A Search for New Synthetic Routes toward Siccanin

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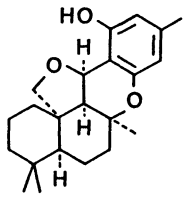
11-Acetoxy-12bα-methoxymethyl-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aβ,12b-decahydro-12*H*-benzo[*a*]xanthene (**34**), which has been expected as a promising key intermediate for the synthesis of siccanin (**1**), was synthesized via acid-catalyzed cyclization of 1α-(2-hydroxy-6-methoxy-4-methylbenzyl)-8aα-methoxymethyl-2,5,5-trimethyl-1,4,4aα,5,6,7,8,8aα-octahydronaphthalene (**13**) and isomeric exo olefin **21**. The phenol acetate **34**, however, was so resistant to oxidation that no corresponding 12-oxo derivative, which was expected to provide 11-acetoxy-12bα-acetoxymethyl-12-oxo-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aα,12b-decahydro-12*H*-benzo[*a*]xanthene (**4**) on epimerization at its C(12a) position as well as hydrofuran ring formation at the C(12) position with its angular methoxymethyl substituent, was obtained.

Siccanin (**1**) is a mold metabolite produced by *Helminthosporium siccans*[1] and exhibits a remarkable antifungal activity against a variety of fungi. In particular, its high activity in low concentrations against *Trichophyton interdigitale* and *T. asteroids*, which cause fungal infection in skin, has been demonstrated to be clinically useful.[2]



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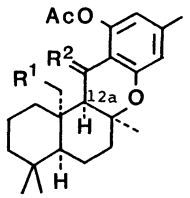
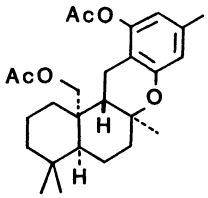


2, R^1=H, R^2=H_2
3, R^1=H, R^2=O
4, R^1=OAc, R^2=O
5, R^1=OAc, R^2=H_2



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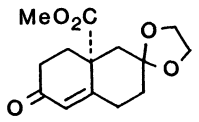
In the course of structural elucidation of **1**, Ishibashi et al.[2] have found that chromium trioxide oxidation of tetracyclic compound **2**, a derivative of **1**, gave dihydro-4*H*-1-benzopyran-4-one derivative **3** in moderate yield. They also demonstrated the cis, cisoid, cis ring system of **2** to be thermodynamically more stable than the corresponding 12aβ-H isomer as indicated by treatment of **3** with various bases giving unchanged material. Oida et al.[3] also reported that lithium aluminium hydride reduction converted tetracyclic ketone **4**, obtained on benzylic oxidation of diacetate **5**, to **1** as a result of concomitant tetrahydrofuran ring formation by internal nucleophilic displacement.

The above Sankyo group's work implies that a compound **6** epimeric with **5** at the C(12a) position would also serve as a synthetic intermediate for **1**, i.e. oxidation of **6** with chromium trioxide at its benzylic position followed by epimerization can be expected to produce **4**. Model syntheses of **1** based on the above presumption were thus reported by the Sankyo group.[3,4]

In preceding papers,[5] we reported the first total synthesis of racemic siccanin (*dl*-**1**), which was achieved from readily available octalone **7** via tetrahydrofuran derivative **8**. Our continuing effort for the synthesis of **1** was then directed to finding an alternative route based on the above presumption in combination with the olefin-phenol cyclization protocol, which seemed to be a more efficacious approach to the characteristic 1-benzopyran-4-one structure of **1** than that reported earlier.[5] We report here our findings in the investigation on this line.



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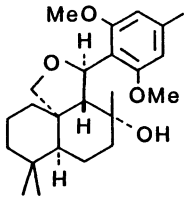

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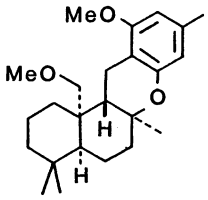
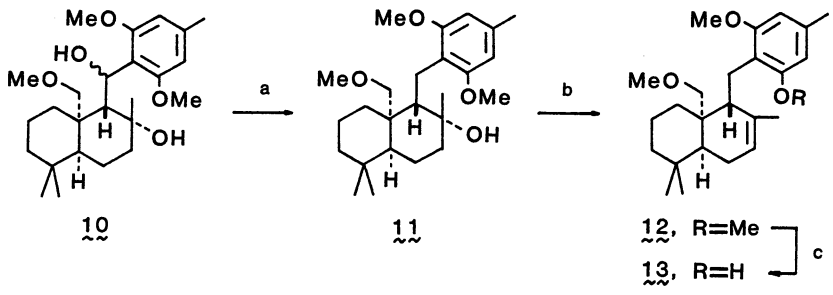


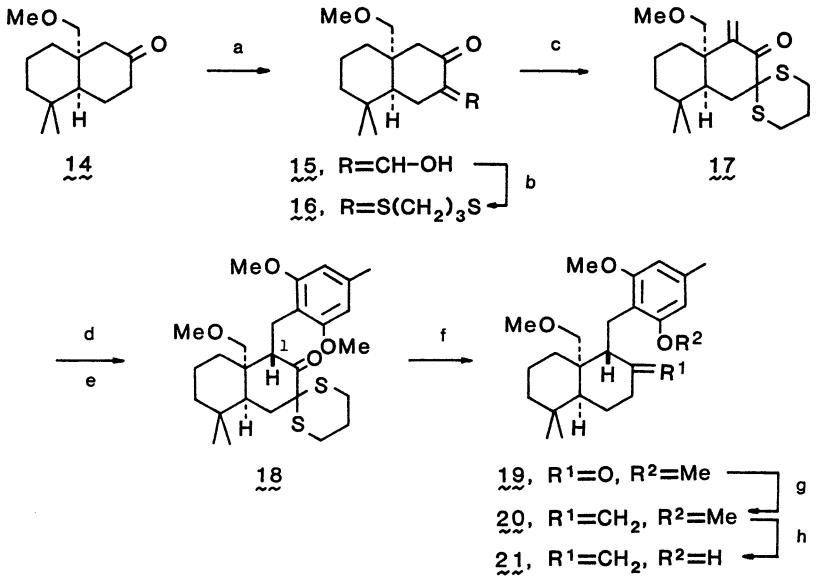
9

We planned to synthesize tetracyclic compound **9**, a synthetic equivalent of the proposed compound **6**, from two olefinic phenols **13** and **21** by the olefin-phenol cyclization. For derivation to the former phenol, benzylic alcohol **10**,[5] epimeric mixture regarding the benzylic hydroxyl, was submitted to hydrogenolysis to give alcohol **11** smoothly (Scheme 1). Sub-



(a) H_2, 10% Pd-C, EtOH: (b) $SOCl_2$, Py: (c) NaSEt, DMF

Scheme 1.



