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A DITERPENE ALCOHOL FROM *HALIMIUM VISCOSUM**

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Key Word Index—*Halimium viscosum*; Cistaceae; new diterpene alcohol; tormesol.

Abstract—A hexane extract of *Halimium viscosum* collected at La Fregeneda (Salamanca, Spain) yielded a new diterpene alcohol, tormesol. Its structure was determined by chemical transformations and NMR spectroscopy with ^1H–^1H (COSY), ^{13}C–^{13}C (2D-inadequate) and ^1H–^{13}C (one bond and long range correlations) two-dimensional experiments.

INTRODUCTION

For several years we have been investigating the chemical composition of different populations of *Halimium viscosum* collected in the west of the Iberian Peninsula: I (Villarino, Salamanca), II (La Fregeneda, Salamanca), III (Valparaiso, Zamora). The three populations differ in the composition of their acid parts: I contains acids with an ent-halimane skeleton with two double bonds [2]; in II the acids have an ent-halimane skeleton with a saturated side chain [3, 4] and from III only labdanic acids with the carboxyl group at C-17 were isolated [1, 5].

In the neutral fraction of *H. viscosum* II (La Fregeneda), apart from the labdanes and *ent*-halimanes previously described [4, 6], we isolated an unsaturated diterpene alcohol with a bicylic-decane[5,3,0] system which we called tormesol **1**. The structural determination of this compound is described in the present paper. Compounds having the same carbon skeleton have been previously isolated from *Pseudolarix kaempferi* (the pseudolaric acids [7]) and from *Anastrophyllum minutum* (Hepaticae) [8]†.

RESULTS AND DISCUSSION

From the neutral part of the hexane extract of *H. viscosum*, chromatography and later crystallization in *n*-hexane yields on unsaturated alcohol **1** (IR 3380, 1640 cm^{-1}). The ^1H NMR spectrum of **1** shows signals corresponding to five Me-singlet groups (three of them on a double bond, one angular and one geminal to a tertiary hydroxyl group) forming part of the following groupings: [Me–C=CH–; HC=C(Me)$_2$, Me–C$\leqslant$, Me–C(OH)$<$]. This spectrum also shows signals of two olefinic hydrogen atoms (5.42, 1H, *br* d; 5. 15 *t*, $J = 7.0$ Hz). The ^{13}C NMR spectrum of **1** has signals of 20 carbon atoms: five methyl groups, seven methylenes, four methynes (two or them sp^2) and four fully substituted carbons (four of them sp^2). In the mass spectrum, the $[M]^+$ *m/z* 290 corresponds to a formula of $C_{20}H_{34}O$, such that it must be a bicyclic diterpene alcohol with two double bonds.

When **1** is reacted with *m*-chloroperbenzoic acid, compounds **2–4** are obtained. The ^1H NMR spectrum of **2** shows signals of a Me–C=CH (δ 1.73) and Me–C$\leqslant$ (δ 0.79) similar to those of **1** and those of a tetrahydrofurane system (δ 3.60 1H, *m*; 1.12 6H, *s*; 1.02 3H, *s*).

Compound **3** is also an unsaturated alcohol (IR 3500, 1650 cm^{-1}); in its ^1H NMR spectrum it is possible to observe signals of the HO–C–Me (1.18, *s*) and –HC=C(Me)$_2$ (δ 5.18 1H, *m*; 1.77 3H, *s* and 1.72 3H, *s*) groupings like those of **1** as well as those corresponding to **D** (δ 2.27 1H, *t*, $J = 7$ Hz); 1.32 3H, *s*). The multiplicity of the oxiranic hydrogen atom of **3** (*t*, $J = 7.1$ Hz) excludes the possibility that this could be situated on a cyclohexane ring.

Compound **4** is a hydroxyderivative whose ^1H NMR spectrum does not show signals of an olefinic hydrogen atom, though there are signals corresponding to the above-mentioned **B** and **D** groupings.

