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DITERPENOIDS OF *HALIMIUM VISCOSUM*

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Key Word Index—*Halimium viscosum*; Cistaceae; diterpenes.

Abstract—Two new diterpenes with a labdane skeleton were isolated as their diacetylderivatives from *Halimium viscosum*. They were characterized as 7α-methoxy-8-labden-3,15-diol and 7-oxo-8-labden-3,15-diol by spectroscopic methods and synthesis.

INTRODUCTION

The three populations of *Halimium viscosum* found in Spain at La Fregeneda (Salamanca), Villarino de los Aires (Salamanca) and Valparaiso (Zamora), respectively, are of different chemical compositions, although all of them afford mainly bicyclic diterpenes.

RESULTS AND DISCUSSION

The neutral part of the hexane extract of *H. viscosum* (La Fregeneda) consists mainly of esters which are difficult to separate [1]. The fractions obtained from the unsaponifiable extract of the hexane extract afforded compounds **1** and **2** and, after acetylation, compounds **3**–**6** [1].

The diacetyl derivative **4** (IR 1750, 1250 cm^{-1}) showed in its ^{13}C NMR spectrum signals of 25 carbon atoms: eight methyl groups (one of them corresponding to an OMe at δ56.61 ppm), seven methylenes, four methines (2CH-O at δ62.97 and 79.83) and six fully substituted carbons (four of them sp^2, two of these with a double tetrasubstituted bond). Its ^1H NMR spectrum showed signals corresponding to the following groupings: HC–OAc (δ4.46, 1H, *dd*), CH_2–CH_2OAc (δ4.06, 2H, *t*), HC–OMe (3.38, 1H, *m*, and 3.32, 3H, *s*), 2 Me-COO (2.02 and 2.01, each 3H, *s*), Me–C= (1.65, 3H, *s*) and four methyl groups (three Me–C and one Me–CH). The mass spectrum of **4** (M^+ *m/z* 422, $C_{25}H_{42}O_5$) corresponded to that of a bicyclic diterpene with two acetoxyl groups, a methoxyl group and one double bond. The base peak at *m/z* 279 corresponded to the loss of $C_8H_{15}O_2$, i.e. the side chain of a bicyclic diterpene in which the primary acetoxyl group and the Me-CH were located.

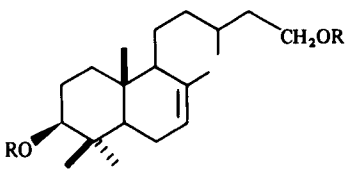
The methyl pattern suggested a labdane skeleton for **4** in which the presence of a methyl group on a tetrasubstituted double bond was only possible by locating the unsaturation at C-8. The δ3.38 shift of the hydrogen geminal to the methoxyl group showed that it was in an allylic position. Indeed, oxidation of **7** (the saponification product of **4**) gave the ketoaldehyde **8** [2] which had no absorption corresponding to an α,β-unsaturated carbonyl in its UV spectrum. The form and shift in the signal of the hydrogen geminal to the secondary acetoxyl was characteristic of labdanes β-substituted at C-3.

The structure of **4** was established by synthesis, as detailed below, from **1**, the major product of this extract. Assignation of the signals of the ^{13}C NMR spectrum of **4** was done by comparison with those of **1** established by 2D-H–C experiments (normal and long range).