(a) NaH, HCO_2Et, PhH: (b) $CH_2(CH_2STs)_2$, KOAc, MeOH, (c) NaH, DMSO, CH_2O(g): (d) BuLi, orcinol dimethyl ether: (e) H_3O^+: (f) Raney-Ni(W-4), EtOH: (g) NaH, DMSO, Ph_3PCH_3Br: (h) NaSEt, DMF

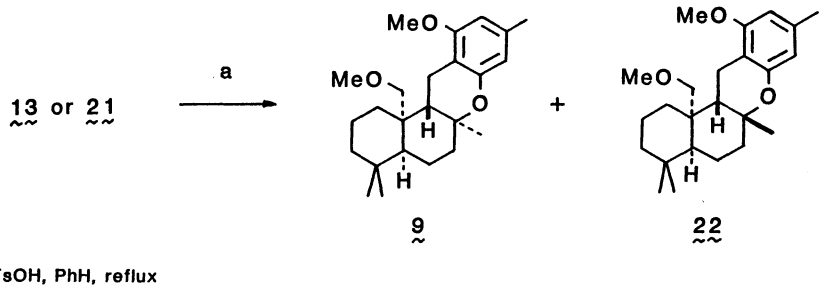
Scheme 2.

sequent dehydration of **11** with thionyl chloride in pyridine provided trisubstituted olefin **12** as the sole product in good yield. The phenol **13** was obtained from **12** by demethylation on heating with sodium ethanethiolate in *N,N*-dimethylformamide,[6] and its structure was confirmed by its physical data (IR and ^{1}H NMR) as well as regeneration of **12** on methylation with dimethyl sulfate under alkaline conditions.

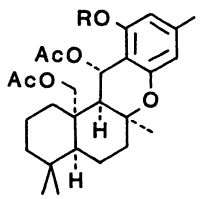
Preparation of the latter phenol **21** was conducted from cis decalone **14**[5] on the application of the reported method.[4] According to our experience,[5] the C(3) position of **14** was protected to prevent preferential alkylation at this position under basic conditions (Scheme 2). Formylation of the sodium enolate of **14** with ethyl formate and subsequent thioacetalization of the resulting hydroxymethylene ketone **15** with 1,3-propanedithiol ditosylate afforded crystalline ketone **16** in 80% overall yield. The enolate anion of the product generated with methylsulfinylmethanide anion was then treated with formaldehyde at −10 °C to give exo-methylene ketone **17** in moderate yield. The ketone **17** was submitted to the Michael addition with the lithium salt of orcinol dimethyl ether[7] and gave oily diastereomeric mixture, from which single epimer **18**[8] was obtained by acid epimerization in high yield. After removal of the thioacetal group in **18** by desulfurization with Raney nickel, methylenation of the resulting ketone **19** by the Wittig reaction with methylenetriphenylphosphorane afforded exo olefin **20** in high overall yield. The desired phenol **21** was derived by demethylation of **20** with sodium ethanethiolate.[6]

Having the olefinic phenols **13** and **21** in hand, we focused our attention on their acid-catalyzed olefin-phenol cyclizations. The cyclization of **13** proceeded smoothly upon heating with *p*-toluenesulfonic acid in benzene to provide two isomeric tetracyclic compounds **9** and **22** in 51 and 16% yields, while **21** similarly produced the same products in 54 and 26% yields, respectively (Scheme 3).

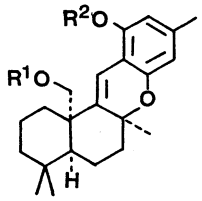
As no informative data were obtained from their



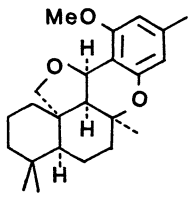
Scheme 3.



23, R=Ac
24, R=Me



25, R^1=R^2=Ac
26, R^1=H, R^2=Me
27, R^1=Ac, R^2=Me



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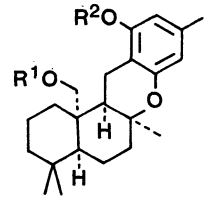
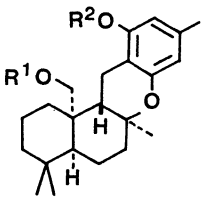
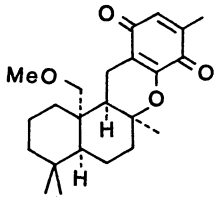


29, R^1=H, R^2=Me
30, R^1=R^2=Me
31, R^1=R^2=H
32, R^1=Me, R^2=H



33, R^1=H, R^2=Me
34, R^1=Me, R^2=Ac
35 R^1=Me, R^2=H



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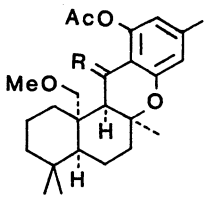


37, R=H_2
38, R=O

^{1}H NMR spectra to distinguish between **9** and **22**, we attempted to define their structures by derivation of the authentic compound from natural siccanin (*l*-**1**).

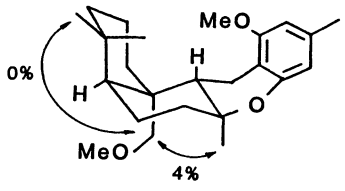
Nozoe et al. reported that siccanin (**1**), on treatment with boron trifluoride etherate in acetic anhydride, underwent cleavage of the C-O bond at the benzylic position to give triacetate **23** and siccanochromene E diacetate (**25**) as major and minor products, respectively.[9] With a view to obtaining siccanochromene E methyl ether (**26**), siccanin methyl ether (**28**)[9] was treated with the above Lewis acid under similar conditions, thus providing diacetoxy methyl ether **24** and acetoxy siccanochromene E methyl ether (**27**) in 80 and 19% yields, respectively. Subsequent reduction of the latter with lithium aluminium hydride afforded **26** quantitatively.

