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Synthesis of 2,6-Dimethyl-6-(8-methyl-4-methylene-7-nonenyl)-2-cyclohexene-1-methanols from α-Santonin[1]

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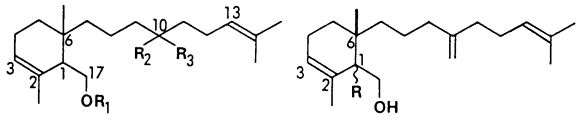
α-Santonin was converted to 2,6-dimethyl-6-(8-methyl-4-methylene-7-nonenyl)-2-cyclohexene-1-methanols (**1a** and **1b**). Both spectral data of **1a** and **1b** were found to be different from those reported for magydar-2,10(20),13-trien-17-ol, a diterpene isolated from *Magydaris panacifolia* (Vahl) Lange. This indicates that the structure of the natural diterpene should be revised; the structure was later revised to *t*-6-hydroxymethyl-1, *t*-3-dimethyl-*t*-2-(3-methyl-2-butenyl)-3-(4-methyl-3-pentenyl)-*r*-1-cyclohexanol.

In 1978 J. de Pascual Teresa and co-workers reported the isolation and the structural elucidation of three new diterpenes, magydar-2,10(20),13-trien-17-ol(I), its acetate(II), and magydar-2,13-diene-10,17-diol(III), from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae).[2] The stereochemistry of these diterpenes with a novel carbon skeleton was however left undetermined. With the object of determining the stereochemistry of these diterpenes including the absolute configuration we synthesized a pair of diastereomers of 2,6-dimethyl-6-(8-methyl-4-methylene-7-nonenyl)-2-cyclohexene-1-methanols, (**1a**) and (**1b**), namely the two possible stereoisomers for the structure of magydar-2,10(20), 13-trien-17-ol (I) or its enantiomer.



I R_1 = H R_2, R_3 = CH_2
II R_1 = $COCH_3$ R_2, R_3 = CH_2
III R_1 = H R_2 = OH, R_3 = CH_3

1a α-H
1b β-H

In this work we chose α-santonin (**2**), easily available sesquiterpene, as the starting material and converted it into **1a** and **1b** via 6,7-secoeudesmane derivatives. Following the known procedures α-santonin (**2**) was transformed into 5α*H*- (**3a**)[3] and 5β*H*-eudesmanolide (**3b**),[4] which have the cyclohexene ring moiety in the diterpene.

In order to convert **3a** into a 6,7-seco derivative functionalization at C-7 was first carried out. Hydroxylation of the enolate of 5α*H*-eudesmanolide (**3a**) with MoO_5·pyridine·HMPT complex[5] gave the hydroxy lactone **4a**[6] in 58% yield. The configuration of the hydroxyl group at C-11 was assigned to be β on the basis of the precedents[7] similar to this case. Reduction of **4a** with lithium aluminium hydride (LAH) in tetrahydrofuran (THF) under reflux afforded the triol **5a** in quantitative yield. Oxidative cleavage of the triol **5a** with sodium periodate in aqueous THF gave the β-hydroxy ketone **6a** in 98% yield. 5β*H*-Eudesmanolide (**3b**) was also converted similarly into the β-hydroxy ketone **6b** in 55% overall yield.

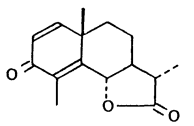
Althogh the Beckmann rearrangement of *O*-mesitylsulfonyloxime **7a**, which was prepared from **6a** and *O*-mesitylsulfonylhydroxylamine, was first attempted using basic alumina (Merck, activity I),[8] the desired amide **8a** was obtained only in 35% yield together with a less polar product. The latter was assumed to be the oxazoline derivative **9** (27% yield) from its spectral data (ν_{max}. 1643 cm^{-1} (C=N); δ=1.98 (d, *J*=1.5 Hz, Me), 3.17 (m, 7α-H), and 3.26 (dd like, *J*=13 and 11 Hz, 6β-H).[9] However, treatment of the oximes, **7a** and **7b**, with activated alumina (Wako) gave the amides, **8a** and **8b**, in 80 and 63% yields, respectively.