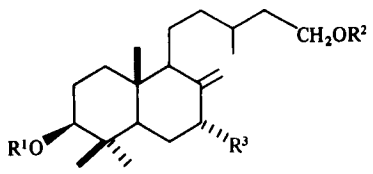
The diacetyl derivative **5**, as well as the acetoxyl groups, also contained an α,β-unsaturated carbonyl (IR 1750, 1670 cm^{-1}; UV 246 nm). Its ^{13}C NMR spectrum showed 24 carbons: seven methyls, seven methylenes, three methines and seven fully substituted carbons (five of which were sp^2: two of a tetrasubstituted olefin, two acetoxyls and one carbonylic). As well as signals of hydrogens geminal to the secondary and primary acetoxyls (4.49, 1H, *dd*; 4.10, 2H, *t*), the ^1H NMR spectrum also showed signals of five methyls (one Me–C=, one Me-CH, and three Me–C). The multiplicities and shifts of these signals were similar to those found for **4** such that **5** had to be a diterpene with a labdane skeleton. In a labdane skeleton, a double tetrasubstituted bond is only possible by locating it at C-8. The shift of Me-17 in the ^1H NMR spectrum (δ1.73 ppm) showed that it was in the α position with respect to an α,β-unsaturated carbonyl, from which it was inferred that the carbonyl group was situated at C-7. The same conclusion was reached with the findings from the study of the UV spectrum. The structure of **5** was established from **1**.

On refluxing **3** in benzene with iodine, **9** was formed, in, quantitative yield (the signal of the olefinic H disappeared; Me–C= remained at δ1.53). Treatment of **9** with sodium dichromate afforded a compound identical to the natural product **5**. Reduction of **5** with sodium borohydride gave **10** and a small amount of **11**. The hydroxyderivative **10** showed in its ^1H NMR spectrum a signal corresponding to the hydrogen geminal to an allylic secondary hydroxyl group (δ4.05, *m*); the broad $W_{1/2}$ of the signal showed that the hydroxyl group was β, in agreement with the entrance of the reductant on the α side i.e. the one showing the least hinderance. Compound **11** was a diol formed as a result of the reduction of the carbonyl group and of the primary acetoxy group of **5**.

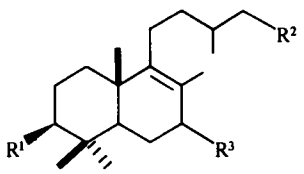
Methylation of **10** with methyl iodide in the presence of sodium hydride afforded **12**. A spectroscopic study of **12** and of its alkaline hydrolysis product **13** showed the presence of a mixture of epimers at C-7, formed in the Williamson synthesis [3]. The signals of the hydrogens geminal to the methoxyl groups appeared at δ3.72 (1H, *t*, J = 4.01 Hz) and 3.38 (1H, *m*, $W_{1/2}$ = 5.9 Hz) in **12** and at



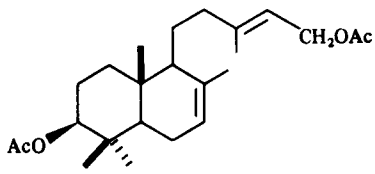
	R
1	H
3	Ac



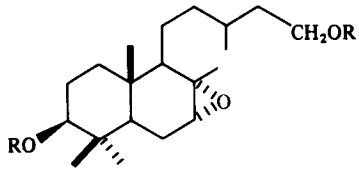
	R^1	R^2	R^3
2	H	H	OH
16	Ac	Ac	OH
19	Ac	Ac	OMe



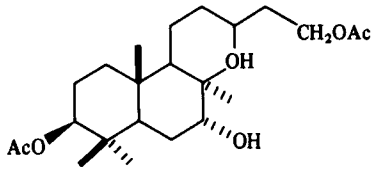
	R^1	R^2	R^3
4	OAc	CH_2OAc	αOMe
5	OAc	CH_2OAc	O
7	OH	CH_2OH	αOMe
8	O	CHO	αOMe
9	OAc	CH_2OAc	H
10	OAc	CH_2OAc	βOH
11	OAc	CH_2OH	βOH
12	OAc	CH_2OAc	α,βOMe
13	OH	CH_2OH	α,βOMe
14	OAc	CH_2OAc	βOMe
17	OAc	CH_2OAc	αOH



6



	R
15	H
20	Ac



18

δ3.73 (1H, *t*, J = 4.01 Hz) and 3.39 (1H, *m*, $W_{1/2}$ = 5.9 Hz) in **13**. These mixtures could not be resolved by chromatography. The isomer **14** with the methoxyl group at β, was also synthesized by methylation of **10** with diazomethane [4]. In the ^{1}H NMR spectrum of **14** the hydrogen geminal to the allylic methoxy group at C-7 appeared at δ3.72 (1H, *t*). The shift and multiplicity of this signal differed from that corresponding to the natural product **4**, which must therefore be the α isomer.