The methyl ether **26** was then submitted to catalytic hydrogenation over Pd-$SrCO_3$, affording two products, oily **29** and crystalline **33**, in a ratio of 81 : 19, and these products were presumed to be isomeric with respect to B/C ring juncture. Anticipation of the stereoselective hydrogenation at the convex face of molecule allowed us to assign the structure **29** to the major product. This surmise was chemically supported; dimethyl ether **30** obtained by methylation of **29** with methyl iodide was identical in all respects, except for optical rotations, with the exhaustive methylation product of the known diol **31**.[9]

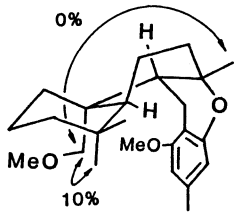
Consequently, the structure **33** could be assigned to the minor hydrogenation product, whose methyl ether was identical with the major cyclization product in comparison of their spectra.[1] This result also indicated that the structure **22** should be assigned to the minor cyclization product.

^{1}H NMR study of these cyclization products were highly suggestive of their conformations. Irradiation at methylene protons at δ 3.24 (CH_3OCH_2) in the spectrum of **9** in C_6D_6 resulted in a 4% NOE of the methyl protons (δ 1.39) on the carbon bearing an oxygen atom, whereas any ^{1}H NOE was not detectable between the methylene and gem. dimethyl protons. This finding seemed to indicate the steroid conformation **9a**[11]

with respect to the A/B rings for this compound. On the other hand, in the spectrum of **22** in $CDCl_3$, irradiation at one (δ 0.98) of methyl signals due to the gem. dimethyl grouping showed a 10% NOE in one of methylene proton signals at δ 2.63 (CH_3OCH_2), whereas no effect was observed between the methylene and the methyl protons (δ 1.20) on the carbon bearing an oxygen atom. In addition, the observed chemical shift (δ 2.63) of a methylene proton in methoxymethyl group of **22** is unusually high in comparison with other related compounds **9** (δ 3.27), **19** (δ 3.22), and **20** (δ 3.4), and this upfield shift would be ascribable to the shielding effect of aromatic ring. Such a stereochemical disposition seems to be allowed by a distorted conformation of its B ring by which one of methylene hydrogen atoms is disposed above the plane of aromatic ring. (cf. **22a**[11]), although we have no other evidence supporting this conformation.



9a



22a

The subsequent step in this synthesis was oxidation of the benzylic position of **9**. In expectation of preliminary information regarding this oxidation, we first submitted **30** to oxidation with chromium trioxide in aqueous acetic acid at 0 °C according to the literature.[1] The product, however, was *p*-quinone **36** formed in 40% yield.[12] Since this result indicated that methoxy was inadequate as a protective group in this oxidation, **9** was then transformed into acetylated phenol **34** by demethylation with sodium ethanethiolate[6] followed by acetylation of the resulting phenol **35**.

The acetylated phenol **34**, unfortunately, was extremely resistant to oxidation under similar conditions and gave rise to recovery of the unchanged substrate. On long duration of the oxidation at room temperature, some unidentified polar products[13] were formed, while no desired 1-benzopyran-4-one derivative was detectable despite of careful inspection of the reaction mixture. Attempted oxidation of **34** with other oxidants (cerium(IV) ammonium nitrate, lead(IV) acetate selenium dioxide, etc.) were also all fruitless. On the other hand, acetylated phenol **37** derived from **30** by demethylation with sodium ethanethiolate followed by acetylation of the resulting phenol **32** was submitted, for comparison, to chromium trioxide oxidation, yielding 1-benzopyran-4-one derivative **38**, albeit in low yield, in harmony with the previous observation.[3] Obviously **34** is suffered from a severe steric hindrance at the benzylic position.

In conclusion, the tetracyclic compound **34**, an equivalent of **6** that has been proposed as a promising synthetic intermediate[3,4] for *dl*-**1**, was synthesized via acid-catalyzed cyclization of the olefinic phenols **13** and **21**. This approach toward **1**, however, seems not to be feasible due to unsuccessful oxidation of **34** to the corresponding 12-oxo derivative.

Experimental

Melting points are uncorrected. IR spectra were obtained with a JASCO A-3 infrared spectrometer. ^1H NMR spectra were recorded on a JEOL FX90Q spectrometer using tetramethylsilane as an internal standard, and chemical shift values are given in δ and coupling constants (J) in hertz. Mass spectra were obtained on a Shimadzu LKB gas chromatograph-mass spectrometer equipped with a column (1 m) packed with OV-1 (1%). Ultraviolet spectra were recorded on a Cary model 14 spectrophotometer. Dry tetrahydrofuran (THF) and ethylene glycol dimethyl ether (DME) were obtained by distillation over lithium aluminium hydride. Other organic solvents, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and benzene were dried according to the standard procedure. All reactions, except for those in aqueous solutions, were carried out under dry N_2 or Ar atmosphere with use of standard procedures for the exclusion of moisture. Extracts obtained on workup of reaction mixtures were washed successively with water and brine, and then dried over $MgSO_4$, unless otherwise stated. Column chromatography was performed on silica gel (Merck, kieselgel 60, 70—230 mesh), and kieselgel GF_{254} was employed for preparative thin-layer chromatography (TLC) as absorbent. Solvents used for elution are shown in parentheses.

1α-(2,6-Dimethoxy-4-methylbenzyl)-8aα-methoxymethyl-2,5,5-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene (12). A mixture of **10**[5] (403 mg, 0.96 mmol), 10% Pd-C (80 mg) and ethanol (8 ml) was stirred at room temperature for 2 d under hydrogen. Filtration and subsequent concentration of the filtrate left an oil (395 mg), whose purification by TLC (1 : 1 ether-hexane) gave **11** (330 mg, 85%) as colorless crystals; mp 149—151 °C (from ether). IR (KBr) 3500, 1610, 1590, 1110, 970, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.92 and 0.98 (3H, s each, $C(CH_3)_2$), 1.08 (3H, s, O-CCH_3), 1.1—2.1 (12H, m), 2.35 (3H, s, $ArCH_3$), 2.47 (1H, t, J=9 Hz, $CHCH_2Ar$), 2.85 (2H, d, J=9 Hz, $ArCH_2$), 3.15 and 4.05 (1H, d, J=10 Hz each, CH_2O), 3.39 (3H, s, OCH_3), 3.85 (6H, s, $ArOCH_3$), 6.40 (2H, s, ArH), and a small amount of **10**.

