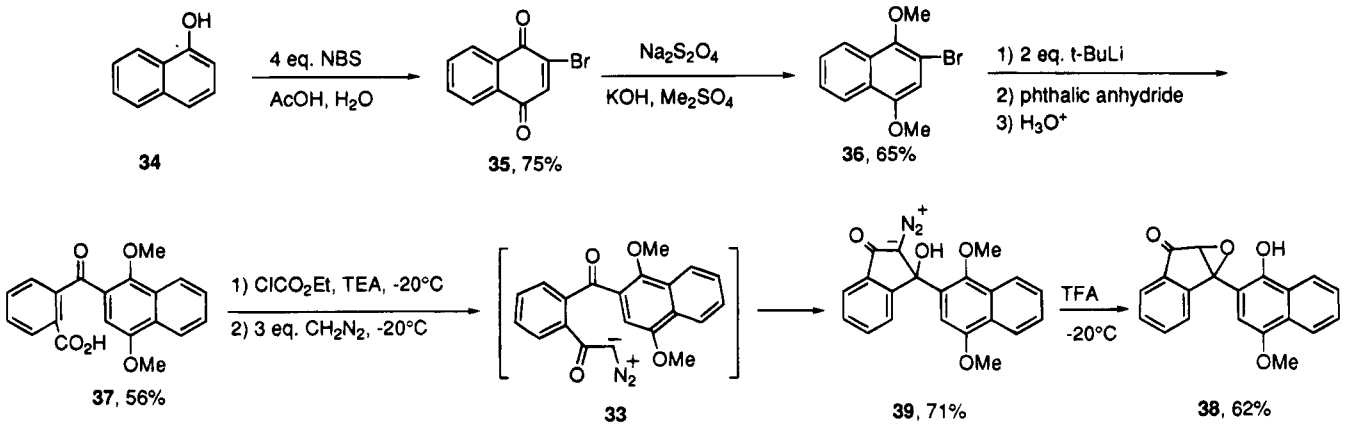
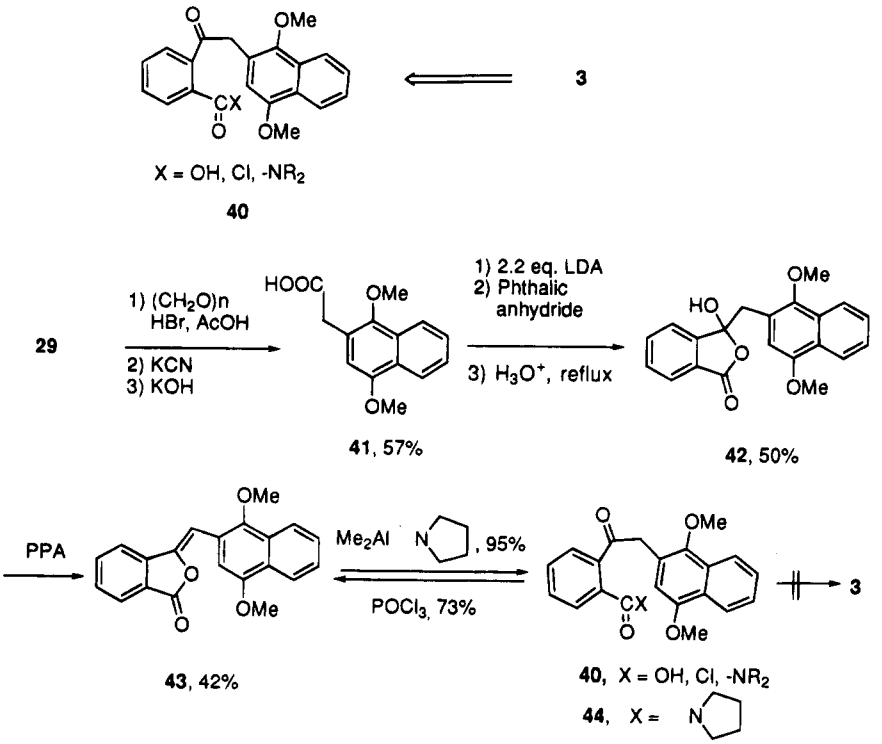
(18) Pettit, G. R.; Nelson, P. S. *J. Org. Chem.* **1986**, *51*, 1282.
(19) Ramasubbu, N.; Bhandary, K.; Joshi, B. S.; Jiang, Q. P.; Pelletier, S. W. *J. Cryst. Spectr. Res.* **1991**, *21*, 533.

Scheme 8



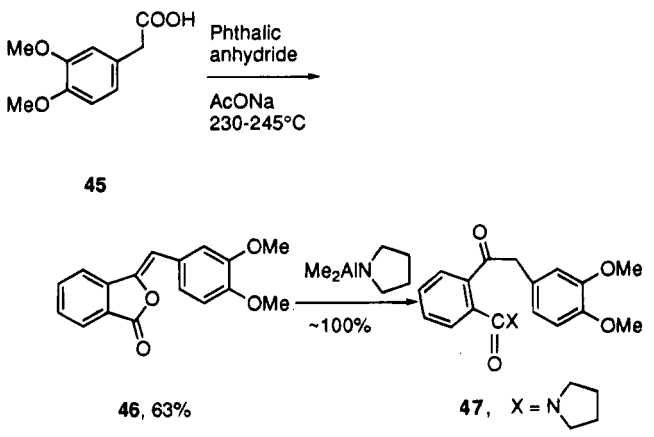
Scheme 9



in favor of the cyclization. First, unlike **33**, the dimethoxynaphthalene ring in the proposed intermediate **40** does not bear any electronegative deactivating group, which frequently causes the Friedel–Crafts cyclization to fail or to proceed in low yields. Second, reaction conditions can be varied for optimization of the yield, using different substrates, e.g. acid (X = OH), acid chloride (X = Cl) and amide (X = NR_2). Our fourth approach began by bromomethylation of 1,4-dimethoxynaphthalene (**29**) with $(CH_2O)_n$ and HBr,[20] treatment with KCN, and hydrolysis with KOH to obtain **41** (Scheme 9). The naphthaleneacetic acid **41** was treated with LDA to generate the dianion.[21] Addition of phthalic anhydride *in situ*, followed by decarboxylation of the resulting β-keto acid, gave a product, which was initially thought to have the structure **40** (X = OH). This assumption turned out to be incorrect, as the ^{13}C NMR spectrum showed the absence of the ketone resonance, around $\delta \sim 200$. Our original goal was to obtain the keto acid **40** (X = OH), but apparently this compound exists mainly in the form of the lactone hemiketal **42**. It is known that 2-acetylbenzoic acid exists in an equilibrium between the keto acid form and the lactone hemiketal form.[22] In the hope that some fraction of the keto acid form **40** will be present in **42**, it was heated with PPA to afford **43** as the major dehydration product; it displayed an intense yellow-green fluorescence. Here, two bulky aromatic groups are assumed to be *trans*-oriented to each other with respect to the double bond. This result reveals that the formation of **43** is more favorable than the formation of the highly strained **3**. As the lactone hemiketal **42** failed to form the cyclization product **3**, our alternative target molecule was the amide **44**, in which the lactone moiety no longer exists. Thus, treatment of **43** with dimethylaluminum pyrrolidinamide, generated *in situ* from trimethylaluminum and pyrrolidine, yielded the keto amide **44** in an excellent yield.[23] The amide **44**, on treatment

(20) Gates, M. *J. Org. Chem.* **1982**, *47*, 578.
(21) Kuo, Y.-N.; Yahner, J. A.; Ainsworth, C. *J. Am. Chem. Soc.* **1971**, *93*, 6321.
(22) *Catalogue Handbook of Fine Chemicals, Aldrich,* Aldrich Chemical Company, Inc.: Milwaukee, 1992–1993, p 13.
(23) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

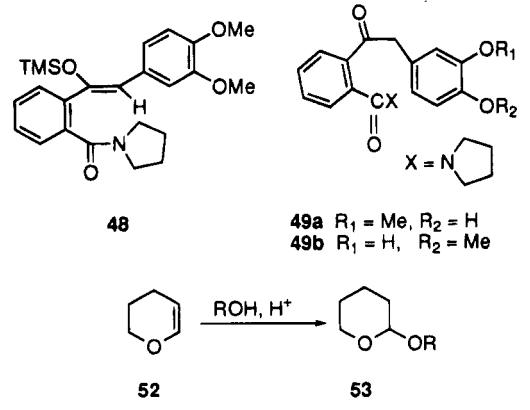
Scheme 10



with $POCl_3$ in C_6H_6,[24] reverted to give **43** in 73% yield (Scheme 9).

It became clear at this stage that under the present set of reaction conditions the keto group in **44** enolized easily to extend the conjugation and the resulting enolate oxide attacked the carbonyl equivalent, forming the stable product **43**. A way to avoid the enolization would be to protect the keto group in **44**. Because of its relative stability to many reagents and the ease of deprotection, 1,3-dithiolane was chosen as a protective group. Accordingly, a number of reagents for protecting the keto group in **44** were tried without success. Because of the paucity of the amide **44**, we decided to synthesize the model compound **47** (Scheme 10).

Heating 3,4-dimethoxyphenylacetic acid (**45**) and phthalic anhydride in the presence of a catalytic amount of NaOAc gave the fluorescent lactone **46**.[25] Treatment of **46** with dimethylaluminum pyrrolidinamide gave **47** in nearly quantitative yield. With the availability of the model compound **47**, we could investigate several conditions for the dithiolanation. Treatment of **47** with 1.5 equiv of 1,2-ethanedithiol in the presence of BF_3 etherate[26,27] or stirring a solution of **47** and 1.1 equiv of Evan's reagent $(CH_2STMS)_2/ZnI_2$[28] in $CHCl_3$ resulted in the recovery of the starting material. However, in the latter case when the solution was heated at 70–80 °C for 18 h, compound **48** was isolated in 54% yield. $TiCl_4$ has been reported as an efficient catalyst for the thio-acetalization of ketones such as β-keto esters[29] which easily enolize. However, when **47** was treated with 1,2-ethanedithiol in the presence of $TiCl_4$, a mixture of **49a** and **49b** was obtained.



