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# Total Synthesis of dl-Siccanin and dl-Siccanochromene E

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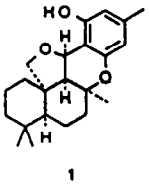
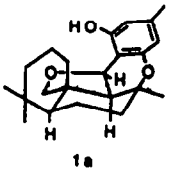
Abstract - The stereoselective synthesis of dl-siccanin (1) and dl-siccanochromene E (2) has been described. Acid isomerization of nonconjugated octalone **11a**, derived from known octalone **5**, stereoselectively provided cis-fused octalone **12**, from which cis-drimane aldehyde **31** was obtained. After condensation of **31** with lithio-orcinol dimethyl ether, the product **32** was treated with pyridinium chloride to give tetrahydrofuran **33** whose complete stereostructure was unambiguously established by an X-ray crystal analysis. While cyclization of monophenol **34**, obtained by partial demethylation of **33**, with sulfuric acid afforded siccanochromene E methyl ether (**35**), reaction of **34** with Lewis acid gave siccanin methyl ether (**36**) along with **35**. In the latter cyclization, the formation of **36** was demonstrated to occur from initially formed **35**. Finally, demethylation of **35** and **36** provided **2** and **1**, respectively. A novel tetrahydrofuran formation by a neighboring participation, which was observed in hydroxy ketone **24** and diol **32**, are also discussed.

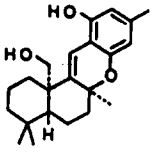
Siccanin (**1**) was isolated by Ishibashi from the culture broth of Helminthosporium siccans Drechesler, one of the plant parasitic fungi of rye-grass, in the course of investigating the antibiotic preparations from fungi.[1] This mold metabolite has been found to exhibit a remarkable antifungal activity against a variety of fungi, particularly pathogenic fungi Trichophyton interdigitale and T. asteroids which cause infection in animal skins, in a low concentration of 1 μg/ml.[2] After extensive scrutiny of the culture broth, several congeners related to **1**, siccanochromenes A-F, were also isolated.[3]




1




1a




2

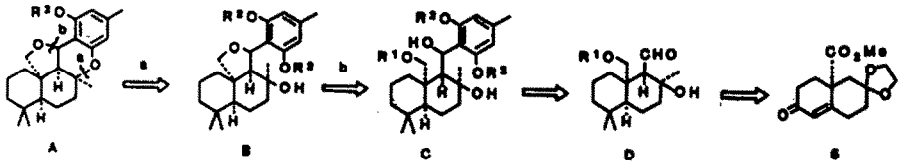
The structure and absolute configuration of **1**, after five years of isolation, were revealed by an X-ray crystallographic study of its p-bromobenzenesulfonate.[4] As depicted, siccanin is formally regarded as a drimane sesquiterpene combined with orcinol, and its structurally distinctive feature is the unique cis, syn, cis-fused alicyclic ring system that has seldom be found in other naturally occurring polycyclic terpenoids (see **1a**).

This novel structure as well as its eminent biological activity of **1** fascinated us as an attractive target for total synthesis. Herein is described details of the first total synthesis

of dl-1 by a novel approach[5] in which dl-siccanochromene E (2) was also synthesized and employed as one of the synthetic intermediates for 1.[6]

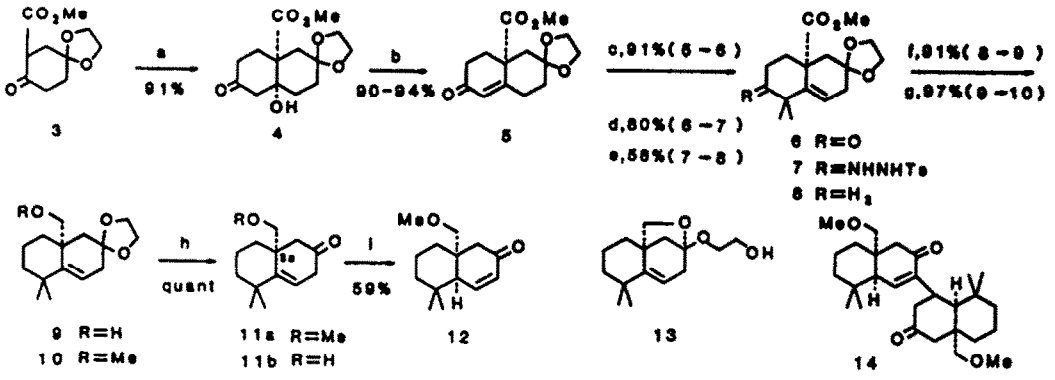
We initially envisioned to construct 1 by the retrosynthesis depicted in Scheme 1. Stepwise cleavage of two ether linkages a and b in A leads to tetrahydrofuran B and then to drimane derivative C, both of which would be visualized as viable precursors of 1. Compound C may be derived from the condensation of aldehyde D and orcinol. Finally, D would be derived by elaboration of known octalone 5. Indeed, this strategy has proven to be successful as described below.

Scheme 1



**Synthesis of cis-decalone 12.** Nonconjugated octalone 11a was prepared via a six-step sequence from the known and readily available octalone 5, and the yield of the latter compound was considerably improved by the following modification of the original procedure[7] (Scheme 2). The Robinson annulation of keto ester 3[8] with methyl vinyl ketone was thus carried out in the presence of 0.1 equiv of sodium methoxide in methanol in place of an amine, resulting in a quantitative yield of hydroxy ketone 4. Subsequent dehydration of 4 with sodium methoxide (1 equiv) in methanol or in boiling benzene in the presence of florisil[9] afforded octalone 5[10] in 82-85% overall yield from 3.

Scheme 2



(a)methyl vinyl ketone,NaOMe(0.1 equiv),MeOH;(b)NaOMe (1.0 equiv),MeOH;(c)MeI,t-BuOK,t-BuOH;(d)p-TsNHNH$_2$, MeOH;(e)NaB(CN)H$_3$,DMF-sulfolane;(f)LiAlH$_4$,DME;(g)MeI, NaH,DMS;(h)p-TsOH,acetone,25 °C;(i)p-TsOH(0.6 equiv), MeOH,60 °C.

Methylation of the potassium enolate of 5 with excess methyl iodide gave the corresponding oily dimethylated ketone 6. Reduction of the hindered ketone carbonyl of 6 was achieved by treatment of tosylhydrazone 7 of 6 with sodium cyanoborohydride,[11] affording octalin 8. This octalin was then converted to crystalline alcohol 9 on lithium aluminum hydride reduction.

During this reduction, we often obtained 9 contaminated with its isomer 13. The latter structure was surmised spectroscopically and confirmed by chemical evidence since hydroxy ketone 11b was obtained by treatment of 13 with hydrochloric acid. It soon became clear that the by-product appears to be formed principally when the extract was dried on commercial magnesium sulfate. This side reaction could be suppressed with ease by extracting the reaction product

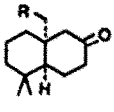
under basic conditions followed by drying the extract over a sodium sulfate-sodium carbonate mixture.

For protection of the newly formed hydroxyl group in **9**, we initially investigated the use of some substituted methyl or benzyl ethers, after all, the simplest methyl ether was our choice as a convenient protective group in our synthetic route, as will be illustrated later. Methylation of **9** in the standard manner and subsequent acetal exchange of the resultant methylated acetal **10** with acetone provided the oily nonconjugated octalone **11a**.

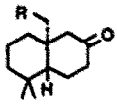
On derivation of the desired cis-fused octalone **12** from **11a**, we expected that under equilibrating conditions for conjugation of the double bond to the carbonyl, the repulsive interaction between the angular substituent and one of the gem. dimethyls in **11a** would act favorably for formation of **12** over the corresponding trans-fused product, and indeed this surmise was the case. After isomerization of **11a** to enone **12** had been extensively examined under a variety of acidic and basic conditions, it was found that the most effective result was obtained when **11a** was warmed with 0.5 equiv of p-toluenesulfonic acid in methanol at 60 °C; thus the reaction provided an equilibrium mixture of **11a** and **12** in a ratio of 1:4, from which **12** was isolated by chromatography in acceptable yield. On long exposure (one day or more) of **11a** to acid, gradual formation of dimer **14** was observed.

