Cytotoxic Hydroxypolygodials. X-Ray Molecular Structure of (1*R*,3*S*,5a*S*,-9a*S*,9b*R*)-1,3,5,5a,6,7,8,9,9a,9b-Decahydro-1,3-dimethoxy-6,6,9a-trimethylnaphtho[1,2-*c*]furan

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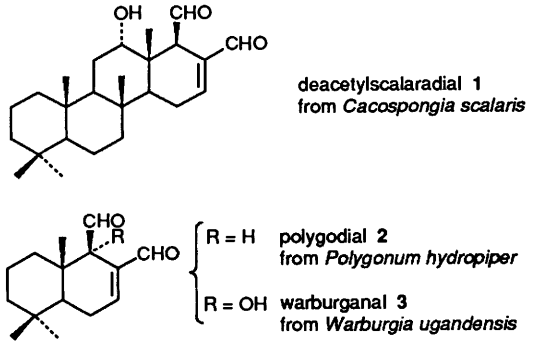
Hydroxypolygodials, designed to have the simplified structure of the cytotoxic sesterterpene deacetylscalaradial isolated from the marine sponge *Cacospongia scalaris*, were synthesized starting from polygodial *via* fungal hydroxylation and chemical modification, and the expected biological activities were obtained. All the structures of the products were determined by mainly spectroscopic means. A simple method for removal of chlorophyll was devised, resulting in considerable improvement in the yield of polygodial.

Our exploratory study of bioactive metabolites from marine sponges led to the discovery of the cytotoxic sesterterpene deacetylscalaradial **1**.[1] However, extensive biological testing could not be carried out due to the limited amount of the metabolite available. We therefore planned the synthesis of 1-hydroxypolygodial with a simplified structure compared with that of the tetracyclic system.[2] The starting material polygodial **2** is available from the plant *Polygonum hydropiper*[3] and optically active products were expected to be obtained. To date, several hydroxypolygodials, represented by warburganal **3**, are known to have antitumour activity.[4] Other hydroxypolygodials are also expected to show bioactivity.

While isolating polygodial from *P. hydropiper*, we noted that on a reversed-phase TLC plate developed with 90% acetonitrile–water, the crude extract showed chlorophylls at the starting line as a condensed green spot. This suggested that chlorophylls could be removed by passage through an octadecylsilanised silica (ODS column). When the acetonitrile solution of the polygodial fractions including chlorophylls was introduced onto an ODS column† and eluted with acetonitrile, chlorophylls were retained completely on the column head, affording a pale yellow eluent. Evaporation of this, followed by recrystallisation, gave the pure compound with a substantial increase in the yield of highly unstable polygodial (0.22%) in comparison with the literature values (0.05[3a] to 0.01%[3b]). For analytical HPLC sample preparation, Bernardi *et al.* reported the elimination of chlorophylls by elution on an ODS cartridge with methanol.[5] However, on a preparative scale, elution with methanol did not lead to retention of chlorophylls on ODS packings.

Hydroxylation at the non-activating carbon of polygodial **2** was achieved by microbial transformation. Since polygodial **2** is an extremely unstable compound which is not suitable as a substrate, both formyl groups must be protected prior to biotransformation. Based on our experience with the purification of deacetylscalaradial **1**, a methanolic solution of polygodial **2** was passed through a column of Dowex™ 50W (H^+-type) to obtain a mixture of epimeric cyclic dimethyl acetal-1 **4** and -2 **5**, which was separated by preparative reversed-phase HPLC (RP-HPLC). The structure difference between the crystalline acetal-1 **4** and the oily acetal-2 **5**, was determined by the ^1H NMR spectra. In both acetals, NOEs were observed between the methyl group at C-10 and the proton at C-11 ([10-Me) → 11-H, 10.3% in **4** and 8.5% in **5**; [11-H] → 10-Me, 5.4% in **4** and 2.4% in **5**), implying the configuration of the methoxy group at C-11 to be α. X-Ray analysis of the acetal-1 **4** confirmed this and showed the methoxy group at C-12 to be α (Fig. 1), which meant that that of compound **5** had to be β disposed (Scheme 1).



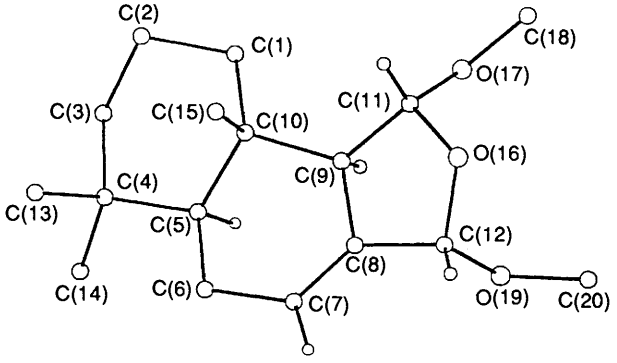
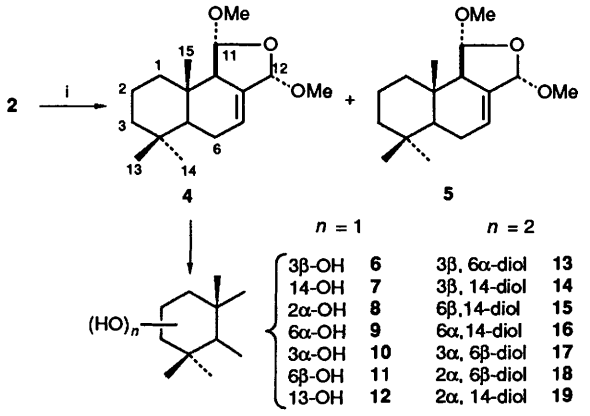


Fig. 1 Perspective view of acetal-1 **4**. Hydrogen atoms of methyl and methylene groups were omitted for clarity.

Type Selection.—In a 0.02 mol dm^{-3} phosphate buffer solution (pH 7.0; 3 cm^3), a methanolic solution of acetal-1 **4** (50 mg in 0.5 cm^3) was shaken with a resting cell suspension of a fungus at 28 °C for 24–48 h. The suspension was filtered, and the filtrate was extracted with dichloromethane. After evaporation of the solvent, the residue was checked on a TLC plate. When polygodial **2** was used as a substrate, neither product nor starting material was detected on the plate.

Of 95 species of fungi studied, six were selected based on the disappearance of the spot of substrate **4** on the TLC plate. Scale-up experiments (5–8 g) were carried out, and the products

† The ODS packings do not have to be new. We used packings (LiChroprep™ RP-18, 25–40 μm) which had been in use for over one year. They were repacked into a GCH™ column, heavy-wall glass column (φ 20 × 500 mm) in the same manner as for open column chromatography.