To a stirred solution of **11** (110 mg, 0.27 mmol) in pyridine (1 ml) was added thionyl chloride (36 μl, ca. 0.5 mmol) at 0 °C, and stirring was continued for 5 h at this temperature and then at room temperature for an additional 5 h. Ether was added and the solution was washed successively with water, aqueous $CuSO_4$, water, and brine, and then dried. The oily residue obtained by evaporation was purified by TLC (4 : 1 hexane-ether) to give **12** (69 mg, 66%) as colorless needles; mp 137—138 °C (from hexane-ether). IR (KBr) 1610, 1590, 1120, 975, 810 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.85 and 0.93 (3H, s each, $C(CH_3)_2$), 1.2—2.2 (10H, m), 1.48 (3H, br s, =C-CH_3), 2.35 (3H, s, $ArCH_3$), 2.67 (2H, d, J=7.2 Hz, CH_2Ar), 3.35 (3H, s, OCH_3), 3.24 and 3.52 (1H, d, J=9 Hz each, CH_2O), 3.81 (6H, s, $ArOCH_3$), 5.38 (1H, br s, =CH), 6.36 (2H, s, ArH).

Found: C, 77.40; H, 9.90%. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91%.

1α-(2-Hydroxy-6-methoxy-4-methylbenzyl)-8aα-methoxymethyl-2,5,5-trimethyl-1,4,4aα,5,6,7,8,8a-octahydronaphthalene (13). A mixture of **12** (176 mg, 0.46 mmol), sodium ethanethiolate (370 mg, 4.4 mmol) and DMF (5 ml) was heated at 110 °C for 4.5 h. After cooling to room temperature, water was added and the resultant solution was extracted with ether. Concentration of the extract and purification of the oily residue by TLC (1 : 1 hexane-ether) gave **13** (164 mg, quantitaive) as a viscous oil. IR ($CHCl_3$) 3300, 1620, 1580, 1110, 815 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.88 and 0.92 (3H, s each, $C(CH_3)_2$), 1.0—2.2 (9H, m), 1.55 (3H, s, $=CCH_3$), 2.24 (3H, s, $ArCH_3$), 2.4—3.05 (3H, m), 3.42 (3H, s, OCH_3), 3.56 and 3.70 (1H, d, J=10 Hz each, CH_2O), 3.77 (3H, s, $ArOCH_3$), 5.35 (1H, br s, =CH), 6.21 and 6.33 (1H, s each, ArH), 7.75 (1H, s, OH). MS (70 eV) m/z 372 (M^+).

Methylation of 13 with Dimethyl Sulfate. To a stirred solution of **13** (10 mg) in ethanol (0.5 ml) was added aqueous NaOH (38%, 0.1 ml) and then dimethyl sulfate (0.1 ml) at room temperature. After stirring for 1 h, the same amounts of dimethyl sulfate and the alkali solution were added and stirring was continued for an additional 1 h. The mixture was diluted with water and extracted with CH_2Cl_2. Concentration of the extract left crystals (10 mg, quantitative), whose IR and ^1H NMR were identical with those of **12**.

5,5-Dimethyl-3-hydroxymethylene-8aα-methoxymethyl-3,4,4aα,-5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (15). A 50% sodium hydride dispersion in mineral oil (1.453 g, 15.14 mmol) was washed with pentane, and benzene (20 ml) was added. A solution of **14**[5] (3.390 g, 15.14 mmol) in benzene (20 ml) was added to the above suspension, and the mixture was stirred at 0 °C for 30 min. A solution of ethyl formate (4.486 g, 60.5 mmol) in benzene (5 ml) was added, and stirring was continued at 0 °C for 1.5 h and then at room temperature for 10 h. The mixture was poured into ice water, and the benzene layer was extracted with aqueous NaOH. The extract was acidified with dilute HCl at 0 °C and extracted with CH_2Cl_2. Concentration of the extract left a semisolid, which was filtered through a short silica gel-column with the aid of hexane-ether (1 : 3) to give **15** (3.550 g, 93%) as colorless needles; mp 76—77 °C (from hexane-ether). IR (KBr) 3300—2500, 1650, 1600, 1120, 890 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.81 and 0.98 (3H, s each, $C(CH_3)_2$), 1.1—1.8 (8H, m), 2.05 (1H, m), 2.3—2.6 (2H, m), 3.00 and 3.10 (1H, d, J=10.0 Hz each, CH_2O), 3.30 (3H, s, OCH_3), 8.27 (1H, s, =CHOH), 13.9—14.4 (1H, br, =CHOH).

Found: C, 71.11; H, 9.19%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%

5,5-Dimethyl-8aα-methoxymethyl-3-(trimethylenedithio)-3,4,4aα,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (16). A mixture of **15** (137 mg, 0.54 mmol), 1,3-propanedithiol ditosylate (225 mg, 0.54 mmol), potassium acetate (180 mg, 1.8 mmol), and methanol (5 ml) was gently refluxed for 15 h. The solvent was mostly removed under reduced pressure, and the residual oil was dissolved in CH_2Cl_2. The solution was washed successively with aqueous $NaHCO_3$, water and brine, and dried. The oily residue obtained on concentration was purified by TLC (1 : 1 ether-hexane) to provide **16** (152 mg, 85%) as colorless needles; mp 95—96 °C (from hexane-ether). IR (KBr) 1700, 1100, 620 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.95 and 1.13 (3H, s each, $C(CH_3)_2$), 1.1—2.6 (16H, m), 2.7—3.7 (1H, m), 3.03 and 3.53 (1H, d, J=10 Hz each, CH_2O), 3.30 (3H, OCH_3).