The stereostructure of **12** was proven to be a cis decalone as mentioned below, while no formation of its trans isomer was found on the careful inspection of the reaction mixture.[12] Hydrogenation of **12** gave decalone **15** in quantitative yield, while **11a** provided a mixture of **15** and **16** in a ratio of 1:4 under the same conditions. In $^1$H NMR spectroscopy, two singlets ($\delta$ 1.03 and 1.08) due to the gem. dimethyls in **15** appeared at a lower field than those ($\delta$ 0.70 and 0.95) in **16**, and this observation is parallel to a chemical shift difference between those of two known trimethyldecalone isomers **17** ($\delta$ 0.98 and 1.06) and **18** ($\delta$ 0.87 and 0.98).[13] This comparison could be highly suggestive of a cis ring juncture in **15**, and consequently that in **12**.

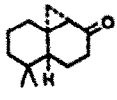
For unambiguous assignment of the cis stereochemistry, **15** was transformed into known **17**. Replacement of the methoxyl group in **15** by a chlorine atom was effected by treatment with saturated hydrogen chloride in ether in the presence of zinc chloride to give chloro ketone **19** in high yield. Conversion of **19** into cyclopropyl ketone **20** was cleanly attained by treatment with sodium hydride in tetrahydrofuran. Finally, reductive cleavage of the cyclopropane ring with lithium in liquid ammonia afforded **17**, which was identified with an authentic sample[13] by spectral comparison.



**15** R=OMe
**17** R=H
**19** R=Cl



**16** R=OMe
**18** R=H

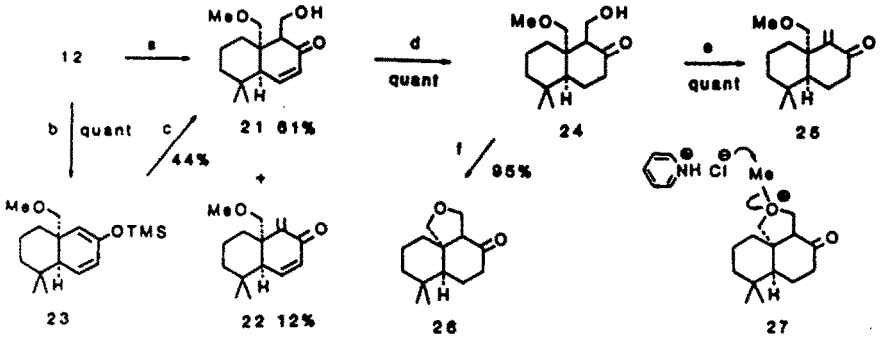


**20**

**Synthesis of formyl decalol 31 and its derivation to tetrahydrofuran 33.** Regioselective hydroxymethylation of **12** was carried out by reaction of its lithium enolate, prepared under kinetically controlled conditions, with gaseous formaldehyde to afford the homogeneous hydroxy octalone **21**[14] in moderate yield together with methylene ketone **22** in a ratio of 74:26 (Scheme 3). These products were chemically correlated by dehydration of **21** on activated alumina leading to **22** in quantitative yield. As an alternative synthesis of **21**, the lithium enolate generated from silyl enol ether **23**, prepared from **12** by an established procedure,[15] with methyllithium was submitted to hydroxymethylation with formaldehyde. The yield of **21**, however, was poor. The hydroxy octalone **21** was then converted to hydroxy decalone **24** by hydrogenation.

We first attempted to employ the conjugated methylene ketone **25**, since its enone system was surmised to play a major role in introducing the aromatic part of **1**.[16] Although enone **25** was

Scheme 3



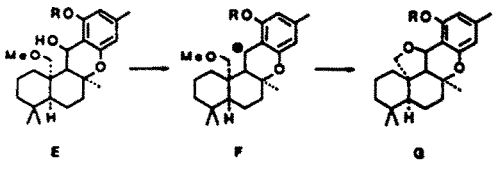

(a)(1)LDA-DME.-78 → -40 °C,(2)$CH_3O(g)$.-78 °C;(b)LDA-DME. $Me_3SiCl$;(c)(1)MeLi-$Et_2O$,(2)$CH_3O(g)$. -78 °C;(d)$H_2$,10%-Pd-C. EtOH,(e)$Al_2O_3$-PhH;(f)p-TsCl,Py.

obtained without difficulty by dehydration of 24 on activated alumina, it gave no detectable amount of the expected 1,4-adduct when treated with the lithium salt of orcinol dimethyl ether;[17] and 25 was completely recovered. This failure would be based on capture of a proton from the active methylene α to the carbonyl with the lithium salt.[18] On the other hand, attempts for regioselective introduction of the aromatic moiety into 12 by condensation with benzaldehyde derivatives also proved fruitless. For example, treatment of 23 with 2,6-dimethoxy-4-methylbenzaldehyde in the presence of equimolar titanium tetrachloride or condensation of the corresponding lithium enolate of 23 prepared with methyllithium with this benzaldehyde gave only the hydrolysis product 12.

Successful results were obtained by utilizing a new type of neighboring group participation reaction. In one attempt to obtain 25, 24 was treated with p-toluenesulfonyl chloride in pyridine, giving an oily compound in almost quantitative yield. This product was not 25 but the unexpected tetrahydrofuran 26. While the enone 25 was inert under the above reaction conditions, treatment of 24 with pyridinium chloride provided 25 in moderate yield as the sole isolable product. Taking into account neighboring effect of the methoxymethyl and hydroxymethyl groups in 24 as well as the above corroborations, the tetrahydrofuran formation would be rationalized by initial tosylation of 24 and subsequent internal displacement to afford an oxonium ion as depicted in 27. Subsequently the oxonium-methyl bond suffers cleavage by the attack of the pyridinium chloride on the least substituted carbon.

This reaction is also highly predictable of the following conceptions; first, this result demonstrates the utility of methyl ether as the convenient protective group for 9, and second, treatment of benzylic alcohol E, a promising progenitor of 1, with pyridinium chloride would lead to tetrahydrofuran G via carbocation F according to the reaction mode described below (Scheme 4)

Scheme 4

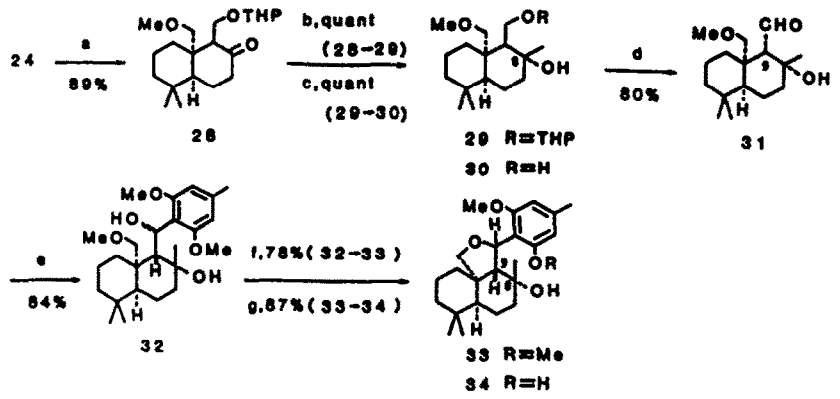



We therefore turned our attention to the synthesis of the formyl decalol 31 (Scheme 5). Protection of the hydroxyl group in 24 as a tetrahydropyranyl (THP) ether and subsequent methylation of the resulting decalone 28 with excess methyllithium produced an oily carbinol 29,[19,20] which was then deprotected. Diol 30 thus obtained was oxidized with pyridinium chlorochromate to provide the desired aldehyde 31[20] in 70% overall yield from 24.