In view of the facile enolization of the keto group in **47**, we intended to protect it as an acetate or as an ether, which requires reduction of the keto group to the alcohol. Reduction of **47** with $NaBH_4$ gave the lactone **50** (Scheme 11) which when treated with dimethylaluminum pyrrolidinamide afforded **51**. However, a routine workup caused the complete conversion to the starting material (**50**).

We explored another approach for thio-acetalization of the keto group in **47** in the form of the THP ether.[30] We thought that compound **46** having an enol ether moiety similar to that of dihydropyrane **52** would undergo the acid-accelerated ether formation. However, the enol double bond in **46** turned out to be very stable and was not protonated by *p*-TsOH, CF_3CO_2H, or BF_3 etherate at either room or elevated temperatures. Finally, **46** was transformed to the desired thioketal **56** by a four-step approach given in Scheme 12. Basic hydrolysis of **46** in aqueous THF in the presence of the phase transfer reagent, *n*-tetrabutylammonium bromide, followed by acidic workup, furnished **54**. Refluxing a C_6H_6 solution of **54** and an excess of 1,2-ethanedithiol in the presence of *p*-TsOH gave the anticipated ketal **55**, which gave **56** when treated with a strong Lewis acid.

With the thioketal **56** in hand, we were ready to proceed with the cyclization. A solution of **56** and excess $SOCl_2$ in $CHCl_3$ was refluxed for 1 h to afford the crude product, thought to be a thioketal acid chloride, which was further treated with $AlCl_3$ in $PhNO_2$. The isolated product showed a molecular ion at m/z 298 in the mass spectrum, instead of at m/z 358 for the desired compound **57**. Besides, it gave a strong fluorescence as in **46** and showed an IR absorption at 1690 cm^{-1} corresponding to a thiolactone group. These data, as well as ^1H and ^{13}C NMR spectra, enabled us to deduce structure **58** for this compound. Separation of the crude product after first treatment of **56** with $SOCl_2$ furnished a pure chlorine-containing compound, as revealed by the isotope effect of chlorine in the MS. The ^1H NMR spectrum showed an AB pattern at δ 3.54 (J = 13.8 Hz), indicating the presence of a chiral center in the molecule. This compound, unlike normal acid chlorides in many aspects, was purified on SiO_2 and was unaffected by H_2O used during workup. On the basis of spectral data and other properties, this compound has been assigned structure **61** (Scheme 13).

A plausible mechanism for the formation of **58** from **56** is rationalized below. The acid chloride **59** of the thioketal carboxylic acid **56,** by a nucleophilic attack of the strong nucleophile sulfur at the carbonyl group, displaces the chloride, forming the sulfonium ion **60**. There are two pathways for the chloride to react with the sulfonium ion center. One is pathway A in which the chloride attacks the methylene group adjacent to the positive charge to give **61**. The other is pathway B in which the chloride attacks alternatively the quaternary center to form **62**. Although one would expect that **61** and **62** should have very similar spectral features, it is

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(26) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
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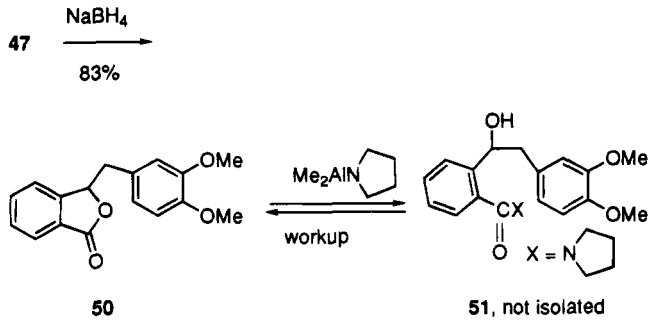
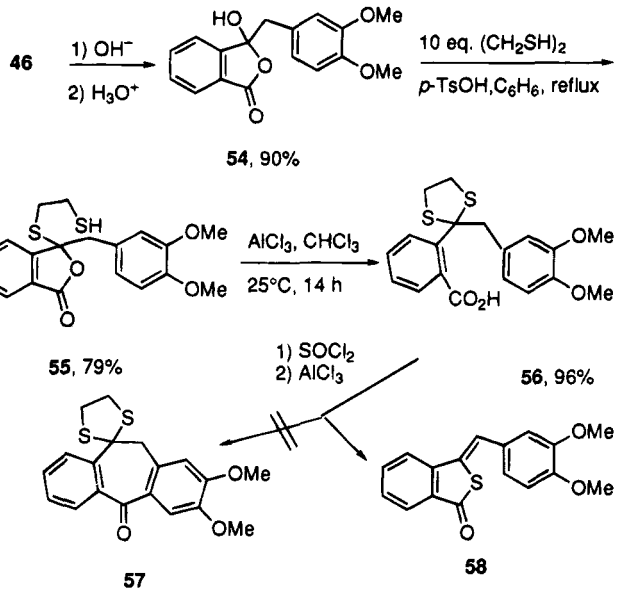
(30) Greene, T. W. *Protective Groups in Organic Synthesis*, John Wiley & Sons: New York, 1981; pp 21–22.

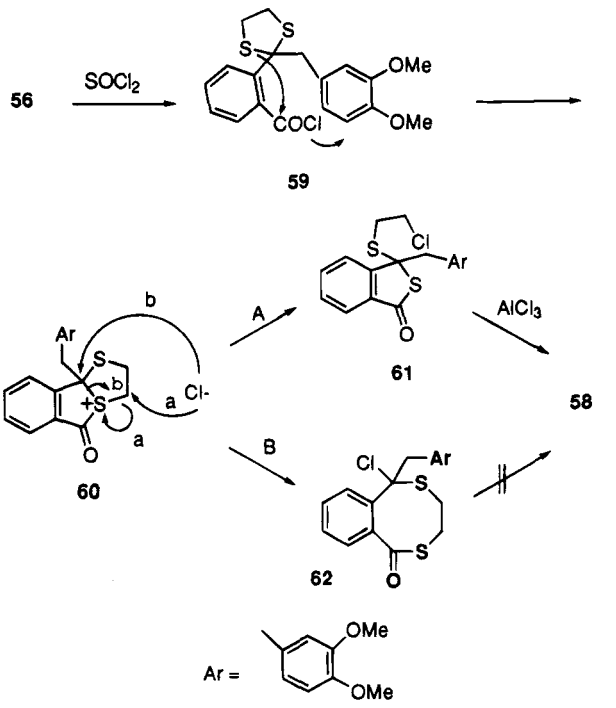
Scheme 11



Scheme 12

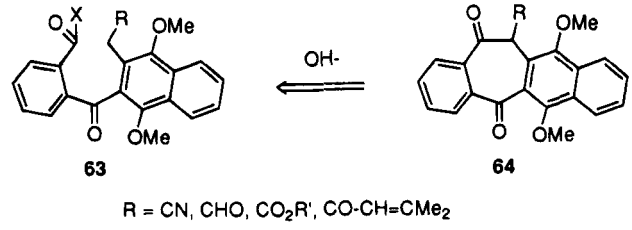


Scheme 13



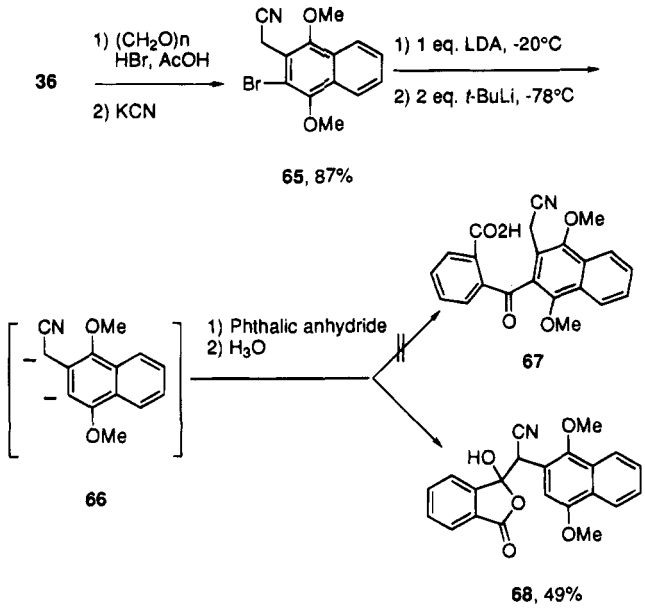
difficult to explain how the final product **58** could be derived from **62**. Therefore, structure **61** in pathway A is proposed as the intermediate. Further treatment of **61** with the strong Lewis acid cleaves the sulfur–carbon bond to afford the stable product **58**.