The hydroxy amides, **8a** and **8b**, were then reduced with LAH to afford hydroxy amines, **10a** (90% yield) and **10b** (88% yield), respectively. Oxidative cleavage of **10a** and **10b** with sodium periodate in aqueous THF followed by reduction with sodium borohydride gave the 6,7-seco derivatives, **11a** (62% yield) and **11b** (74% yield), respectively.

Completion of the side chain transformation was brought as follows. The diol **11a** was transformed into the monoiodide **13a** via the monotosylate **12a** in 46% overall yield. After tetrahydropyranylation of **13a**, the resulting iodide **14a** was treated with 2-lithio-1,3-dithiane at 0 °C to give the dithiane **15a** in 73% yield. The carbanion generated from **15a** with butyllithium was then treated with 4-methyl-3-pentenyl iodide[10] to give compound **16a** in 60% yield.[11] Hydrolysis of **16a** with copper(II) chloride-copper(II) oxide in acetone[12] gave the hydroxy ketone **17a** in 40% yield. Finally the Wittig reaction of **17a** with methylenetriphenylphosphorane ($Ph_3P=CH_2$) afforded **1a** in ca. 30% yield. The ^1H NMR spectral data of **1a** were found to differ from those reported for the diterpene (I) (see Table).

The diol **11b** was converted similarly to the monoiodide **14b** in 26% overall yield. Treatment of **14b** with 2-lithio-2-(4-methyl-3-pentenyl)-1,3 dithiane gave compound **16b** in 52% yield.[11] Hydrolysis of **16b** gave the hydroxy ketone **17b** in 40% yield.[12] The Wittig reaction of **17b** with $Ph_3P=CH_2$ gave **1b** in 30% yield. The ^1H NMR spectral data of **1a** were obviously different from those reported for magydar-2,10(20),13-trien-17-ol (I) (see Table).

Since the two stereoisomers, **1a** and **1b**, are found to



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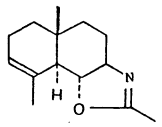

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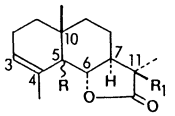
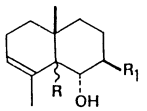
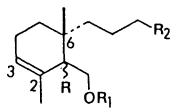


3a, 3b R_1 = H
4a, 4b R_1 = OH



5a, 5b R_1 = C(OH)(Me)CH_2OH
6a, 6b R_1 = COMe
7a, 7b R_1 = C(Me)=$NOSO_2Mst$
8a, 8b R_1 = NHCOMe
10a, 10b R_1 = NHEt



11a, 11b R_1 = H R_2 = OH
12a, 12b R_1 = H R_2 = OTs
13a, 13b R_1 = H R_2 = I
14a, 14b R_1 = THP R_2 = I
15a R_1 = THP R_2 =
16a, 16b R_1 = THP
R_2 =
17a, 17b R_1 = H
R_2 =

3a - 8a, 10a - 17a R = α-H
3b - 8b 10b - 14b, 16b, 17b R = β-H

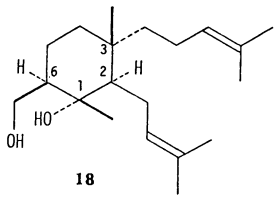
Table 1. ^{1}H NMR Spectral Data ($CDCl_3$, δ values)

Compounds	6-Me	C=C-Me	CH_2OH	$C=CH_2$	$CH=C(Me)_2$	3-H
I	0.71(s)	1.53(s, 6H), 1.63(s, 3H)	3.65 (ABdq)	4.76(s), 4.62(s)	5.03(m)	5.03(m)
1a	0.99(s)	1.60(s), 1.69(s), 1.74(d, J=1.5 Hz)	3.73(m)	4.70(s)	5.11(m)	5.61(m)
1b	0.85(s)	1.62(s), 1.70(s), 1.74(s)	3.73(m)	4.72(s)	5.16(m)	5.62(m)

differ from magydar-2,10(20),13-trien-17-ol, the structure of the natural diterpene should be revised.