Introduction of the aromatic ring was carried out by condensation of 31 with lithiated orcinol dimethyl ether,[17] and the expected diol 32 was obtained in high yield as a C-11 epimeric

mixture with a minor quantity of its epimer regarding the benzylic hydroxyl group. Having the desired 32 in hand, the tetrahydrofuran formation reaction was immediately examined by treatment

Scheme 5




(a)DHP,PPTS,$CH_2Cl_2$;(b)MeLi,$Et_2O$;(c)PPTS,EtOH;(d)PCC, $CH_2Cl_2$;(e)n-BuLi,orcinol dimethyl ether, DME,-78 - 0 °C; (f)$C_5H_5N$·HCl,$CH_2Cl_2$;(g)NaSEt,DMF,100 °C.

of the epimeric mixture with 1 equiv of pyridinium chloride in dichloromethane. The anticipated reaction proceeded smoothly at room temperature and on short treatment afforded crystalline 33 in high yield. Compound 33 was also obtained by treatment of 32 with titanium tetrachloride in satisfactory yield. Subsequent partial demethylation of 33 could be accomplished by heating with sodium ethylthiolate in N,N-dimethylformamide[21] to give monophenol 34 in high yield.

Although $^1$H NMR did not allow us to assign the stereochemistry of the newly formed tetrahydrofuran ring, X-ray crystallographic analysis of 33 definitely established its stereostructure as shown, and further revealed the following new feature; the crystal structure of 33 consists of pairs of two independent molecules, e.g. enantiomers A and B, as shown in Fig. 1, and they are connected by the hydrogen bond, thus forming an infinite sequence of molecules A--B--A--B along the c axis. The distance of O--O are 2.72 and 2.93 Å for A--B and B--A, respectively. The geometries of A and B are essentially the same and in comparison with those of similar compounds, no significant difference was observed in the bond lengths and angles. The six-membered ring fused with the tetrahydrofuran ring exists in a boat conformation and the other cyclohexane ring in a chair conformation. The hydroxyl group is thus in an axial position, and this conformation

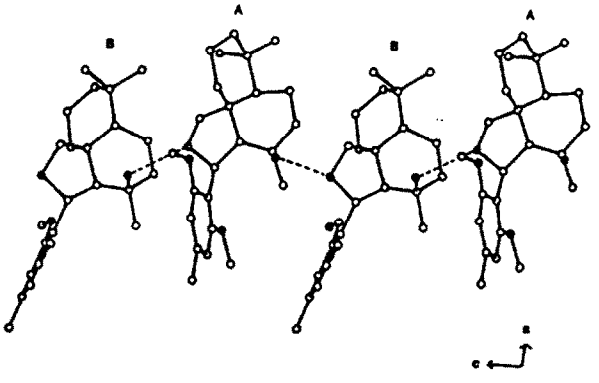
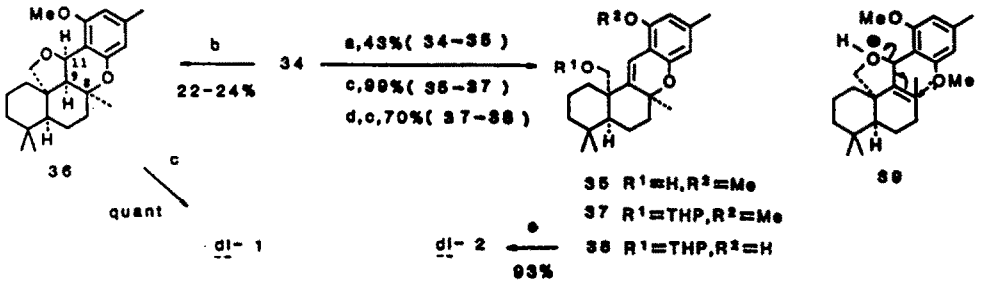



Figure 1. The crystal structure of 33 viewed along b axis. The hydrogen bonding scheme is shown by describing the molecules A and B, and their molecules translated by (x, y, 1+z).

is favorable for hydrogen bonding and excluded the interference of the sterically crowded phenyl ring. The phenyl ring is oriented almost diagonal to the tetrahydrofuran ring.

**Synthesis of dl-siccanin (1) and dl-siccanochromene E (2).** Returning to our total synthesis, the procurement of **34** prompted us to complete the synthesis of **1**. There are two tasks remaining; inversion of the C(9) hydrogen atom to the same configuration as that of **1** and formation of the second ether linkage with the proper stereochemistry of the methyl group at C(8). To this end, we planned to utilize a $\Delta^{8,9}$-tetrasubstituted double bond via dehydration of **34** and subsequent olefin-phenol cyclization in a one-pot operation. While no fruitful result was obtained on exposure of **34** to p-toluenesulfonic acid or oxalic acid,[22] treatment with concentrated sulfuric acid in 1-nitropropane at room temperature afforded colorless crystals along with a small amount of a mixture of unidentified highly less polar products (Scheme 6). The crystals were shown to be dl-**35** by spectral comparison with an authentic sample of siccanochromene E methyl ether.[23]

Scheme 6




(a)$H_2SO_4$,$PrNO_2$,-26 - 25 °C;(b)$BF_3 \cdot OEt_2$,$CH_2Cl_2$,25 °C or $SnCl_4$,PhH,25 °C;
(c)DHP,PPTS,$CH_2Cl_2$;(d)NaSEt,DMF, 100 °C;(e)PPTS,EtOH.

Judging from the fact that authentic siccanin methyl ether (**36**)[4b] was recovered unchanged under the same conditions, **35** would be derived through the following sequence of reactions: dehydration of **34** to the expected tetrasubstituted olefin; protonation of the ether oxygen doubly activated by both the aromatic ring and the newly introduced double bond; and synchronous carbon-oxygen bond cleavage in the tetrahydrofuran ring and chromene ring formation by attack of the phenolic oxygen atom, as shown in **39**.

Excellent results were obtained when a Lewis acid was employed in place of a protonic acid. Treatment of **34** with boron trifluoride etherate or stannic chloride in dichloromethane at room temperature gave rise to a second product, dl-siccanin methyl ether (**36**)[4b] along with **35**. TLC monitoring indicated that the former product appears to be formed via the latter.[24] The solid obtained, albeit in low yield, was a mixture of both compounds in a ratio of 4:1, from which pure **36** was isolated as crystals by preparative TLC and identified by spectral comparison with an authentic sample. No evidence was found for formation of stereoisomers of **35** and **36**. As was anticipated by the above TLC analysis, treatment of **35** with the same Lewis acids provided a similar equilibrium mixture of **35** and **36**, from which the latter was also separated.[25] Regarding the stereochemical stability of the ring system of **1**,[2] it is worthy to mention that the one-step construction of three consecutive chiral centers at the C(8), C(9) and C(11) positions in **36** was achieved under the above thermodynamically controlled conditions.

Finally, demethylation of **36** with sodium ethylthiolate[21] produced dl-**1** without difficulty. On the other hand, demethylation of **35** in a similar manner led to only unidentified product.[26] dl-Siccanochromene E (**2**) was eventually derived in moderate overall yield by a three-step sequence: protection of the hydroxyl in **35** as a THP ether affording diether **37**; demethylation with sodium ethylthiolate followed by deprotection of the resulting phenol **38** giving **2**. dl-Siccanin (**1**) and dl-siccanochromene E (**2**) thus obtained were indistinguishable from the natural specimens in TLC, IR, and $^1H$ NMR.

**Acknowledgment.** This work was supported by a Grant-in-Aid for Scientific Research (354,187). We acknowledge Prof. S. Nozoe (Tohoku University) and Dr. G. Ohloff (Firmenich SA) for providing

us with authentic samples of siccanochromene E methyl ether and trimethyldecalone 17, respectively. Our thanks are also due to Sankyo Co. for a generous gift of natural siccanin.

## Experimental

Melting points are uncorrected (Mitamura Riken NRK-VOLTSTAT). IR spectra were obtained with a JASCO A-3 infrared spectrophotometer and spectral bands are reported in $cm^{-1}$. $^1H$ NMR spectra were recorded on a JEOL FX90Q spectrometer, except where noted, in deuterochloroform. Chemical shifts are given in parts per million ($\delta$) downfield from internal tetramethylsilane and coupling constants (J) in hertz. Gas chromatography was carried out on a JEOL JGL-20K gas chromatograph. Dry tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl. Other organic solvents were purified and dried by using standard procedures. All reactions were carried out under dry $N_2$ or Ar atmospheres with use of standard procedures for the exclusion of moisture, except those in aqueous solution. Column chromatography was performed by using silica gel (Merck, Kieselgel 60, 70-230 mesh), and kieselgel $GF_{254}$ was employed for preparative thin-layer chromatography (TLC). Solvents for elution are shown in parentheses. $MgSO_4$ was employed for drying extracts, unless otherwise stated.