Found: C, 62.44; H, 8.45; S, 19.17%. Calcd for $C_{17}H_{28}O_2S_2$: C, 62.17; H, 8.59; S, 19.14%.

1α-(2,6-Dimethoxy-4-methylbenzyl)-5,5-dimethyl-8aα-methoxymethyl-3-(trimethylenedithio)-3,4,4aα,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (18). A 50% sodium hydride dispersion in mineral oil (983 mg, 9.75 mmol) was washed with pentane, and DMSO (20 ml) was added. The mixture was warmed at 65 °C with stirring for 1.5 h and then cooled to 0 °C. To the resulting solution, a solution of **16** (3.20 g, 9.75 mmol) in THF (30 ml) was added dropwise, and the whole was stirred for an additional 30 min. Formaldehyde vapor generated by heating paraformaldehyde (ca. 3 g) at 160—170 °C was passed through the well-stirred, above mixture at −10 °C with the aid of a dry N_2 stream over 40 min. The reaction was then quenched with aqueous NH_4Cl, and the mixture was extracted with benzene. Concentration of the extract left a semisolid, which was chromatographed over 50 g of silica gel (1 : 3 hexane-ether) to give **17** (1.94 g, 58%) as colorless crystals; mp 80—82 °C (from hexane-ether). IR (KBr) 1680, 1595, 1100, 950 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.97 and 1.00 (6H in total, s, $C(CH_3)_2$), 1.1—2.75 (15H, m), 3.25 and 3.60 (1H, d, J=10 Hz each, CH_2-O), 3.30 (3H, OCH_3), 5.42 and 6.13 (1H, finely splitted s each, $=CH_2$). MS (70 eV) m/z 340 (M^+).

1.5 M butyllithium in hexane (5.1 ml, 7.63 mmol) was added to a stirred solution of orcinol dimethyl ether (1.48 g, 9.72 mmol) in THF (20 ml) at 0 °C and the resulting mixture was stirred at room temperature for an additional 30 min. The mixture was cooled at −40—−50 °C and a solution of **17** (1.18 g, 3.47 mmol) in THF (10 ml) was added dropwise. Stirring was continued for an additional 2 h, and the reaction was quenched with ice water. The product was extracted with ether, and the oily residue obtained by concentration of the extract was dissolved in $CHCl_3$ (30 ml). A $CHCl_3$ solution (0.1 ml) saturated with dry HCl was added to the above solution, and the mixture was stirred at room temperature for 30 min. Removal of the solvent under reduced pressure gave a semisolid, which was then chromatographed over 50 g of silica gel (1 : 3 ether-hexane) to give **18** (1.52 g, 89%) as colorless crystals; mp 148—149 °C (from ether). IR (KBr) 1710, 1610, 1580, 1110, 810, 580 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.93 and 1.03 (3H, s each, $C(CH_3)_2$), 1.1—4.0 (18H, m), 2.30 (3H, s, $ArCH_3$), 3.35 (3H, s, OCH_3), 3.43 (2H, s, CH_2O), 3.80 (6H, s, $ArOCH_3$), 6.28 (2H, s, ArH). MS (70 eV) m/z 492 (M^+).

Found: C, 65.63; H, 8.40; S, 12.74%. Calcd for $C_{27}H_{40}O_4S_2$: C, 65.83; H, 8.19; S, 13.00%.

1α-(2,6-Dimethoxy-4-methylbenzyl)-5,5-dimethyl-8aα-methoxymethyl-3,4,4aα,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone (19). A mixture of W-4 Raney-Ni (ca. 4 g) and a solution of **18** (320 mg, 0.64 mmol) in ethanol (10 ml) was gently refluxed for 2.5 h with stirring. After cooling to room temperature, precipitates were filtered and washed with ethanol. The combined filtrates were evaporated and the residue was dissolved in CH_2Cl_2. Concentration of the solution left a solid, which was purified by TLC (3 : 1 hexane-ether) to give **19** (230 mg, 91%) as colorless needles; mp 130—131 °C (from ether). IR (KBr) 1710, 1605, 1590, 810 cm^{-1} ^1H NMR ($CDCl_3$) δ=1.02 and 1.15 (3H, s each, $C(CH_3)_2$), 1.0—2.9 (14H, m), 2.28 (3H, s, $ArCH_3$), 3.28 (3H, s, OCH_3), 3.22 and 3.33 (1H, d, J=10 Hz each, CH_2O), 3.78 (6H, s, $ArOCH_3$), 6.30 (2H, s, ArH).

Found: C, 74.16; H, 9.40%. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34%.

1α-(2,6-Dimethoxy-4-methylbenzyl)-5,5-dimethyl-8aα-methoxymethyl-2-methylene-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (20). A 50% sodium hydride dispersion in mineral oil (65 mg, 1.36 mmol) was washed with pentane, and DMSO (2 ml) was added. The resulting suspension was warmed at 60 °C for 1.5 h with stirring. A solution of methyltriphenylphosphonium bromide (480 mg, 1.36 mmol) in DMSO (1.5 ml) was added to the above solution at 0 °C, and stirring was continued at the same temperature for 30 min and then at room temperature for 30 min. A solution of **19** (250 mg, 0.64 mmol) in THF (1.5 ml) was added to the above ylide solution, and the mixture was stirred for an additional 15 h. The reaction was quenched with aqueous NH_4Cl, and the product was extracted with ether. Concentration of the extract gave an oil, which was purified by TLC (4 : 1 hexane-ether) to give **20** (199 mg, 80%) and recovered **19** (20 mg). **20**: colorless needles; mp 79—81 °C (from hexane-ether). IR (KBr) 1650, 1600, 1120, 980, 870, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.97 and 1.05 (3H, s each, $C(CH_3)_2$), 1.1—2.3 (12H, m), 2.30 (3H, s, $ArCH_3$), 2.6—2.9 (2H, m), 3.28 (3H, s, OCH_3), 3.40—3.43 (2H, m, CH_2-O), 3.77 (6H, s, $ArOCH_3$), 4.26 and 4.45 (1H, br d, J=3 Hz each, $=CH_2$), 6.27 (2H, s, ArH).

Found: C, 77.60; H, 9.89%. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91%.