Scheme 1 *Reagents:* i, H^+, MeOH

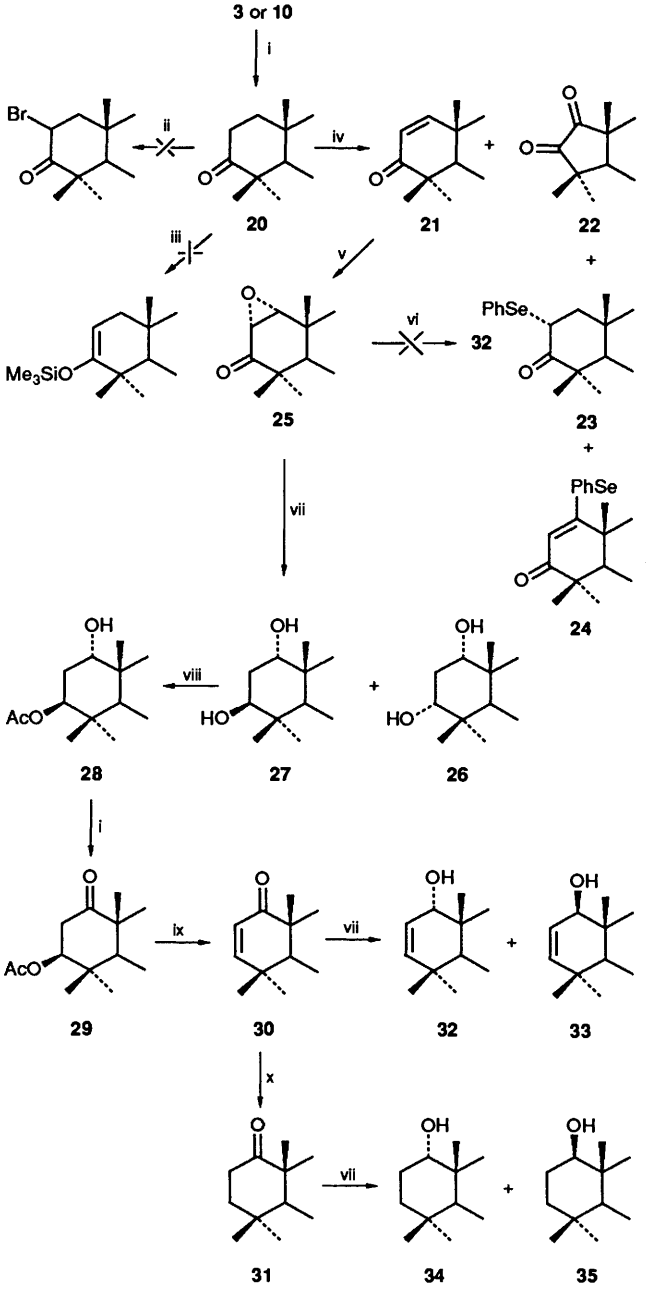
were successfully separated by preparative RP-HPLC to afford seven mono-ols and seven diols (Scheme 1). The metabolic pattern is summarised in Table 1. *Syncephalostrum racemosa* was found to be the best for producing the 3β-hydroxy derivative **6** (58% yield), which is the starting material for the 1-hydroxy compound.

Position of Hydroxy Groups Introduced.—All the hydroxy groups introduced could be acetylated (IR and ^{1}H NMR spectra), implying that they are primary and/or secondary. The number and position of the hydroxy groups introduced were determined by examination of the ^{1}H and the ^{13}C NMR spectra (Tables 2–9). Signals in the ^{13}C NMR spectra of the hydroxypolygodial acetals were assigned by comparison of the chemical shifts with those of acetal **4** and by the contribution values ($\Delta\delta$) of the hydroxy group(s) introduced (Tables 3, and 5–9).

In the ^{1}H NMR spectrum of the mono-ol **6**, the hydroxymethine signal appeared as a double doublet (J 10 and 5 Hz), indicating that the hydroxy group is oriented at C-1β (eq) or C-3β (eq). On the other hand, the hydroxymethine signal in the mono-ol **10** appeared as a narrow triplet, implying the hydroxy group to be situated at C-1α (ax) or C-3α (ax) (Table 2). Both compounds **6** and **10** gave the same ketone **20** on CrO_3 oxidation. The position of the hydroxy group of compound **6** was determined to be C-3 by comparison with the chemical-shift differences ($\Delta\delta$-values in ^{13}C NMR spectra) between it and compound **4** (**6** – **4**) and (lanostanol – podocarpane) as a contribution of the C-3β hydroxy group, and with the substituent effects of the neighbouring carbons; therefore isomer **10** is the 3α-hydroxy compound (Table 6). This was also supported by comparison with the substituent effects at C-13, C-14 and C-15 of the 3- and 1-hydroxy compounds (Table 6). The hydroxy groups in the mono-ol **7** and the mono-ol **12** were both primary and substituted at C-13 or C-14 (Tables 2 and 3). Comparison of $\Delta\delta$-values of ^{13}C NMR data between (**7** – **4**) and (isopimarol – isopimaradiene) as a contribution of the C-14 hydroxy group indicated that compound **7** is a C-14 derivative (Table 7), which meant that compound **12** is a C-13 derivative. This was also supported by the NOEs observed between 10-Me and one of the hydroxylated methylene protons ([13-H] → 10-Me, 8.2% and [10-Me] → 13-H, 9.3%). The hydroxylated methine proton in the mono-ol **8** appeared as a triple triplet (J 11.5 and 4 Hz). Only the C-2β (ax) proton can be expected to give this signal pattern (Tables 2, 4 and 8). In the spectra of the mono-ols **9** and **11**, the olefin proton signal appeared as a triplet, suggesting that these mono-ols are C-6 hydroxy derivatives. The signal width at half-height of the methine signal at C-6 made it clear that compound **9** contains a 6β (ax) proton (more broad) and that there is a 6α (eq) proton in compound **11** (Table 2). The values of the substitution effects in the ^{13}C NMR spectra of isomers **9** and **11** supported these assignments (Table 9).

The position of the hydroxy groups of the diols were also determined in the same manner as for mono-ols [examination of ^{1}H NMR signal pattern and comparison of the contribution values ($\Delta\delta$) of the hydroxy groups in the ^{13}C NMR spectra (Tables 4–9)].

Transhydroxylation of the C-3 Hydroxy Group to C-1.—Starting with the ketone **20**, which was obtained by Collins oxidation of the 3β-mono-ol **6**, dehydrogenation to the enone **21** was achieved with benzeneseleninic anhydride[8] in moderate yield. By-products of this reaction were ring-contracted diketone **22**, α-phenylseleno ketone **23**, and β-phenylseleno didehydroketone **24**. Other attempts to obtain the enone **21** failed: (1) α-bromination of the ketone **20** using pyridinium perbromide (PPB) gave an intractable resin, (2) preparation of the silylenol ether with trimethylsilyl chloride or (3) de-



Scheme 2 *Reagents:* i, CrO_3–pyridine; ii, PPB; iii, Me_3SiCl, DMAP; iv, $(PhSeO)_2O$; v, H_2O_2 OH^-; vi, $NH_2NH_2{\cdot}H_2O$; vii, $LiAlH_4$; viii, Ac_2O, pyridine; ix, Al_2O_3; x, H_2/Pd $SrCO_3$

Table 1 Metabolic pattern of microbial hydroxylation

	Mono-ol							Diol						
Fungus	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Rhizopus javanicus[a]	++	+	+	+			+	+	+					
Helminthosporium sigmoideum[b]		++	+							++	+		+	+
Syncephalostrum racemosa[c]	++													
Corynespora cassiicola[d]	++	+							+					
Fusarium roseum[e]					+	++						+		
Fusarium solan[f]					+	+						++		

++: major product; +: minor product.
All the strains are preserved in a liquid nitrogen server in this laboratory: Laboratory numbers are: [a] SRL-1105; [b] SRL-1097; [c] RF-3189; [d] SRL-1121; [e] SRL-1164; [f] SRL-1200.