Scheme 14



R = CN, CHO, CO_2R', CO-CH=CMe_2

Scheme 15

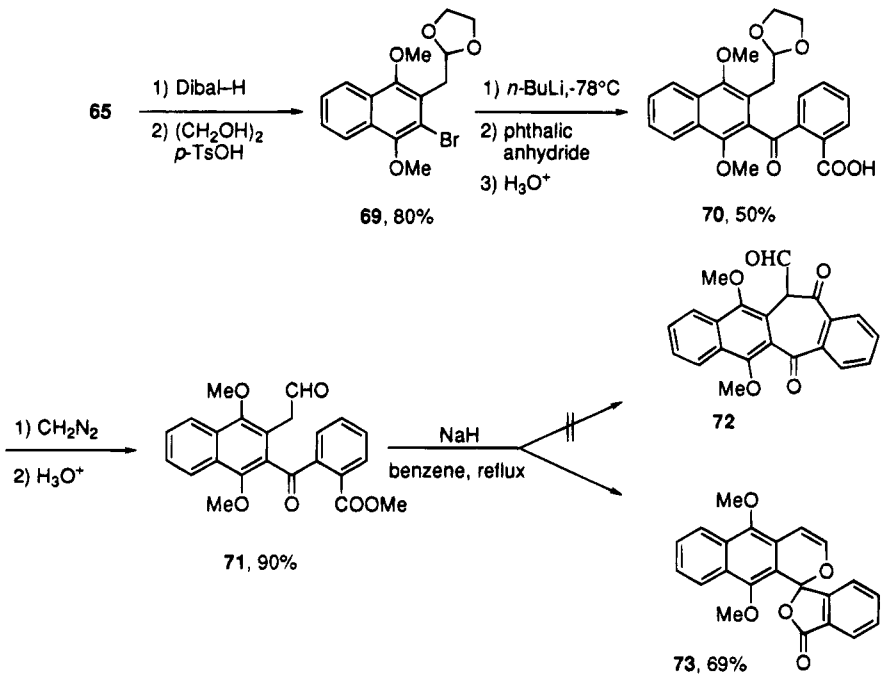


Intramolecular Claisen Condensation Approach. Several examples have been reported for the syntheses of seven-membered ketones *via* intramolecular Claisen condensation, though reactions of this type are generally considered unfavorable for the construction of medium-sized rings. A general approach using intramolecular Claisen condensation was designed and is given in Scheme 14 where R stands for nitrile, aldehyde, ester, or a 3,3-dimethylacryloyl group. It appears from Scheme 14 that when **63** is treated with a base, the resulting anion should undergo a cyclization to give **64,** in which the anion is stabilized by the keto and R groups. If a 3,3-dimethylacryloyl group was introduced in this way, the product, upon demethylation and acidic or basic treatment, should directly give the final product (**1**).

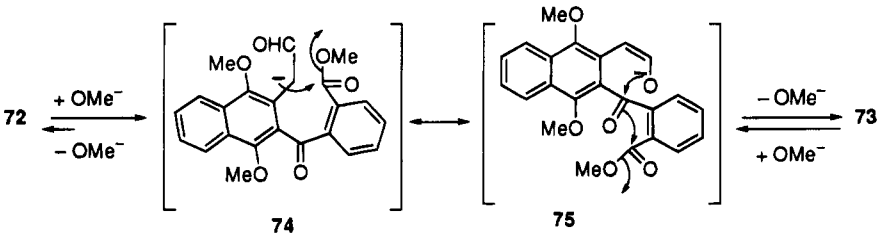
To this end, we proposed a short route to intermediate **63,** which again employed dianion chemistry (Scheme 15). Bromomethylation of **36,** followed by displacement of the bromide in the resulting product with the cyano group gave **65**, which when treated with LDA produced the first anion at the α-position of the cyano group; bromine–lithium exchange generated the second aryl anion. Addition of phthalic anhydride to the dianion, followed by acidic workup, resulted in the formation of **68** as the major product, and not **67**.

The cyano group in **65** was reduced to the aldehyde with DIBALH (Scheme 16) and converted to the 1,3-dioxolane **69**. The bromine–lithium exchange and subsequent addition of phthalic anhydride to the resulting anion, followed by acidic workup, gave **70**. Methylation of the carboxyl group with CH_2N_2 and acidic hydrolysis of the acetal afforded the precursor **71**. Cyclization of **71** with NaH in benzene did not furnish the desired product **72** but an unexpected spirolactone (**73**). The ^1H NMR spectrum of **73** showed an AB system at δ 6.60 and

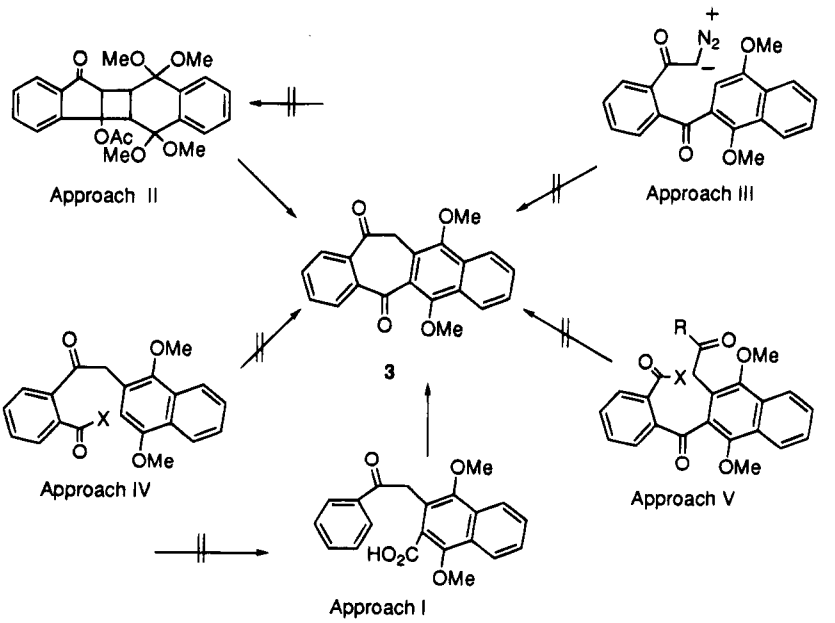
Scheme 16



Scheme 17



Scheme 18



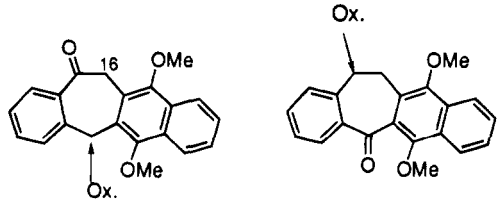
6.85 (J = 5.9 Hz), respectively, in accord with a pair of *cis*-olefinic protons on a dihydropyran ring.

A surprising and unusual observation is that the oxygen anion of the enolate **75** generated with base attacks the diaryl keto group and the resulting spiro oxygen anion attacks in turn the ester group (Scheme 17). We hoped that two compounds **72** and **73** would equilibrate in a basic solution in favor of the formation of **72**, which has a very acidic proton present between the carbonyl and aldehyde groups. However, when **73** was further treated with NaOMe, it did not equilibrate to **72**.

The five approaches for the synthesis of cycloheptanedione **3**, the key intermediate in the total synthesis of radermachol, are summarized in Scheme 18. In each case we failed to obtain the cycloheptanedione **3**. From

these negative experimental results, three important conclusions can be drawn: (i) a common and major problem in approaches III, IV, and V is the high strain embodied in the cycloheptanedione moiety of the target compound **3**, which makes the Scheme 18 cyclization very difficult. This conclusion follows from an examination of a Dreiding model and is confirmed by analysis of the X-ray structure of **3** (*vide infra)*; (ii) it is largely because of this strain that the neighboring group effects play a major role for failure of the cyclization; (iii) these effects are directly related to the presence of two carbonyl groups in the precursors of the cyclizations. Consequently, it is crucial that the two keto groups in the cycloheptanedione **3** should be introduced separately.

Synthesis of Radermachol (1). In light of the observations discussed earlier, our general strategy for formation of **3** consisted of the synthesis of a monoketone and then introduction of a second carbonyl group in the molecule. Between the two monoketones **76** and **77**, we chose **76** as our synthetic target. This selection was based on the idea that the two methylene positions in **76** have widely different properties and can be manipulated differentially, while the two methylenes in **77** have very similar features.



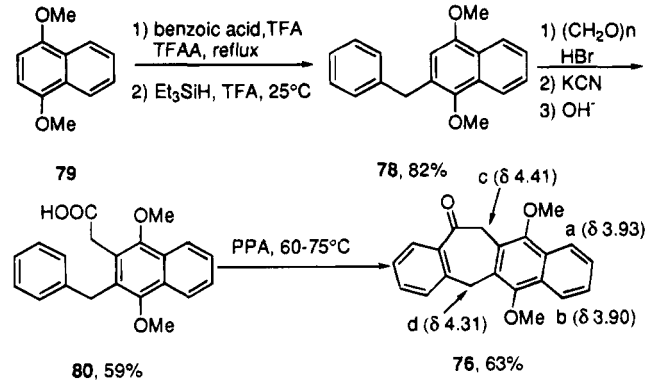
76

77

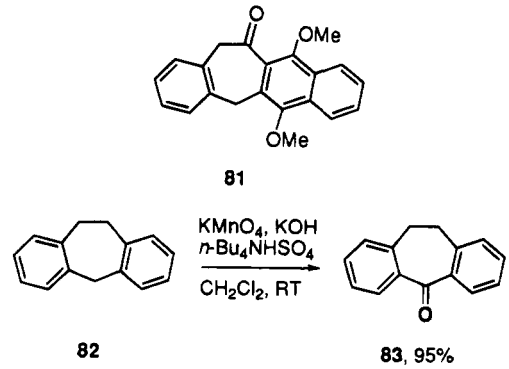
The total synthesis of radermachol, based on Scheme 19, began with the formation of the intermediate **78.** Refluxing a mixture of 1,4-dimethoxynaphthalene (**79**) and benzoic acid in TFAA and TFA,[31] and reducing the resulting diaryl ketone with triethylsilane in an acidic medium,[32,33] affords **78** in an overall yield of 82%. Introduction of the carboxylic acid side chain in the dimethoxynaphthalene **78** was accomplished by bromomethylation, displacement, and hydrolysis. This three-step transformation, which has been applied earlier in the synthesis of 1,4-dimethoxy-2-naphthaleneacetic acid, gave the carboxylic acid **80** in 59% overall yield. Cyclization proceeded smoothly by heating **80** in PPA at 65–70 °C for 1 h to furnish a yellowish monoketone (**76**) in 63% yield.