5,5-Dimethyl-1α-(2-hydroxy-6-methoxy-4-methylbenzyl)-8aα-methoxymethyl-2-methylene-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (21). A mixture of **20** (120 mg, 0.31 mmol), sodium ethanethiolate (250 mg, 2.97 mmol) and DMF (3 ml) was gently refluxed for 1.5 h. After cooling to room temperature, water was added and the solution was extracted with ether. Concentration of the extract gave a semisolid, which was purified by TLC (3 : 1 hexane-ether) to afford **21** (95 mg, 82%) and recovered **20** (5 mg). **21:** mp 145—146 °C (from ether). IR (KBr) 3300, 1650, 1620, 1595, 1110, 925, 880, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.91 and 1.07 (3H, s each, $C(CH_3)_2$), 1.1—2.6 (14H, m), 2.27 (3H, s, $ArCH_3$), ca. 3.5 (2H, m, CH_2O), 3.50 and 3.60 (3H, s each, OCH_3 and $ArOCH_3$), 4.0 and 4.45 (1H, finely splitted s each, $=CH_2$), 6.15 and 6.35 (1H s each, ArH), 7.63 (1H, s, ArOH). MS (70 eV) m/z 372 (M^+).

Found: C, 77.56; H, 10.07%. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74%.

11-Methoxy-12bα-methoxymethyl-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aβ,12b-decahydro-12*H*-benzo[*a*]xanthene (9) and 11-Methoxy-12bα-methoxymethyl-4,4,6aβ,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aα,12b-decahydro-12*H*-benzo[*a*]xanthene (22). a) A solution of **21** (46 mg, 0.12 mmol) and *p*-toluenesulfonic acid (2 mg) in benzene (2 ml) was gently refluxed for 2 h. After cooling to room temperature, the mixture was diluted with benzene and washed successively with aqueous $NaHCO_3$, water and brine, and then dried. The oily residue obtained by concentration was purified by TLC (14 : 1 hexane-ether) to provide **9** (25 mg, 54%) as crystals, mp 111—112 °C (from hexane-ether). IR (KBr) 1615, 1585, 1130, 1105, 810 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.98 and 1.10 (3H, s each, $C(CH_3)_2$), 1.2—2.8 (14H, m), 1.28 (3H, s, O-CCH_3), 2.25 (3H, s, $ArCH_3$), 3.27 (5H, s, CH_2OCH_3), 3.78 (3H, s, $ArOCH_3$), 6.20 (2H, br s, ArH); ^1H NMR (C_6D_6) δ= 0.97 and 1.09 (3H, s each, $C(CH_3)_2$), 1.2—3.0 (14H, m), 1.39 (3H, s, O-CCH_3), 2.28 (3H, s, $ArCH_3$), 3.09 (3H, s, OCH_3), 3.24 (2H, s, CH_2O), 3.53 (3H, s, $ArOCH_3$), 6.24 and 6.72 (1H, s each, ArH). MS (70 eV) m/z 372 (M^+), and **22** (12 mg, 26%) as crystals, mp 175—176 °C (from ether). IR (KBr) 1615, 1590, 1115, 810 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.98 and 1.10 (3H, s each, $C(CH_3)_2$), 1.20 (3H, s, O-CCH_3), 1.27—2.8 (14H, m), 2.23 (3H, s, $ArCH_3$), 2.63 and 3.50 (1H, d, J=10 Hz each, CH_2O), 2.92 (3H, s, OCH_3), 3.77 (3H, s, $ArOCH_3$), 6.17 and 6.20 (1H, br s each, ArH). MS (70 eV) m/z 372 (M^+).

Found for **9:** C, 77.16; H, 10.04%. Found for **22:** C, 76.94; H, 9.50%. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74%.

b) A solution of **13** (172 mg, 0.46 mmol) and *p*-toluenesulfonic acid (5 mg) in benzene (4 ml) was gently refluxed for 2 h. Workup and subsequent purification of the oily residue obtained by the same procodure as described in a) gave **9** (86 mg, 51%) and **22** (28 mg, 16%).

Siccanochromene E Methyl Ether (26). A solution of 640 mg (1.80 mmol) of siccanin methyl ether (**28**)[9] in acetic anhydride (4 ml) was treated with a catalytic amount of boron trifluoride etherate at 0 °C. After stirring for 10 min, the mixture was poured into ice water and extracted with ether. The extract was successively washed with aqueous $NaHCO_3$, water, and brine, and then dried. Concentration left a semisolid, which was chromatographed over 15 g of silica gel (1 : 4 ether-hexane) to provide **27** (135 mg, 19%), mp 137—138 °C (from hexane-ether). IR (KBr) 1735, 1625, 1610, 1580, 1240, 1140, 1050, 830 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 and 1.03 (3H, s, $C(CH_3)_2$), 1.35 (3H, s, O-CCH_3), 1.9—2.2 (11H, m), 2.02 (3H, s, CH_3C=O), 2.28 (3H, s, $ArCH_3$), 3.81 (3H, s, OCH_3), 3.87 and 4.10 (1H, d, J=10 Hz each, CH_2O), 6.24 and 6.28 (2H in total, s each, ArH), 6.62 (1H, s, =CH), and **24** (646 mg, 80%) as colorless needels, mp 208—209 °C (from ether). IR (KBr) 1735, 1620, 1600, 1500, 1250, 1120, 1050, 820 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 and 1.20 (3H, s each, $C(CH_3)_2$), 1.32 (3H, s, O-CCH_3), 1.0—1.9 (12H, m), 1.98 and 2.07 (6H in total, s each, CH_3C=O), 2.26 (3H, s, $ArCH_3$), 3.75 (3H, s, OCH_3), 4.57 (2H, s, CH_2O), 6.00 (1H, s, ArCH-O), 6.22 and 6.29 (2H in total, s each, ArH).

Found for **27**: C, 75.60; H, 8.69%. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60%. Found for **24:** C, 70.40; H, 8.53%. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35%.

A mixture of **27** (282 mg, 0.71 mmol) and lithium aluminium hydride (54 mg) in THF (4 ml) was stirred at room temperature for 10 h, and the reaction was quenched with wet ether. Precipitates were filtered and washed with ether. Concentration of the combined filtrates left a semisolid, which was filtered through a short silica-gel column with the aid of ether-hexane (1 : 1) to afford **26** (247 mg, 98%) as colorless needles. The IR and ^1H NMR spectra of the product was identical with those of an authentic sample.