Table 2 ^{1}H NMR data for mono-ols δ (J in Hz)

	6	**7**	**8**	**9**	**10**	**11**	**12**
2β-H			3.89 tt (11.5, 4)				
3-H	3.28 dd(α) (10, 5)				3.48 t(β) (2)		
6-H				4.29 dt(β) (10, 3)		4.55 m(α)	
7-H	5.82 q (3.5)	5.78 q (3.5)	5.82 q (3.5)	5.81 t (3.5)	5.81 q (3.5)	5.87 t (3.5)	5.76 q (3.5)
9-H	2.42 m	2.49 m	2.53 m	2.53 m	2.54 m	2.38 m	2.48 m
11-H	4.92 d (4)	4.92 d (4)	4.94 d (4)	4.87 d (4)	4.93 d (4)	4.94 d (4)	4.90 d (4)
12-H	5.14 s	5.13 s	5.13 s	5.17 s	5.14 s	5.19 s	5.11 s
13-H							3.82, 3.56 ABq (12)
14-H		3.96, 3.34 ABq (11)					
Me	0.99, 0.88, 0.77	0.87, 0.81	0.96, 0.94, 0.82	1.13, 1.04, 0.80	0.96, 0.93, 0.79	1.32, 1.08, 1.05	0.98, 0.77

Table 3 ^{13}C NMR chemical shifts for acetals and mono-ols

	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
C-1	39.7	39.9	37.6	39.4	48.8	39.8	31.7	41.9	39.9
C-2	18.5	18.5	27.1	17.8	64.4	18.7	25.0	18.5	18.2
C-3	42.4	42.4	78.6	35.7	51.4	43.5	75.8	45.0	35.9
C-4	*32.9	*32.8	38.7	37.5	*34.6	33.4	37.1	*34.1	38.2
C-5	49.7	49.6	49.1	43.2	49.0	58.6	43.0	54.1	50.8
C-6	23.6	23.8	23.4	23.4	23.5	68.7	23.2	65.9	23.2
C-7	121.0	121.6	121.1	121.1	121.3	124.1	121.4	123.3	121.6
C-8	137.4	136.7	137.1	137.2	137.0	139.2	137.4	138.8	137.6
C-9	57.9	59.0	57.8	57.7	57.9	57.7	57.5	59.0	58.2
C-10	*33.2	*33.6	33.0	32.9	*34.8	38.8	32.9	*33.3	33.4
C-11	106.9	105.0	106.8	107.0	106.7	106.9	106.9	107.2	107.4
C-12	104.5	102.5	104.4	104.5	104.4	104.3	104.5	104.2	104.9
C-13	21.4	21.5	14.9	17.3	22.4	22.3	21.8	24.7	65.0
C-14	32.9	33.3	27.7	71.7	32.9	36.1	27.9	32.5	26.6
C-15	14.0	14.4	14.1	14.6	14.9	15.2	14.0	16.5	15.1

* Assignments marked with an asterisk are interconvertible within one column.

hydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinane (DDQ)–collidine (2,4,6-trimethylpyridine) resulted in no reaction. Since separation of the enone **21** from the starting ketone **20** was very laborious, a fraction of a mixture of compounds **20** and **21** was subjected to H_2O_2 oxidation. The epoxy ketone **25** was easily separated from the ketone **20**. Since reaction of the epoxy ketone **25** with hydrazine hydrate, which was expected to afford the allyl alcohol **32**, gave only a complex mixture, a classical route [9] was applied to derive the 1-hydroxy compounds from the epoxy ketone **25** (Scheme 2).

Although the chemical procedure in this report was not so new, we would like to emphasise: (1) selection of an available natural product as a starting material to obtain optically active products, (2) combination of chemical procedure with biotransformation, which is useful for introduction of a functional group at a non-activating carbon atom, (3) preparative-scale HPLC was introduced effectively to separate the product(s) from even complex mixtures.

As shown in Table 10, several hydroxypolygodial dimethyl acetals, including 1-hydroxy compounds, have strong biological activity but, contrary to our expectation, deprotection of the acetal moiety led to lower activity except for compound **25** (Table 11). Further trials to search for more active derivatives are in progress.

Table 4 ^{1}H NMR data for diols δ (J in Hz)

	13	14	15	16	17	18	19
2β-H						3.98 tt (11.5, 4)	3.90 tt (11, 4)
3-H	3.29 dd(α) (10, 5)	3.68 dd(α) (10, 5)			3.45 t(β) (2)		
6-H	4.39 dt(β) (9, 3)		4.61 m(α)	4.29 ddd(β) (9, 3.5, 2.5)	4.61 m(α)	4.58 m(α)	
7-H	5.84 t (3)	5.78 q (3)	5.87 t (3)	5.83 t (3.5)	5.87 t (3.5)	5.88 t (3.5)	5.76 q (3)
9-H	2.50 m	2.44 m	2.32 m	2.52 m	2.49 m	2.46 m	2.60 m
11-H	4.87 d (3.5)	4.91 d (4)	4.95 d (4)	4.89 d (4)	4.96 d (4)	4.96 d (4)	4.90 d (4)
12-H	5.19 s	5.13 s	5.22 s	5.20 s	5.20 s	5.20 s	5.09 s
14-H		3.64, 3.41 ABq (10.5)	3.55, 3.35 ABq (11)	3.34, 3.19 ABq (11.5)			3.36, 3.10 ABq (12)
Me	1.26, 1.01, 0.80	0.98, 0.82	1.33, 0.99	1.00, 0.79	1.33, 1.14, 1.07	1.36, 1.13, 1.09	0.88, 0.85

Table 5 ^{13}C NMR chemical shifts for diols

	13	14	15	16	17	18	19
C-1	37.2	37.2	40.7	39.3	33.7	50.6	48.7
C-2	27.0	26.4	18.0	17.7	24.8	64.2	64.5
C-3	78.7	76.0	38.8	37.3	77.6	53.8	45.1
C-4	*39.3	42.0	38.6	*37.9	38.1	*35.7	[illegible]2
C-5	58.2	43.4	52.0	55.4	47.0	53.4	42.2
C-6	68.2	23.3	66.1	67.0	66.2	65.4	23.2
C-7	123.7	120.9	123.7	122.9	123.5	123.4	121.2
C-8	139.6	137.1	138.1	139.5	138.7	138.3	137.0
C-9	57.7	57.7	58.7	57.6	58.5	59.0	57.8
C-10	*38.9	32.7	32.5	*38.9	32.8	*34.7	34.6
C-11	106.9	106.8	107.5	107.1	107.2	106.9	106.4
C-12	104.3	104.4	104.4	104.4	104.2	104.1	104.4
C-13	15.8	11.0	20.3	17.7	24.9	32.3	18.3
C-14	30.2	70.1	74.1	74.7	27.4	25.6	71.0
C-15	15.3	14.6	15.8	15.2	16.5	17.2	15.5

* Assignments marked with an asterisk are interconvertible within one column.

