1,3-Diol Fragmentation Using a Reactive Benzylic Hydroxyl Group as a Nucleofuge. Synthesis of a Tobacco Sesquiterpene

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A benzylic hydroxyl group activated by electron-donative aromatic function was found to be a remarkably reactive nucleofuge for 1,3-diol fragmentation. Thus, treatment of α-(2,6-dimethoxy-4-methylphenyl)-2β-hydroxy-2α,5,5,8aβ-tetramethyl-4aα-decahydro-1β-naphthalenemethanol with pyridinium chloride or pyridinium *p*-toluenesulfonate in dichloromethane underwent the 1,3-diol fragmentation smoothly to produce *r*-1-[(*E*)-2-(2,6-dimethoxy-4-methylphenyl)ethenyl]-*t*-2-(3-oxobutyl)-1,3,3-trimethylcyclohexane (**24**) in quantitative yield. Starting from **24**, a tobacco sesquiterpene, 4-(2,2,6-trimethyl-6-vinylcyclohexyl)-2-butanone, was synthesized in racemic form by seven steps.

As one of C–C bond cleavage reactions, fragmentation reaction has been extensively utilized in structural elucidation and synthetic study in the natural product chemistry.[1] On the C(2)–C(3) bond cleavage in 1,3-diol i by fragmentation reaction, a primary hydroxyl group itself is generally less effective as a nucleofuge,[2] as can be judged from the consideration that the more stable a carbonium ion formed is, the easier the 1,3-diol fragmentation reaction occurs. When the diol i is converted to the corresponding benzyl alcohol ii possessing a phenyl group (Ar) substituted by electron-donative groups at ortho and para positions, the benzylic hydroxyl group in ii eliminates easily to give a stable carbonium ion, and therefore, the fragmentation reaction would proceed, to our expectation, providing the desired product iii.

The above conception was founded on the following observation made earlier in the course of our synthetic study on siccanin,[3] an antibiotic mold metabolite. We examined deprotection of the tetrahydropyranyl(THP) ether **1**. Under mild hydrolytic conditions (AcOH–THF–H_2O), well-known for cleavage of THP ethers,[4] not only deprotection of **1** but also concomitant 1,3-diol fragmentation proceeded smoothly to give olefinic ketone **2** in quantitative yield.[5] Surprisingly, treatment of **1** with pyridinium *p*-toluenesulfonate (PPTS) in ethanol also provided **2** in almost quantitative yield.[5] Moreover, oxidation of benzyl alcohol **3** with pyridinium chlorochromate in dichloromethane (CH_2Cl_2) furnished a ring-opened product **4** as one of the products. The olefin **4** could be accounted for by fragmentation, when presuming that a chromate ester group initially formed at the benzylic position of **3** would act as a nucleofuge.[5] These results indicate that generation of a carbonium ion assisted by electron-donative aromatic function causes the remarkably facile 1,3-diol fragmentation of this type. We wish to describe here results of our studies on the 1,3-diol fragmentation using a reactive benzylic hydroxyl group as a nucleofuge, and its application to the synthesis of (±)-4-(2,2,6-trimethyl-6-vinylcyclohexyl)-2-butanone (**5**),[6] a seco-sesquiterpene isolated from sun-cured Greek tobacco, *Nicotiana tabacum* L.[7]

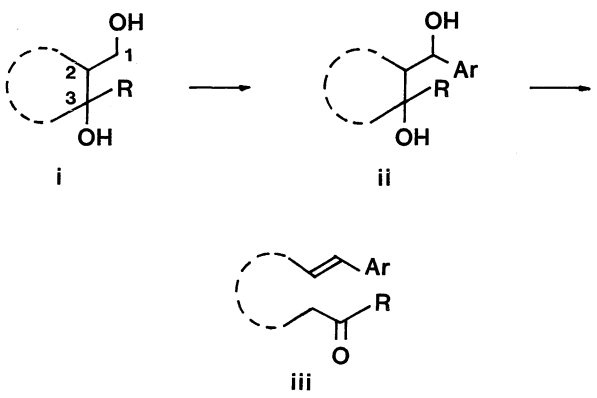


Fig. 1.

Results and Discussion

Our key compound selected for this work was drimane-8β,11-diol (**17**),[8] and its synthesis began with

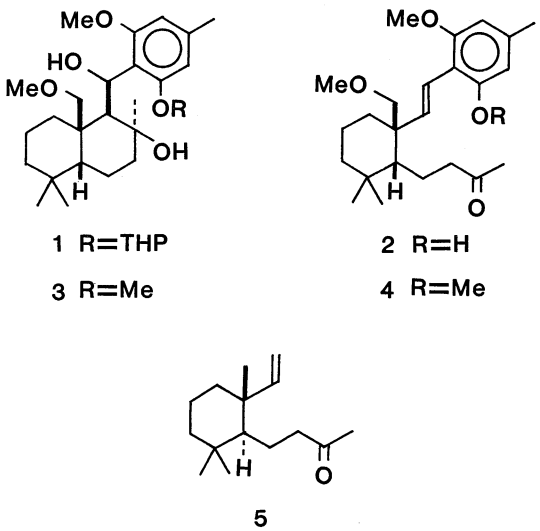


Fig. 2.