12bα-Hydroxymethyl-11-methoxy-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aα,12b-decahydro-12*H*-benzo[*a*]xanthene (29) and 12bα-Hydroxymethyl-11-methoxy-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aβ,12b-decahydro-12*H*-benzo[*a*]xanthene (33). A mixture of **26** (85 mg, 0.24 mmol), Pd-$SrCO_3$ (20 mg) and ethanol (5 ml) was stirred at room temperature for 20 h under hydrogen. The catalyst was filtered and washed with a small amount of ethanol, and the combined filtrates were concentrated under reduced pressure to give an oil. The oil was purified by TLC (1 : 1 ether-hexane) to provide **29** (R_f 0.57, 64 mg, 75%), **33** (R_f 0.5, 15 mg, 18%), and unchanged **26** (R_f 0.43, 5 mg). **29** (viscous oil): IR (neat) 3400, 1620, 1590, 1110, 1030, 810 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.0 and 1.22 (9H in total, s each, $C(CH_3)_2$ and

O-CCH$_3$), 1.1—2.1 (13H, m), 2.31 (3H, s, ArCH$_3$), 2.73 (2H, d, J=7 Hz, CH$_2$Ar), 3.83 (3H, s, ArOCH$_3$), 3.67 and 4.10 (1H, d, J=10 Hz each, CH$_2$O), 6.20 and 6.25 (2H in total, s each, ArH). MS (70 eV) m/z 358 (M$^+$). **33** (colorless crystals): mp 155—156 °C (from hexane-ether). IR (KBr) 3500, 1620, 1590, 1120, 1100, 810 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=1.04, 1.12, and 1.30 (9H in total, s each, C(CH$_3$)$_2$ and O-CCH$_3$), 1.0—2.9 (15H, m), 2.25 (3H, s, ArCH$_3$), 3.52 and 3.72 (1H, d, J=10 Hz each, CH$_2$O), 3.83 (3H, s, ArOCH$_3$), 6.25 and 6.29 (2H in total, s each, ArH). MS (70 eV) m/z 358 (M$^+$).

Found for **29:** C, 77.39; H, 9.36%. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56%.

11-Methoxy-12bα-methoxymethyl-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aα,12b-decahydro-12*H*-benzo[*a*]xanthene (30). a) To a stirred mixture of 50% sodium hydride in mineral oil (14 mg, 0.3 mmol) and DME (0.5 ml) was added a solution of **29** (57 mg, 0.16 mmol) in DME (0.5 ml) at room temperature. After stirring for 20 min, a solution of methyl iodide (50 mg, 0.35 mmol) in DME (0.5 ml) was added and stirring was continued for an additional 10 h. Ether was added, and the oily residue obtained by workup the solution was purified by TLC (2 : 1 hexane-ether) to give **30** (45 mg, 77%) as colorless crystals; mp 157—158 °C (from hexane-ether). IR (KBr) 1620, 1590, 1115, 820 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=0.90 and 1.12 (3H, s each, C(CH$_3$)$_2$), 1,18 (3H, s, O-CCH$_3$), 1.1—2.1 (12H, m), 2.27 (3H, s, ArCH$_3$), 2.68 (2H, d, J=6 Hz, CH$_2$Ar), 3.30 and 3.72 (1H, d, J=10.5 Hz each, CH$_2$O), 3.29 (3H, s, OCH$_3$), 3.80 (3H, s, ArOCH$_3$), 6.2 and 6.24 (2H in total, s each, ArH); MS (70 eV) m/z 372 (M$^+$).

Found: C, 77.64; H, 9.62%. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74%.

b) To a stirred mixture of 50% sodium hydride in mineral oil (30 mg, 0.6 mmol) and DME (1 ml) was added a solution of **31**[9] (69 mg, 0.2 mmol) in DME (0.5 ml), and stirring was continued for 30 min at room temperature. A solution of methyl iodide (92 mg, 0.64 mmol) in DME (0.5 ml) was added, and the mixture was stirred for an additional 10 h. Workup and subsequent purification by the same procedure as described in a) gave **30** (59 mg, 80%).

Conversion of 33 to 9. A mixture of **33** (35 mg, 0.09 mmol), 50% sodium hydride in mineral oil (10 mg, 0.18 mmol), methyl iodide (29 mg, 0.18 mmol) and DME (1.5 ml) was stirred at room temperature for 12 h. Purification of the resulting oily residue, obtained by workup, by TLC (5 : 1 hexane-ether) gave crystals (31 mg, 86%), whose IR and ^{1}H NMR were identical with those of authentic **9** derived by acid-catalyzed cyclization of **13** or **21**.

Chromium Trioxide Oxidation of 30. To a stirred solution of **30** (25 mg, 67.1 mol) in acetic acid (0.4 ml) was added a 25% chromium trioxide solution in 80% aqueous acetic acid (92 µl) at 0 °C, and the mixture was stired at 0 °C for 15 h. After dilution with brine, the product was extracted with ether, and the extract was washed successively with aqueous NaHCO$_3$, water and brine, and dried. The oily residue obtained by evaporation was purified by TLC (10 : 1 hexane-ether) to afford, along with unreacted **30** (4 mg), **36** (10 mg, 40%) as pale yellow needles; mp 159—160 °C (from hexane-ether). IR (KBr) 1672, 1650, 1634, 1612, 1120, 980 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=1.00 and 1.08 (6H in total, s each, C(CH$_3$)$_2$), 1.2—2.3 (14H, m), 1.27 (3H, s, O-CCH$_3$), 2.03 (3H, d, J=1.4 Hz, CH=C-C<u>H</u>$_3$), 3.05 (3H, s, OCH$_3$), 3.1—3.3 (2H, m, OCH$_2$), 6.47 (1H, q, J=1.4 Hz, =CH). UV (EtOH) 262 (ε 11,400), 405 (ε 760) nm. MS (70 eV) m/z 372 (M$^+$).

Found: C. 74.12; H. 8.45%. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66%.