Table 6 Contributions of C-1 and C-3 hydroxy groups ($\Delta\delta$) in ^{13}C NMR spectra

Contribution of 1- and 3-OH	Lanostanol − podocarpane 3β	6 − 4 3β	13 − 9 3β	14 − 7 3β	10 − 4 3α	17 − 11 3α	34 − 4 1α	35 − 4 1β
C-1	−1.4	−2.1	−2.6	−2.2	−8.0	−8.2	+32.2	+40.5
C-2	+8.7	+8.6	+8.3	+8.6	+6.5	+6.3	+5.1	+8.1
C-3	+36.7	+36.2	+35.2	+40.3	+33.4	+32.6	−7.9	−1.6
C-4	+5.7	+5.8	+5.9	+4.5	+4.2	+4.0	−0.3	−0.3
C-5	−0.4	−0.6	−0.4	+0.2	−6.7	−4.1	−6.0	−1.2
C-9		−0.1	0.0	0.0	−0.4	−0.5	−7.3	−3.5
C-10	+0.3	−0.2	+0.1	−0.2	−0.3	−0.5	+4.2	+6.0
C-13	−6.4	−6.5	−6.5	−6.3	+0.4	+0.2	−0.1	+0.8
C-14	−5.3	−5.2	−5.9	−1.6	−5.0	−5.1	−0.3	0.0
C-15	−0.4	+0.1	+0.1	0.0	0.0	0.0	+0.4	−5.8

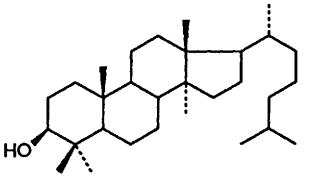
Experimental

General.—Unless otherwise specified, the specific rotations (given in units of 10^{-1} deg cm^2 g^{-1}) were measured in methanol (c 1) at 22–24 °C. The NMR spectra were recorded (Varian VXR-200) at 200 MHz (δ_H) and 50 MHz (δ_C) in $CDCl_3$ containing Me_4Si as internal reference, and J-values are given in Hz. For preparative HPLC, the columns were made by the slurry packing method using appropriate packings (ODS or CN) in a GCH™-20, heavy-wall glass column, φ 20 × 250 mm (N ~4000).

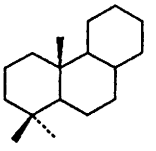
Isolation of Polygodial **2** *from* Polygonum hydropiper.—Fresh tops of *P. hydropiper* (17 kg), collected in August, were extracted twice with Et_2O. The combined extract was evaporated under reduced pressure to give a residue (200 g), which was triturated with CH_2Cl_2 to remove insoluble material. The CH_2Cl_2 extract (170 g) was then subjected to a silica gel open column (850 g) and eluted with CH_2Cl_2 for group separation. The combined polygodial fractions gave a residue (77.6 g), which was dissolved in acetonitrile (380 cm^3) and filtered from insoluble material. The dark green acetonitrile solution (divided into six portions) was applied to an ODS column and eluted with acetonitrile (6 cm^3/min), with UV detection. After elution of polygodial, CH_2Cl_2 (40 cm^3) was injected to elute out the chlorophylls retained on the column. The combined yellow acetonitrile eluent was evaporated under reduced pressure to leave a solid (66.4 g), which on recrystallisation from heptane gave pure polygodial **2** (37.5 g, 0.22%), m.p. 58 °C (lit.,[3a] 53 °C,

Table 7 Contributions of C-14 hydroxy group ($\Delta\delta$) in ^{13}C NMR

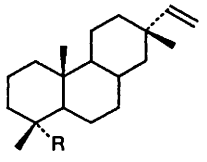
	Isopimarol – isopimaradiene	7 – 4	14 – 6	15 – 11	16 – 9	19 – 8
C-1	−0.5	−0.3	−0.4	−1.2	−0.5	−0.1
C-2	−0.5	−0.7	−0.7	−0.5	−1.0	+0.1
C-3	−6.7	−6.7	−2.6	−6.2	−6.2	−6.3
C-4	+4.5	+4.6	+3.3	+4.5	+4.5	+4.6
C-5	−6.8	−6.5	−5.7	−2.1	−3.2	−6.8
C-10	−0.2	−0.3	−0.3	−0.8	+0.1	−0.2
C-13	−4.1	−4.1	−3.9	−4.4	−4.6	−4.1
C-14	+38.0	+38.8	+42.4	+41.6	+38.6	+38.1
C-15	+0.7	+0.6	+0.5	−0.7	0.0	+0.6



lanostanol [6a]



podocarpane [6b]



isopimarol R = CH_2OH [7]
isopimaradiene R = Me [7]

Numbering of the methyl groups is tentative, corresponding to the polygodial series.

Table 8 Contribution of C-2α hydroxy group ($\Delta\delta$) in ^{13}C NMR

	18 – 11	8 – 4	19 – 7
C-1	+8.7	+9.1	+9.3
C-2	+45.7	+45.9	+46.7
C-3	+8.8	+9.0	+9.4
C-4	+1.6	+1.7	+1.7
C-10	+1.4	+1.6	+1.7
C-13	+0.9	+1.0	+1.0
C-14	−0.2	0.0	−0.7
C-15	+0.7	+0.9	+0.9

0.01%; lit.,[3b] 52 °C, 0.05%). Higher yields can be obtained if the second crops are collected.

Preparation of Polygodial Dimethyl Acetals.—A methanolic solution of polygodial (10 g in 100 cm^3) was passed through the column (φ 20 × 500 mm) of Dowex™ 50W × 8 (100–200 mesh, H^+-type) to afford an epimeric acetal mixture of compounds **4** and **5**. A test separation of the mixture (200 mg) on an ODS column (LiChroprep™ RP-18 25–40 μm; MeOH, 4 cm^3/min) under the conditions of base-line separation gave compound **4** (144 mg, 72%) and compound **5** (55 mg, 27%). To avoid deterioration during prolonged chromatography (*e.g.*, change into dial or monomethyl acetal, *etc.*), practical separation was carried out under heavy overload conditions (1–2 g per injection), and crystals from fractions rich in isomer **4** were filtered off. The residual fractions were applied again to a Dowex™ column to change the ratio **4**:**5**, followed by rechromatography.

Acetal-1 **4**: m.p. 69–70 °C (from 90% MeOH–water) (Found: C, 72.9; H, 10.1. $C_{17}H_{28}O_3$ requires C, 72.82; H, 10.06%); $[\alpha]_D$ +2.1 ± 0.4; δ_H 5.79 (q, *J* 3.5, 7-H), 5.11 (s, 12-H), 4.91 (d, *J* 4, 11-H), 3.47 and 3.40 (MeO), 2.45 (m, 9-H) and 0.91, 0.87 and 0.77 (Me); EIMS *m/z* M^+ (not detected), 279 (M^+ − 1), 249 (M^+ − MeO), 220 (base peak, M^+ − MeOCH=O), 205 (220 − Me), 135, 111, 91 and 55.

Acetal-2 **5**: oil (Found: C, 72.9; H, 10.0%); $[\alpha]_D$ − 109.9 ± 1.9; δ_H 5.79 (m, 7-H), 5.39 (br s, 12-H), 4.91 (d, *J* 6, 11-H), 3.49 and 3.45 (MeO), 2.24 (m, 9-H) and 0.91, 0.88 and 0.86 (Me); EIMS *m/z* M^+ (not detected), 279 (M^+ − 1), 249 (M^+ − MeO), 220 (base peak, M^+ − MeOCH=O), 205 (220 − Me), 135, 111, 91 and 55.