protection of the oxo group in the known keto ester **6**[9] (Scheme 1). Acetalization of **6** with ethylene glycol followed by reduction of the resulting ethylenedioxyl ester **7** with lithium aluminium hydride provided crystalline alcohol **8**. Reaction of **8** with PPTS in acetone at 40 °C led to the exclusive formation of hydroxy ketone **9**, whereas treatment of **8** with catalytic *p*-toluenesulfonic acid at room temperature gave a mixture of **9** (45%) and the known enone **18** (32%).[9] Subsequent protection of the hydroxyl group in **9** with 3,4-dihydro-2*H*-pyran gave the THP ether **10** in 73% overall yield from **6**. The compound **10** was also prepared by an alternate route. Hydroxymethylation of the lithium enolate of *trans*-octalone **11**[10] with gaseous formaldehyde under the kinetically controlled conditions occurred stereoselectively from the α-side, affording the α-hydroxymethyl enone **12** in good yield, which was then converted to the corresponding THP ether **13**. Inversion of stereochemistry of the oxygenated side chain in **13** to equatorial configuration was carried out by regioselective deprotonation of **13** with lithium diisopropylamide (LDA) followed by kinetically controlled protonation with 10% citric acid, giving the desired enone **14** and dienone **15** in 45 and 41% yield, respectively. Catalytic hydrogenation of the former **14** afforded **10** in 34% overall yield from **11**. The decalone **10** upon methylation with excess methylmagnesium iodide in ether at −60 °C gave a single alcohol **16**. The stereochemistry of **16** was predicted from the consideration that the Grignard reagent would approach preferentially from the less hindered α face of **10**. This prediction was confirmed as follows. Deprotection of **16** afforded the required diol **17** (mp 133—134 °C) in 86% overall yield from **10**. The physical constants (mp, IR, and ^{1}H NMR) of **17** were identical with those of (±)-drimane-8β,11-diol reported by Pelletier and co-workers.[8]

In order to confirm the consideration mentioned in the beginning, a number of preliminary experiments were undertaken. The diol **17** was treated with pyridinium chloride or PPTS in CH_2Cl_2 at room temperature or under refluxing. However, it was completely recovered unchanged. Hence, **17** was transformed into the tosylate **19**. When **19** was treated with sodium hydride in 1,2-dimethoxyethane (DME) at 60 °C for 15 h, the sole product obtained in 30% yield was the oxetane **20**, and no formation of the fragmentation product, i.e. **5**, was detectable on the careful inspection of the reaction mixture.

At this juncture, we turned our attention to utilization of a reactive benzylic hydroxyl group as a nucleofuge. According to the published procedure,[8] the diol **17** was oxidized by Collins reagent to give the drimanic aldehyde **21** in 47% yield (lit,[8] 42% yield).

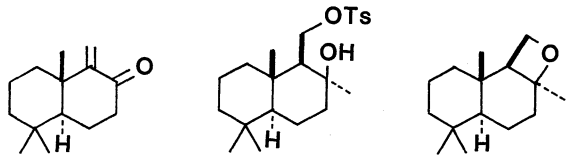
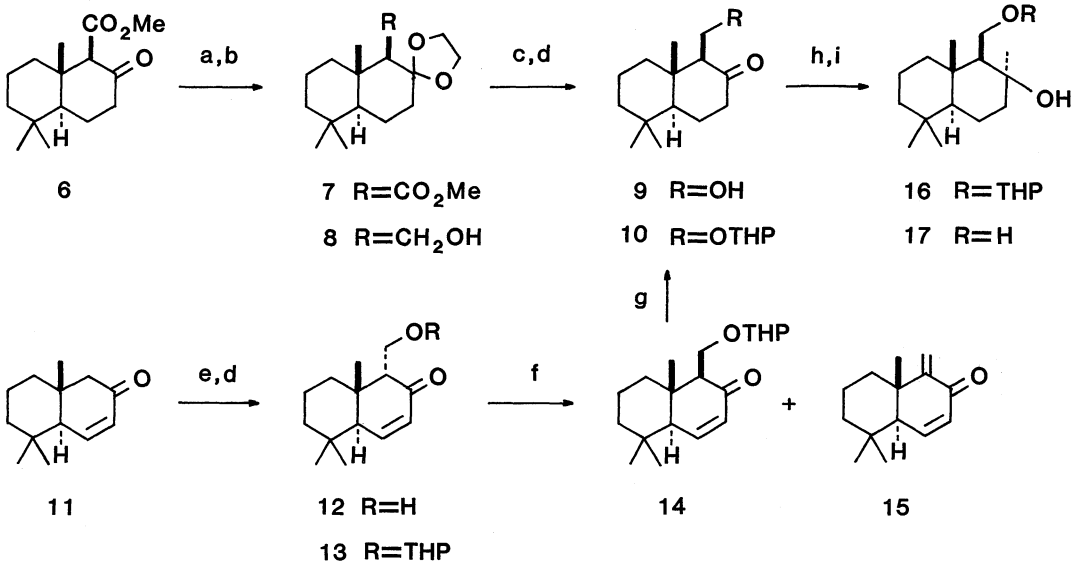
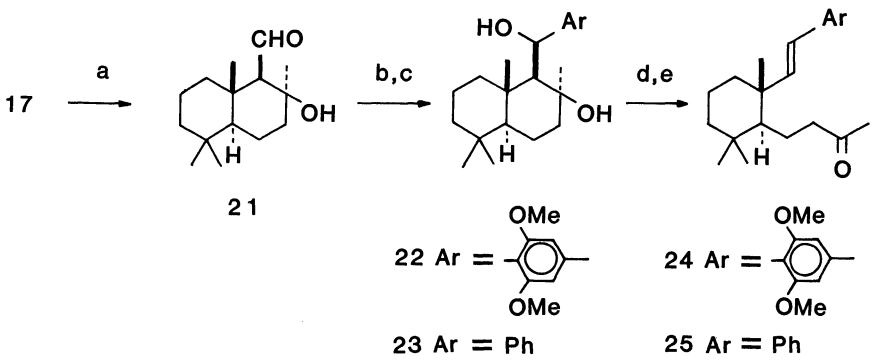


Fig. 3.