Attempts to isomerize the double bond 8(17) of **19** obtained from **2** [4] using diazomethane and later acetylation did not afford **4**. It was decided, therefore, to use another route starting out from **1**.

Reaction of **1** with *m*-chloroperbenzoic acid followed by acetylation afforded a mixture of epoxides which were resolved by crystallization and/or column chromatography of the corresponding diacetylderivatives, to give **15** (92 %) and **20**, which corresponded to the α-epoxide [1].

Cleavage of the epoxide **20** in acid medium afforded **16**, **17** and **18** [5]. Apart from the signals of the hydrogens geminal to the acetoxyl groups at δ4.51 (1H, *dd*) and 4.10 (2H, *m*), the ^{1}H NMR spectrum of **17** also showed the following groupings: –C=C(Me)–CH–OH (3.93, 1H, *m*, $W_{1/2}$ = 6.50 Hz, 1.71, 3H, *s*) and four methyls (three Me-C and one Me-CH). The broad $W_{1/2}$ of the signal of the hydrogen geminal to the allylic secondary hydroxyl showed the α configuration of the hydroxyl group at C-7.

Alkaline hydrolysis of **16** afforded **2**, also present in the neutral part [1]. The diol **18** was the product resulting from the *trans*-diaxial cleavage of the epoxide. The signal of the hydrogen geminal to the secondary hydroxyl appeared in the ^{1}H NMR spectrum of **18** at δ3.61 (1H, *t*, J = 2.8 Hz) and the Me-17 that is geminal to the tertiary hydroxyl group appeared deshielded at δ1.21.

Methylation of **17** with diazomethane/silica gel afforded a compound identical to the natural product **4** [4].

EXPERIMENTAL

Mps: uncorr; ^{1}H NMR: 200 MHz, $CDCl_3$, TMS as int. standard; ^{13}C NMR: 50.3 MHz (Table 1).

Table 1. ^{13}C NMR data of compounds **1–5**, **9–11**, **14**, **16** and **18** (50.3 MHz, $CDCl_3$, TMS as int. standard)

c	1	3	2	16	4	5	9	10	11	14	18
1	36.82	37.01	36.97	36.66	37.38	36.01	37.63	36.96	37.18	36.98	37.08
2	27.47	23.94	27.47	24.34	24.01	23.77	24.16	26.96	23.97	23.97	23.32
3	79.20	81.07	78.80	80.80	79.83	79.81	81.04	80.58	80.65	80.64	80.94
4	38.72	37.57	39.68	39.53	39.47	40.67	38.71	39.52	39.52	39.30	38.71
5	49.79	49.89	46.94	47.08	45.43	49.34	51.29	49.13	49.14	48.89	46.14
6	23.55	23.34	20.60	20.72	22.48	34.04	18.77	29.45	29.43	24.28	22.27
7	122.01	121.80	73.92	73.79	80.70	199.20	33.70	72.83	72.85	81.06	75.60
8	135.35	135.28	149.67	144.48	126.35	130.20	125.81	128.77	128.66	127.61	75.15
9	55.44	55.22	51.18	51.06	145.38	167.03	140.10	144.03	144.18	144.94	53.70
10	37.41	36.55	38.71	37.62	37.00	37.65	37.82	37.49	37.49	37.65	37.33
11	24.46	24.39	30.65	30.47	25.63	27.26	25.59	25.84	25.91	25.25	25.68
12	39.69	39.59	35.98	35.34	34.41	34.69	34.97	35.01	35.00	35.04	40.75
13	30.59	30.78	30.31	30.66	31.14	31.21	31.12	31.16	30.83	31.18	30.88
14	39.98	35.30	39.68	35.69	35.44	35.34	35.52	35.48	39.80	35.50	35.40
15	61.23	62.93	61.12	63.00	62.97	62.71	63.03	62.95	61.09	62.47	63.01
16	19.82	19.67	19.90	19.76	19.30	19.22	19.37	19.33	19.46	19.33	19.58
17	21.95	21.87	109.82	110.00	18.52	18.45	20.28	20.35	20.35	20.23	26.98
18	27.94	27.82	28.10	26.02	27.87	27.45	28.13	28.02	28.02	28.01	27.95
19	15.09	16.17	15.29	16.37	17.37	16.18	16.58	16.58	16.58	16.57	16.62
20	13.68	13.68	13.49	13.54	16.73	11.31	19.37	14.65	14.68	14.82	15.16
Me-COO		20.89		20.97	20.93	20.93	20.93	20.96	21.21	20.98	20.98
Me-COO		21.17		21.21	21.18	21.14	21.20	21.20		21.22	21.23
Me-COO		170.73		170.78	170.68	170.72	170.84	170.81	170.92	170.84	170.85
Me-COO		170.73		170.81	171.00	170.99	170.84	171.07		170.84	170.85
Me-O					56.61					55.20	