Although this transformation is a simple reaction, we were cautious of the result. The initial step in the cyclization generates the carbocation (or PPA ester), which should lead to the direct formation of the product **76**. It was important to determine the structure of the cyclization product since it would be difficult to distinguish the isomeric product **81** by normal ^1H and ^{13}C NMR, mass, and infrared spectra. Needless to say, severe consequences result if the wrong isomer of **81** is used for the next step. In order to fully characterize the structure of the product, a differential NOE experiment was carried out. When two methoxy groups at δ 3.93

Scheme 19



Scheme 20



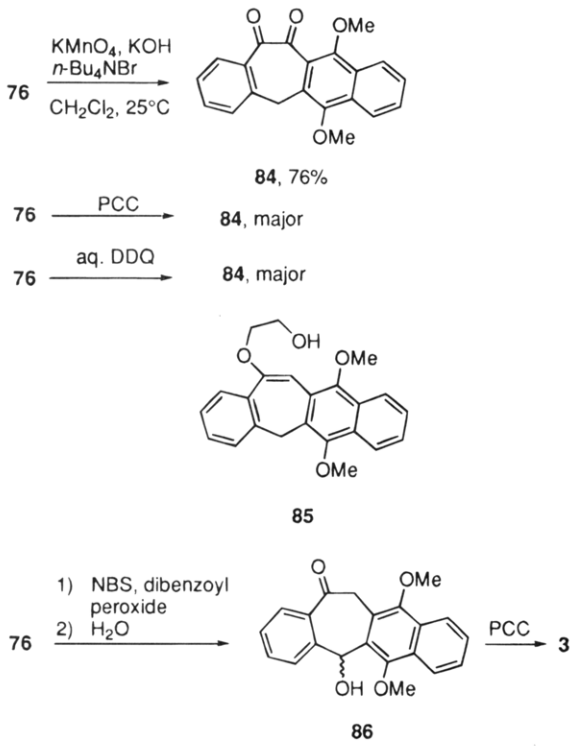
and 3.90 were irradiated separately, two methylene singlets at δ 4.41 and 4.51 showed enhancements, respectively. These assignments were also confirmed by a NOESY experiment. This result demonstrated that both methylene groups in the product must be located at the positions benzylic to the 1,4-dimethoxynaphthalene ring, as in structure **76**. In contrast to **76**, one would expect that only one methylene group in structure **81** can have an NOE enhancement to a methoxy group. The assignment of a, b, c, and d to individual groups in **76** is based on the differential NOE spectra as well as a deuterium base exchange experiment. In the latter experiment, a two-proton singlet at δ 4.41 disappeared upon addition of KOD to the sample solution and hence can be assigned to the position α to the carbonyl group. On the basis of these results, the cyclization product is assigned structure **76**.

In a recent investigation, the phase transfer $KMnO_4$ oxidation of benzylic positions has been studied and an example is given in Scheme 20. In this case, the doubly-benzylic position in **82** is selectively and efficiently oxidized, affording dibenzosuberone **83** in 95% yield.[34]

We decided to apply the above oxidation to **76** since it has double and single benzylic positions in the molecule. However, when a solution of **76** in CH_2Cl_2 was treated with basic $KMnO_4$ in the presence of *n*-tetrabutylammonium bromide at rt for 1 h, the 1,2-diketone **84**, rather than the diketone **3**, was isolated in 76% yield. It appears that under basic conditions, the keto group is readily enolized and the double bond of the resulting enolate is then selectively oxidized. When the oxidation was carried out under nearly neutral condition using PCC,[35] the same result was obtained. Oxidation of the benzylic positions with DDQ in aqueous media has been reported

(31) Penco, S.; Angelucci, F.; Ballabio, M.; Barchielli, G.; Suarato, A.; Vanotti, E.; Vigevani, A.; Arcamone, F. *Tetrahedron* **1984**, *40*, 4677.
(32) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.
(33) Swenton, J. S.; Anderson, D. K.; Coburn, C. E.; Haag, A. P. *Tetrahedron* **1984**, *40*, 4633.
(34) Gannon, S. M.; Krause, J. G. *Synthesis* **1987**, 915.
(35) Parish, E. J.; Chitrakorn, S.; Wei, T.-Y. *Synth. Commun.* **1986**, *16*, 1371.

Scheme 21



to give aryl ketones in moderate yields.[36] Application of this method to substrate **76** yielded the 1,2-diketone **84** as the major product. These reactions are shown in Scheme 21.

An attempt to protect the keto group with 1,2-glycol resulted in the formation of the enol ether **85** in addition to some recovered starting material. The double bond of the resulting enolate ether appears to be unreactive to further protonation. As pointed out earlier, the two methylene positions in **76** have widely different properties, and this feature allows us to selectively introduce the second carbonyl group at the doubly-benzylic position. Thus, this position was first selectively brominated through a free radical reaction by refluxing a solution of **76** and NBS in CCl_4 in the presence of dibenzoyl peroxide.[37] The bromo group in the resulting product was very labile and therefore was easily hydrolyzed by water during aqueous workup or separation on silica gel. The resulting doubly-benzylic alcohol **86** was readily oxidized with PCC, generating the yellowish crystalline ketone **3**. The overall yield of three steps was 50%.

Figure 1 shows the single-crystal X-ray diffraction structure (Chem 3-D drawing) of **3**. The high strain of the cycloheptanedione ring can be clearly seen from the folded shape of the molecule, in which two planes formed through two different aromatic rings have a dihedral angle of nearly 100°. This result is in good accord with our observation from a Dreiding model. Despite the rigid seven-membered ring system, the whole molecule in solution is not chiral, as revealed by the presence of a singlet at δ 4.41 in the ^{1}H NMR spectrum for the methylene group. This may be due to the rapid flipping of two carbonyl groups in solution, causing the loss of the chirality generated from two unsymmetric planes.

The next step in our retrosynthetic analysis features introduction of the side chain at the benzylic position in

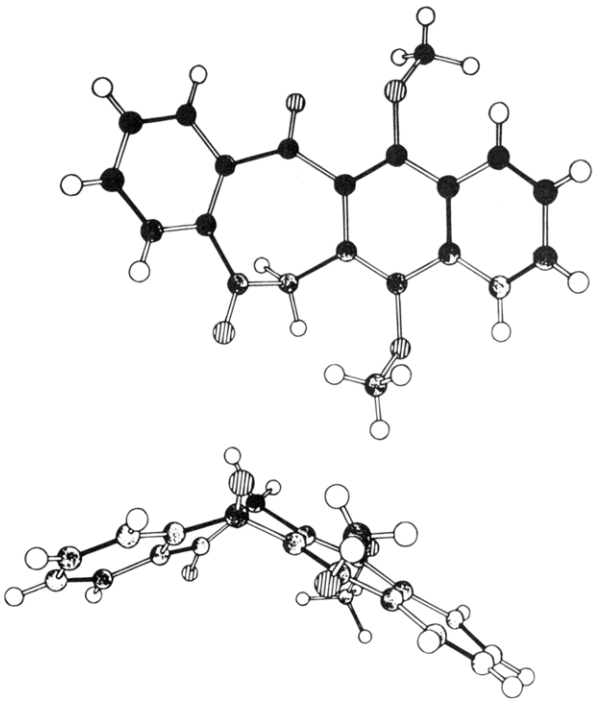
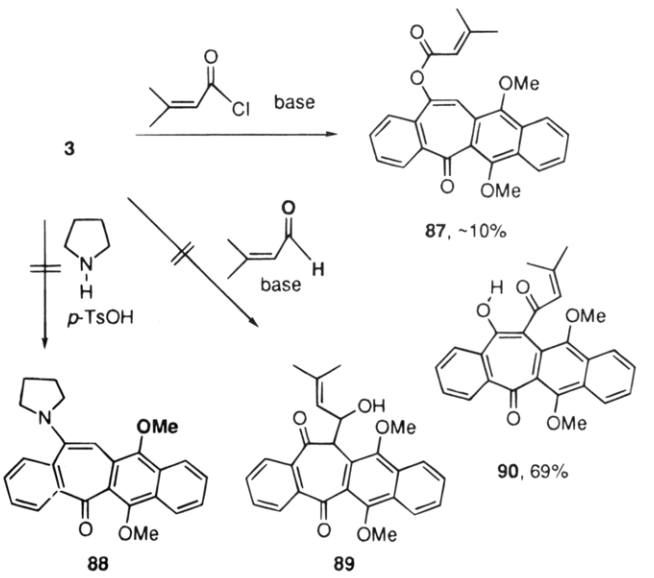


Figure 1. Two projections of the molecular structure of 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuborane (**3**).

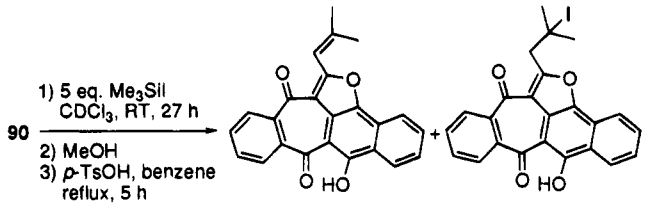
Scheme 22



3. Theoretically, this coupling can be achieved by an intermolecular Claisen condensation. However, treatment of **3** with a base followed by addition of 3,3-dimethylacryloyl chloride gave the enol ester **87** (Scheme 22) in a low yield along with unreacted starting material. Several conditions were studied, including different acylation reagents, temperatures, and solvents, but in every case the desired *C*-alkylation product was not formed. Formation of **87** is due mainly to the generation of the very stable enolate, which upon formation of the ester extends the conjugation. In order to prevent *O*-acylation, 3-methylbutenal was used, but essentially no reaction took place. Next, an effort was made to prepare the enamine **88**, which upon treatment with 3,3-dimethylacryloyl chloride should place the side chain at the benzylic position. However, after several trials, only the starting material was recovered. These results reveal that once generated, the enolate remains predominantly

(36) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1983**, *48*, 749.
(37) Huang, R. L.; Williams, P. *J. Chem. Soc.* **1958**, 2637.