**4aα-Carbomethoxy-8aα-hydroxy-3,4,4a,7,8,8a-hexahydronaphthalene-2,6-(1H,5H)-dione 6-ethylene acetal (4).** A solution of 3 (4.634 g, 21.65 mmol) in anhydrous methanol (10 ml) was added to a sodium methoxide solution prepared from Na (50 mg, 2.17 mg atom) and anhydrous methanol (50 ml), and the resulting mixture was cooled at ice-bath temperature. A solution of methyl vinyl ketone (4.634 g, 21.65 mmol) in methanol (10 ml) was added with stirring. After 1 h, the cooling bath was removed and stirring was continued at room temperature for an additional 15 h. The solvent was mostly removed in vacuo and the resulting oil was dissolved in $CH_2Cl_2$. The solution was washed successively with water and brine, and dried. Evaporation gave a semisolid, whose $CH_2Cl_2$ solution was then filtered through a short silica gel column. Evaporation of the filtrate 4 (5.591 g, 91%) as colorless needles, mp 154-155 °C: IR (KBr) 3450, 1710 $cm^{-1}$; $^1H$ NMR 1.5-2.7 (m, 12H), 3.78 (s, 3H), 3.95 (br, 4H), 4.5 (br s, 1H, OH). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.03; H, 7.23.

**4a-Carbomethoxy-4,4a,7,8-tetrahydronaphthalene-2,6(3H,5H)-dione 6-ethylene acetal (5).** (a) The compound 4 (6.117 g, 21.54 mmol) was added to a sodium methoxide solution prepared from Na (495 mg, 21.53 mg atom) and anhydrous methanol (40 ml), and the resulting suspension was stirred at room temperature for 15 h. After evaporating most of the solvent, the residue was diluted with water, extracted with $CH_2Cl_2$, and dried. Concentration in vacuo and recrystallization of the resulting semisolid from ether gave 5 (5.183 g, 90%), mp 121-122 °C (lit.[10,7] mp 122-124, 124-126 °C), as colorless needles. This compound was identified by comparison of spectral data with those reported.[7]

(b) A mixture of 4 (251 mg), florisil (1.0 g) and benzene (10 ml) was gently refluxed for 5 h. After cooling, the content was poured onto a short silica gel column. Elution with $CH_2Cl_2$ gave 5 (222 mg, 94%).

**4a-Carbomethoxy-1,1-dimethyl-3,4,4a,5-tetrahydronaphthalene-2,6(1H,7H)-dione 6-ethylene acetal (6).** Small pieces of K metal (3.2 g, 82 mg atom) was dissolved in anhydrous t-butyl alcohol (80 ml) with gentle heating. After cooling, the resulting solution was added dropwise to a stirred solution of 5 (10.57 g, 40 mmol) in t-butyl alcohol (70 ml) at room temperature. After 1 h, methyl iodide (31.7 g, 223 mmol) was added dropwise and the whole was stirred for an additional 4 h. The solvent was mostly removed in vacuo at 30 °C and the residue was diluted with water, and extracted with $CH_2Cl_2$. The combined extracts were washed successively with water and brine, and dried. The residue obtained by evaporation was purified by column chromatography on 50 g of silica gel (1:1 ether-hexane) to afford 6 (10.60 g, 91%) as a colorless oil, IR (liquid) 1720, 1710, 1660 $cm^{-1}$; $^1H$ NMR 1.30 and 1.40 (s, 3H each), 1.3-2.7 (m, 8H), 3.60 (s, 3H), 3.93 (br s, 4H), 5.75 (t, 1H, J 4.0). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.10; H, 7.91.

**8a-Carbomethoxy-5,5-dimethyl-1,5,6,7,8,8a-hexahydro-2(3H)-naphthalenone 2-ethylene acetal (8).** A mixture of 6 (8.66 g, 29 mmol), p-toluenesulfonyl hydrazine (6.58 g, 35 mmol) and methanol(16 ml) was warmed at 55 °C for 15 h with stirring. After cooling in an ice bath, precipitates were collected by filtration and washed with a small quantity of cold methanol to give 7 (11.07 g, 80%), mp 217-219 °C, IR (KBr) 3200, 1710, 1600, 1170 $cm^{-1}$; $^1H$ NMR 1.20 and 1.37 (s, 3H each), 1.1-2.6 (m, 8H), 2.41 (s, 3H), 3.20 (s, 3H), 3.92 (m, 4H), 5.72 (t, 1H, J 4.0), 7.30 and 7.90 (d, 1H, J 8.0 each).

A solution of 7 (11.07 g, 24 mmol) and $NaBH_3CN$ (6.05 g, 96 mmol) in a mixture of N,N-dimethylformamide (DMF)(30 ml) and sulfolane (30 ml) was heated at 110 °C with stirring. p-Toluenesulfonic acid (3.37 g, 19.6 mmol) was added to the solution in small portions over 4 h. After cooling, the mixture was poured into water, and extracted with ether. The combined extracts were washed successively with water and brine and dried. The residue obtained after evaporation was purified by column chromatography on 60 g of silica gel (1:1 ether-hexane) to furnish 8 (3.89 g, 58%) as colorless needles, mp 43-44 °C, IR (KBr) 1715 $cm^{-1}$; $^1H$ NMR 1.05 and 1.15 (s, 3H each), 1.0-2.2 (m, 8H), 2.40 (br d, 2H), 3.67 (s, 3H), 3.90 (s, 4H), 5.67 (t, 1H, J 4.0). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.80; H, 8.78.

**8a-Hydroxymethyl-5,5-dimethyl-1,5,6,7,8,8a-hexahydro-2(3H)-naphthalenone 2-ethylene acetal (9).** A suspension of 8 (1.241 g, 4.4 mmol) and $LiAlH_4$ (420 mg, 11.1 mmol) in anhydrous 1,2-dimethoxyethane (DME)(55 ml) was stirred at room temperature for 1 h, and then at 60 °C for 10 h. After cooling in an ice-bath, the excess reagent was decomposed with wet ether and a small quantity of water. The content was poured into aqueous NaOH and the product was extracted with ether, and then the combined extracts were dried over $Na_2SO_4$ containing a small amount of $Na_2CO_3$.

Evaporation left a viscous oil, and after filtration through a short silica gel column (1:1 ether-hexane) afforded **9** (1.018 g, 91%) as colorless needles, mp 38-40 °C, IR (KBr) 3400 $cm^{-1}$, $^1H$ NMR 1.09 and 1.15 (s, 3H each), 1.0-2.0 (m, 8H), 2.40 (d, 2H, J 4.0), 3.4-3.9 (m, 3H), 3.95 (m, 4H), 5.55 (t, 1H, J 4.0). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.07; H, 9.41.

**8a-Methoxymethyl-5,5-dimethyl-1,5,6,7,8,8a-hexahydro-2(3H)-naphthalenone 2-ethylene acetal (10).** A 50% suspension of NaH in mineral oil (1.30 g, 27.0 mmol) was washed with pentane, and DME (30 ml) was added. A solution of **9** (3.189 g, 12.7 mmol) in DME (10 ml) was added to the above suspension with stirring and the resulting mixture was warmed at 60 °C for 1 h. After cooling to room temperature, methyl iodide (4.56 g, 32.1 mmol) was added and stirring was continued for an additional 15 h. The mixture was poured into water and extracted with ether. The combined extracts were washed successively with water and brine and dried. Removal of the solvent left an oil, whose filtration through a short silica gel column (1:1 ether-hexane) gave **10** (3.26 g, 97%) as colorless needles, mp 52-54 °C, IR (KBr) 1100 $cm^{-1}$, $^1H$ NMR 1.10 and 1.15 (s, 3H each), 0.9-2.9 (m, 10H), 3.33 (s, 3H), 3.50 and 3.63 (d, 1H, J 10.0 each), 3.95 (m, 4H), 5.55 (t, 1H, J 4.0). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.48; H, 10.17.