Treatment of **2**, **3** or **4** with Na_2CrO_4 affords the γ-lactone **5** [9] (IR 1790 cm^{-1}), whose ^{13}C NMR spectrum shows signals of 17 carbon atoms: three methyl groups, seven methylenes, two methynes (one of them CH–O–) and four fully substituted (one of them sp^2). Apart from the *D* grouping and the Me–C$\leqslant$, the ^1H NMR spectrum of **5** exhibits the signal of a Me geminal to the γ-lactone oxygen (grouping **C**) (δ 1.05, 3H, *s*). The occurrence of the γ-lactone implies the presence of a side chain *A* in **1**. The existence and structure of the above side chain is confirmed by the mass spectra of **1** and **3** *m/z* 109 (100%, $C_8H_{15}O$–H_2O), of **4** *m/z* 143 (100%, $C_8H_{15}O_2$) and of **5** *m/z* 99 (100%, $C_5H_7O_2$). Treatment of **5** with $BF_3{\cdot}Et_2O$ yields a carbonyl compound with a γ-lactone grouping **6** (IR 1705 and 1780 cm^{-1}).

The side of one of the rings of the biannular system was determined as follows: catalytic hydrogenation of **1** afforded **7** from which dehydration with $POCl_3$ gave **8**, **9** and **10**. Oxidative degradation of the side chains of the olefins

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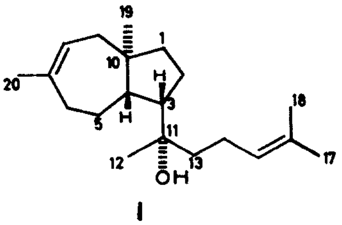
* Part 7 in the series 'Constituents of *Halimium viscosum*'. For Part 6 see ref. [6].

† We maintain the numbering system of ref. [7].



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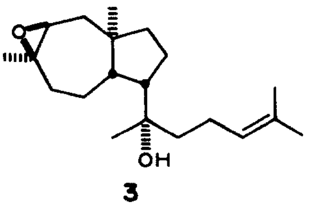

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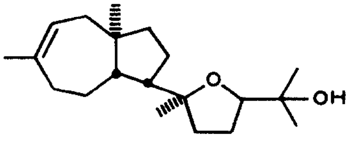

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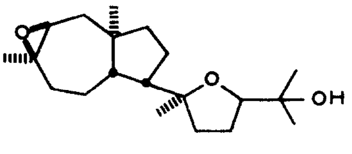

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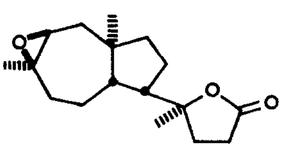

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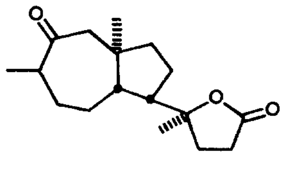

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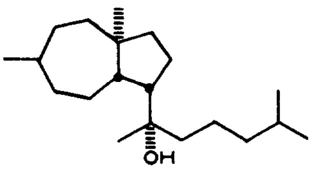

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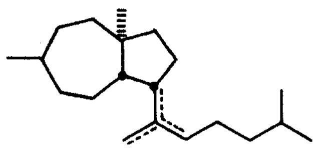
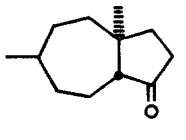


	Δ
8	3,11
9	11,13
10	11,12



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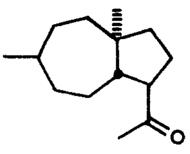
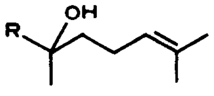


12

8 and **9** by ozonolysis or permanganate oxidation in the presence of dicyclohexyl 18-crown-6 yielded **11** and **12** respectively, which also confirmed the presence of the side chain **A** in **1**. The IR spectrum of compound **11** shows absorption at 1745 cm^{-1}, corresponding to a cyclopentanone. Accordingly, the biannular system of **1** could correspond to a bicyclic[5,3,0]decane which would support the side chain in the five-membered ring. There would also be an angular methyl group and another in the Me–C=CH– grouping on the seven-membered ring.

Homonuclear (COSY) and heteronuclear (HC-COSY and HC-Long-range COSY) two-dimensional NMR experiments did not normally yield interpretable results owing to the large overlap between the signals of the ^{1}H NMR spectrum. Accordingly, in order to establish unequivocally the carbon skeleton of tormesol **1** a two-dimensional ^{13}C–^{13}C correlation experiment (2D-Inadequate) was performed; the results of this directly visible from the spectrum or from analysis of its different segments are shown in Table 1. As may be seen, of a maximum of 21 connectivities, the 18 shown in structure E, were detected.

Establishment of connectivities between carbon atoms 4 and 10, 1 and 10 and 2 and 3 was performed by studying of the long-range heteronuclear correlations (^{1}H/^{13}C); the results are summarized in Table 2. In view of these findings the carbon skeleton of tormesol **1** is established as a bicyclic[5, 3, 0]decane by simultaneously assigning the ^{1}H and ^{13}C spectra (Tables 2 and 3).