Scheme 23



in the stable enol form, does not form the *C*-acylation product, and reacts neither with the aldehyde nor the amine.

Finally, assembly of the 3,3-dimethylacryloyl group on the benzylic position was successfully achieved by acylation under acidic condition. Thus, a solution of the diketone **3** in CH_2Cl_2 was heated under reflux for 4 h with 2.2 equiv of 3,3-dimethylacryloyl chloride and 2.2 equiv of $AlCl_3$, followed by quenching with saturated NH_4Cl. Purification afforded compound **90** in 69% yield. The ^1H NMR spectrum of **90** shows the chelated hydroxy group at δ 17.00.

The last problem to be dealt is the formation of the furan ring. This includes two major operations, i.e. demethylation and cyclization. After many efforts, demethylation finally succeeded by treatment of **90** with 5 equiv of trimethylsilyl iodide in $CHCl_3$ at rt for 27 h.[38] The presumably-formed trimethylsilyl ether was readily hydrolyzed by addition of excess MeOH. The crude product was refluxed for 5 h with a catalytic amount of *p*-TsOH in dry C_6H_6 in a Dean–Stark apparatus, leading to the formation of the target molecule **1** as the major product, as well as a side product (**91**) (Scheme 23). More conveniently, the crude product **90** was used as the starting material without further purification. In a 50-mg-scale run, the formation of radermachol (**1**) from **3** gave an overall 51% yield for the four steps. The synthetic radermachol was characterized by its identity with an authentic sample in all respects, including the co-TLC behavior, mixture mp, ^1H and ^{13}C NMR, FT-IR, and mass spectra. The ^1H NMR spectrum of **91** is similar to that of **1**, except for the presence of two *gem*-dimethyl groups at δ 1.46 and the absence of the vinyl proton present in **1**.

It is necessary to point out that the demethylation is not as straightforward as presented in Scheme 23. A stepwise mechanism, including the hydrolysis and cyclization, is shown in Scheme 24. A multiple-step transformation from **90** to **94** is proposed according to the result of the ^1H NMR study, in which the process of the demethylation in $CDCl_3$ was followed by taking the ^1H NMR spectrum from time to time. Addition of 5 equiv of trimethylsilyl iodide led to the immediate formation of **92**, in which a two-proton AB pattern was observed at δ 2.90 and 3.28 (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 two magnetically-nonequivalent protons of the methylene group in **92**; nonequivalence is due to the rigid chiral ring system. After 1 h, this AB system disappeared, giving **93** in which two protons of the methylene group become equivalent. The last phenomenon observed in the ^1H NMR study, as expected, was the demethylation. The total synthesis of radermachol was completed in 14 steps from 1,4-naphthoquinone in an overall yield of 6.7%.

(38) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

Summary

Radermachol (**1**), the red pigment of *R. xylocarpa*, has a uniquely fused aromatic ring system not encountered previously in any other natural product. Five different approaches are described for the synthesis of the key intermediate 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (**3**). These approaches involve (a) the Diels–Alder reaction, (b) [2 + 2] photoaddition and retro-Aldol condensation, (c) intramolecular Friedel–Crafts alkylation, (d) intramolecular Friedel–Crafts acylation, and (e) intramolecular Claisen condensation. All the routes failed to give the intermediate **3**. These experiments led to the following conclusions: (i) the high strain embodied in the cyclohepatanedione **3** makes the cyclizations difficult; (ii) because of this strain, the neighboring group effects play a major role for failure of the cyclization; (iii) these effects are directly related to the two carbonyl groups in the precursors of the cyclization; and (iv) it is crucial that the two keto groups in **3** should be introduced separately.

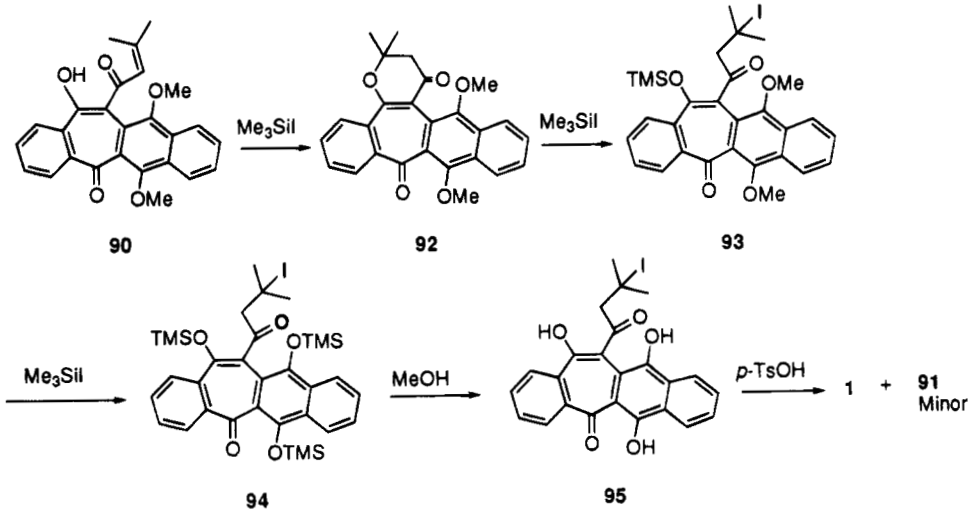
1,4-Dimethoxynaphthalene (**79**) was converted to 3-benzyl-1,4-dimethoxynaphthalene-2-acetic acid (**80**) in five steps and cyclized to give 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1-oxosuberane (**76**). The monoketone **76** was brominated with NBS, hydrolyzed and oxidized with PCC to afford the desired intermediate 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (**3**), the structure of which was established by an X-ray crystal structure determination. Treatment of **3** with 3,3-dimethylacryloyl chloride under acidic conditions gave **90** which was demethylated with Me_3SiI and cyclized with *p*-TsOH to afford radermachol (**1**) in an overall yield of 6.7% in 14 steps.

Experimental Section

General Procedure. Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. FT NMR spectra were recorded in the specified solvent on a Bruker AM-250 250 MHz (^1H)/62.5 MHz (^{13}C), a Bruker WM-300 300 MHz (^1H)/75.0 MHz (^{13}C), a JEOL FX-270 270 MHz (^1H)/67.5 MHz (^{13}C), a JEOL FX-90Q 90 MHz (^1H)/22.5 MHz (^{13}C), or a JEOL FX-60 60 MHz (^1H)/15.0 MHz (^{13}C) spectrometer. Chemical shifts are reported in ppm relative to TMS at 0.00 ppm. ^1H NMR data are presented as follows: chemical shift (number of protons, multiplicity, coupling constant in hertz). Carbon multiplicities, if specified, were determined by DEPT experiments with ^1H decoupling, and most quaternary carbons were deduced from DEPT sequence, otherwise determined by QUAT experiments which give ^1H-decoupled spectra for proton-unattached ^{13}C nuclei. Low-resolution MS were determined on a Finnegan Quadrupole 4023 chromatograph–mass spectrometer by a direct probe at an ionizing voltage of 70 eV and are expressed in m/z units (relative intensity). Dispersive IR spectra were taken on a Perkin-Elmer Model 1420 spectrophotometer in Nujol or thin films between polished NaCl plates, as specified. FT IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer coupled with a Spec-Tech IR-Plan IR microscope on a KBr matrix with a resolution of 4 cm^{-1}. All dispersive IR absorption bands are reported in wavenumber (cm^{-1}), which were calibrated against the 1601 cm^{-1} absorption band of polystyrene.

Materials. For chromatographic separation on a Chromatotron, rotors were coated with 1-mm-thick SiO_2 PF 254+365 (EM Art. 7741); for vacuum liquid chromatography (VLC) and column chromatography, SiO_2 (EM Art. 7744) was used; for TLC and PTLC, SiO_2 PF 254+365 (EM Art. 7741) was used.

Scheme 24



Unless otherwise noted, all chemicals were obtained from commercial suppliers and used without further purification. Anhyd THF, Et_2O, and C_6H_6 were prepared by refluxing with and distillation from Na/benzophenone under a N_2 atm in a recycling still. Anhyd CH_2Cl_2, $CHCl_3$, and CCl_4 were dried over and distilled from $CaCl_2$ under a N_2 atm and stored over molecular sieve (4 Å). All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atm.

2-Benzoyl-1,4-dimethoxynaphthalene. A solution of 1,4-dimethoxynaphthalene (**79**) (25.0 g, 133.0 mol) and benzoic acid (24.3 g, 199.2 mol) in TFAA (300 mL) and TFA (150 mL) was refluxed at 60 °C for 12 h and the reaction product concentrated *in vacuo*. The residue was taken in 200 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ (5 × 200 mL), H_2O (2 × 200 mL), and brine (200 mL), and dried over anhyd $MgSO_4$. Removal of the solvent *in vacuo* gave an oily product (38.61 g), which crystallized from Me_2CO/hexane to yield 33.59 g (87%) of yellow crystals, mp 100–102 °C. MS (rel int): *m/z* 292 ([M]$^+$, 58.2), 278 (4.7), 262 (16.7), 249 (10.2), 234 (16.2), 218 (11.6), 201 (10.8), 189 (5.4). IR (Nujol): ν_{max} 1660, 1620, 1590, 1450 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.77 (3H, s), 4.00 (3H, s), 6.82 (1H, s), 7.48 (2H, t, *J* = 7.9 Hz), 7.61 (3H, m), 7.94 (2H, d, *J* = 7.9 Hz), 8.19 (1H, m), 8.33 (1H, m). ^{13}C NMR (67.4 MHz, DEPT, $CDCl_3$): δ 55.7 (q), 63.6 (q), 102.9 (d), 122.4 (d), 122.7 (d), 127.0 (d, × 2), 127.7 (s), 128.3 (d, ×2), 128.4 (s), 129.9 (d, ×2), 133.2 (d), 137.5 (s), 148.6 (s), 151.6 (s), 196.9 (s).