**8a-Methoxymethyl-5,5-dimethyl-1,5,6,7,8,8a-hexahydro-2(3H)-naphthalenone (11a).** A mixture of **10** (9.718 g, 36.5 mmol) and p-toluenesulfonic acid (30 mg) in acetone (50 ml) was stirred at room temperature for 3 h. The solvent was mostly removed in vacuo and the oily residue was diluted with ether. The solution was washed successively with aqueous $NaHCO_3$, water, and brine, and then dried. Concentration followed by filtration of the residue through a short silica gel column (3:1 hexane-ether) provided oily **11a** (8.055 g, 99%), IR (liquid) 1725 $cm^{-1}$, $^1H$ NMR 1.13 and 1.20 (s, 3H each), 0.8-2.0 (m, 6H), 2.19 and 2.41 (d, 1H, J 14 each), 2.83 (d, 2H, J 4), 3.20 (s, 3H), 3.15 and 3.53 (d, 1H, J 10 each), 5.70 (t, 1H, J 4). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.76; H, 9.73.

**8aα-Methoxymethyl-5,5-dimethyl-4aα,5,6,7,8,8a-hexahydro-2(1H)-naphthalenone (12) and dimer 14.** A solution of **11a** (2.736 g, 12.32 mmol) and p-toluenesulfonic acid (1.06 g, 6.16 mmol) in methanol (20 ml) was warmed at 65 °C with stirring for 15 h. The solvent was mostly evaporated in vacuo and the oily residue was diluted with ether. The ether solution was washed successively with aqueous $NaHCO_3$, water and brine, and then dried. Filtration and concentration of the filtrate provided an oil, whose analysis by gas chromatography (10% SE-30 column, 2 m x 1 mm; vaporizer, 240 °C; column temperature, 180 °C; He flow, 1 kg/$cm^2$) showed two peaks (1:4 in area) due to **11a** and **12** with retention times 2.5 and 3.6 min, respectively. Purification of the oil by column chromatography on 75 g of silica gel (2:1 hexane-ether) gave **11a** (410 mg) and **12** (1.607 g, 59%) as a colorless oil; IR (liquid) 1675, 1616 $cm^{-1}$, $^1H$ NMR 0.90 and 1.10 (s, 3H each), 1.0-1.8 (m, 6H), 2.00 and 2.68 (d, 1H, J 18), 2.25 (br d, 1H, J 5.7), 2.95 and 3.19 (d, 1H, J 10.0), 3.28 (s, 3H), 6.10 (dd, 1H, J 10.3 and 1.0), 6.95 (dd, 1H, J 10.3 and 5.7). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.75; H, 9.69.

On longer warming (1-2 days) of a similar solution of **11a** gave **14** as crystals from polar fractions on silica gel chromatography (2:1 ether-hexane), mp 151-153 °C; IR (KBr) 1705, 1660, 1620 $cm^{-1}$, $^1H$ NMR 0.8 (s, 3H), 0.9 (s, 6H), 1.07 (s, 3H), 1.2-2.4 (m, 2H), 2.75-3.58 (m, 4H), 3.17 and 3.30 (s, 3H each), 6.80 (d, 1H, J 3); MS, m/z 444 ($M^+$). Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.63; H, 9.97. Found: C, 75.54; H, 10.43.

**By-product 13.** A mixture of **8** (915 mg, 3.27 mmol), $LiAlH_4$ (248 mg, 7.6 mmol) and THF (7 ml) was stirred at 60 °C for 15 h. After cooling, the excess reducing agent was destroyed by the addition of wet ether followed by a small amount of water. Solids were collected by filtration and washed with ether. The combined filtrates were washed successively with water and brine, and dried. Concentration and subsequent separation of the oily residue by column chromatography on 50 g of silica gel (1:1 ether-hexane) provided **9** (500 mg) and **13** (300 mg) slightly contaminated with **9**. **13**, IR (liquid) 3400 $cm^{-1}$, $^1H$ NMR 1.10 and 1.15 (s, 3H each), 1.30-2.5 (m, 8H), 2.98 (br s, 1H, OH), 3.40-4.16 (m, 6H), 5.50 (t, 1H, J 3.4). The oil was used in the next reaction without further purification.

**5,5-Dimethyl-8a-hydroxymethyl-1,5,6,7,8,8a-hexahydro-2(3H)-naphthalenone (11b).** A mixture of **13** (165 mg), 0.5 M HCl (1 ml) and THF (5 ml) was stirred at 40 °C for 3 h and then dilute brine was added. Extraction with $CH_2Cl_2$ and subsequent concentration of the extracts left an oil. Purification by TLC (1:1 ether-hexane) gave **11b** (95 mg, 70%) as colorless needles, mp 125-126 °C; IR (KBr) 3350, 1715 $cm^{-1}$, $^1H$ NMR 1.12 (s, 3H), 1.22 (s, 3H), 1.0-1.8 (m, 7H), 2.22 and 2.38 (d, 1H, J 13 each), 2.8-3.0 (m, 2H; changed to 3.40 and 3.72 (d, 1H, J 10.8 each) on the addition of $D_2O$), 3.3-3.8 (m, 2H), 5.88 (t, 1H, J 3.6). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.69; H, 9.64.

**8aα-Methoxymethyl-5,5-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (15).** A mixture of **12** (1.013 g, 4.6 mmol), 10% Pd-C (240 mg), and ethanol (4 ml) was stirred under $H_2$ at room temperature for 15 h and filtered. The residue obtained by evaporation was passed through a short silica gel column (ether) to provide **15** (1.048 g, quantitative) as a colorless oil; IR (liquid) 1710 $cm^{-1}$, $^1H$ NMR 1.03 and 1.08 (s, 3H each), 1.2-1.8 (m, 6H), 1.8-2.8 (m, 7H), 3.00 and 3.10 (d, 1H, J 10.0 each), 3.28 (s, 3H). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.75. Found: C, 74.97; H, 10.72.

**8aα-Methoxymethyl-5,5-dimethyl-3,4,4aβ,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (16).** A mixture of **11a** (113 mg, 0.5 mmol), 10% Pd-C (22 mg) and ethanol (3 ml) was stirred under $H_2$ at room temperature for 15 h. Filtration followed by evaporation left an oil (112 mg), whose analysis by gas chromatography (10% SE-30, 2 m x 1 mm; vaporizer, 240 °C; column temperature, 190 °C; He flow, 1 kg/$cm^2$) indicated two peaks (1:4) due to **15** and **16** with retention times 2.6 and 3.0 min, respectively. Purification by TLC (1:9 ether-hexane) gave **15** (17 mg) and **16** (70 mg); IR (liquid) 1710 $cm^{-1}$, $^1H$ NMR 0.98 and 1.06 (s, 3H each), 1.2-2.6 (m, 13H), 3.21 (s, 3H), 3.42 (br s, 2H). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.75; H, 10.51.

**1α,8aα-Methano-5,5-dimethyl-1,4,4aα,5,6,7,8,8a-octahydro-2(3H)-naphthalenone (20).** To a

stirred solution of **15** (92 mg, 0.4 mmol) and $ZnCl_2$ (148 mg, 1.1 mmol) in ether (10 ml) was slowly bubbled a stream of dry HCl at room temperature for 3 h. The reaction mixture was poured into ice-water and extracted with ether. The combined extracts were successively washed with 5% $NaHCO_3$, water and brine, and then dried ($Na_2SO_4$). Evaporation left an oil, which was purified by TLC (1:9 ether-hexane) to provide **19** (68 mg, 73%) as a colorless oil; IR (liquid) 1710, 725 $cm^{-1}$; $^1H$ NMR 1.12 (s, 6H), 0.9-1.9 (m, 8H), 2.2-2.8 (m, 5H), 3.35 and 3.45 (d, 1H, J 10.0 each). Without further purification, the oil was used in the next reaction.