We therefore reinvestigated the structure of magydar-2,13-diene-10,17-diol (II) and established the structure of the diterpene, renamed magydardienediol, to be *t*-6-hydroxymethyl-1,*t*-3-dimethyl-*t*-2-(3-methyl-2-butenyl)-3-(4-methyl-3-pentenyl)-*r*-1-cyclohexanol (**18**) on the basis of the detailed analysis of its 400 MHz ^{1}H NMR spectrum.[13] The structure of the diterpene was also elucidated by J. de Pascual Teresa and co-workers. They proposed the structure **18** including the absolute configuration (1*S*, 2*R*, 3*S*, 6*R*).[14]

M. Bruno et al. have recently reported the isolation and the structure elucidation of a diterpene of *Bonannia graeca* (L.) Halacsy (Umbelliferae).[15] The diterpene, named bonandiol, is identical with magydardienediol (**18**).



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Experimental

Melting points were determined on a hot block melting point apparatus and are uncorrected. ^{1}H NMR spectra of all the compounds except for **1a** and **1b** were recorded on a JEOL C-60 (60 MHz) spectrometer and those of **1a** and **1b**

were recorded on a JEOL FX-90Q spectrometer. Chloroform-*d* and tetramethylsilane were used as solvent and internal standard, respectively. IR spectra were taken on a JASCO A-3 spectrometer. Mass spectra were obtained on JEOL DX-300, Hitachi 50-GC, or Hitachi M80-A mass spectrometer using electron impact (70 ev) mode. Optical rotations were determined on a JASCO DIP-181 polarimeter. Pre-coated Merck Kieselgel 60 F_{254} was used for general analytical purposes and silica gel (Wakogel C-200) was used for column chromatography.

Hydroxylation of 3a. To a solution of lithium diisopropylamide, prepared from diisopropylamine (1.5 ml) and butyllithium (1.7 mol dm^{-3} hexane solution, 6.5 ml) in THF (6 ml) under a nitrogen atmosphere, was added a solution of **3a** (2.17 g) in dry tetrahydrofuran (18 ml) at −78 °C. The reaction mixture was stirred for 1 h at this temperature. To the solution was then added Mo_5 · pyridine · HMPT complex (6.0 g) in one portion. The suspension was stirred for 2 h at −78 °C and then warmed to room temperature. Usual work-up gave a yellow residue, which was chromatographed on silica gel (30 g; eluant: hexane-ethyl acetate 10 : 1 v/v) to give 11β-hydroxy-5αH-eudesmanolide (**4a**) (1.36 g) in 58% yield. Recrystallization of the product from diethyl ether gave colorless needles; mp 185.0—186.5 °C; $[\alpha]_D^{34}$ +132°(*c* 0.33, $CHCl_3$); IR (KBr): 3470 and 1755 cm^{-1}; ^1H NMR δ=0.92 (3H, s, 10-Me), 1.44 (3H, s, 11-Me), 1.81 (3H, m, 4-Me), 4.37 (1H, dd, *J*=12 and 9 Hz, 6-H), and 5.37 (1H, m, 3-H); MS: *m/z* 250 (rel intensity 9%, M^+) and 43 (100). Found: *m/z* 250.1555. Calcd for $C_{15}H_{22}O_3$: M, 250.1569.

5βH-Eudesmanolide (**3b**) was similarly hydroxylated to give **4b** in 75% yield. **4b**: colorless needles; mp 131.0—132.5 °C (from diethyl ether); $[\alpha]_D^{34}$ 0° (*c* 0.45, $CHCl_3$); IR: 3430 and 1755 cm^{-1}; ^1H NMR δ=1.11 (3H, s, 10-Me), 1.42 (3H, s, 11-Me), 1.64 (3H, m, 4-Me), 4.73 (1H, dd, *J*=10.5 and 4.5 Hz, 6-H), and 5.45 (1H, broad(br) s, 3-H); MS: *m/z* 250 (4%), 109 (100), and 43 (100). Found: *m/z* 250.1594.