Assignments based on DEPT experiments and, particularly in the case of **1**, on C/H (HCCORR) normal and long range two dimensional correlations.

Extraction and isolation. The aerial parts of *H. viscosum* (5 kg) collected in La Fregeneda (Salamanca), were dried and extracted with *n*-hexane in a Soxhlet for 24 hr to give 306 g of extract, which was dewaxed with MeOH (18%) and then extracted with 6% $NaHCO_3$ (5.3%), 12% Na_2CO_3 (32.4%) and 4% NaOH (13.6%). The neutral fraction remaining represented 38.5% of the original extract.

Saponification of the neutral fraction. A portion (115 g) of the neutral fraction was treated with 100 ml KOH in MeOH (10%) for 24 hr at room temp. After evapn of the MeOH, H_2O and HCl were added, and the mixture extracted with Et_2O. The ethereal soln was washed with NaOH (4%) and with H_2O, yielding an acid fraction (24 g, 19.7%) and a neutral fraction (93 g, 78.9%).

The neutral fraction was chromatographed on silica gel (*n*- hexane–EtOAc) giving four fraction (I–IV). CC of fraction I and IV on silica gel gave **1–3** and **6** [1].

By acetylation of fraction II and III and after CC on silica gel, compound **4** (73 mg, *n*-hexane–EtOAc, 9:1) and compound **5** (250 mg, *n*-hexane-EtOAc, 7:3) were isolated.

3β,15-Diacetoxy-7α-methoxy-8-labdene (**4**). Colourless oil. $[\alpha]_D^{22}$ +24.3° ($CHCl_3$, *c* 0.8); IR ν_{max}^{film} cm^{-1}: 1750, 1250, 1090, 1040, 990, 910, 860; ^1H NMR: δ4.46 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.06 (2H, *t*, J = 6.35 Hz), 3.38 (1H, *m*, $W_{1/2}$ = 5.90 Hz), 2.02 (3H, *s*), 2.01 (3H, *s*), 1.65 (3H, *s*), 0.91 (3H, *s*), 0.87 (6H, *s*), 0.86 (3H, *d*, J = 6.35 Hz). EIMS 70 eV, *m/z* (rel. int.): 422 $[M]^+$ (4), 408 (13), 279 (100), 219 (23), 203 (71), 149 (77).