Scheme 1. (a) Ethylene glycol, *p*-TsOH, PhH (99%): (b) $LiAlH_4$, THF (69%): (c) PPTS, acetone (96%): (d) DHP, PPTS (quant): (e) LDA, THF, −78 °C, then CH_2O(g) (78%): (f) LDA, THF, −78 °C, then 10% citric acid (45%): (g) H_2, 10% Pd-C, dioxane (95%): (h) MeMgI, Et_2O, −60 °C (94%): (i) PPTS, MeOH (91%).



Scheme 2. (a) NCS, Me_2S, toluene (63%): (b) 1,3-dimethoxy-5-methylbenzene (**26**), BuLi, DME (92%): (c) PhLi, DME (90%): (d) Py·HCl or PPTS, CH_2Cl_2, rt, a few minutes (quant): (e) *p*-TsCl, Py, 60 °C, 2d (58%).

After a few attempts to improve the yield of **21**, it was found that oxidation by Corey–Kim method[11] employing *N*-chlorosuccinimide (NCS) and dimethyl sulfide was more effective to provide crystalline **21** in 63% yield (Scheme 2). For the purpose of constructing a reactive benzyl alcohol moiety, the use of 1,3-dimethoxy-5-methylbenzene (**26**)[12] was deemed most favorable, because its precursor, 5-methyl-1,3-benzenediol(orcinol) monohydrate, was commercially available and moderate in price, and readily convertible to **26** with dimethyl sulfate.[12] The lithium salt prepared from **26** with butyllithium in DME was submitted to condensation with **21**, providing **22** as an epimeric mixture with a minor quantity of one epimer regarding the newly formed hydroxyl group, from which a major epimer **22**[13] was obtained as crystals in 92% yield. For comparison, benzyl alcohol **23**,[13] a major epimer of stereoisomers, was prepared in high yield by treatment of **21** with phenyllithium followed by recrystallization of products. On exposure to pyridinium chloride in CH_2Cl_2 at room temperature, **22** underwent the 1,3-diol fragmentation within a few minutes to afford olefinic ketone **24**[14] in almost quantitative yield. In similar fashion, almost conversion of **22** into **24** was detected on treatment with PPTS. In contrast to **22**, benzyl alcohol **23** was recovered unchanged under the same reaction conditions described above. On prolonged heating of **23** with *p*-toluenesulfonyl chloride in pyridine at 60 °C, a fragmentation product **25** was obtained in 58% yield. The stereochemistry of the double bond in **25** was assigned to be E on the basis of a coupling constant (J=16.2 Hz) of two olefinic protons in the ^1H NMR spectrum. Obviously unsubstituited phenyl group as an activator was insufficient to cause the fragmentation under the above mild conditions, and difference in reactivity observed in the above two types of reactions is dependent on liability to generate a carbonium ion. After all, it was found that 2,6-dimethyoxy-4-methylphenyl function remarkably assists elimination of the benzylic hydroxyl group in the 1,3-diol fragmentation even under the mild conditions. The reaction conditions used here would be practically useful, especially when the substrate is an acid-labile compound.

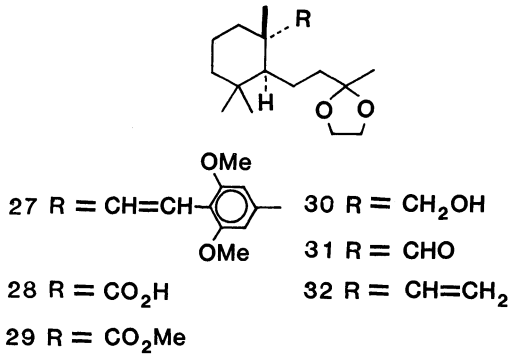


Fig. 4.

As an extension of this study to the natural product synthesis, we envisioned the olefinic ketone **24** to be a resonable intermediate for the synthesis of Tobacco sesquiterpene **5**. Transformation of **24** to **5** was accomplished by a conventional but straightforward sequence of reactions. Acetalization of **24** followed by ozonolysis of the resulting acetal **27** in CH_2Cl_2 directly provided carboxylic acid **28** in 55% overall yield. Esterification of **28** with diazomethane yielded ester **29**. As attempt to reduce the ester **29** with diisobutylaluminium hydride to the corresponding aldehyde **31** failed, **29** was converted to alcohol **30** by lithium aluminium hydride reduction. Collins oxidation of **30** afforded **31** in good yield, and methylenation of the latter with methylenetriphenylphosphorane provided olefin **32**. Finally, deprotection of **32** gave the target molecule (±)-4-(2,2,6-trimethyl-6-vinylcyclohexyl)-2-butanone (**5**), whose physical data (IR and NMR) were identical with those of the natural **5**.[6,15]

Experimental

Melting points are uncorrected. IR spectra were obtained with a JASCO A-3 infrared spectrometer. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer with tetramethylsilane as an internal standard. Dry THF and DME were obtained by distillation over lithium aluminium hydride, and other organic solvents were purified according to the standard procedure. All reactions were carried out under dry N_2 or Ar atmosphere. Extracts obtained on aqueous workup were dried over Na_2SO_4. Column chromatography was performed by using silica gel (Merck, kieselgel 60, 70—230 mesh), and kieselgel GF_{254} was employed for preparative thin-layer chromarography (TLC) as an absorbent. Solvents used for elution are shown in parentheses.