Reduction of 4a with Lithium Aluminium Hydride. To a suspension of lithium aluminium hydride (280 mg) in dry THF (10 ml) was added a solution of **4a** in dry THF (20 ml). The reaction mixture was heated at reflux temperature under a nitrogen atmosphere for 4 h. After work-up as usual the crude product was chromatographed on silica gel (40 g; diethyl ether) to give the triol **5a** (885 mg) together with the partially reduced hemiacetal (545 mg). The hemiacetal was again reduced to **5a** in quantitative yield. **5a**: Colorless viscous oil; $[\alpha]_D^{34}$ +59° (*c* 0.91, $CHCl_3$); IR (neat): 3350 cm^{-1}; ^1H NMR δ=0.76 (3H, s, 10-Me), 1.18 (3H, s, 11-Me), 1.90 (3H, br s, 4-Me), 3.37 (1H, A part of an AB-type quartet, *J*=(−)12 Hz, 12-H), 3.53 (1H, B part of an AB-type quartet, *J*=(−)12 Hz, 12-H), 3.92 (1H, t, *J*=10 Hz, 6-H), and 5.36 (1H, m, 3-H); MS: *m/z* 254 (1%, M^+), 236 (4, M^+-H_2O) 218 (21, M^+-2H_2O), and 43 (100); Found: *m/z* 236.1707. (Calcd for $C_{15}H_{24}O_2$, *m/z* 236.1775).

The hydroxy lactone **4b** was also reduced with lithium aluminium hydride to give the triol **5b** in 75% yield. **5b**: Colorless needles; mp 129.0—129.5 °C (from hexane-diethyl ether); $[\alpha]_D^{34}$ −44° (*c* 0.5, $CHCl_3$); IR (KBr): 3300 cm^{-1}; ^1H NMR δ=0.93 (3H, s, 10-Me), 1.14 (3H, s, 11-Me), 1.80 (3H, br s, 4-Me), 2.60 (3H, br s, OH), 3.37 (1H, A part of an AB-type quartet, *J*=(−)10.5 Hz, 12-H), 3.47 (1H, B part of an AB-type quartet, *J*=(−)10.5 Hz, 12-H), 4.25 (1H, m, 6-H), and 5.55 (1H, m, 3-H); MS: *m/z* 254 (0.1%), 236 (14), 218 (62), and 109 (100).

Oxidative Cleavage of 5a with Sodium Periodate. To a solution of **5a** (615 mg) in THF (30 ml)-H_2O (10 ml) was added dropwise a solution of sodium periodate (623 mg) in water (5 ml). The reaction mixture was stirred for 1.2 h at room temperature. After work-up as usual the crude product was chromatographed (3 g; hexane-ethyl acetate 1 : 1) to give the hydroxy ketone **6a** (527 mg, 98% yield); colorless needles; mp 66.0—67.0 °C (from hexane); $[\alpha]_D^{34}$ +35° (*c* 0.34, $CHCl_3$); IR (KBr): 3420 and 1708 cm^{-1}; ^1H NMR δ=0.82 (3H, s, 10-Me), 1.88 (3H, br s, 4-Me), 2.18 (3H, s, COMe), 4.00 (1H, t, *J*=ca. 10 Hz, 6-H), and 5.35 (1H, m, 3-H); MS: *m/z* 222 (9%, M^+), 204 (10, M^+-H_2O), 189 (15, M^+-H_2O—Me), 161 (62, M^+-H_2O—MeCO), and 43 (100). Found: *m/z* 222.1622. Calcd for $C_{14}H_{22}O_2$: M, 222.1620.

The triol **5b** (201 mg) was also oxidized with sodium periodate (190 mg) to yield the hydroxy ketone **6b** in 98% yield. **5b**: Colorless oil; IR (neat): 3550 and 1710 cm^{-1}; ^1H NMR δ=0.80 (3H, s, 10-Me), 1.74 (3H, d, *J*=1.5 Hz, 4-Me), 2.18 (3H, s, COMe), 2.85 (1H, m, 7-H), 4.20 (1H, t, *J*=3.5 Hz, 6-H), and 5.65 (1H, m, 3-H); MS: *m/z* 222 (0.9%), 204 (68), 189 (30), 161 (100), and 145 (57); Found: *m/z* 204.1542. (Calcd for $C_{14}H_{20}O$, *m/z* 204.1515).