General Procedure for Culture and Fermentation.—Fungus was cultured in a liquid culture medium containing 0.3% corn steep liquor, 3.5% glucose and 2.0% polypeptone in distilled water (adjusted to pH 7.0 by NaOH). After 3–4 days of growth in Sakaguchi flasks at 28 °C, the mycelium was filtered off using a cloth. To a Sakaguchi flask containing 0.02 mol dm^{-3} phosphate buffer (pH 7.0) (100 cm^3) were added wet mycelium (4–7 g) and a solution of acetal-1 **4** (100–200 mg) in methanol (1.0–1.5 cm^3). Thirty to fifty flasks were then shaken reciprocally (120 cycles) for 24 h at 28 °C after which CH_2Cl_2 (50 cm^3/flask) was added and the flasks were shaken for 30 min. The culture liquor was filtered off and the CH_2Cl_2 layer was separated, then the aqueous layer was extracted with CH_2Cl_2. After evaporation of the combined organic solutions, the residue was subjected to a silica gel column (residue 1 g/SiO_2 5 g; elution with CH_2Cl_2 and an increasing proportion of acetonitrile) to separate it into unchanged acetal **4** and the hydroxylated acetal fraction. Chromatography of the latter on an ODS column (Develosil™ ODS 15–30 μm; MeOH–water 8:2, 4 cm^3/min) gave a diol fraction and the respective mono-ol. The diol fraction was rechromatographed on the same ODS column (MeOH–water, 7:3) to yield the respective diol.

3β-*Mono-ol* **6**: m.p. 120–121 °C (from heptane) (Found: C, 68.7; H, 9.5. $C_{17}H_{28}O_4$ requires C, 68.89; H, 9.52%); $[\alpha]_D$ − 1.7 ± 0.4; ν_{max}(KBr)/cm^{-1} 3440 (OH). 14-*Mono-ol* **7**: amorphous powder (Found: C, 68.5; H, 9.45%). 2α-*Mono-ol* **8**: m.p. 142 °C (from CH_2Cl_2–Et_2O) (Found: C, 68.6; H, 9.4%). 6α-

Table 9 Contributions of C-6 hydroxy groups ($\Delta\delta$) in ^{13}C NMR spectra

Contribution of 6-OH	9 – 4 6α	13 – 6 6α	16 – 7 6α	11 – 4 6β	15 – 7 6β	17 – 10 6β	18 – 8 6β
C-1	+0.1	−0.4	−0.1	+2.2	+1.3	+2.0	+1.8
C-2	+0.2	−0.1	−0.1	0.0	+0.2	−0.2	−0.2
C-3	+1.1	+0.1	+1.6	+2.6	+3.1	+1.8	+2.4
C-4	+0.5	+0.6	+0.4	+1.2	+1.1	+1.0	+1.1
C-5	+8.9	+9.1	+8.2	+4.4	+8.8	+4.0	+4.4
C-6	+45.1	+44.8	+43.6	+42.3	+42.7	+43.0	+41.9
C-7	+3.1	+2.6	+1.8	+2.3	+2.6	+2.1	+2.2
C-8	+1.8	+2.5	+2.3	+1.4	+0.9	+1.3	+1.3
C-9	−0.2	−0.1	−0.1	+1.1	+1.0	+1.0	+1.1
C-10	+5.6	+5.9	+6.0	+0.1	−0.4	−0.1	−0.1
C-13	+0.9	+0.9	+0.4	+3.3	+3.0	+3.1	+3.2
C-14	+3.2	+2.5	+3.0	−0.4	+2.4	−0.5	−0.6
C-15	+1.2	+1.2	+0.6	+2.5	+1.2	+2.5	+2.3

Mono-ol **9**: m.p. 97–98 °C (from Et_2O–pentane) (Found: C, 68.6; H, 9.4%). 3α-*Mono-ol* **10**: m.p. 89–90 °C (from Et_2O–heptane) (Found: C, 68.8; H, 9.3%). 6β-*Mono-ol* **11**: m.p. 113–115 °C (from Et_2O–heptane) (Found: C, 68.8; H, 9.5%). 13-*Mono-ol* **12**: oil (Found: C, 68.7; H, 9.3%). 3β,6α-*Diol* **13**: m.p. 145–147 °C (from Et_2O) (Found: C, 65.2; H, 8.9. $C_{17}H_{28}O_5$ requires C, 65.36; H, 9.03%). 3β,14-*Diol* **14**: m.p. 145–147 °C (from Et_2O) (Found: C, 65.4; H, 9.2%). 6β,14-*Diol* **15**: oil (Found: C, 65.4; H, 9.1%). 6α,14-*Diol* **16**: m.p. 123–124 °C (from Et_2O–heptane) (Found: C, 65.1; H, 9.3%). 3α,6β-*Diol* **17**: m.p. 129–130 °C (from CH_2Cl_2–Et_2O) (Found: C, 65.5; H, 9.0%). 2α,6β-*Diol* **18**: amorphous powder (Found: C, 65.0; H, 8.75%). 2α,14-*Diol* **19**: m.p. 170 °C (decomp.) (from Et_2O) (Found: C, 65.45; H, 9.1%).

Collins Oxidation of 3β-*Mono-ol* **6**.—A CH_2Cl_2 solution of CrO_3–pyridine complex (300 mg of CrO_3, 3 mmol) was added dropwise to a solution of the 3β-ol **6** (133 mg, 0.45 mmol) in CH_2Cl_2 (1 cm^3). After being stirred for 40 min at room temperature, the reaction mixture was treated as usual to yield the *ketone* **20** (129 mg, 97%), m.p. 90–91 °C (from Et_2O–heptane) (Found: C, 69.2; H, 8.9. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%); $[\alpha]_D$ −44.5 ± 0.9; ν_{max}(KBr)/cm^{-1} 1710 (CO); δ_H 5.84 (q, *J* 3.5, 7-H), 5.15 (s, 12-H), 4.97 (d, *J* 4, 11-H), 3.47 and 3.40 (MeO), 2.73 (td, *J* 14.5 and 5.5, 2α-H), 2.51 (m, 9-H), 2.30 (dt, *J* 14.5 and 4, 2β-H) and 1.13, 1.08 and 1.02 (Me); δ_C 215.2 (CO).

Dehydrogenation of 3-*One* **20**.—To a solution of the ketone **20** (832 mg, 2.8 mmol) in toluene (6 cm^3) were added pyridine (0.6 cm^3) and benzeneseleninic anhydride (1.0 g, 2.8 mmol). After being stirred for 2 h at 100 °C, the reaction mixture was diluted with CH_2Cl_2 and washed successively with aq. sodium hydrogen carbonate and water. Evaporation of the organic solvent afforded a solid (1.6 g), which was subjected to chromatography (SiO_2 16 g) to yield fr. 1 (from CH_2Cl_2, 553 mg) and fr. 2 [from CH_2Cl_2–MeOH (9:1) 293 mg]. The former eluate, fr. 1 (553 mg) was rechromatographed on a CN column [YMCgel™ CN 15–30 μm; 2% MeCN-in-hexane–CH_2Cl_2 (95:5), 4 cm^3/min] and gave (i) a mixture of compounds **20** and **21** (353 mg), (ii) 1-phenylselenodidehydro ketone **24** (84 mg, 7%), (iii) 2α-phenylseleno ketone **23** (31 mg, 2%), and (iv) dials which were hydrolysed during chromatography (53 mg). The mixture of compounds **20** and **21** was subjected to further chromatography under the same conditions to separate the components (**20**: 194 mg, 23% and **21**: 143 mg, 17%).

The latter eluate, fr. 2 (293 mg), from the above silica gel chromatography was also rechromatographed on a CN column [YMCgel™ CN 15–30 μm; 2% MeCN-in-hexane–CH_2Cl_2 (8:2), 4 cm^3/min] to yield diketone **22** (177 mg, 21%).