Methyl 2,2-Ethylenedioxy-5,5,8aβ-trimethyl-4aα-decahydro-1β-naphthalenecarboxylate (7). A solution of **6**[9] (1.665 g, 6.61 mmol), ethylene glycol (492 mg, 7.93 mmol), and *p*-toluenesulfonic acid (5 mg) in benzene (70 ml) was refluxed azeotropically for 30 h. After cooling, the mixture was washed successively with aqueous $NaHCO_3$, water, and brine, and dried. Removal of the solvent left a semicrystalline residue, which was filtered through a short silica-gel column with hexane–ether (1:1) to give **7** (1.946 g, 99%) as crystals: Mp 103—104 °C (from hexane–ether); IR (KBr) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.85 and 0.88 (6H in total, s each $C(CH_3)_2$), 1.22 (3H, s, C–CH_3), 0.9—2.0 (12H, m), 3.63 (3H, s, O–CH_3), 3.7—4.15 (4H, m, $O(CH_2)_2O$).

Found: C, 68.77; H, 9.27%. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52%.

2,2-Ethylenedioxy-5,5,8aβ-trimethyl-4aα-decahydro-1β-naphthalenemethanol (8). To a stirred mixture of lithium aluminium hydride (230 mg, 5.97 mmol) in THF (20 ml) wad added a solution of **7** (1.767 g, 5.97 mmol) in THF (2 ml), and the mixture was gently refluxed for 5 h. After cooling, the reaction mixture was quenched by addition of wet ether followed by water, and filtered. The solid was washed with ether, and the combined filtrate and wash were dried. Concentration gave an oil which was chromatographed on silica gel with hexane–ether (1:1) to give **8** (1.103 g, 69%) as crystals: Mp 90—91 °C (from hexane–ether); IR (KBr) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.81, 0.83, and 0.89 (9H, in total, s each, $C(CH_3)_2$ and C–CH_3), 1.0—2.0 (12H, m), 2.95 (1H, dd, J=7.2 and 3 Hz, OH), 3.5—4.2 (6H, m, CH_2–OH and $O(CH_2)_2O$).

Found: C, 71.44; H, 10.84%. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%.

1β-[(Tetrahydropyranyloxy)methyl]-5,5,8aβ-trimethyl-4aα-octahydro-2(1*H*)-naphthalenone (10). (a) A solution of **8** (890 mg, 3.32 mmol) and PPTS (5 mg) in acetone (15 ml) was warmed with stirring at 40 °C for 15 h. The solvent was mostly taken off under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with brine and dried. Removal of the solvent left an oil which was filtered through a short silica-gell column with hexane–ether (1:1) to give ketol **9** (714 mg, 96%): IR (film) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.80, 0.85, and 0.97 (9H in total, s each, $C(CH_3)_2$ and C–CH_3), 1.0—2.6 (13H, m), 3.8—4.1 (2H, m, CH_2–OH). This material was used for the next reaction without further purification. A mixture of **9** (714 mg, 3.18 mmol), 3,4-dihydro-2*H*-pyran (267 mg, 3.18 mmol), PPTS (5 mg), and CH_2Cl_2 (15 ml) was stirred at room temperature for 15 h, and washed with brine, and dried. Evaporation followed by filtration of an oily residue through a short silica-gel column with hexane–ether (3:2) gave **10** (950 mg, 97%): IR (film) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75, 0.85, and 0.95 (9H in total, s each, $C(CH_3)_2$ and C–CH_3), 1.1—2.4 (18H, m), 3.3—4.2 (4H, m, CH_2–O–CH–O–CH_2), 4.58 (1H, br s, O–CH–O).

Found: C, 73.90; H, 10.60%. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%.

(b) A mixture of **14** (41 mg, 0.13 mmol), 10% Pd-C (5 mg), and dioxane (1 ml) was stirred at room temperature under H_2 for 20 h, and filtered. Concentration of the filtrate left an oil which was purified by preparative TLC (hexane–ether, 2:1) to give **10** (38 mg, 95%).

1α-Hydroxymethyl-5,5,8aβ-trimethyl-4aα,5,6,7,8,8a-hexahydro-2(1*H*)-naphthalenone (12). To a stirred solution of diisopropylamine (156 mg, 1.10 mmol) in THF (4 ml) was added dropwise at −78 °C a solution of 1.5 M butyllithium in hexane (0.96 ml, 1.43 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 **11**[9] (212 mg, 1.10 mmol) in THF (4 ml) was added dropwise and stirring was continued for an additional 1.5 h. To this solution, Gaseous formaldehyde, generated by heating paraformaldehyde (ca. 3 g) at 160—170 °C, was passed through by means of a stream of dry N_2 for 30 min. The reaction was quenched by addition of aqueous NH_4Cl and the product was extracted with ether. The combined extracts were washed with brine and dried. Evaporation left an oil which was purified by preparative TLC (hexane–ether 1:1) to give **12** (191 mg, 78%) and **11** (15 mg, 7%).