11-Acetoxy-12bα-methoxymethyl-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,6a,12aβ,12b-decahydro-12*H*-benzo[*a*]xanthene (34). A solution of **9** (39 mg, 0.10 mmol), sodium ethanethiolate (66 mg, 0.78 mmol) and DMF (2 ml) was gently refluxed for 6 h. After cooling to room temperature, water was added and the product was extracted with benzene. The oily residue obtained by concentration was purified by TLC (7 : 1 hexane-ether) to give **35** (31 mg, 83%) as a colorless oil. IR (neat) 3350, 1623, 1590, 1100, 1050, 820 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=0.97 and 1.10 (6H in total, s each, C(CH$_3$)$_2$), 1.27 (3H, s, O-CCH$_3$), 1.3—2.9 (14H, m), 2.18 (3H, s, ArCH$_3$), 3.28 (3H, s, OCH$_3$), 3.31 (2H, s, CH$_2$O), 4.98 (1H, s, OH), 6.17 and 6.20 (2H in total, br s each, ArH).

A solution of **35** (30 mg, 0.08 mmol), acetic anhydride (0.5 ml) and pyridine (0.5 ml) was stirred at room temperature for 5 h. The mixture was poured into ice water and extracted with ether. A semisolid obtained by concentration was purified by TLC to give **34** (24 mg, 72%) as colorless crystals; mp 160—162 °C (from hexane-ether). IR (KBr) 1760, 1625, 1585, 1205, 1100, 1050 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=0.97 and 1.08 (3H, s each, C(CH$_3$)$_2$), 1.27 (3H, s, O-CCH$_3$), 1.3—2.8 (14H, m), 2.23 and 2.28 (3H, s each, ArCH$_3$ and CH$_3$C=O), 3.29 (5H, m, CH$_2$OCH$_3$), 6.43 and 6.50 (2H in total, br s each, ArH).

Found: C, 74.81; H, 9.15%. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.09%.

Attempted Oxidation of 34 with Chromium Trioxide. a) To a solution of **34** (24 mg, 0.06 mmol) in acetic acid (1 ml) was added a 25% chromium trioxide solution in 80% aqueous acetic acid (82 µl) at 0 °C, and the mixture was stirred at 0 °C for 20 h. After dilution with brine, the product was extracted with ether, and the extract was washed successively with aqueous NaHCO$_3$, water and brine, and dried. The oily residue obtained by concentration was purified by TLC (10 : 1 hexane-ether) to provide unchanged **34** (18 mg).

b) A 25% chromium trioxide solution in 80% aqueous acetic acid (90 µl) was added to a solution of **34** (25 mg, 0.06 mmol) in acetic acid (1 ml), and the mixture was stirred at room temperature for 20 h. Workup followed by purification in a similar manner provided unchanged **34** (4 mg) and unidentified polar oily products.

11-Acetoxy-12bα-methoxymethyl-4,4,6aα,9-tetramethyl-1,2,3,4,4aα,5,6,12aα,12b-decahydro-12*H*-benzo[*a*]xanthene (37). A mixture of **30** (116 mg, 0.31 mmol), sodium ethanethiolate (235 mg, 2.8 mmol) and DMF (3 ml) was heated at 110 °C for 7 h. After cooling to room temperature, water was added and the resulting solution was extracted with ether. Evaporation followed by purification of the oily residue by TLC (2 : 1 hexane-ether) provided phenol **32** (97 mg, 87%) as an amorphous powder. IR (KBr) 3500, 1630, 1595, 1110, 1080, 1060 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=0.90, 1.10 and 1.15 (3H, s each, C(CH$_3$)$_2$ and O-CCH$_3$), 1.1—2.0 (m, 12H), 2.20 (3H, s, ArCH$_3$), 2.68 (2H, d, J=6 Hz, CH$_2$Ar), 3.32 (3H, s, OCH$_3$), 3.35 and 3.70 (1H, d, J=10.0 Hz each, CH$_2$O), 5.0 (1H, s, OH), 6.15 and 6.20 (1H, s each, ArH).

A solution of **32** (66 mg, 0.18 mmol), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was stirred at room temperatutre for 15 h. The mixture was poured into water and extracted with ether. Concentration of the extract afforded an oil, which was purified by TLC (2 : 1 hexane-ether) to give **37** (70 mg, 96%) as an amorphous powder. IR (KBr) 1760, 1630,

1580 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90, 1.10 and 1.18 (3H, s each, $C(CH_3)_2$ and O-CCH_3), 1.0—2.2 (m, 12H), 2.25 (3H, s, $ArCH_3$), 2.32 (3H, s, CH_3C=O), 2.60 (2H, d, J=3.6 Hz, CH_2Ar), 3.18 and 3.68 (1H, d, J=10.0 Hz each, CH_2O), 3.30 (3H, s, OCH_3), 6.38 and 6.47 (1H, s each, ArH).

Found; C, 74.70; H, 9.03%. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06%.

Oxidation of 37. A 25% chromium trioxide solution in 80% aqueous acetic acid (0.3 ml) was added to a solution of **37** (88 mg, 0.23 mmol) in acetic acid (1 ml), and the mixture was stirred at 0 °C for 15 h. After dilution with water, the product was extracted with ether, and the combined extracts were washed successively with aqueous $NaHCO_3$, water, and brine, and dried. Removal of the solvent left an oil, which was purified by TLC (1 : 1 hexane-ether) to give **38** (19 mg, 23%) as a viscous oil. IR (neat) 1765, 1675, 1620, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.92, 1.13, and 1.22 (3H, s each, $C(CH_3)_2$ and O-CCH_3), 1.0—2.1 (m, 11H), 2.30 (3H, s, $ArCH_3$), 2.39 (3H, s, CH_3C=O), 2.54 (1H, s, CHC=O), 3.22 and 3.63 (1H, d, J=10.0 Hz each, CH_2O), 3.35 (3H, s, OCH_3), 6.40 and 6.61 (1H, s each, ArH). MS (70 eV) m/z 414 (M^+).

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13) Although structural elucidation of these products were not attempted, they seemd to be degradation products resulting from an aromatic ring cleavage. The oxidative fission of an aromatic ring has been reported for **5** (Ref. 3).