2-Benzyl-1,4-dimethoxynaphthalene (78). To a solution of 2-benzoyl-1,4-dimethoxynaphthalene (29.0, 99.3 mol) in TFA (115 mL) kept at 0–5 °C was slowly added EtSiH (34.8 mL, 218.5 mol); the solution was stirred at 25 °C for 6 h until the brown color disappeared. The solvent was removed *in vacuo* and the residue dissolved in 150 mL of CH_2Cl_2. The solution was washed with H_2O (5 × 100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 40.1 g of the crude product which was divided into two portions. The first portion (20.0 g) was purified on a SiO_2 VLC column by elution with hexane and an increasing percentage of CH_2Cl_2 to give 10.6 g of **78** and 5.23 g of a mixture. This mixture and the second portion (total 25.33 g) were combined and purified on a SiO_2 VLC column by elution with hexane to give 22.87 g of pure **78**, which crystallized spontaneously. The crystals were washed with hexane to afford 14.76 g of a colorless crystalline product, mp 61–62 °C; evaporation of the mother liquor *in vacuo* gave a residue (8.10 g) that was purified on a SiO_2 VLC column by elution with hexane with an increasing percentage of CH_2Cl_2 to afford 0.99 g of pure product. A total of 26.29 g (95%) of pure product was obtained. MS (rel int) *m/z* 278 ([M]$^+$, 100.0), 263 (97.7), 231 (73.2), 203 (33.3), 202 (51.6), 189 (11.2). IR (film): ν_{max} 1625, 1590, 1500, 1490, 1420 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.84 (3H, s), 3.86 (3H, s), 4.19 (2H, s), 6.52 (1H, s), 7.24 (5H, m), 7.44 (1H, t, *J* = 8.2 Hz), 7.52 (1H, t, *J* = 8.2 Hz), 8.05 (1H, d, *J* = 8.2 Hz), 8.20 (1H, d, *J* = 8.2 Hz). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 35.8 (t), 55.5 (q), 62.1 (q), 106.0 (d), 121.9 (d), 122.3 (d), 125.0 (d), 125.6 (s), 126.0 (d), 126.6 (d), 128.4 (d, ×2), 128.6 (s), 128.8 (d, ×2), 141.0 (s), 147.1 (s), 151.8 (s).

2-Benzyl-3-(bromomethyl)-1,4-dimethoxynaphthalene. A solution of 2-benzyl-1,4-dimethoxynaphthalene (25.5 g, 91.7 mol) in glacial AcOH (123 mL) was treated with paraformaldehyde (74.0 g) and 30% HBr in AcOH (246 mL); the mixture was stirred at 45–50 °C for 9 h. The cooled solution was diluted with 800 mL of H_2O and extracted with Et_2O (4 × 500 mL). The Et_2O extract was washed with H_2O (2 L), 5% $NaHCO_3$ (2 × 500 mL), saturated $NaHSO_3$ (2 × 500 mL), and brine (500 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 37.75 g of crude product. This was divided into two roughly-equal portions and purified on a SiO_2 VLC column by elution with hexane. A total of 27.44 g (81%) of the amorphous product, which was homogeneous by TLC, was obtained. MS (rel int): *m/z* 372 ([M]$^+$ + 2, 42.9), 370 ([M]$^+$, 37.7), 291 (100.0), 259 (78.0), 244 (31.3), 228 (29.7), 215 (37.1), 202 (21.4). IR (film): ν_{max} 1620, 1590, 1490, 1410, 1270, 1210, 1190 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (3H, s), 4.03 (3H, s), 4.43 (2H, s), 4.60 (2H, s), 7.12 (3H, m), 7.19 (2H, m), 7.50 (2H, m), 8.09 (2H, m). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 26.3 (t), 31.4 (t), 62.2 (q), 62.3 (q), 122.6 (d), 122.8 (d), 126.1 (d), 126.6 (s), 126.9 (d), 127.7 (d, ×3), 128.1 (s), 128.5 (d, ×2), 129.0 (s), 140.1 (s), 151.1 (s), 152.0 (s).

2-Benzyl-3-(cyanomethyl)-1,4-dimethoxynaphthalene. A solution of 2-benzyl-3-(bromomethyl)-1,4-dimethoxynaphthalene (27.14 g, 73.35 mol) and KCN (9.54 g, 146.7 mol) in *p*-dioxane (450 mL) and H_2O (190 mL) was refluxed for 10 h. The cooled solution was slowly poured into ice–H_2O (200 mL) with stirring; the precipitate was collected and dried to afford 23.20 g (~100%) of an amorphous title compound which was homogeneous by TLC. A crystalline sample (mp 98–100 °C) was obtained by elution of a small portion of the material on a SiO_2 rotor plate with CH_2Cl_2/hexane. MS (rel int): *m/z* 317 ([M]$^+$, 100.0), 302 (35.7), 270 (41.1), 262 (37.1), 247 (23.7), 243 (14.2), 230 (13.1), 215 (15.7), 202 (19.0). IR (film): ν_{max} 2240, 1590, 1490, 1450, 1410, 1350 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (2H, s), 3.86 (3H, s), 3.97 (3H, s), 4.41 (2H, s), 7.10 (2H, d, *J* = 6.9 Hz), 7.20 (3H, m), 7.63 (2H, m), 8.12 (2H, m). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 14.8 (t), 32.1 (t), 62.5 (q, ×2), 118.0 (s), 119.9 (s), 122.5 (d), 122.7 (d), 126.3 (d, ×2), 126.9 (d), 127.5 (s), 127.9 (d, ×2), 128.7 (d, ×2), 139.1 (s), 151.3 (s).

3-Benzyl-1,4-dimethoxynaphthalene-2-acetic Acid (80). A solution of 2-benzyl-3-(cyanomethyl)-1,4-dimethoxylnaphthalene (23.0 g, 72.55 mol) and KOH (80.0 g) in MeOH (160 mL) and H_2O (110 mL) was refluxed for 22 h. The MeOH was removed *in vacuo*, and the residue was poured into 400 mL of H_2O. The aqueous solution was acidified in an ice–H_2O bath with concd HCl to pH 3 and extracted with Et_2O (4 × 300 mL). The combined Et_2O layer was washed with H_2O (4 × 500 mL) and brine (500 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 18.86 g of the crude product. This was purified on a SiO_2 VLC column by elution with CH_2Cl_2 with an increasing percentage of MeOH, to afford **80** (17.58 g, 73%).

The homogeneous product (TLC) was crystallized from MeOH/CH_2Cl_2, mp 210.5–212.5 °C. MS (rel int): m/z 336 ([M]$^+$, 58.4), 305 (65.3), 245 (36.0), 215 (38.5), 202 (31.9), 129 (23.1). IR (film): ν_{max} ~3000 (br), 1710, 1590, 1490, 1450 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.76 (2H, s), 3.84 (3H, s), 3.91 (3H, s), 4.27 (2H, s), 7.11 (3H, m), 7.20 (2H, m), 7.50 (2H, m), 8.09 (2H, m), 9.39 (1H, br s, D_2O ~). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 32.4 (t, ×2), 62.2 (q), 62.4 (q), 122.6 (d), 122.7 (d), 123.4 (s), 126.0 (d), 126.3 (d), 127.6 (s), 128.1 (d), 128.4 (d), 128.6 (s), 139.7 (s), 150.9 (s), 151.4 (s), 177.8 (s).

6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1-oxosuberane (76). The acid **80** (100 mg, 298 mmol) was heated with PPA (2 g) at 60–70 °C with mechanical stirring for 1.5 h. Upon cooling, the mixture was poured into 20 mL of ice–H_2O and extracted with Et_2O (2 × 20 mL). The Et_2O extract was washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 85 mg of the crude product, which was purified on a SiO_2 rotor plate by elution with hexane/CH_2Cl_2 and CH_2Cl_2 to yield crystalline **76** (60 mg, 63%), mp 134–136 °C. MS (rel int): m/z 318 ([M]$^+$, 100.0), 303 (60.0), 271 (27.4), 244 (30.7), 215 (42.9), 202 (28.4). IR (film): ν_{max} 1670, 1590, 1450, 1350, 1330 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (3H, s), 3.93 (3H, s), 4.41 (2H, s), 4.51 (2H, s), 7.33 (1H, t, J = 6.2 Hz), 7.35 (4H, m), 8.05 (2H, m), 8.14 (1H, d, J = 7.6 Hz). Deuterium base exchange experiment: on addition of 40% KOD (2 drops) to a solution of **76** (5 mg) in $CDCl_3$ (0.5 mL), the two-proton singlet at δ 4.41 observed in **76** disappeared, indicating a methylene group adjacent to the carbonyl group. ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 34.7 (t), 44.0 (t), 62.8 (q), 63.0 (q), 122.2 (d), 122.4 (d), 126.1 (d), 126.2 (d), 127.2 (d), 127.9 (s), 128.9 (s), 130.2 (d), 130.4 (d), 133.5 (d), 134.8 (s), 142.2 (s), 148.8 (s), 150.4 (s), 194.5 (s).