3β,15-Diacetoxy-7-oxo-8-labdene (**5**). Colourless oil. $[\alpha]_D^{22}$ +26.2° ($CHCl_3$, *c* 0.72); UV λ_{max}^{EtOH} nm (log ε): 246 (4.17). IR ν_{max}^{film} cm^{-1}: 1750, 1615, 1250, 1030; ^1H NMR: δ4.49 (1H, *dd*, J = 10.79 and 4.39 Hz), 4.10 (2H, *t*, J = 6.35 Hz), 2.05 (3H, *s*), 2.03 (3H, *s*), 1.73 (3H, *s*), 1.09 (3H, *s*), 0.96 (3H, *d*, J = 6.35 Hz), 0.95 (3H, *s*), 0.87 (3H, *s*).

Alkaline hydrolysis of **4**. **4** (35 mg) was treated with 3 ml NaOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **7** (29 mg). Colourless oil; IR ν_{max}^{film} cm^{-1}: 3400, 1100, 1050; ^1H NMR: δ3.68 (2H, *m*), 3.39 (1H, *m*), 3.35 (3H, *s*), 3.26 (1H, *dd*, J = 11.23 and 5.37 Hz), 1.67 (3H, *s*), 0.90 (6H, *s*), 0.91 (3H, *d*, J = 6.35 Hz), 0.81 (3H, *s*).

Oxidation of **7** *with* CrO_3. To a soln of CH_2Cl_2 (2 ml) and C_5H_5N (0.1 ml), CrO_3 (28 mg) was added. After shaking for 0.5 hr, 29 mg of **7** in 1 ml CH_2Cl_2 were added. The reaction mixture was kept at room temp. for 2 hr, then filtered and evapd. The residue was dissolved in Et_2O and the soln washed with NaOH, HCl and H_2O. After evapn off the solvent, 23 mg of the reaction product were obtained. Prep. TLC (*n*-hexane–EtOAc, 1:1) gave **8** (10 mg). Colourless oil. IR ν_{max}^{film} cm^{-1}: 2760, 1740, 1720, 1620, 1100; ^1H NMR: δ9.77 (1H, *t*, J = 1.95 Hz), 3.44 (1H, *m*), 3.38 (3H, *s*), 1.71 (3H, *s*), 1.11 (3H, *s*), 1.07 (3H, *s*), 1.00 (3H, *s*) 0.99 (3H, *d*, J = 6.35 Hz).

Isomerization of **3** *with* I_2. Compound **3** (900 mg) in dry C_6H_6 (15 ml) and I_2 (10 mg) was refluxed for 12 hr. After this time, the ^1H NMR of the reaction mixture showed that compound **3** was completely transformed. The reaction mixture was purified on silica gel CC yielding **9** (900 mg). Colourless oil. IR ν_{max}^{film} cm^{-1}: 1750, 1240, 1030; ^1H NMR: δ4.45 (1H, *dd*, J = 11.10 and 4.80 Hz), 4.08 (2H, *m*), 2.04 (3H, *s*), 1.53 (3H, *s*), 0.95 (3H, *s*), 0.92 (3H, *d*, J = 6.35 Hz), 0.87 (3H, *s*), 0.86 (3H, *s*).

Oxidation of **9** *with* Na_2CrO_4. To 900 mg **9** in 20 ml C_6H_6, 1.04 g dry Na_2CrO_4, 8 ml Ac_2O, 6 ml HOAc and 820 mg dry NaOAc were added. The mixture was kept at 60° for 24 hr, then H_2O was added and after 1 hr the mixture was extracted with Et_2O. The ethereal extract was washed with $NaHCO_3$ and H_2O to give 890 mg of material which on silica gel CC (*n*-hexane–EtOAc 4:1) yielded 540 mg **5**.

Reduction of **5** *with* $NaBH_4$. To **5** (540 mg) dissolved in MeOH (15 ml), $NaBH_4$ (156 mg) was added. The mixture was kept at room temp. for 7 hr. Then H_2O and some drops of 2 M HCl were added. After this the mixture was extracted with Et_2O and washed with H_2O. Evapn of the solvent gave 497 mg reaction products which on silica gel CC gave **10** (390 mg, *n*-hexane–EtOAc, 7:3) and **11** (50 mg, *n*-hexane–EtOAc, 1:1).