Beckmann Rearrangement of 6a. To a solution of **6a** (485 mg) in dichloromethane (15 ml), stirred at 0 °C, was added *O*-mesitylsulfonylhydroxylamine (813 mg) and the solution was stirred for 30 min at room temperature. The reaction mixture was absorbed on a column of activated alumina (Wako, for column chromatography, 50 g) and allowed to stand for 2 h. The eluate from methanol (200 ml) was evaporated under reduced pressure. Ethyl acetate was added and the resulting suspension was put on a column of silica gel (20 g). Elution with ethyl acetate gave the hydroxy amide **8a** (402 mg, 80% yield). The formation of **9** was not detected. **8a**: Mp 125.0—127.0 °C (from acetone); IR (KBr): 3400, 3330, 1655, and 1545 cm^{-1}; ^1H NMR δ=0.82 (3H, s, 10-Me), 1.78 (3H, br s, 4-Me), 2.01 (3H, s, COMe), 3.0—3.8 (3H, OH, 6-H, and 7-H), 5.34 (1H, m, 3-H), and 6.00 (1H, br s, NH); MS: *m/z* 237 (33%, M), 219 (100, M^+-H_2O), 178 (52), 163 (52), 145 (69), 109 (85). Found: *m/z* 237.1722. Calcd for $C_{14}H_{23}NO_2$: M, 237.1727.

The Beckmann rearrangement of the hydroxy ketone **6b** was similarly performed to yield the hydroxy amide **8b** in 63% yield. The formation of the corresponding oxazoline derivative was not detected. **8b**: Colorless oil; IR (neat): 3320, 1745, 1645, and 1545 cm^{-1}; ^1H NMR δ=0.87 (3H, s, 10-Me), 1.70 (3H, d, *J*=ca. 1 Hz, 4-Me), 2.02 (3H, s, COMe), 3.83 (1H, t, *J*=3.5 Hz, 6-H), 4.23 (1H, m, 7-H), 5.70 (1H, m, 3-H), and 6.00 (1H, br s, NH); MS: *m/z* 237 (0.3%), 219 (6), and 83 (100). Found: *m/z* 237.1797.

The Beckmann rearrangement of **6a** (59 mg) using basic alumina (Merck, activity I, 3 g) gave **8a** (22 mg) together with **9** (16 mg). **9**: Colorless oil; IR (neat): 1643 cm^{-1}; ^1H NMR δ=0.88 (3H, s, 10-Me), 1.78 (3H, m, 4-Me), 1.98 (3H, d, *J*=1.5 Hz, Me), 3.17 (1H, m, 7-H), 3.26 (1H, dd like, *J*=13 and 11 Hz, 6-H), and 5.33 (1H, m, 3-H).

Reduction of 8a with Lithium Aluminium Hydride. A mixture of **8a** (390 mg) and lithium aluminium hydride (470 mg) in dry diethyl ether (30 ml) was heated at reflux temperature for 3 h under a nitrogen atmosphere. Usual work-up gave the hydroxy amine **10a** (90% yield), which was recrystallized to give colorless needles; mp 64.0—65.0 °C; IR (KBr): 3400 cm^{-1}; ^1H NMR δ=0.82 (3H, s, 10-Me), 1.07 (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.88 (3H, br s, 4-Me), 2.3—2.9 (3H, m, 7-H and

$C\underline{H}_2CH_3$), 3.24 (1H, dd, J=10 and 8 Hz, 6-H), and 5.31 (1H, br s, 3-H); MS: m/z 223 (2%, M^+), 205 (18, M^+-H_2O), and 84 (100). Found: m/z 223.1910. Calcd for $C_{14}H_{23}NO$: M, 223.1935.

The amide **8b** (93 mg) was similarly reduced with lithium aluminium hydride (177 mg) to yield the hydroxy amine **10b** in 88% yield. Although the product solidified in a refrigerator, its recrystallization was not successful. **10b**: IR (neat): 3400 cm^{-1}; ^1H NMR δ=0.85 (3H, s, 10-Me), 1.12 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.67 (2H, br s, OH and NH), 1.72 (3H, d, J=1.5 Hz, 4-Me), 2.69 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 2.95 (1H, q, J=3 Hz, 7-H), 3.77 (1H, t, J=ca. 3 Hz, 6-H), and 5.68 (1H, br s, 3-H); MS: m/z 223 (M^+).