12: a colorless crystals; mp 104—105 °C (from hexane–ether); IR (KBr) 3350 and 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.94, 1.04, and 1.08 (9H in total, s each, $C(CH_3)_2$ and C–CH_3), 1.1—1.8 (6H, m), 2.10 (1H, ddd, J=8.2, 4.8, and 1.0 Hz, CH–CH_2O), 2.28 (1H, br t, J=1.7 Hz, CH–C=C), 2.3 (1H, br, OH), 3.65—4.18 (2H, m, CH_2–O), 6.04 (1H, ddd, J=10.4, 3.2, and 1.0 Hz, C=CH–CO), 6.96 (1H, dd, J=10.4 and 1.8 Hz, CH=C–CO). Upon irradiation at 6.04 ppm, the absorptions at 2.10, 2.28, and 6.96 ppm changed a double doublet (J=8.2, 4.8 Hz), a doublet (J=1.8 Hz), and a doublet (J=1.8 Hz), respectively. ^{1}H NMR ($CDCl_3$–D_2O) δ=3.76 (1H, dd, J=10.8, 8.2 Hz, CHH–O), 4.05 (1H, dd, J=10.8, 4.8 Hz, CHH–O).

Found: C, 75.78; H, 9.80%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

1α-[(Tetrahydropyranyloxy)methyl]-5,5,8aβ-trimethyl-4aα,5,6,7,8,8a-hexahydro-2(1*H*)-naphthalenone (13). A mixture of **12** (50 mg, 0.23 mmol), 3,4-dihydro-2*H*-pyran (29 mg, 0.34 mmol), catalytic amount of PPTS, and CH_2Cl_2 (2 ml) was stirred at room temperature for 6 h, and washed with brine. Removal of the solvent left an oil which was purified by preparative TLC (hexane–ether, 3:2) to give **13** (68 mg, quantitative): IR (film) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.93, 1.02, and 1.07 (9H in total, s each, $C(CH_3)_2$ and C–CH_3), 1.1—1.9 (12H, m), 2.13 (1H, br t, J=5.4 Hz), 2.57 and 2.68 (1H in total, br t, C=C–CH), 3.3—4.2 (4H, m, CH_2–O–CH–O–CH_2), 4.55 (1H, br s, O–CH–O), 6.02 (1H, dd, with fine splittings, J=10.4 and 3.2 Hz, C=CH–CO), 6.90 (1H, dd, J=10.4 and 1.9 Hz, CH=C–CO).

1β-[(Tetrahydropyranyloxy)methyl]-5,5,8aβ-trimethyl-4aα,

5,6,7,8,8a-hexahydro-2(1*H*)-naphthalenone (14) and dienone 15. By the same procedure described in the preceding experiment, LDA solution was prepared from 1.5 M (1 M=1 mol dm^{-3}) butyllithium in hexane (0.52 ml, 0.76 mmol) and diisopropylamine (93 mg, 0.90 mmol) in THF (3 ml). A solution of **13** (120 mg, 0.46 mmol) in THF (2 ml) was added dropwise to the above solution at −78 °C. After stirring for 10 min, 10% citric acid (1 ml) was added and stirring was continued at −78 °C for an additional 30 min. Water was added, and the product was extracted with ether. Evaporation left an oil which was purified by preparative TLC (hexane–ether, 2:1) to give **14** (54 mg, 45%) and **15** (49 mg, 41%).

14: IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.84, 0.95, and 1.05 (9H in total, s each, $C(CH_3)_2$ and C-CH_3), 1.0—2.0 (12H, m), 2.2—2.4 (2H, m, C=C-CH and CH-CO), 3.4—4.44 (4H, m, $C\underline{H}_2$-O-CH-O-$C\underline{H}_2$), 4.65 (1H, br s, O-CH-O), 6.08 (1H, dd. J=10.2 and 3.0 Hz, C=CH-CO), 6.92 (1H, dd, J=10.2 and 2.2 Hz, CH=C-CO).

Found: C, 74.57; H, 10.13%. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%.

15: IR (film) 1675 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98, 1.03, and 1.17 (3H, s each, $C(CH_3)_2$ and C-CH_3), 1.1—1.9 (6H, m), 2.22 (1H, br t, C=C-CH), 5.16 and 5.87 (1H s with fine splittings each, $C=CH_2$), 6.20 (1H, dd, J=10.4 and 3.2 Hz, C=CH-CO), 7.01 (1H, dd, J=10.4 and 2.1 Hz, CH=C-CO).

Drimane-8β,11-diol (17). To a stirred solution of **10** (490 mg, 1.59 mmol) in ether (10 ml) was added dropwise at −78 °C a solution of 0.95 M methylmagnesium iodide in ether (7 ml, 4.0 mmol) and stirring was continued for an additional 5 h over a range of −78 to −10 °C. The reaction was quenched by the addition of aqueous NH_4Cl and the product was extracted with ether. Evaporation of the combined extracts gave an oil, which was chromatographed on silica gel with hexane–ether (7:3) to give alcohol **16** (485 mg, 94%): IR (film) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.85 (6H, s, $C(CH_3)_2$), 1.15, 1.22, and 1.30 (6H in total, s each, C-CH_3 and O-C-CH_3), 0.9—2.0 (19H, m), 3.2—4.3 (4H, m, $C\underline{H}_2$O-CH-O-$C\underline{H}_2$), 4.35 (1H, br s, O-CH-O). A mixture of **16** (485 mg, 1.50 mmol), PPTS (5 mg), and methanol (7 ml) was stirred at 60 °C for 15 h. The solvent was removed under reduced pressure to give a semicrystalline residue which was chromatographed on silica gel with hexane–ether (3:7), giving **17** (328 mg, 91%) as crystals: Mp 133—134 °C [lit,[8] 133.8—134.5 °C (from hexane–ether)]; IR (KBr) 3280 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.87 (6H, s, $C(CH_3)_2$), 1.23 (3H, s, C-CH_3), 1.35 (3H, s, O-C-CH_3), 1.0—2.1 (13H, m), 2.94 (1H, br s, OH), 4.06 (2H, d, J=3 Hz, CH_2-O). The physical constants (mp, IR, and ^1H NMR) were identical with those of drimane-8β,11-diol reported by Pelletier.[8]