Compound **10**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3300, 1740, 1240, 1030; ^1H NMR: δ4.44 (1H, *dd*, J = 11.20 and 4.60 Hz), 4.08 (2H, *m*), 4.05 (1H, *m*), 2.03 (3H, *s*), 2.02 (3H, *s*), 1.64 (3H, *s*), 1.01 (3H, *s*), 0.90 (3H, *d*, J = 6.35 Hz), 0.87 (6H, *s*).

Compound **11**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3300, 1740, 1240, 1030; ^1H NMR: δ4.44 (1H, *dd*, J = 11.20 and 4.28 Hz), 4.03 (1H, *t*, J = 8.30 Hz), 3.63 (2H, *dt*, J = 6.89 and 2.44 Hz), 2.03 (3H, *s*), 1.69 (3H, *s*), 1.01 (3H, *s*) 0.91 (3H, *d*, J = 6.35 Hz), 0.87 (6H, *s*).

Methylation of **10**. To 200 mg NaH (80%) in 1 ml THF, 2 ml MeI were added under dry N_2 followed by 94 mg **10** dissolved in 2 ml THF. The mixture was kept at 60° for 6 hr, after which time it was diluted with ice and extracted with Et_2O. The Et_2O was washed with H_2O, dried and evapd to give 100 mg of an extract which on silica gel CC (*n*-hexane–EtOAc, 4:1) yielded 51 mg **12**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 1740, 1670, 1240, 1100, 1030; ^1H NMR: δ4.49 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.46 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.09 (2H, *t*, J = 6.78 Hz), 4.06 (2H, *t*, J = 6.35 Hz), 3.72 (1H, *t*, J = 4.01 Hz), 3.38 (1H, *m*, $W_{1/2}$ = 5.9 Hz), 3.34 (3H, *s*), 3.32 (3H, *s*) 2.06 (6H, *s*), 2.05 (6H, *s*), 1.65 (3H, *s*) 1.61 (3H, *s*), 1.02 (3H, *s*) 0.93 (3H, *d*, J = 6.35 Hz), 0.91 (3H, *s*), 0.90 (3H, *s*), 0.89 (3H, *s*), 0.87 (6H, *s*), 0.86 (3H, *d*, J = 6.35 Hz).

Alkaline hydrolysis of **12**. 30 mg **12** were treated with 3 ml NaOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **13** (26 mg). Colourless oil. IR ν_{max}^{film} cm^{-1}: 3340, 1100, 1050; ^1H NMR: δ3.73 (1H, *t*, J = 4.01 Hz), 3.68 (4H, *m*), 3.39 (1H, *m*), 3.34 (3H, *s*), 3.33 (3H, *s*), 3.23 (4H, *dd*, J = 11.23 and 4.39 Hz), 1.71 (3H, *s*), 1.61 (3H, *s*), 1.02 (3H, *s*), 1.01 (3H, *s*), 1.00 (3H, *s*), 0.94 (3H, *d*, J = 6.35 Hz), 0.91 (6H, *s*), 0.82 (3H, *s*), 0.81 (3H, *s*).

Methylation of **10**. **10** (69 mg) dissolved in Et_2O (2 ml) was absorbed on to 5 g silica gel. The mixture was treated with gaseous CH_2N_2 generated from 15 g *N*-methyl-*N*-nitroso-*p*-toluene-sulphonamide [4] dissolved in Et_2O. The reaction product (62 mg) was extracted with Et_2O and purified by silica gel CC. Elution with *n*-hexane–EtOAc (9:1) gave 22 mg **14** while *n*-hexane–EtOAc (7:3) gave 28 mg of unreacted product.