A mixture of **19** (68 mg, 0.3 mmol), 50% NaH dispersion in mineral oil (30 mg) and THF (3 ml) was stirred in an ice-water bath for 1 h and at room temperature for an additional 3 h, and then poured into ice-water. The product was extracted with ether and the combined extracts were washed with brine, and then dried ($Na_2SO_4$). Concentration and subsequent purification of the oily residue by TLC (1:4 ether-hexane) furnished **20** (42 mg, 74%) as colorless plates, mp 49-50 °C; IR (KBr) 1690, 900 $cm^{-1}$; $^1H$ NMR 0.83 and 0.98 (s, 3H each), 0.6-1.10 (m, 2H), 1.2-2.5 (m, 12H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 79.93; H, 10.40.

**Reductive cleavage of 20.** To a stirred liquid $NH_3$ (50 ml) was added small pieces of Li wire (50 mg, 7.2 mg atom) followed by a solution of **20** (127 mg, 0.7 mmol) in ether (10 ml). After stirring had been continued for an additional 1 h, the reaction was quenched by the addition of saturated $NH_4Cl$. Removal of the liquid $NH_3$ left an oil, which was dissolved in ether. The ether solution was washed successively with water and brine, and dried. Evaporation and subsequent purification of the residue by TLC (1:4 ether-hexane) gave **17** (75 mg, 58%) as colorless needles, mp 54-56 °C. The IR and $^1H$ NMR spectra of **17** were identical with those of an authentic sample.[12]

**1ξ-Hydroxymethyl-8aα-methoxymethyl-5,5-dimethyl-4aα,5,6,7,8,8a-hexahydro-2(1H)-naphthalenone (21) and 8aα-methoxymethyl-5,5-dimethyl-1-methylene-4aα,5,6,7,8,8a-hexahydro-2(1H)-naphthalenone (22).** (a) To a stirred solution of diisopropylamine (2.331 g, 23.03 mmol) in DME (70 ml) at -78 °C was added dropwise a 1.5 M solution of butyllithium in hexane (14.3 ml, 21.36 mmol). The bath was replaced by an ice bath and the mixture was stirred for 30 min, then recooled at -78 °C. A solution of **12** (3.654 g, 16.46 mmol) in DME (10 ml) was added dropwise and the reaction temperature was gradually raised to -45 °C over 15 h, and then recooled to -78 °C. Gaseous formaldehyde, generated by heating paraformaldehyde (ca. 3 g) at 160-170 °C, was passed through the well-stirred mixture by means of a stream of dry $N_2$ over 40 min. The reaction was quenched by the addition of aqueous $NH_4Cl$ and the product was extracted with ether. The combined extracts were washed successively with water and brine, and dried. Filtration and evaporation of the filtrate afforded an oil, which was chromatographed on 40 g of silica gel (1:1 ether-hexane) gave **21** (2.516 g, 61%) as a colorless oil and **22** (798 mg, 21%) as needles, mp 97-98 °C. **27**, IR (liquid) 3400, 1665 $cm^{-1}$; $^1H$ NMR 0.95 and 1.10 (s, 3H each), 1.2-1.9 (m, 6H), 2.30 (br d, 1H, J 6), 2.9-3.1 (m, 2H), 3.15 (s, 3H), 3.5-3.8 (m, 3H), 6.10 (dd, 1H, J 10 and 2), 6.90 (dd, 1H, J 10 and 6). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.01; H, 9.55. **22**, IR (KBr) 1670, 1600, 880 $cm^{-1}$; $^1H$ NMR 0.75 and 1.00 (s, 3H each), 0.9-2.3 (m, 6H), 2.40 (br d, 1H, J 6.0), 2.80 and 3.30 (d, 1H, J 10 each), 3.23 (s, 3H), 5.43 and 6.30 (br s, 1H each), 6.26 (br d, 1H, J 10), 6.97 (dd, 1H, J 10 and 6.0). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.65; H, 9.74.

(b) To a stirred LDA solution, prepared from 1.5 M butyllithium in hexane (0.64 ml, 0.95 mmol) and diisopropylamine (102 mg, 0.95 mmol) in DME (4 ml) according to the same procedure as above, was added dropwise a solution of **12** (200 mg, 0.95 mmol) in DME (3 ml) at -78 °C and stirring was continued for an additional 1 h at -40 °C, and then recooled to -78 °C. A solution of triethylamine (40 mg, 0.4 mmol) in DME (1 ml) was added to a solution of trimethylsilyl chloride (198 mg, 1.8 mmol) in DME (1 ml) and precipitates thereby formed were removed by a centrifuge. The solution was added dropwise to the reaction mixture prepared above. The whole was stirred in an ice bath for 1 h, and the reaction was quenched by the addition of 10% $NaHCO_3$. The product was extracted with ether, washed successively with water and brine, and dried. Removal of the solvent in vacuo gave **23** (274 mg, quantitative) as a colorless oil; IR (liquid) 1640, 1580, 1100, 900, 840 $cm^{-1}$; $^1H$ NMR ($CCl_4$) 0.12 (s, 9H), 0.90 (s, 6H), 0.9-2.3 (m, 6H), 2.65 and 2.95 (d, 1H, J 8 each), 3.12 (s, 3H), 4.24 (m, 1H), 5.65 (m, 2H). The oil was used in the next reaction without further purification.

1.4 M Methyllithium in ether (2 ml, 2.8 mmol) was added to a solution of **23** (563 mg, 1.9 mmol) in ether (10 ml). The mixture was stirred at room temperature for 1 h and then cooled to -78 °C. Formaldehyde vapor, generated by heating paraformaldehyde (ca. 2 g) at 160-170 °C, was passed through the mixture by means of a stream of dry $N_2$ over 30 min. Workup by the same manner described in (a) gave an oil, whose preparative TLC (1:1 ether-hexane) afforded **21** (210 mg, 44%) together with a small amount of **22**.

**1ξ-Hydroxymethyl-8aα-methoxymethyl-5,5-dimethyl-3,4,4aα,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (24).** A mixture of **21** (70 mg, 0.3 mmol), 10% Pd-C (13 mg) and ethanol (3 ml) was stirred under $H_2$ at room temperature for 15 h. Workup followed by filtration of an oily residue through a short silica gel column (1:1 ether-hexane) afforded **24** (72 mg, quantitative) as a colorless oil; IR (liquid) 3450, 1700, 1150 $cm^{-1}$; $^1H$ NMR 1.00 and 1.13 (s, 3H each), 1.1-1.8 (m, 8H), 1.9-2.9 (m, 4H), 3.03 (s, 2H), 3.13 (s, 3H), 3.6-4.0 (m, 3H). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.51; H, 10.52.

**8aα-Methoxymethyl-5,5-dimethyl-1-methylene-3,4,4aα,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (25).** A suspension of **24** (60 mg, 0.2 mmol) and basic alumina (830 mg; Brockmann I) in benzene (2 ml) was stirred at room temperature for 10 h. Filtration followed by evaporation left an oil, which was filtered through a short silica gel column (1:1 ether-hexane) to give **25** (56 mg, quantitative) as a colorless oil; IR (liquid) 1690, 1610, 880 $cm^{-1}$; $^1H$ NMR 0.90 and 1.00 (s, 3H each), 1.1-2.7 (m, 11H), 3.05 and 3.15 (d, 1H, J 10.0), 3.27 (s, 3H), 5.35 and 6.15 (d, 1H, J 2 each). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.04; H, 10.34.

**6,6-Dimethyl-3-oxo-2,2aξ,3,4,5,5a,6,7,8,9,9a,10-dodecahydronaphtho[1,8a-c]furan (26).** A

solution of **24** (72 mg, 0.3 mmol) and p-toluenesulfonyl chloride (114 mg, 0.6 mmol) in pyridine (2 ml) was stirred at room temperature for 1 day and then poured into ice-water. The product was extracted with ether and the combined extracts were washed successively with aqueous $CuSO_4$, water, and brine and dried. Removal of the solvent followed by purification by TLC (1:2 ether-hexane) provided **26** (60 mg, 95%) as colorless plates, mp 72-73 °C; IR (KBr) 1690 $cm^{-1}$; $^1H$ NMR 0.93 and 0.96 (s, 3H each), 1.1-2.6 (m, 12H), 2.9-4.3 (m, 4H), MS m/z 222 (M ). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.60; H, 9.61.