1β-[(*p*-Tolylsulfonyloxy)methyl]-2α,5,5,8aβ-tetramethyl-4aα-decahydronaphthalen-2β-ol (19). A solution of **17** (60 mg, 0.25 mmol) and *p*-toluenesulfonyl chloride (71 mg, 0.37 mmol) in pyridine (1 ml) was stirred at room temperature for 10 h and diluted with ether. The ethereal solution was washed successively with aqueous copper(II) sulfate, water, and brine, and dried. Evaporation left a solid, which was filtered through a short silica-gel column with hexane–ether (1:1) to give **19** (85 mg, 88%) as crystals: Mp 96—97 °C (from hexane–ether); ^1H NMR ($CDCl_3$) δ=0.80, 0.85, and 0.89 (9H in total, s each, $C(CH_3)_2$ and C-CH_3), 1.12 (3H, s, O-C-CH_3), 0.9—1.8 (13H, m), 2.44 (3H, s, Ar-CH_3), 4.10 (1H, d, J=10.8 and 2.8 Hz, O-C$\underline{H}$H), 4.32 (1H, d, J=10.8 and 3.9 Hz, O-CH$\underline{H}$), 7.32 and 7.78 (1H, dd each, J=8.6 Hz, Ar-H).

Found: C, 66.93; H, 8.79%. Calcd for $C_{22}H_{34}O_4$: C, 66.96; H, 8.63%.

Reaction of 19 with Sodium Hydride. To a stirred mixture of 60% sodium hydride dispersion in mineral oil (6 mg, 0.14 mmol) in DME (1 ml) was added a solution of **19** (50 mg, 0.13 mmol) in DME (1 ml), and the mixture was stirred at 60 °C for 15 h. After cooling, ether was added and the ethereal solution was washed successively with water and brine, and dried. Removal of the solvent left an oil, which was purified by preparative TLC (hexane–ether, 3:1) to give oxetane **20** (10 mg, 30%) and **19** (35 mg, 70%).

20: IR (film) 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83, 0.95, and 1.17 (3H, s each, $C(CH_3)_2$ and C-CH_3), 1.98 (3H, s, O-C-CH_3), 1.0—2.0 (11H, m), 2.24 (1H, t, J=6.8 Hz, O-CH_2-C$\underline{H}$), 4.55 (2H, d, J=6.8 Hz, O-$C\underline{H}_2$-CH).

Found: C, 86.39; H, 8.45%. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55%.

2β-Hydroxy-2α,5,5,8aβ-tetramethyl-4aα-decahydro-1β-naphthalenecarbaldehyde (21). To a stirred solution of NCS (400 mg, 3.0 mmol) in toluene (10 ml) was added dropwise at 0 °C a solution of dimethyl sulfide (0.3 ml, 4.1 mmol), and stirring was continued for an additional 30 min. The reaction mixture was cooled at −25 °C, and a solution of **17** (480 mg, 2.0 mmol) in toluene (5 ml) was added. After stirring for 3 h, triethylamine (0.5 ml) was added and the whole was stirred for 30 min, and diluted with ether. The ethereal solution was washed successively with 1% HCl, water and brine, and dried. Removal of the solvent gave an oil, which was chromatographed on silica gel with hexane–ether (4:1) to give **21** (295 mg, 63%) and **17** (50 mg).

21: Crystals; mp 72—73 °C (from hexane–ether); IR (KBr) 3400 and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.82 and 0.89 (6H in total, s each, $C(CH_3)_2$), 1.15 and 1.18 (6H in total, s each, C-CH_3 and O-C-CH_3), 1.0—2.8 (11H, m), 2.10 (1H, d, J=3.2 Hz, C$\underline{H}$-CHO), 2.90 (1H, br s, OH), 10.1 (1H, d, J=3.2 Hz, CHO).

Found: C, 75.41; H, 10.86%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

α-(2,6-Dimethyoxy-4-methylphenyl)-(2β-hydroxy-2α,5,5,8aβ-tetramethyl-4aα-decahydro-1β-naphthalenemethanol (22). To a stirred solution of 1,3-dimethoxy-5-methylbenzene[12] (1.272 g, 8.37 mmol) in DME (15 ml) was added dropwise at −60 °C a solution of 1.6 M butyllithium in hexane (5.26 ml, 8.37 mmol). The reaction mixture was stirred at −60 °C for 30 min, and at room temperature for 2 h, and recooled at −60 °C. A solution of **21** (249 mg, 1.05 mmol) in DME (2 ml) was added and the whole was allowed to stir for 2 h over a range of −60 to 0 °C, and then at room temperature for 30 min. After cooling at 0 °C, wet ether followed by water were added, and the product was extracted with ether. The combined extracts were washed with brine and dried. Removal of the solvent left a crystalline residue, whose ^1H NMR spectrum indicated that it is a mixture of stereoisomers with regard to a benzylic hydroxyl group. The residue was chromatographed on silica gel with hexane–ether (1:1) to give **22** (378 mg, 92%) as crystals: Mp 131—133 °C (from hexane–ether); IR (KBr) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (6H, s, $C(CH_3)_2$), 1.17 (3H, s, C-CH_3), 1.35

(3H, s, O-C-CH_3), 1.0—2.1 (12H, m), 2.32 (3H, s, Ar-CH_3), 3.82 (6H, s, O-CH_3), 4.80 (1H, br s, C-OH), 5.38 (1H, d, J=4.3 Hz, CH-OH), 5.75 (1H, m, CH-OH), 6.35 (2H, s, Ar-H).