Compound **14**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 1750, 1240, 1130; ^1H NMR: δ 4.47 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.09 (2H, *t*, J = 6.78 Hz), 3.72 (1H, *t*, J = 4.01 Hz), 3.34 (3H, *s*), 2.05 (3H, *s*), 2.04 (3H, *s*), 1.60 (3H, *s*), 1.02 (3H, *s*), 0.93 (3H, *d*, J = 6.78 Hz), 0.90 (3H, *s*), 0.89 (3H, *s*).

Methylation of **2**. 600 mg **2** absorbed on silica gel (6 g) were treated with gaseous CH_2N_2 generated from 6 g of *N*-methyl-*N*-nitroso-*p*-toluene–sulphonamide [4]. Silica gel CC of the reaction product, eluting with *n*-hexane–EtOAc (1:1), yielded a mixture (50 mg) which after treatment with Ac_2O and C_5H_5N followed by prep. TLC (*n*-hexane–Me_2CO, 9:1, 2 elutions) yielded 25 mg **19**.

Treatment of **1** *with* m-*chloroperbenzoic acid*. *m*-Chloroperbenzoic acid (230 mg) dissolved in 2 ml CH_2Cl_2 was added slowly to a soln of 410 mg **1** in 10 ml CH_2Cl_2. The mixture was then shaken at room temp. for 3 hr, after which work-up in the usual fashion yielded 402 mg of a mixture of two substances. The major component, **15** was separated by crystallization in EtOAc (320 mg) [1]. C_5H_5N (2 ml) and Ac_2O (2 ml) were added to 320 mg of **15** to give 320 mg of **20**.

Treatment of **20** *with* $HClO_4$. 320 mg **20** were dissolved in 1,2-dimethoxyethane (10 ml) cooled to −4°. $HClO_4$ (5%, 3 drops) was added and the mixture kept at −4° for 1.5 hr. The reaction mixture was extracted with Et_2O and the Et_2O washed with 10% Na_2CO_3, H_2O, dried and evapd to give 310 mg of a mixture which on silica gel CC yielded the following compounds: *n*-hexane–EtOAc (9:1) **20** (120 mg), *n*-hexane–EtOAc (4:1) **16** (40 mg), *n*-hexane–EtOAc (7:3) **18** (26 mg).

Compound **16**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3440, 3080, 1745, 1240, 1040, 890; ^1H NMR: δ5.04 (1H, *s*), 4.62 (1H, *s*), 4.53 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.37 (1H, *t*, J = 2.44 Hz), 4.08 (2H, *m*), 2.03 (6H, *s*), 0.90 (3H, *d*, J = 6.35 Hz), 0.87 (3H, *s*), 0.84 (3H, *s*), 0.67 (3H, *s*).

Compound **17**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3440, 1745, 1240; ^1H NMR: δ4.51 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.10 (2H, *m*), 3.93 (1H, *m*, $W_{1/2}$ = 6.5 Hz), 2.05 (3H, *s*), 2.04 (3H, *s*), 1.71 (3H, *s*), 0.94 (3H, *d*, J = 6.37 Hz), 0.94 (3H, *s*), 0.91 (3H, *s*), 0.89 (3H, *s*).

Compound **18**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3440, 1745, 1240; ^1H NMR: δ4.51 (1H, *dd*, J = 11.23 and 4.39 Hz), 4.09 (2H, *m*), 3.61 (1H, *t*, J = 2.8 Hz), 2.05 (3H, *s*), 2.04 (3H, *s*), 1.21 (3H, *s*), 0.96 (3H, *s*), 0.92 (3H, *d*, J = 6.07 Hz), 0.86 (6H, *s*).

Methylation of **17**. Compound **17** (32 mg) absorbed on silica gel (3 g) was treated with gaseous CH_2N_2 generated from 10 g of *N*-methyl-*N*-nitroso-*p*-toluene-sulphonamide. The mixture was extracted with Et_2O to give 30 mg reaction product, which on prep. TLC (*n*-hexane–EtOAc, 4:1) yielded **4** (11 mg).

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