**Treatment of 24 with pyridinium chloride.** A mixture of **24** (70 mg, 0.27 mmol), pyridinium chloride (80 mg) and $CH_2Cl_2$ (2 ml) was stirred at room temperature for 1 day, and then washed with brine, and dried. Evaporation followed by purification of the residue by TLC (2:3 ether-hexane) gave **25** (40 mg, 63%) and recovered **24** (17 mg) as identified spectroscopically.

**2α-Hydroxy-1ξ-hydroxymethyl-8aα-methoxymethyl-2β,5,5-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (30).** A mixture of **24** (1.00 g, 3.94 mmol), dihydropyran (662 mg, 7.88 mmol), and pyridinium tosylate (20 mg) in $CH_2Cl_2$ (10 ml) was stirred at room temperature for 15 h. The mixture was washed with brine and dried ($Na_2SO_4$), and then concentrated in vacuo. An oily residue was chromatographed on 40 g of silica gel (1:2 ether-hexane) to give **28** (1.183 g, 89%) as a colorless oil; IR (liquid) 1710, 1120 $cm^{-1}$; $^1H$ NMR 1.06 and 1.20 (s, 3H each), 1.25-2.5 (m, 18H), 2.8-4.5 (m, 6H), 3.20 (s, 3H), 4.58 (br s, 1H). The oil was used in the next reaction without further purification.

A solution of 1.5 M methyllithium in ether (7 ml, 10.5 mmol) was added to a solution of **28** obtained above in ether (10 ml) in an ice-water bath. The mixture was stirred at 0 °C for 5 h and then at room temperature for an additional 3 h. The reaction was quenched by the addition of aqueous $NH_4Cl$. The product was extracted with ether and the combined extracts were washed successively with water and brine, and dried ($Na_2SO_4$). Removal of the solvent left a viscous oil, whose filtration through a short silica gel column (1:1 ether-hexane) provided **29** (1.251 g, 99%) as a viscous oil; IR (liquid) 3450 $cm^{-1}$; $^1H$ NMR 0.95 and 1.02 (s, 3H each), 1.25 (s, 3H), 1.2-2.1 (m, 19H), 3.25 (s, 3H), 3.0-4.4 (m, 6H), 4.55 (br s, 1H). The oil was submitted to the next reaction.

A solution of the above oil **29** and pyridinium tosylate (20 mg) in ethanol (5 ml) was warmed at 50 °C for 4 h with stirring. The solvent was mostly removed in vacuo and the oily residue was chromatographed on 40 g of silica gel (2:1 ether-hexane) to give **30** (952 mg, quantitative) as a colorless oil; IR 3350 $cm^{-1}$; $^1H$ NMR 0.90 and 1.04 (s, 3H each), 1.1-2.5 (m, 12H), 1.32 (s, 3H), 2.85 and 3.09(d, 1H, J 9 each), 3.33 (s, 3H), 4.0 (m, 2H), 4.93 (br s, 2H). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.29; H, 11.19.

**1α-Formyl-2α-hydroxy-8aα-methoxymethyl-2β,5,5-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthalene (31).** To a stirred suspension of pyridinium chlorochromate (881 mg, 4.07 mmol) in $CH_2Cl_2$ (8 ml) at room remperature was added a solution of **30** (647 mg, 2.40 mmol) in the same solvent (2 ml) and stirring was continued for an additional 3 h. The mixture was filtered through a short silica gel column (ether) and the filtrate was concentrated in vacuo to leave an oil which was mostly solidified. Chromatagraphy of the solid on 35 g of silica gel (1:1 ether-hexane) gave **31** (512 mg, 80%) as colorless needles, mp 102-103.5 °C; IR (KBr) 3400, 2750, 1700 $cm^{-1}$; $^1H$ NMR 1.02 and 1.06 (s, 3H each), 1.05-2.2 (m, 11H), 1.30 (s, 3H), 2.45 (d, 1H, J 3), 3.27 (s, 3H), 3.30 and 3.80 (d, 1H, J 9 each), 3.75 (br s, 1H), 9.96 (d, 1H, J 3). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.51; H, 10.34.

**(2,6-Dimethoxy-4-methyl)phenyl-1-(8aα-methoxymethyl-2β,5,5-trimethyl-1,2,3,4,4aα,5,6,7,8,8a-decahydronaphthyl)methanol (32).** A solution of 1.5 M butyllithium in ether (13.5 ml, 20.26 mmol) was added to a solution of orcinol dimethyl ether (3.272 g, 21.53 mmol) in DME (20 ml) at -78 °C with stirring. The cooling bath was removed and stirring was continued at room temperature for 30 min, and then the mixture was recooled to -78 °C. A solution of **31** (679 mg, 2.53 mmol) in DME (10 ml) was added to the above mixture, and the whole was stirred for 2 h and then warmed to room temperature over 3 h. The mixture was quenched with wet ether and water, and extracted with ether. Evaporation of the solvent left an oil, whose analysis by TLC (1:1 ether-hexane) indicated two spots with $R_f$ 0.33 for the major and 0.28 for the minor. The oil was chromatographed on 70 g of silica gel (1:1 ether-hexane) provided **32** (893 mg, 84%) as a semisolid. A pure sample of the major was obtained as needles by recrystallization from ether, mp 152-153 °C; IR (KBr) 3400, 1608, 1580 $cm^{-1}$; $^1H$ NMR 0.98 and 1.05 (s, 3H each), 1.0-2.0 (m, 12H), 1.30 (s, 3H), 2.33 (s, 3H), 3.37 (s, 3H), 3.82 (s, 6H), 3.53 and 3.87 (d, 1H, J 10 each), 4.90 (d, 1H, J 6), 5.33 (s, 1H), 5.70 (dd, 1H, J 6 and 4), 6.35 (s, 2H). Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.12; H, 9.44.

**3β,6,6-Trimethyl-3α-hydroxy-2β-(2,6-dimethoxy-4-methyl)phenyl-2α,2aβ,3,4,5,5aα,6,7,8,9,9a,-10-dodecahydronaphtho[1,8a-c]furan (33).** (a) Pyridinium chloride (258 mg, 2.24 mmol) was added to a solution of **32** (856 mg, 2.04 mmol) in $CH_2Cl_2$ (25 ml) and the mixture was stirred at room temperature for 1 h. Removal of the solvent in vacuo left a semisolid, which was filtered through a short silica gel column (ether) to give **33** (620 mg, 78%) as crystals. An analytically pure sample was obtained by recrystallization from 1:3 ether-hexane, mp 167-168 °C; IR (KBr) 3400, 1610, 1580, 1120, 810 $cm^{-1}$; $^1H$ NMR 0.93 and 0.96 (s, 3H each), 1.0-2.0 (m, 12H), 1.03 (s, 3H), 2.17 (d, 1H, J 10), 2.33 (s, 3H), 3.72 and 4.14 (d, 1H, J 9 each), 3.81 (s, 6H), 5.37 (d, 1H, J 10), 6.39 (s, 2H). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.41; H, 9.41.

(b) A mixture of **32** (42 mg, 0.1 mmol), $TiCl_4$ (35 mg, 0.18 mmol) and $CH_2Cl_2$ (1 ml) was stirred at -60 ° C for 1.5 h and the reaction was quenched with aqueous $NaHCO_3$. The product was extracted with ether and the combined extracts were washed with brine, and dried ($Na_2SO_4$). An oil obtained by concentration was purified by TLC (1:1 ether-hexane) to afford crystals (28 mg, 72%), whose IR and $^1H$ NMR were identical with those of **33** prepared above.