Oxidation of 6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1-oxosuberane (76). (a) With $KMnO_4$. To a solution of **76** (73 mg, 0.2296 mmol) in CH_2Cl_2 (2 mL) was added a solution of $KMnO_4$ (54.4 mg, 0.3443 mmol), KOH (6.4 mg, 0.1148 mmol), and *n*-tetrabutylammonium bromide (7.4 mg, 0.1148 mmol) in H_2O (2 mL). The purple mixture, which turned dark brown after 3 min, was stirred at 25 °C for 1 h and quenched with 0.5 mL of AcOH. $NaHSO_3$ was added in several portions until the brown color disappeared. CH_2Cl_2 (15 mL) and H_2O (15 mL) were added, the orange-colored organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layer was washed with H_2O (20 mL) and brine (20 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,2-dioxosuberane (**84**) (58 mg, 76%) as orange crystals, mp 141–145 °C. IR (film): ν_{max} 1700, 1665, 1620, 1590, 1570, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (3H, s), 4.02 (3H, s), 4.42 (2H, s), 7.40 (1H, t, J = 7.4 Hz), 7.51 (4H, m), 8.05 (1H, d, J = 8.3 Hz), 8.14 (2H, t, J = 7.4 Hz). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 32.6 (t), 63.1 (q), 64.6 (q), 122.5 (d), 123.7 (d), 124.3 (s), 125.1 (s), 126.7 (d), 127.7 (d), 128.3 (s), 128.6 (d), 129.8 (d), 130.3 (s), 131.3 (d), 132.6 (s), 134.9 (d), 141.9 (s), 148.0 (s), 153.2 (s), 189.5 (s), 194.8 (s).

(b) With PCC. To a solution of **76** (20 mg, 0.063 mmol) and several piecies of dry molecular sieves (4 Å) in CH_2Cl_2 (4 mL) was added PCC (815 mg, 3.77 mmol). The mixture was stirred at 50 °C for 15 h, followed by dilution with 3 mL of Et_2O. The mixture was passed through a small Florisil VLC column and washed with Et_2O (30 mL). Removal of the solvent *in vacuo* gave a yellowish material. Separation of this material on a SiO_2 rotor plate by elution with hexane/Et_2O yielded the pure 1,2-diketone (**84**) (8 mg, 38%) and a mixture (7 mg), which contained mainly the starting material and ~10% of the 1,4-diketone **3**, as seen from the ^{1}H NMR spectrum.

(c) With DDQ. A solution of **76** (20 mg, 0.063 mmol) and DDQ (43 mg, 0.1886 mmol) in aqueous *p*-dioxane (3 mL) was refluxed for 24 h. The cooled solution was passed through a short VLC column of Al_2O_3 and eluted with *p*-dioxane. Removal of the solvent *in vacuo* gave 10 mg of a residue, which was purified on a SiO_2 rotor plate by elution with Et_2O/hexane to give **84** (2 mg) and an unidentified compound (3 mg).

Attempted Ketalization of 6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1-oxosuberane (76). A solution of **76** (77 mg, 0.242 mmol), 1,2-ethylene glycol (0.3 mL), and *p*-TsOH (5 mg) in dry C_6H_6 (5 mL) was refluxed for 14 h; the H_2O formed was collected with a Dean–Stark trap. The cooled solution was diluted with 15 mL of C_6H_6 and then washed with a 5% $NaHCO_3$ solution (2 × 20 mL), H_2O (2 × 20 mL), and brine (20 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 79 mg of a mixture. Separation of this mixture on a SiO_2 rotor plate, by elution with CH_2Cl_2/hexane and CH_2Cl_2 with an increasing percentage of MeOH, afforded the starting material (11 mg) and 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,2-dehydro-1-(2-hydroxyethoxy)suberane (**85**) (26 mg, 30%) which was homogeneous by TLC. MS (rel int): m/z 362 ([M]$^+$, 28.9), 303 (13.6), 259 (10.7), 243 (11.1), 202 (10.2), 45 (62.4), 40 (100.0). IR (film): ν_{max} 3440, 1620, 1600, 1580, 1560, 1480, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (1H, br s, D_2O ~), 3.87 (3H, s), 4.00 (3H, s), 4.09 (1H, t, J = 4.5 Hz), 4.10 (2H, br s), 4.27 (1H, t, J = 4.5 Hz), 6.73 (1H, s), 7.28 (1H, dd, J_1 = 7.6, J_2 = 1.4 Hz), 7.35 (1H, dt, J_1 = 7.2, J_2 = 1.2 Hz), 7.44 (3H, m), 7.69 (1H, dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz), 8.06 (2H, m). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 33.3 (t), 61.3 (q), 61.4 (t), 62.8 (q), 69.3 (t), 100.3 (d), 122.1 (d), 122.2 (d), 124.8 (s), 125.4 (d), 125.6 (d), 126.3 (d), 127.0 (s), 127.5 (s), 128.1 (d), 129.4 (d), 133.6 (s), 139.0 (s), 148.0(s), 148.7 (s), 155.4 (s).

6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-5-hydroxy-1-oxosuberane (86). A solution of **76** (200 mg, 0.629 mmol), NBS (134 mg, 0.753 mmol), and dibenzoyl peroxide (5 mg) in dry CCl_4 (20 mL) was gently refluxed for 4.5 h. The cooled solution was poured into 30 mL of H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O (2 × 30 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* furnished a mixture, which was separated on a SiO_2 plate by elution with hexane/CH_2Cl_2 and CH_2Cl_2 with an increasing percentage of MeOH, to afford amorphous 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-5-hydroxy-1-oxosuberane (143 mg, 68%) which was homogeneous by TLC. MS (rel int): m/z 334 ([M]$^+$, 49.1), 289 (30.4), 288 (30.9), 274 (16.6), 273 (64.9), 259 (34.9), 258 (27.1), 243 (26.3), 231 (20.1), 215 (16.1), 202 (39.5). IR (film): ν_{max} 3400, 1680, 1660, 1590, 1500, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (1H, s, D_2O ~), 3.89 (3H, s), 3.91 (3H, s), 4.43 (1H, d, J = 15.5 Hz), 5.14 (1H, d, J = 15.5 Hz), 6.59 (1H, s), 7.40 (1H, dt, J_1 = 7.6, J_2 = 1.5 Hz), 7.50 (3H, m), 7.61 (1H, d, J = 7.6 Hz), 8.06 (3H, m). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 42.2 (t), 62.8 (q), 63.4 (q), 72.0 (d), 121.6 (s), 122.5 (d, ×2), 126.7 (d), 126.9 (d), 127.8 (s), 128.8 (d, ×2), 130.8 (d), 133.4 (d), 150.9 (s), 196.5 (s).

6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (3). To a suspension of PCC (97 mg, 0.4491 mmol) and Celite (97 mg) in dry CH_2Cl_2 (2 mL) was added a solution of 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-5-hydroxy-1-oxosuberane (100 mg, 0.2994 mmol) in 8 mL of CH_2Cl_2. The mixture was stirred at 25 °C for 3 h and then diluted with 20 mL of Et_2O. The mixture was decanted and the residue washed with 100 mL of Et_2O. The solution was passed through a short Florisil column and eluted with Et_2O. Removal of the solvent *in vacuo* gave 91 mg of the crude product. Separation on a SiO_2 rotor plate by elution with hexane/CH_2Cl_2 and CH_2Cl_2 with an increasing percentage of MeOH afforded 28 mg of the starting material and 53 mg of **3**, which crystallized from MeOH, mp 121.5–122.5 °C. Compound **3** was obtained in a yield of 74% on the basis of the recovered starting material. MS (rel int): m/z 332 ([M]$^+$, 100.0), 317 (42.0), 301 (53.3), 189 (32.9), 104 (27.4), 76 (45.7). IR (film): ν_{max} 1680 (br.), 1590, 1580, 1500, 1450, 1410, 1350, 1280, 1250, 1220, 1190, 1170, 1080, 1045, 1020, 975, 965, 940, 835, 780, 760, 745, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (3H, s), 4.03 (3H, s), 4.41 (2H, s), 7.52–7.75 (4H, m), 7.98 (1H, dd, J_1 = 7.4, J_2 = 1.6 Hz), 8.14 (3H, m). ^{13}C NMR (67.5 MHz, DEPT, $CDCl_3$): δ 42.8 (t), 63.3 (q), 64.6 (q), 116.7 (s), 122.7 (d), 123.7 (d), 126.9 (d), 128.1 (d), 128.8 (s), 129.2 (d, ×2), 130.2 (s), 130.7 (s), 132.6 (d), 133.0 (s), 133.6 (d), 141.4 (s), 149.6 (s), 150.7 (s), 193.5 (s), 195.8 (s). For the X-ray structure, see Figure 1.

Attempted *C*-Acylation of 6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (3) with 3,3-Dimethylacryloyl Chloride. To a solution of **3** (10 mg, 0.030 mmol) in THF (4 mL) was added LDA (monoTHF) (24 μL, 1.5 M in cyclohexane, 0.036 mmol) at −78 °C; the orange solution was

stirred at −78 °C for 10 min, followed by addition of 7 mL of 3,3-dimethylacryloyl chloride. The solution was stirred at −78 °C for 40 min, followed by quenching with 4 mL of saturated NH_4Cl solution. The two layers were separated; the aqueous layer was extracted with Et_2O (10 mL). The combined THF and Et_2O solution was washed with brine (10 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 12 mg of material. Purification on a SiO_2 rotor plate by elution with hexane/CH_2Cl_2 gave the starting material (6 mg) and 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,2-dehydro-1-((3,3-dimethylacryloyl)oxy)-5-oxosuberane (**87**) (1 mg) which was homogeneous by TLC. IR (film): ν_{max} 1730, 1280, 1120, 1070, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.05 (3H, d, J = 1.2 Hz), 2.25 (3H, d, J = 1.1 Hz), 4.00 (3H, s), 4.13 (3H, s), 6.04 (1H, q, J = 1.3 Hz), 7.33 (1H, s), 7.55 (3H, m), 7.60 (2H, m), 7.79 (1H, m), 8.18 (1H, dd, J_1 = 7.1, J_2 = 1.3 Hz), 8.25 (1H, dd, J_1 = 7.4, J_2 = 1.5 Hz).