Conversion of 10a to 11a. To a solution of **10a** (238 mg) in THF (6 ml), stirred at 0 °C, was added a solution of sodium periodate (516 mg) in water (6 ml). The solution was stirred at this temperature for 1 h under a nitrogen atmosphere. A solution of sodium borohydride (371 mg) in water (5 ml) was then added and the resulting solution was stirred for 45 min. The product was extracted with diethyl ether. The ethereal solution was washed successively with water, dilute hydrochloric acid, 5% aqueous sodium hydrogencarbonate, water, and saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography (8 g; hexane-ethyl acetate 1 : 1) gave the diol **11a** (99 mg) and the hydroxy amine **10a** (58 mg). **11a**: Colorless oil; $[\alpha]_D^{34}$ +97° (c 0.86, $CHCl_3$); IR (neat): 3340 cm^{-1}; ^1H NMR δ=1.00 (3H, s, 6-Me), 1.23 (3H, m, 2-Me), 3.5—3.8 (4H, m, two $C\underline{H}_2OH$), and 5.62 (1H, m, 3-H); MS: m/z 198 (nil, M^+), 180 (3%, M^+-H_2O), and 121 (100, $M^+-H_2O-(CH_2)_3OH$); Found: m/z 180.1448. (Calcd for $C_{12}H_{20}O$: m/z 180.1513).

The hydroxy amine **10b** (70 mg) was similarly transformed into the diol **11b** (46 mg; 74% overall yield), colorless oil; IR (neat): 3350 cm^{-1}; ^1H NMR δ=0.85 (3H, s, 6-Me), 1.73 (3H, d, J=1.5 Hz, 2-Me), 2.27 (2H, br s, OH), 3.65 (4H, m, two $C\underline{H}_2OH$), and 5.55 (1H, m, 3-H).

Conversion of 11a to 14a. A solution of **11a** (33 mg) and p-toluenesulfonyl chloride (39 mg) in pyridine (1 ml) was allowed to stand overnight at 4 °C. Then dilute hydrochloric acid was added and the product was extracted with diethyl ether. The crude product (60 mg), containing the monotosylates, the ditosylate, and **11a**, was dissolved in acetone (4 ml). To the solution was added a solution of sodium iodide (34 mg) in acetone (1 ml) and reaction mixture was heated under reflux for 2.2 h. After evaporation of the solvent the residue was chromatographed to yield the monoiodide **13a** (18 mg; 46% yield). The diol **11a** (8.6 mg) was recovered. **13a**: Colorless oil; IR (neat): 3400 cm^{-1}; ^1H NMR δ=1.00 (3H, s, 6-Me), 1.75 (3H, m, 2-Me), 3.13 (2H, t, J=7 Hz, CH_2I), 3.72 (2H, d, J=3 Hz, $C\underline{H}_2OH$), and 5.60 (1H, m, 3-H); MS: m/z 308 (4%, M^+), 290 (8, M^+-H_2O), 277 (51, M^+-CH_2OH), 121 (64), 93 (94), and 81 (100). Found: m/z 308.0541. Calcd for $C_{12}H_{21}IO$: M, 308.0638.

A solution of **13a** (56 mg) and freshly distilled dihydropyran (6 mg) in dry THF (3 ml) was stirred in the presence of a catalytic amount of p-toluenesulfonic acid. Purification of the product using a column of Florisil (10 g; hexane-diethyl ether 80 : 3) gave **14a** in 82% yield. **14a**: Colorless oil; ^1H NMR δ=0.93 (3H, s, 6-Me), 1.73 (3H, br s, 2-Me), 3.11 (2H, t, J=7 Hz, CH_2I), 3.2—4.0 (4H, m, CH_2OCH_2), 4.52 (1H, m, O-CH-O), and 5.40 (1H, m, 3-H).