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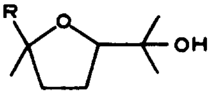

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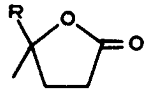

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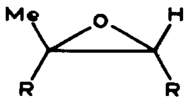

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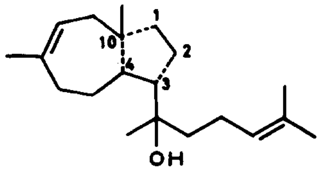

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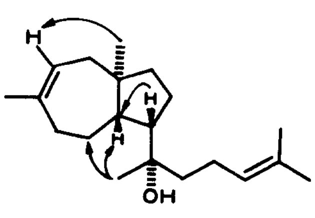

F

Table 1. 2D-Indadequate correlation for compound **1**

C	δ (ppm)	Conectivities
1	42.49	2
2	26.30	1
3	52.64	4, 11
4	56.81	3, 5, 10
5	24.06	4, 6
6	36.11	5, 7
7	139.08	6, 8, 20
8	122.93	7, 9
9	41.48	8, 10
10	42.41	4, 9, 19
11	75.73	3, 12, 13
12	27.80	11
13	40.31	11, 14
14	22.89	13, 15
15	124.88	14, 16
16	131.52	15, 17, 18
17	25.72	16
18	17.70	16
19	19.25	10
20	26.96	7

Table 2. Long-range 2D ^1H–^{13}C correlations for compound **1**

C	H	C	H
1	19	11	2, 3, 4, 12
2	—	12	13
3	2, 4, 12	13	3, 12
4	6, 19	14	13
5	6	15	17, 18
6	4, 20	16	17, 18
7	6, 20	17	18
8	6, 20	18	17
9	19	19	4, 9
10	1, 19	20	—

The relative configuration of 1 was established by applying differential NOE spectroscopy; by saturation of the Me-19, NOE over H-8 is observed but not with H-4 nor with H-3. From this it may be inferred that the inter-ring bonding is *trans*. After saturation of H-3 NOE over H-4 is seen such that H-3 and H-4 must be in the *cis* position (structure **F**). The two-dimensional COSY spectrum of **1** shows the existence of long range coupling (^4J) between the methyl H-19 and the H-9α, H-1α and H-4; this confirms the *trans* inter-ring bonding. Taking into account that the CD curve of **11** has a negative EC [10] ($\Delta\varepsilon_{296} = -1.57$), the absolute configuration of the biannular system of 1 must be as shown in E and F. NOE is observed over H-3 and αH-5 when Me-12 is irradiated, taking into account the most probable conformation with the minimum interactions for the side chain (using Dreiding models), we propose the *S*-configuration for C-11.

EXPERIMENTAL

Mps: uncorr. ^1H NMR: 200 MHz, $CDCl_3$, TMS as int. standard; ^{13}C NMR: 50.3 MHz. 2D-Inadequate. 128 FID (2048 data points) of 768 scans each were acquired, with quadrature detection and phase cycling as in the INADSYM. AU Bruker pulse sequence, on a 2.53 M sample (10 mm tube) in $CDCl_3$ soln at 24°. The recycle delay was 2 sec; the evolution time was changed from 2 μsec to 37.9 msec in 128 steps, P_3 pulse was selected for better quadrature image suppression (135°) and the spin-echo period was adjusted for couplings of about 80 Hz. 2D-FT was performed with one degree of zero-filling in the t_1 domain after sine-bell filtration in both domains, yielding a matrix which was analysed before and after symmetrization. Digital resolution (DR) 6.6 Hz/pt. ^1H–^{13}C correlations. One-bond corr. 256 FIDS (1024 data points) of 128 scans each were acquired, with quadrature detection and phase cycling as in the HCCORR Bruker pulse sequence, on a 0.71 M sample (5 mm tube) in $CDCl_3$ soln, at 27°. The recycle delay was 1 sec; the evolution time was incremented from 3 μsec to 128 msec in 256 steps. Modulation was tuned for $^1J_{H,C} = 135$ Hz. 2D-FT was performed after sine-bell filtration in both domains and DR was 3.4 Hz/pt. The long-range correlation expt was performed on the same sample and under the same conditions as in the one-bond correlation, except for modulation tuning which was optimized for $^nJ_{H,C} = 10$ Hz and for the number of scans, which was doubled.