Δ^1-3-*One* **21**: m.p. 89–90 °C (from Et_2O–heptane) (Found: C, 69.7; H, 8.3. $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%); $[\alpha]_D$ −40.4 ± 0.8; ν_{max}(KBr)/cm^{-1} 1680 (conj. CO); δ_H 6.80 and 5.94 (ABq, *J* 10, 1- and 2-H), 5.91 (q, *J* 3.5, 7-H), 5.17 (s, 12-H), 5.11 (d, *J* 4, 11-H), 3.53 and 3.42 (MeO), 2.72 (m, 9-H) and 1.15, 1.11 and 1.06 (Me); δ_C 203.9 (CO).

A-Nor-1,2-*dione* **22**: m.p. 148–149 °C (Found: C, 64.8; H, 7.4. $C_{16}H_{22}O_5$ requires C, 65.29; H, 7.53%); ν_{max}(KBr)/cm^{-1} 1740 (CO); δ_H 5.94 (q, *J* 3.5, 7-H), 5.22 (d, *J* 3.5, 11-H), 5.17 (s, 12-H), 3.43 and 3.17 (MeO), 3.02 (m, 9-H) and 1.14, 1.07 and 1.02 (Me); δ_C 203.4 and 192.9 (CO); EIMS *m/z* 294 (M^+), 263 (M^+ − MeO), 234 (M^+ − MeOCH=O), 206 (234 − CO), 191, 138, 105, 91 and 73.

2α-*Phenylseleno*-3-*one* **23**: m.p. 114–116 °C (from CH_2Cl_2–Et_2O (Found: C, 61.0; H, 6.7. $C_{23}H_{30}O_4Se$ requires C, 61.46; H, 6.73%); ν_{max}(KBr)/cm^{-1} 1710 (CO); δ_H 7.56 (2 H, m, Ph), 7.37 (3 H, m, Ph), 5.81 (q, *J* 3.5, 7-H), 5.11 (s, 12-H), 4.75 (d, *J* 4, 11-H), 4.52 (dd, *J* 14 and 6, 2β-H), 3.38 and 3.35 (MeO), 2.46 (m, 9-H), 1.84 (t, *J* 14, 1α-H) and 1.18, 1.15 and 0.92 (Me); δ_C 211.1 (CO); EIMS *m/z* 450 (M^+), 418 (M^+ − MeOH), 261 (418 − PhSeH), 233 (M^+ − MeOCH=O − PhSeH), 201 (233 − MeOH), 173 (201 − CO), 157 (PhSeH), 135, 105, 91 and 77.

1-*Phenylseleno*-Δ^1-3-*one* **24**: m.p. 174–177 °C (from CH_2Cl_2–Et_2O) (Found: C, 61.81; H, 6.35. $C_{23}H_{28}O_4Se$ requires C, 61.74; H, 6.31%); ν_{max}(KBr)/cm^{-1} 1660 (conj. CO); δ_H 7.58 (2 H, m, Ph), 7.37 (3 H, m, Ph), 6.16 (s, 2-H), 5.86 (q, *J* 3.5, 7-H), 5.10 (s, 12-H), 4.76 (d, *J* 4, 11-H), 3.37 and 3.23 (MeO), 2.58 (m, 9-H) and 1.21, 1.15 and 0.93 (Me); δ_C 200.4 (CO); EIMS *m/z* 448 (M^+), 417 (M^+ − MeO), 292 (M^+ − PhSe), 231 (292 − MeOCH=O − H), 199 (231 − MeOH) and 171 (199 − CO).

Epoxidation of Δ^1-3-*One* **21**.—To the above mentioned mixture of compounds **20** and **21** (382 mg) in MeOH (10 cm^3) were added 30% H_2O_2 (0.5 cm^3) and 10% NaOH (0.1 cm^3) in MeOH (2.7 cm^3). After the reaction mixture had been stirred for 4 h at room temperature, diethyl ether was added and the mixture was then washed with water. Evaporation of the solvent gave a solid (374 mg), which was subjected to a porous polymer column (GS-310™, φ 20 × 500 mm; 3 cm^3/min, MeOH) to yield the ketone **20** (164 mg) and the *epoxy ketone* **25** (162 mg), m.p. 101–102 °C (from Et_2O–heptane) (Found: C, 66.1; H, 7.8. $C_{17}H_{24}O_5$ requires C, 66.21; H, 7.85%); $[\alpha]_D$ +92.3 ± 1.3; ν_{max}(KBr)/cm^{-1} 1700 (CO); δ_H 5.82 (q, *J* 3.5, 7-H), 5.15 (s, 12-H), 5.04 (d, *J* 5, 11-H), 3.53 and 3.47 (ABq, *J* 5, 1-and 2-H), 3.52 and 3.43 (MeO), 3.11 (m, 9-H) and 1.17, 1.07 and 0.83 (Me); δ_C 211.2 (CO).

$LiAlH_4$ *Reduction of* 1α,2α-*Epoxy*-3-*one* **25**.—To a solution of the epoxy ketone **25** (445 mg, 1.44 mmol) in absolute diethyl ether was added $LiAlH_4$ (220 mg, 5.8 mmol), and the mixture

Table 10 Proliferation effect of acetals *in vitro* [IC_{50} (μg/cm^{-3})]

	4	5	10	26	28	25	32	33	34	35
Human origin										
A-549[a]	76	42		74		>100	70	86	65	83
SK-HEP-1[b]	12	15	29	25	33	60	23	13	27	8.5
Daudi[c]			9.4	7.2	9.3	12	5.6	4.2	3.5	3.6
KATO III[d]	25	27	28	42	25	49	26	19	30	16
SK-MEL-1[e]	25	26	25	31	24	53	27	18	23	13
HL-60[f]	5.7	7.8		12		27	5.5	2.7	1.7	2.6
CCD-19Lu[g]	7.8		41			56		15	11	12
Murine origin										
B-16[h]	21	21	42	30	48	>100	21	14	11	12
Meth A[i]	14	16	11	11	8.5	15	7.8	4.2	3.5	4.0
L-1210[j]			12	15	6.4	39	7.3	3.9	2.6	3.4
MH-134[k]	21	27	25	13	24	29	11	7.6	3.9	6.1

All the cell lines are maintained in this laboratory. [a] Lung carcinoma. [b] Liver adenocarcinoma. [c] Burkitt lymphoma. [d] Gastric carcinoma. [e] Melanoma. [f] Promyelocytic leukaemia. [g] Lung fibrobrast-like. [h] Melanoma. [i] Methylcholanthrene-induced fibrosarcoma. [j] Mouse leukaemia. [k] Mouse hepatoma.

Table 11 Proliferation effect of aldehydes *in vitro* [IC_{50} (μg/cm^3)]

	2 (= 4a = 5a)	10a	25a	33a	34a	35a
Human origin						
SK-HEP-1	7.4	49	2.0	69	59	31
Daudi		50	1.7	77	34	24
HL-60	61	57	3.9	>100	59	44
CCD-19Lu	45	42	2.6	50	54	48
Murine origin						
Meth A	59	28	1.8	44	20	11
L-1210		70	1.9	28	14	9.6
MH-134	>100	20	1.2	46	24	15

The letter '**a**' of the compound number denotes the corresponding aldehyde of the respective acetal.

was stirred for 25 min at room temperature. The crude product (453 mg), subjected to silica gel chromatography, gave 1α,3α-diol **26** (140 mg, 31%) and 1α,3β-diol **27** (290 mg, 64%).