Found: C, 73.67; H, 9.85%. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81%.

α-Phenyl-2β-hydroxy-2α,5,5,8aβ-tetramethyl-4aα-decahydro-1β-naphthalenemethanol (23). To a stirred solution of **21** (101 mg, 0.42 mmol) in DME (7 ml) was added at −60 °C a solution of 1.8 M phenyllithium in cyclohexane-ether (0.95 ml, 1.69 mmol), and the mixture was stirred for 1 h over a range of −60 to −20 °C, and then at 0 °C for 1 h. The reaction was quenched by addition of aqueous NH_4Cl and the product was extracted with ether. The combined extracts were washed with brine and dried. Evaporation followed by purification of the oily residue by preparative TLC (hexane-ether, 3:1) gave **23** (126 mg, 94%), which crystallized on standing. The ^1H NMR spectrum indicated that it is a mixture of stereoisomers regarding a benzylic hydroxyl group. Recrystallization of the crystals from hexane-ether (5:1) gave analytically pure sample: Mp 155—156 °C; IR (KBr) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.91 (6H s, $C(CH_3)_2$), 1.01 (3H, s, C-CH_3), 1.35 (3H, s, O-C-CH_3), 1.0—2.0 (11H, m), 2.98 (1H, s, C-OH), 4.23 (1H, d, J=3.6 Hz, CH-OH), 5.35 (1H, br d, J=4 Hz, CH-OH), 7.2—7.58 (5H, Ar-H).

Found: C, 79.82; H, 10.43%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

***r*-1-[(*E*)-2-(2,6-Dimethoxy-4-methylphenyl)ethenyl]-*t*-2-(3-oxobutyl)-1,3,3-trimethylcyclohexane (24).** (a) A solution of **22** (483 mg, 1.24 mmol) and pyridinium chloride (71 mg, 0.62 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 10 min, and washed with brine, and dried. Removal of the solvent gave an oil, which was chromatographed on silica gel with hexane-ether (3:1) to give **24** (459 mg, quantitative) as crystals: Mp 102—103 °C (from hexane-ether); IR (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 and 0.95 (6H in total, s each, $C(CH_3)_2$), 1.15 (3H, s, C-CH_3), 1.2—1.7 (7H, m), 1.98 (3H, s, CO-CH_3), 2.33 (3H, s, Ar-CH_3), 2.4—2.6 (2H, m, CH_2-CO), 3.90 (6H, s, O-CH_3), 6.37 (4H, br s, CH=CH and Ar-H).

Found: C, 77.37; H, 9.53%. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74%.

(b) A solution of **22** (91 mg, 0.23 mmol) and PPTS (5 mg) in CH_2Cl_2 (2 ml) was stirred at room temperature for 20 min. The solvent was removed and a crystalline residue was purified by preparative TLC (hexane-ether, 1:1) to give **24** (83 mg, 97%).

***t*-2-(3-Oxobutyl)-1,3,3-trimethyl-*r*-1-[(*E*)-styryl]cyclohexane (25).** A solution of **23** (34 mg, 0.11 mmol) and *p*-toluenesulfonyl chloride (31 mg, 0.2 mmol) in pyridine (1 ml) was stirred at 60 °C for 2 d. After cooling, water was added and the product was extracted with ether. The combined extracts were washed successively with aqueous copper(II) sulfate, water, and brine and dried. Evaporation left an oil, which was purified by preparative TLC (hexane-ether, 2:3) to give **25** (18 mg, 58%): IR (film) 1710 and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 and 0.94 (6H in total, s each, $C(CH_3)_2$), 1.14 (3H, s, C-CH_3), 1.95 (3H, s, CO-CH_3), 1.0—2.3 (11H, m), 5.95 and 6.23 (2H in total, d each, J=16.2 Hz, CH=CH), 7.3 (5H, br s, Ar-H).

Found: C, 84.45; H, 10.05%. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13%.

Methyl *t*-2-[3,3-(Ethylenedioxy)butyl]-1,3,3-trimethyl-*r*-1-cyclohexanecarboxylate (29). A mixture of **24** (83 mg, 0.22 mmol), ethylene glycol (28 mg, 0.44 mmol), *p*-toluenesulfonic acid (5 mg) and benzene (10 ml) was refluxed azeotropically for 5 h. After cooling, aqueous $NaHCO_3$ was added and the product was extracted with ether. The combined extracts were washed with brine and dried. The oily residue obtained by evaporation was filtered through a short silica-gel column with hexane-ether (1:1) to give acetal **27** (84 mg, 91%) as crystals: Mp 107—108 °C (from hexane-ether); ^1H NMR ($CDCl_3$) δ=0.94 and 0.97 (6H in total, s each, $C(CH_3)_2$), 1.13 (3H, s, C-CH_3), 1.22 (3H, s, O-CH_3), 1.0—1.8 (11H, m), 2.32 (3H, s, Ar-CH_3), 3.80 (4H, s, O-$(CH_2)_2$-O), 6.38 and 6.40 (4H in total, s each, CH=CH and Ar-H).