Table 3. ^1H NMR spectral data of compounds **1–8** and **11**

H	1	2	3	4	5	6	7	8	11
3	2.44 *ddd* (11.5,10.0,5.0)	—	—	—	—	—	—	—	—
8	5.42 *br d*	5.32 *m*	2.76 *t* (7.1)	2.72 *t* (7.1)	2.77 *t* (7.1)	—	—	—	—
12	1.22 *s*	1.02 *s*	1.18 *s*	1.08 *s*	1.28 *s*	1.31 *s*	1.20 *s*	1.61 *s*	—
15	5.15 *t* (7.0)	3.60 *m*	5.18 *t* (7.0)	3.65 *m*	—	—	—	—	—
17	1.71 *s*	1.12 *s*	1.77 *s*	1.17 *s*	—	—	0.89 *d* (6.8)	0.87 *d* (6.8)	—
18	1.65 *s*	1.12 *s*	1.72 *s*	1.13 *s*	—	—	0.89 *d* (6.8)	0.87 *d* (6.8)	—
19	0.82 *s*	0.79 *s*	0.98 *s*	0.94 *s*	0.98 *s*	0.95 *s*	0.91 *s*	0.89 *s*	0.98 *s*
20	1.75 *s*	1.73 *s*	1.32 *s*	1.29 *s*	1.32 *s*	1.00 *d* (6.8)	0.89 *d* (6.8)	0.87 *d* (6.8)	0.99 *d* (6.8)

Coupling constants to parentheses.

Extraction and isolation. Aerial parts of *H. viscosum* collected at La Fregeneda (herbarium samples of plants from the three populations available from Dept. of Botany, University of Salamanca, Spain) were dried and extracted with *n*-hexane in a Soxhlet over 24 hr (6.05%). This ext. was dewaxed with MeOH (20.5%) and then extracted with 6% $NaHCO_3$ (9.8%), 10% Na_2CO_3 (39.1%) and 4% NaOH (13.4%). The neutral fraction represented 35.4% of the original ext. CC of 58 g of the neutral fraction and elution with *n*-hexane–Et_2O (9:1) yielded 1.5 g of **1**.

Tormesol **1**. Colourless crystals, mp 60–61° (*n*-hexane) $[\alpha]_D^{22}$ + 30.8° ($CHCl_3$; *c* 1.10). IR ν_{max}^{BrK} cm^{-1}: 3380, 1640, 1100, 950, 890; ^1H NMR (see Table 3); ^{13}C NMR (see Table 1). EIMS 70 eV, *m/z* (rel. int.): 290 $[M]^+$ (0.5), 272 (6), 207 (22), 203 (7), 189 (8), 163 (17), 148 (71), 133 (71), 127 (4), 109 (100), 83 (9), 69 (20).

Reaction of **1** *with* m*-chloroperbenzoic acid. m*-Chloroperbenzoic acid (305 mg) (previously washed in KH_2PO_4–NaOH buffer, pH 7.5, and dried under red. pres. dissolved in 4 ml of CH_2Cl_2 were added to 514 mg of **1** dissolved in 5 ml of CH_2Cl_2 with continuous stirring over 2.5 hr. Following this, Na_2SO_3 was added (10%) until the oxidant had disappeared. The organic phase was decanted and washed with $NaHCO_3$ (5%) and with satd NaCl. After evapn of solvent 512 mg of the reaction product were recovered from which, following CC over silica gel, 130 mg (*n*-hexane–Et_2O, 9:1) of **1**, 140 mg (*n*-hexane–Et_2O, 4:1) of **2**, 110 mg (*n*-hexane–Et_2O, 7:3) of **3** and 110 mg (*n*-hexane–Et_2O, 3:2) of **4** were obtained.

Compound **2**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3480, 1650, 1145, 1080, 960, 900, 850, 810, ^1H NMR (see Table 3).

Compound **3**. Colourless oil $[\alpha]_D^{22}$ + 0.18° ($CHCl_3$; *c* 1.11); IR ν_{max}^{film} cm^{-1}: 3500, 1650, 1140, 1115, 1085, 965, 940, 885, 830; ^1H NMR (see Table 3). EIMS 70 eV, *m/z* (rel. int.): 306 $[M]^+$ (0.5), 288 (1.5), 288 (1.5), 244 (1.5), 179 (3), 161 (12), 143 (35), 109 (100), 107 (34), 95 (35), 85 (35), 83 (42), 71 (37), 69 (61), 59 (33), 43 (40).