Tosylation of the diol **11b** (39 mg) with p-toluenesulfonyl chloride (38 mg) in pyridine (0.5 ml) gave the monotosylate **12b** (22 mg; 31% yield), which was then converted to the monoiodide in quantitative yield. **13b**: Colorless oil; IR (neat): 3420 cm^{-1}; ^1H NMR δ=0.86 (3H, s, 6-Me), 1.75 (3H, br s, 2-Me), 3.19 (2H, t, J=6.5 Hz, CH_2I), 3.72 (2H, d, J=3.5 Hz, $C\underline{H}_2OH$), and 5.61 (1H, m, 3-H). The alcohol **13b** was then treated with dihydropyran in the presence of p-toluenesulfonic acid to give **14b** in 84% yield. **14b**: Colorless oil, MS: m/z 392 (0.1%, M^+), 290 (4), 201 (18), and 85 (100); Found: m/z 290.0501 (Calcd for $C_{12}H_{19}I$: $M^+-C_5H_{10}O_2$, 290.0532).

Treatment of 14a with 2-Lithio-1,3-dithiane. To a solution of **14a** (42 mg; 0.11 mmol) in dry ether (2 ml), stirred at 0 °C, was added a solution of 2-lithio-1,3-dithiane (0.4 mmol) under a nitrogen atmosphere. The crude product was chromatographed on Florisil (4 g; hexane-ether 60 : 3) to yield the dithiane **15a** (30 mg; 73% yield); colorless oil; ^1H NMR δ=0.94 (3H, s, 6-Me), 2.7—3.0 (4H, m, SCH_2), 3.1—4.2 (6H, m), 4.52 (1H, m, O-CH-O), and 5.39 (1H, m, 3-H); MS: m/z 384 (nil, M^+), 282 (15%, $M^+-C_5H_{10}O_2$), and 85 (100).

4-Methyl-3-pentenylation of 15a. To a solution of **15a** (17 mg; 0.044 mmol) in dry THF (0.8 ml), stirred at −30 °C, was added butyllithium (0.27 mmol) under a nitrogen atmosphere. The solution was stirred for 2 h at this temperature. A solution of 4-methyl-3-pentenyl iodide (57 mg; 0.27 mmol) in dry THF (0.5 ml) was added and the reaction mixture was stirred at 0 °C for 2 h. After work-up as usual, the crude product was passed through a column of Florisil (1 g; hexane-ether 30 : 1) to yield **16a** (12 mg; 60% yield); colorless oil; ^1H NMR δ=0.95 (3H, s, 6-Me), 1.5—1.8 (9H, m, three olefinic methyls), 2.6—2.9 (4H, m, SCH_2), 3.0—4.1 (4H, m, $C\underline{H}_2O$), 4.55 (1H, m, O-CH-O), 5.10 (1H, m, CH=), and 5.40 (1H, m, 3-H); MS: m/z 466 (0.6%, M), 364 (5, $M^+-C_5H_{10}O_2$), 229 (23), 85 (83), and 71 (100).

Hydrolysis of 16a with Copper(II) Chloride-Copper(II) Oxide. A suspension of **16a** (12 mg) and $CuCl_2 \cdot 2H_2O$ (17 mg), and CuO (16 mg) in acetone (4 ml) was heated under reflux for 20 min. The reaction mixture was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel (0.5 g; hexane-ether 10 : 1) to yield the hydroxy ketone **17a** (3 mg); colorless oil; IR (neat): 3450 and 1710 cm^{-1}; ^1H NMR δ=1.00 (3H, s, 6-Me), 1.5—1.75 (9H, m, three olefinic methyls), 2.34 (4H, m, CH_2COCH_2), 3.72 (2H, d, J=3 Hz, $C\underline{H}_2OH$), 5.05 (1H, m, CH=), and 5.60 (1H, m, 3-H); MS: m/z 292 (nil, M^+), 274 (1.7%, M^+-H_2O), 205 (3), 121 (100), and 69 (82); Found: m/z 205.1676 (Calcd for $C_{14}H_{21}O$: $M^+-H_2O-C_5H_9$, m/z 205.1593).