1α,3α-*Diol* **26**: m.p. 149–151 °C (from CH_2Cl_2–hexane) (Found: C, 65.1; H, 9.0. $C_{17}H_{28}O_5$ requires C, 65.36; H, 9.03%); $[\alpha]_D$ +35.6 ± 0.8; δ_H 5.83 (q, *J* 3.5, 7-H), 5.22 (s, 12-H), 4.97 (d, *J* 5, 11-H), 3.80 (t-like, *J* 3, 1β-H), 3.44 (t-like, *J* 3, 3β-H), 3.51 and 3.42 (MeO), 3.16 (m, 9-H) and 1.02, 0.91 and 0.81 (Me).

1α,3β-*Diol* **27**: oil (Found: C, 65.1; H, 9.2%); $[\alpha]_D$ + 31.6 ± 0.9; δ_H 5.81 (q, *J* 3.5, 7-H), 5.22 (s, 12-H), 4.97 (d, *J* 5, 11-H), 3.79 (dd, *J* 10 and 7, 3α-H), 3.76 (t-like, *J* 3, 1β-H), 3.53 and 3.43 (MeO), 3.06 (m, 9-H) and 1.02, 0.89 and 0.79 (Me).

Acetylation of 1α,3β-*Diol* **27**.—The diol **27** (244 mg, 0.8 mmol) was acetylated with Ac_2O (0.5 cm^3) and pyridine (1 cm^3) for 1 h at room temperature. Group separation of the crude solid (291 mg) on a column of silica gel (3 g) gave an acetylated fraction (211 mg) and the recovered diol **27** (70 mg, 28%). The former fraction was rechromatographed using a CN column [YMC-gel™ CN 15–30 μm; 2% MeCN-in-hexane–CH_2Cl_2 (9:1), 4 cm^3/min] to give 3-monoacetate **28** (166 mg, 60%) and the diacetate (40 mg, 13%).

1α,3β-*Diol* 3-*monoacetate* **28**: m.p. 123–124 °C (from CH_2Cl_2–hexane) (Found: C, 64.3; H, 8.5. $C_{19}H_{30}O_6$ requires C, 64.38; H, 8.53%); $\nu_{max}(CHCl_3)$/cm^{-1} 3600 (OH) and 1730 (CO); δ_H 5.79 (q, *J* 3.5, 7-H), 5.21 (s, 12-H), 5.07 (dd, *J* 11 and 5, 3α-H), 4.97 (d, *J* 5, 11-H), 3.76 (t-like, *J* 3, 1-H), 3.50 and 3.41 (MeO), 3.09 (m, 9-H), 2.06 (AcO) and 0.96, 0.91 and 0.81 (Me).

Δ^2-1-*One* **30**.—Collins oxidation of the 3-monoacetate **28** (120 mg, 0.34 mmol) at 0 °C for 1 h, followed by chromatography on silica gel (1.2 g), gave the 3-acetoxy ketone **29** (37 mg) and a mixture of compounds **28** and **29** (79 mg). In practice, Collins oxidation of the alcohol **28** (158 mg, 0.45 mmol), followed by adsorption on neutral Al_2O_3 (8 g) and slow elution with hexane to hexane–EtOAc gave the unsaturated ketone **30** (103 mg, 78%). Elution with EtOAc gave the starting material **28** (28 mg, 21%).

3β-*Acetoxy*-1-*one* **29**: m.p. 102–103 °C (from CH_2Cl_2–hexane) (Found: C, 64.5; H, 8.0. $C_{19}H_{28}O_6$ requires C, 64.75; H, 8.01%); $\nu_{max}(CHCl_3)$/cm^{-1} 1720 (CO); δ_H 5.84 (q, *J* 3.5, 7-H), 5.20 (d, *J* 3, 11-H), 5.14 (s, 12-H), 4.84 (dd, *J* 9.5 and 6, 3α-H), 3.56 and 3.41 (MeO), 2.78 (m, 9-H), 2.07 (AcO) and 1.09, 1.01 and 0.99 (Me).

Δ^2-1-*One* **30**: m.p. 67 and 93–94 °C (dimorph, from CH_2Cl_2–hexane) (Found: C, 69.5; H, 8.5. $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%); $[\alpha]_D$ +66.7 ± 2.1 (*c* 0.5); $\nu_{max}(CHCl_3)$/cm^{-1} 1670 (conj. CO); δ_H 6.64 and 5.88 (ABq, *J* 10, 3- and 2-H), 5.90 (q, *J* 3.5, 7-H), 5.41 (d, *J* 3, 11-H), 5.15 (s, 12-H), 3.60 and 3.42 (MeO), 2.80 (m, 9-H) and 1.14, 1.14 and 1.00 (Me).

Hydrogenation of Δ^2-1-*One* **30**.—An EtOAc solution (2 cm^3) of the unsaturated ketone **30** (50 mg, 0.17 mmol) was hydrogenated with 5% Pd–$SrCO_3$ (5 mg). Chromatography of the product, eluted by hexane–EtOAc 90:10, gave the *saturated ketone* **31** (35 mg, 70%), m.p. 80–81 °C (from CH_2Cl_2–hexane) (Found: C, 69.3; H, 8.9. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%); $[\alpha]_D$ +74.2 ± 2.2 (*c* 0.5); $\nu_{max}(CHCl_3)$/cm^{-1} 1710 (CO); δ_H 5.80 (q, *J* 3.5, 7-H), 5.14 (d, *J* 3, 11-H), 5.13 (s, 12-H), 3.57 and 3.41 (MeO), 2.84 (m, 9-H), 2.71 (ddd, *J* 15, 12.5 and 6.5, 2β-H), 2.31 (dt, *J* 15 and 4, 4, 2α-H) and 1.11, 1.00 and 0.98 (Me).

$LiAlH_4$ *Reduction of* Δ^2-1-*One* **30**.—An ethereal solution of the unsaturated ketone **30** (50 mg, 0.17 mmol) with $LiAlH_4$ (10 mg, 0.26 mmol) was stirred for 25 min at room temperature, followed by HPLC [Develosil™ ODS 10–20 μm; MeOH–water (7:3), 4 cm^3/min] to afford Δ^2-1α-ol **32** (11 mg, 23%) and Δ^2-1β-ol **33** (35 mg, 70%).

Δ^2-1α-*Ol* **32**: m.p. 51–52 °C (from CH_2Cl_2–heptane) (Found: C, 69.0; H, 8.9. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%); $[\alpha]_D$ +111.5 ± 5.0 (*c* 0.3); $\nu_{max}(CHCl_3)$/cm^{-1} 3500 (OH); δ_H 5.81 (q, *J* 3.5, 7-H), 5.76 (dd, *J* 10.5 and 5.5, 2-H), 5.64 (d, *J* 10.5, 3-H), 5.23 (s, 12-H), 5.04 (d, *J* 5, 11-H), 3.80 (d, *J* 5.5, 1β-H), 3.54 and 3.43 (MeO), 3.25 (m, 9-H) and 1.04, 0.96 and 0.77 (Me).