To a stirred solution of **27** (143 mg, 0.35 mmol) in CH_2Cl_2 (20 ml) was passed ozone at −78 °C for 20 min. After the excess ozone was removed by bubbling through with N_2, dimethyl sulfide (0.5 ml) was added, and the mixture was stirred at −78 °C for 1 h and at room temperature for 30 min. Evaporation left an oil, which was chromatographed on silica gel with hexane-ether (1:2) to give **28** (46 mg, 52%): IR (film) 3300—2800, 1700, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 and 0.92 (6H in total, s each, $C(CH_3)_2$), 1.18 (3H, s, C-CH_3), 2.09 (3H, s, O-C-CH_3), 1.0—1.8 (11H, m), 3.90 (4H, s, O-$(CH_2)_2$-O), 7.7 (1H, br, CO_2H).

To a stirred solution of **28** (40 mg, 0.15 mmol) in ether (5 ml) was added at 0 °C a solution of diazomethane in ether. Evaporation and purification of the oily residue by preparative TLC (hexane-ether, 3:1) gave **29** (41 mg, quntitative): IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 and 0.93 (6H in total, s each, $C(CH_3)_2$), 1.18 (3H, s, C-CH_3), 1.28 (3H, s, O-C-CH_3), 1.0—2.0 (11H, m), 3.63 (3H, s, O-CH_3), 3.91 (4H, s, O-$(CH_2)_2$-O).

Found: C, 68.40; H, 10.29%. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13%.

4-(2,2,6-Trimethyl-*t*-6-vinylcyclohex-*r*-1-yl)-2-butanone Ethylene Acetal (32). To a stirred mixture of lithium aluminium hydride (14 mg, 0.36 mmol) in THF (4 ml) was added at 0 °C a solution of **29** (54 mg, 0.18 mmol) in THF (1 ml), and the reaction mixture was stirred at room temperature for 7 h, and quenched by addition of wet ether. A solid was filtered and washed with ether. The combined filtrate and wash were dried and evaporated to give an oil. Filtration through a short silica-gel column with hexane-ether (1:1) gave **30** (48 mg, quantitative): IR (film) 3300 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.80 and 0.89 (9H in total, s each, $C(CH_3)_2$ and C-CH_3), 1.0—1.9 (12H, m), 1.33 (3H, s, O-C-CH_3), 3.0—3.3 (2H, m, CH_2-OH), 3.96 (4H, s, O-$(CH_2)_2$-O).

Chromium(VI) oxide (118 mg) was added at 0 °C to a stirred solution of pyridine (0.2 ml) in CH_2Cl_2 (4 ml). After stirring for 1 h, Celite 545 (400 mg) followed by a solution of **30** (32 mg, 0.12 mmol) in CH_2Cl_2 (2 ml) was added. After stirring for 10 min, sodium hydrogensulfate monohydrate (400 mg) was added and the whole was stirred for 10 min. Filtration followed by evaporation of the filtrate left an oil, which was purified by preparative TLC (hexane-ether, 3:1) to give **31** (30 mg, quantitative): IR (film) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 and 0.97 (6H in total, s each, $C(CH_3)_2$), 1.10 (3H, s, C-CH_3), 1.28 (3H, s, O-C-CH_3), 1.0—1.8 (11H, m), 3.90 (4H, s, O-$(CH_2)_2$-O), 9.30 (1H, s, CHO).

To a stirred suspension of 60% sodium hydride dispersion in mineral oil (10 mg, 0.25 mmol) in toluene (0.5 ml) was added a solution of 1-pentanol (23 mg) in toluene (0.5 ml), and the mixture was stirred at 60 °C for 1 h. After cooling, methyltriphenylphosphonium bromide (98 mg, 0.27 mmol) was added, and the resulting mixture was stirred at room temperature for 1 h. To a yellow suspension obtained, a solution of **31** (32 mg, 0.12 mmol) in toluene (0.5 ml) was added, and the whole was allowed to stir for 10 h, and then quenched by addition of wet ether. The ethereal solution was washed successively with water and brine, and dried. Removal of the solvent gave an oil, which was purified by preparative TLC (hexane–ether, 2:1) to give **32** (24 mg, 77%): IR (film) 3060, 1630, and 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.90 (6H, s, $C(CH_3)_2$), 1.08 (3H, s, $C-CH_3$), 1.38 (3H, s, $O-C-CH_3$), 1.0—1.8 (11H, m), 3.98 (4H, s, $O-(CH_2)_2-O$), 4.90, 5.02, and 5.77 (3H in total, ABX system, J=18, 9, and 1.8 Hz, $CH=CH_2$).

4-(2,2,6-Trimethyl-*t*-6-vinylcyclohex-*r*-1-yl)-2-butanone (5). A solution of **32** (20 mg, 0.08 mmol) and PPTS (5 mg) in acetone (2 ml) was stirred at 40 °C for 5 h. Removal of the solvent left an oil, whose purification by preparative TLC (hexane–ether, 4:1) gave **5** (18 mg, quantitative). The physical data (IR and ^1H NMR) were identical of those of natural **5** reported by Enzell.[6]

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