Treatment of 14b with 2-Lithio-2-(4-methyl-3-pentenyl)-1,3-dithiane. To a solution of 2-lithio-1,3-dithiane (ca. 1 mmol) in dry THF (2.5 ml), stirred at −6 °C under a nitrogen atmosphere, was added a solution of 4-methyl-3-pentenyl iodide (221 mg) in dry THF (0.2 ml). The solution was stirred at 0 °C for 3 h and then cooled to −30 °C. Butyllithium (ca. 1 mmol) was added. A part of the solution (1.5 ml) was added to a solution of **14b** (26 mg) in dry THF (1.5 ml) at −5 °C under a nitrogen atmosphere. The solution was stirred overnight at −5—0 °C. After work-up as usual the crude product was chromatographed on silica gel (2.5 g; hexane-diethyl ether 97 : 3) to yield the dithiane **16b** (16 mg); colorless oil; MS: m/z 466 (0.6%, M^+), 381 (4), 364 (2, $M^+-C_5H_{10}O_2$), and 69 (100).

Hydrolysis of 16b with Copper(II) Chloride-Copper(II) Oxide. The dithiane **16b** was hydrloyzed with $CuCl_2 \cdot$

$2H_2O$-Cu_2O in acetone to give the hydroxy ketone **17b** in 39% yield. **17b**: Colorless oil; IR (neat): 3470 and 1710 cm^{-1}; ^1H NMR δ=0.87 (3H, s, 6 Me), 1.70 (9H, m, three olefinic methyls), 2.38 (4H, m, CH_2COCH_2), 3.73 (2H, d, J=3 Hz, $C\underline{H}_2OH$), 5.08 (1H, m, CH=), and 5.60 (1H, m, 3-H); MS: m/z 292 (nil, M^+), 274 (3%, M^+-H_2O), 109 (100), 107 (46), and 69 (99); Found: m/z 205.1660 (Calcd for $C_{14}H_{21}O$: $M^+-H_2O-C_5H_9$, m/z 205.1593).

Wittig Reaction of 17a with Methylenetriphenylphosphorane. To a solution of methylenetriphenylphosphorane, prepared from methyltriphenylphosphonium bromide (73 mg) and butyllithium (ca. 0.3 mmol) in dry diethyl ether (1 ml), was added a solution of **17a** (3 mg) in dry ether (1 ml) under a nitrogen atmosphere. The reaction mixture was then stirred for 2 h at room temperature. After work-up as usual the product was purified using column chromatography to yield **1a** (ca. 1 mg); colorless oil; IR (neat): 3400 and 890 cm^{-1}; ^1H NMR (90 MHz) δ=0.99 (3H, s, 6-Me), 1.61 (3H, s, Me), 1.69 (3H, s, Me), 1.74 (3H, d, J=1.5 Hz, Me), 3.74 (2H, m, $C\underline{H}_2OH$), 4.71 (2H, br s, $=CH_2$), 5.16 (1H, m, CH=), and 5.62 (1H, m, 3-H); MS: m/z 290 (5%, M^+), 272 (12, M^+-H_2O), 149 (26), 135 (27), 122 (52), 121 (48), 119 (27), 109 (94), 95 (48), 93 (54), 91 (23), 81 (57), 79 (23), and 69 (100). Found: m/z 290.2629. Calcd for $C_{20}H_{34}O$: M, 290.2610.

The hydroxy ketone **17b** (3 mg) was similarly methylenated with $PH_3P=CH_2$ to yield **1b** (ca. 1 mg); colorless oil; IR (neat): 3450 and 885 cm^{-1}; ^1H NMR (90 MHz) δ=0.85 (3H, s, 6-Me), 1.62 (3H, br s, Me), 1.70 (3H, br s, Me), 1.74 (3H, br s, Me), 3.73 (2H, m, $C\underline{H}_2OH$), 4.72 (2H, br s, $=CH_2$), 5.16 (1H, m, CH=), and 5.62 (1H, m, 3-H); MS: 290 (7%, M^+), 272 (8), 135 (23), 123 (20), 122 (38), 121 (38), 110 (24), 109 (83), 107 (54), 95 (37), 93 (46), 81 (46), 79 (20), and 69 (100). Found: m/z 290.2620.

Gas chromatography (20% Carbowax 20M, 3 mm×2 m, N_2 (1.2 kg cm^{-2})) of the final products showed that the contamination due to a more volatile component (t_R=4.5 min) was less than 10%; t_R(**1a**)=9.2 min and t_R(**1b**)=9.0 min.

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