Δ^2-1β-*Ol* **33**: m.p. 100–101 °C (from CH_2Cl_2–hexane) (Found: C, 69.3; H, 8.9%); $[\alpha]_D$ −32.8 ± 1.5 (*c* 0.5); $\nu_{max}(CHCl_3)$/cm^{-1} 3480 (OH); δ_H 5.88 (q, *J* 3.5, 7-H), 5.45 (d, *J* 10.5, 2-H), 5.40 (dd, *J* 10.5 and 1.5, 3-H), 5.13 (s, 12-H), 5.07 (d,

Table 12 Atomic coordinates and equivalent isotropic temperature factors

	x	*y*	*z*
Molecule 1			
C1	0.1989(1)	0.5732(3)	0.0955(2)
C2	0.1324(1)	0.5563(4)	0.0229(3)
C3	0.0862(1)	0.6820(4)	0.0824(2)
C4	0.1059(1)	0.8752(3)	0.0772(2)
C5	0.1766(1)	0.8936(3)	0.1368(2)
C6	0.2022(1)	1.0808(3)	0.1289(2)
C7	0.2714(1)	1.0974(3)	0.1819(2)
C8	0.3061(1)	0.9591(3)	0.2149(2)
C9	0.2832(1)	0.7742(3)	0.1982(2)
C10	0.2261(1)	0.7588(3)	0.0916(2)
C11	0.3453(1)	0.6738(3)	0.1808(2)
C12	0.3760(1)	0.9502(3)	0.2594(2)
C13	0.0936(1)	0.9429(4)	−0.0646(2)
C14	0.0617(1)	0.9800(5)	0.1629(3)
C15	0.2483(1)	0.7986(3)	−0.0452(2)
O16	0.3970(1)	0.7967(2)	0.1979(2)
O17	0.3512(1)	0.5421(3)	0.2768(2)
C18	0.4077(1)	0.4398(5)	0.2698(5)
O19	0.3830(1)	0.9421(3)	0.3970(2)
C20	0.4478(1)	0.9367(6)	0.4500(3)
Molecule 2			
C1	0.8068(1)	0.6643(3)	0.3212(2)
C2	0.8744(1)	0.6264(3)	0.3814(2)
C3	0.9171(1)	0.7842(3)	0.3662(2)
C4	0.8936(1)	0.9489(3)	0.4334(2)
C5	0.8221(1)	0.9825(3)	0.3830(2)
C6	0.7931(1)	1.1446(3)	0.4448(2)
C7	0.7230(1)	1.1673(3)	0.4056(2)
C8	0.6901(1)	1.0496(3)	0.3338(2)
C9	0.7169(1)	0.8809(3)	0.2902(2)
C10	0.7759(1)	0.8234(3)	0.3821(2)
C11	0.6581(1)	0.7595(3)	0.2774(2)
C12	0.6196(1)	1.0436(4)	0.2962(2)
C13	0.9062(1)	0.9295(5)	0.5830(2)
C14	0.9348(1)	1.1037(4)	0.3910(2)
C15	0.7552(1)	0.7784(4)	0.5201(2)
O16	0.6039(1)	0.8635(3)	0.3064(2)
O17	0.6510(1)	0.6941(3)	0.1494(2)
C18	0.6023(1)	0.5643(6)	0.1302(4)
O19	0.6079(1)	1.1070(3)	0.1679(2)
C20	0.5419(1)	1.1041(6)	0.1191(4)

J 6, 11-H), 4.11 (d, *J* 1.5, 1α-H), 3.55 and 3.42 (MeO), 2.63 (m, 9-H) and 0.99, 0.97 and 0.82 (Me).

$LiAlH_4$ *Reduction of* 1-*One* **31**.—An ethereal solution of the ketone **31** (42 mg, 0.14 mmol) was treated with $LiAlH_4$ (10 mg, 0.26 mmol) as above, to yield the 1α-ol **34** (21 mg, 50%) and 1β-ol **35** (18 mg, 43%).

1α-*Ol* **34**: m.p. 89–90 °C (from CH_2Cl_2–heptane) (Found: C, 68.8; H, 9.6. $C_{17}H_{28}O_4$ requires C, 68.89; H, 9.52%); $[\alpha]_D$ + 41.6 ± 1.6 (*c* 0.5); $\nu_{max}(CHCl_3)/cm^{-1}$ 3550 (OH); δ_H 5.77 (q-like, 7-H), 5.20 (s, 12-H), 4.96 (d, *J* 5, 11-H), 3.60 (t, *J* 3, 1β-H), 3.52 and 3.41 (MeO), 3.08 (m, 9-H) and 0.93, 0.90 and 0.79 (Me).

1β-*Ol* **35**: m.p. 64–65 °C (from CH_2Cl_2–heptane) (Found: C, 68.7; H, 9.6%); $[\alpha]_D$ +7.7 ± 1.6 (*c* 0.3); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH); δ_H 5.85 (q, *J* 3, 7-H), 5.12 (s, 12-H), 5.06 (d, *J* 5.5, 11-H), 3.52 and 3.42 (MeO), 3.42 (dd, *J* 10 and 6, 1α-H), 2.56 (m, 9-H) and 0.93, 0.88 and 0.85 (Me).

General Procedure for Hydrolysis of Dimethyl Acetals.—A solution of a dimethyl acetal (0.1 mmol) in 10% aq. acetone (3 cm^3) was stirred with a catalytic amount of *p*-TsOH at room temperature for 10 min. The reaction mixture was diluted with water containing sodium hydrogen carbonate and extracted with CH_2Cl_2. Evaporation of the solvent gave the corresponding dial in quantitative yield, which was characterised by IR and ^1H NMR spectra.

X-Ray Crystallographic Analysis of Compound **4**.—*Crystal data.* $C_{17}H_{28}O_3$, *M* = 280.41, monoclinic, space group $P2_1$, *a* = 20.900(3), *b* = 7.668(1), *c* = 10.183(1) Å, β = 94.63(1)°, *V* = 1626.5(3) $Å^3$ [from 2θ-values for 25 reflections in the range 30 < 2θ < 45°, λ = 1.541 78 Å], *Z* = 4, D_{calc} = 1.145 g/cm^3. Prism crystals obtained from aq. ethanol. Crystal dimensions: 0.3 × 0.3 × 0.3 mm, μ(Cu-Kα) = 0.61 mm^{-1}, *F*(000) = 616.

Data collection and processing. Rigaku AFC-5R diffractometer, graphite-monochromated Cu-Kα radiation, *T* = 295 K. ω/2θ scan mode with ω scan width (1.3 + 0.2 tan θ)°, 3242 unique reflections (2θ ≤ 140°; *h* 0/25, *k* −9/0, *l* −12/12), giving 3013 with $|F_0| > 3\sigma(F_0)$ for structure solution and refinement. No significant crystal decay was observed.

Structure analysis and refinement. Direct methods, MULTAN84.[10] All positional parameters and anisotropic thermal parameters for non-H atoms were refined by block-diagonal least-squares. Temperature factors of each H-atom were set as B_{eq} of the bonded atom. $\Sigma(w|\Delta F|^2)$ were minimised, $w^{-1} = \sigma^2(F_0) + 0.001\,55|F_0|^2$, $w = 0$ for 81 reflections with $w^{\frac{1}{2}}|\Delta F| \geqslant 3$. Final *R* = 0.041, R_w = 0.049, *S* = 1.062 for 529 refined parameters. The final Δ*F* synthesis showed $\Delta\rho_{max}$ 0.29 e $Å^{-3}$ and $\Delta\rho_{min}$ −0.29 e $Å^{-3}$. The $(\Delta/\sigma)_{max}$ in the final cycle was 0.1. The atomic scattering factors were taken from *International Tables for X-Ray Crystallography*.[11] Atomic coordinates for non-H atoms are given in Table 12.* Atomic positional parameters, anisotropic displacement parameters, and bond lengths and angles have been deposited with the Cambridge Crystallographic Data Centre.

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* *Supplementary publication* (see section 5.6.3 of Instructions for Authors, in the January issue).

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