**3β,6,6-Trimethyl-3α-hydroxy-2β-(2-hydroxy-4-methyl)phenyl-2α,2aβ,3,4,5,5aα,6,7,8,9,9a,10-dodecahydronaphtho[1,8a-c]furan (34).** A solution of **33** (606 mg, 1.56 mmol) and sodium ethylthiolate (1.180 g, 14.06 mmol) in DMF (15 ml) was stirred at 100-110 °C for 4.5 h. After cool-

ing, the solution was concentrated to ca. two-thirds in vacuo on warming. The residue was diluted with water and extracted with $CH_2Cl_2$. The combined extracts were washed successively with water and brine, and dried ($Na_2SO_4$). Evaporation and purification of the oily residue by column chromatography on silica gel (1:1 ether-hexane) gave **34** (510 mg, 87%) as crystals, mp 185-186 °C, together with a small amount of starting **33**. **34**: IR (KBr) 3500, 3300, 1620, 1590 $cm^{-1}$; $^1H$ NMR 0.87 and 0.95 (s, 3H each), 1.0-2.0 (m, 12H), 1.05 (s, 3H), 2.28 (s, 3H), 2.59 (s, 1H), 3.50 and 4.25 (d, 1H, J 9 each), 3.83 (s, 3H), 5.13 (d, 1H, J 10), 6.27 and 6.40 (s, 1H each), 8.34 (s, 1H). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.71; H, 9.43.

**Conversion of 34 into siccanochromene E methyl ether (35).** A suspension of **34** (1.267 mg, 3.34 mmol) in 1-nitropropane (30 ml) was gently warmed until completely dissolved. After cooling to -25 °C, concentrated sulfuric acid (10 l) was added to the solution and the whole was warmed to room temperature over 3 h, and stirring was continued for an additional 2 h. The mixture was poured into water and products were extracted with $CH_2Cl_2$. The combined extracts were washed successively with water and brine and dried. Evaporation left an oil, which was purified by TLC (2:1 ether-hexane) provided **35** (514 mg, 43%) as needles, mp 144-145 °C, which was identified by comparison of mobility in TLC and of the IR and $^1H$ NMR spectra with those of the authentic compound.[22] From less polar fractions, small amount of two unidentified products were separated.

**Conversion of siccanochromene E methyl ether (35) into siccanin methyl ether (36).** (a) $BF_3$ etherate (0.5 µl) was added to a solution of **35** (40 mg, 0.11 mmol) in $CH_2Cl_2$ (2 ml). The mixture was stirred at room temperature for 6 h, and washed successively with water and brine, and then dried. Evaporation of the solvent left an oil which was purified by TLC (2:1 ether-hexane) to give **36** (8 mg, 22%) as needles, mp 134-135 °C, along with recovered **35** (4 mg). Mobility in TLC and the IR and $^1H$ NMR spectra of the product were identical with those of authentic **36**.[4b]

(b) A mixture of **35** (85 mg, 0.24 mmol), $SnCl_4$ (0.5 µl) and benzene (2 ml) was stirred at room temperature for 10 h. Workup in the same manner as described in (a) and subsequent purification by TLC (2:1 ether-hexane) gave **36** (19 mg, 22%) along with recovered **35** (10 mg).

**Treatment of 34 with stannic chloride.** A solution of **34** (122 mg, 0.33 mmol) and $SnCl_4$ (10 µl) in benzene (5 ml) was stirred at room temperature for 11 h. The mixture was washed successively with water and brine, and dried. Removal of the solvent left a semisolid, which was chromatographed on 25 g of silica gel (1:1 ether-hexane) to give a solid (24 mg). $^1H$ NMR indicated the solid to be a mixture of **35** and **36** in a ratio of 5:1. The solid was separated by TLC (1:4 ether-hexane) on three repetitions to provide **35** (15 mg) and **36** (3 mg).

**Treatment of 34 with boron trifluoride etherate.** A mixture of **34** (40 mg, 0.11 mmol), $BF_3$ etherate (0.5 µl) and $CH_2Cl_2$ (4 ml) was stirred at room temperature for 9 h. Workup gave a solid (9 mg), whose analysis by $^1H$ NMR showed it to be a mixture of **35** and **36** in a ratio of 4.5:1.

**dl-Siccanin (1).** A mixture of **36** (51 mg, 0.14 mmol), sodium ethylthiolate (110 mg) and DMF (1 ml) was heated at 100 °C for 3 h with stirring. After cooling, water was added and the product was extracted with $CH_2Cl_2$. The combined extracts were washed successively with water and brine, and dried. Concentration in vacuo provided **dl-1** (48 mg, quantitative) as crystals. Recrystallization from methanol gave pure **dl-1** as needles, mp 154-155 °C. Spectral date (IR, $^1H$ NMR) and behavior in TLC were all identical with those of the natural specimen.

**dl-Siccanochromene E (2).** A mixture of **35** (71 mg, 0.2 mmol), dihydropyran (34 mg, 0.4 mmol), a trace of pyridinium tosylate and $CH_2Cl_2$ (2 ml) was warmed at 50 °C with stirring. After workup in the usual manner, removal of the solvent and purification of the oily residue by TLC (1:2 ether-hexane) gave **37** (87 mg, 99%) as an oil: $^1H$ NMR 0.97 and 1.02 (s, 3H each), 1.37 and 1.40 (s each, 3H in total), 1-2.2 (m, 17H), 2.26 (s, 3H), 3.0-3.9 (m, 5H), 3.82 (s, 3H), 4.53 (br, 1H), 6.24 and 6.28 (s, 1H each), 6.61 (s, 1H). The oil was used in the next reaction without further purification.

A mixture of **37** (80 mg, 0.18 mmol), sodium ethylthiolate (135 mg, 1.63 mmol) and DMF (1.5 ml) was heated at 100-110 °C for 4 h with stirring. Workup in the usual manner followed by purification of the oil obtained by TLC (1:1 ether-hexane) gave **38** (54 mg, 70%) as a colorless oil along with a small amount of starting **37**. **38**: $^1H$ NMR 0.98 and 1.02 (s, 3H each), 1.37 and 1.41 (s each, 3H in total), 1-2.2 (m, 17H), 2.21 (s, 3H), 3.0-4.0 (m, 4H), 4.35 (br, 1H), 5.48 (br s, 1H), 6.18 and 6.23 (s, 1H each), 6.57 (s, 1H). The oil was used in the next reaction without further purification.

A mixture of **38** (54 mg, 0.13 mmol), a trace of pyridinium tosylate and ethanol (1 ml) was warmed at 50 °C for 15 h with stirring. The solvent was mostly removed in vacuo and the resulting oil was purified by TLC (3:1 ether-hexane) to give **dl-2** (40 mg, 93%) as crystals, mp 114-115 °C. **2** was identified by comparison of behavior in TLC and of the IR and $^1H$ NMR spectra with those of an authentic sample.

**X-ray study of 33.** Colorless crystals with the sizes of 0.20 x 0.20 x 0.25 mm were used for the study, and the intensity data were measured on a Rigaku Denki four circle diffractometer (AFC-3) with graphite monochomated Cu-Kα radiation ($\lambda$ =1.5418 Å). The crystals belong to the monoclinic space group $P2_1/n$ and the cell dimensions are a=23.656(2), b=15.668(2), c=12.062(1) Å and β =96.21 (1), and $\rho_{calcd}$=1.22 g/cm$^3$ for z=8 (Mr; 388.53). A total of 5916 independent reflections up to 2θ =128 were collected and corrected for the Lorenz and polarization effect but not for the absorption. The structure was solved by the direct method and the successive weighted Fourier techniques using the program MULTAN80. The non-hydrogen atoms were initailly allowed to refine isotropically and then anisotropically by the block-diagonal least-squares method. No attempt to locate the hydrogen atoms was made since the difference map contained no distinct peaks in the geometrically reasonable positions. The final R value is 0.09 ($R_w$=0.11) for 3420 reflections with $F_o > 2(F_o)$ used in the refinement. The crystal data, listing of final atomic coordinates, anisotropic temperature factors, bond lengths together with the estimated standard derivations, and listing of final Fo-Fc, have deposited with the Cambridge Crystallographic Data Centre.

**References and Notes**

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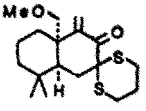


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(19) Direct methylation of **24** with methyllithium resulted in recovery of the starting material owing to complete precipitation of the lithium alkoxide formed.

(20) The stereochemistry of C(8) in **29** and C(9) in **31** was concluded from the unambiguously assigned stereochemistry of **33** (vide post).

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