Attempted Synthesis of 90 from 6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (3). To a solution of **3** (10 mg, 0.030 mmol) in THF (4 mL) was added LDA (monoTHF) (22 μL, 1.5 M in cyclohexane, 0.033 mmol) at -78 °C; the orange solution was stirred for 5 min, followed by addition of a solution of 3.2 μL (0.033 mmol) of 3-methyl-2-butenal in 2 mL of THF. The solution was stirred at −78 °C for 3 h; TLC showed that no reaction took place.

Attempted Synthesis of 88 from 6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane (3). A solution of **3** (12 mg, 0.036 mmol), pyrrolidine (2 drops, excess amount), and *p*-TsOH (catalytic amount) in 10 mL of dry C_6H_6 in a flask fitted with a Dean−Stark trap was refluxed for 12 h; TLC showed a single spot corresponding to the starting material.

6,7-Benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,2-dehydro-1-hydroxy-2-(3,3-dimethylacryloyl)-5-oxosuberane (90). To a solution of **3** (50 mg, 0.151 mmol) and 3,3-dimethylacryloyl chloride (**4**; X = Cl) (37.3 μL, 0.331 mmol) in CH_2Cl_2 (5 mL) was added $AlCl_3$ (44 mg, 0.331 mmol); the orange-brown solution was refluxed at 55 °C for 4 h, followed by quenching with 10 mL of saturated NH_4Cl solution. Two layers were separated; the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The CH_2Cl_2 extract was washed with H_2O (2 × 20 mL) and brine (10 mL) and dried over anhyd Na_2SO_4. Removal of the solvent *in vacuo* gave 58 mg of the crude product, which was purified on a SiO_2 rotor plate by elution with CH_2Cl_2 with an increasing percentage of MeOH, to give amorphous **90** (43 mg, 69%) which was homogeneous by TLC. MS (rel int): m/z 414 ([M]$^+$, 41.7), 399 (5.5), 383 (63.1), 358 (8.8), 343 (36.3), 315 (14.2), 286 (14.2), 259 (11.4), 41 (100.0). IR (film): ν_{max} 1690, 1630, 1580, 1530, 1440 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.76 (3H, d, J = 0.9 Hz), 2.27 (3H, d, J = 1.0 Hz), 3.70 (3H, s), 4.17 (3H, s), 5.86 (1H, br s), 7.59 (5H, m), 8.00 (1H, m), 8.15 (2H, m), 17.00 (1H, s, D_2O ~). ^{13}C NMR (62.5 MHz, DEPT, $CDCl_3$): δ 21.6 (q), 28.5 (q), 61.3 (q), 65.3 (q), 108.3 (s), 119.5 (s), 121.6 (d), 123.0 (d), 123.5 (d), 125.1 (d), 127.0 (d), 128.0 (d), 128.6 (d), 128.7 (s), 129.6 (s), 131.0 (d), 131.3 (s), 132.1 (d), 143.8 (s), 147.7 (s), 150.4 (s), 156.8 (s), 175.8 (s), 192.3 (s), 195.5 (s).

Radermachol (1) and 22-Iodo-21,22-dihydroradermachol (91). (a) From 3. To a solution of **3** (50 mg, 0.151 mmol) and 3,3-dimethylacryloyl chloride (**4**; X = Cl) (37.3 μL, 0.331 mmol) in CH_2Cl_2 (5 mL) was added $AlCl_3$ (44 mg, 0.331 mmol); the orange-brown solution was refluxed at 55 °C for 4 h, followed by quenching with 10 mL of saturated NH_4Cl. Two layers were separated; the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The CH_2Cl_2 extract was washed with H_2O (2 × 20 mL) and brine (10 mL) and dried over anhyd Na_2SO_4; removal of the solvent *in vacuo* gave a residue that was passed through a short SiO_2 VLC column by elution with CH_2Cl_2 (150 mL). Removal of the solvent *in vacuo* gave the crude product **90** (61 mg). To a solution of this sample (61 mg, 0.147 mmol) in $CDCl_3$ (1.5 mL) in a 5 mm NMR tube was added Me_3SiI (105 μL, 0.738 mmol). The solution was kept at 25 °C for 27 h when the ^1H NMR spectrum showed that the two methoxy groups had disappeared. The solution was treated with excess MeOH; removal of the solvent *in vacuo* yielded the crude product **95** (72 mg). This material and *p*-TsOH (5 mg) were dissolved in 25 mL of dry C_6H_6. The solution was heated under reflux for 5 h in a Dean−Stark apparatus and evaporated *in vacuo* to give a red colored solid (52 mg). This was purified on a SiO_2 preparative TLC plate (20 cm × 20 cm × 1 mm thick) by elution with C_6H_6 and the red-colored band was eluted with CH_2Cl_2 (40 mL). Removal of the solvent *in vacuo* afforded the homogeneous product **1** (29 mg, 52% from **3**), which crystallized from hexane/CH_2Cl_2, mp 214.5−216.5 °C. This synthetic compound was identical with an authentic sample of radermachol in the co-TLC behavior, mixture mp, IR, MS, ^1H NMR and ^{13}C NMR spectra. MS (rel int): m/z 368 ([M]$^+$, 36.8), 353 (100.0), 177 (31.7), 77 (23.5), 57 (29.9), 55 (27.9), 44 (48.0), 43 (56.7), 41 (40.7). FT-IR (crystal): ν_{max} 1627, 1602, 1571, 1556, 1539, 1527, 1505, 1487, 1469, 1440, 1414, 1396, 1386, 1379, 1350, 1326, 1301, 1280, 1267, 1258, 1232, 1194, 1185, 1167, 1158, 1111, 1086, 1070, 1026, 996, 921, 910, 900, 883, 862, 855, 817, 809, 797, 765 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.18 (3H, s), 2.43 (3H, s), 7.22 (1H, m), 7.57 (1H, dt, J_1 = 7.0 Hz, J_2 = 1.3 Hz), 7.78 (3H, m), 8.14 (1H, d, J = 8.2 Hz), 8.39 (1H, m), 8.57 (2H, m), 15.30 (1H, s, D_2O ~). ^{13}C NMR (62.5 MHz, DEPT, $CDCl_3$): δ 21.9 (q), 28.6 (q), 107.8 (s), 114.2 (d), 117.9 (s), 119.6 (d), 123.4 (s), 124.9 (s), 125.6 (d), 125.9 (d), 129.3 (s), 130.9 (d), 131.5 (d), 132.0 (d), 132.6 (d), 133.3 (d), 135.9 (s), 138.6 (s), 141.6 (s), 148.3 (s), 160.8 (s), 164.1 (s), 185.8 (s), 192.7 (s).

(b) From 90. To a solution of **90** (2 mg, 0.0048 mmol) in $CDCl_3$ (0.5 mL) in a 5-mm NMR tube was added Me_3SiI (3.4 μL, 0.025 mmol). The solution was kept at 25 °C and checked by taking the ^1H NMR. After 30 h, the reaction was quenched with excess MeOH; the solvent was removed *in vacuo*. The dried material and *p*-TsOH (catalytic amount) were dissolved in 8 mL of dry C_6H_6; the solution was refluxed for 5 h in a Dean−Stark apparatus. Removal of the solvent *in vacuo* yielded a residue, which was purified on a short SiO_2 column by elution with CH_2Cl_2. The first fraction obtained from 5 mL of CH_2Cl_2 gave **1** (1.5 mg) as the major product. The second fraction gave **91** (0.5 mg). ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (6H, s), 3.52 (2H, s), 7.63 (1H, t), 7.83 (3H, m), 8.24 (1H, d), 8.40 (1H, d), 8.62 (2H, m), 15.16 (1H, s, D_2O ~).

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Supplementary Material Available: ^1H NMR spectra of compounds **9, 20, 21, 37, 38, 44, 49$_{a+b}$, 55, 68, 71, 73**, and 2-[(1,4-dimethoxy-3-(2-carbomethoxybenzyl)-2-naphthyl)methyl]-1,3-dioxolane and ^{13}C NMR spectra of compounds **16, 23, 30$_a$, 36, 37, 39, 42, 43, 44, 46, 47, 48, 49$_{a+b}$, 50, 54, 55, 56, 58, 61, 65, 69, 70**, and 2-bromo-3-(bromomethyl)-1,4-dimethoxynaphthalene. Experimental procedures together with analytical and spectral data for the compounds **5, 9, 11, 14, 13, 16, 18, 20, 22, 7, 8, 10, 12, 15, 17, 19, 21, 23, 24, 29, 25, 30$_a$, 35, 36, 37, 39, 38, 41, 42, 43, 44, 46, 47, 48, 49, 50, 51, 54, 55, 56, 61, 58**, 2-bromo-3-(bromomethyl)-1,4-dimethoxynaphthalene, **65, 68**, (3-bromo-1,4-dimethoxy-2-naphthyl)acetaldehyde, **69, 70**, 2-[(1,4-dimethoxy-3-(2-carbomethoxybenzyl)-2-naphthyl)methyl]-1,3-dioxolane, **71**, and **73**. ^1H NMR spectra of compounds **14, 15, 16, 20**. ^{13}C NMR spectra of compounds **5** and **7**. ^1H and ^{13}C NMR spectra of compounds **1, 2, 3, 13, 19**, 2-benzoyl-1,4-dimethoxynaphthalene, and 2-benzyl-3-(bromomethyl)-1,4-dimethoxynaphthalene (87 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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