Compound **4**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3480, 1135, 1090, 960, 880. ^1H NMR (see Table 3). EIMS 70 eV, *m/z* (rel. int.) : 307 $[M-H_2O]^+$ (1), 289 (0.5), 286 (1), 143 (100), 125 (35), 109 (16), 95 (25), 93 (28), 85 (95), 81 (34), 71 (55), 69 (25), 67 (27), 59 (45), 55 (37), 43 (42).

Oxidation of **2**, **3** and **4** with Na_2CrO_4. Dry Na_2CrO_4 (55 mg) 1 ml of HOAc, 1 ml of $(AcO)_2O$ and 20 mg of dry NaOAc were added to 27.3 mg of **2** dissolved in 1 ml of C_6H_6. The mixt was stirred for 44 hr at 44°. Ice was then added and after 1 hr extraction was performed with Et_2O. The Et_2O extract was washed with $NaHCO_3$ and then with H_2O. After evapn of solvent 21.4 mg of reaction product were recovered from which prep. TLC yielded 19 mg of **5**. Upon subjecting 21.7 mg of **3** and 40 mg of **4** to the above treatment, 17.5 and 29.1 mg, respectively, of **5** were obtained. Colourless crystals, mp 121–122° $[\alpha]_D^{22}$ – 4.1° ($CHCl_3$; *c* 0.73). IR ν_{max}^{film} cm^{-1}: 1790, 1260, 1220, 1195, 1140, 1080, 965, 945, 880; ^1H NMR (see Table 3). EIMS 70 eV, *m/z* (rel. int.): 278 $[M]^+$ (0.5), 161(7), 99 (100), 95 (19), 93 (25), 91 (19), 81 (28), 79 (28), 77 (16), 71 (27), 69 (18), 67 (26), 55 (48), 43 (72).

Rearrangement of **5** *with* BF_3 *etherate.* Freshly dist. BF_3 etherate (0.02 ml) was added to 53 mg of **5** dissolved in 1 ml of C_6H_6. After 20 min a few drops of H_2O were added and extn performed with Et_2O. The mixt. was then washed with Na_2CO_3 and H_2O; 42 mg of reaction product were obtained which after CC yielded 30 mg of **6**. Colourless crystals, mp 115°. $[\alpha]_D^{22}$ – 88.6° ($CHCl_3$; *c* 0.53); IR ν_{max}^{film} cm^{-1}: 1780, 1705, 1125, 1090, 970, 940, 820; ^1H NMR (see Table 3). EIMS 70 eV *m/z* (rel. int.): 278 $[M]^+$ (3), 260 (1.5), 161 (7), 99 (100), 95 (35), 93 (20), 91 (23), 81 (28), 79 (32), 77 (20), 71 (31), 69 (19), 67 (40), 55 (50), 53 (20), 43 (84).

Hydrogenation of **1**. PtO_2 (20 mg) was added to 500 mg of **1** dissolved in 25 ml of dry Et_2O and the mixt. hydrogenated at normal pres. for 5.5 hr. Following this the mixt. was filtered and the solvent evapd to yield 474 mg of **7**. Colourless oil $[\alpha]_D^{22}$ – 4.5° ($CHCl_3$; *c* 1.80); IR ν_{max}^{film} cm^{-1}: 3410, 1100, 910; ^1H NMR (see Table 3); EIMS 70 eV *m/z* (rel. int.): 294 $[M]^+$ (0.5), 276 (4), 191 (94), 165 (14), 129 (100), 111 (45).

Dehydration of **7**. To a soln of 510 mg of **7** in 6 ml of C_6H_5N at 0°, 1.5 ml of $POCl_3$ was added dropwise. The mixt. was then kept at room temp. for 20 hr, poured onto ice and extracted with Et_2O. The resulting Et_2O soln was washed with 2 N HCl, $NaHCO_3$ (5%) and H_2O, dried (Na_2SO_4) and the solvent evapord to yield 440 mg of reaction product. After CC on silica gel impregnated with 15% $AgNO_3$ and elution with dry hexane 65 mg of **8**, 95 mg of **9** and 55 mg of **10** were obtained. **8**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 1450, 1370. ^1H NMR (see Table 3). **9**. Colourless oil IR ν_{max}^{film} cm^{-1}: 3020, 1450, 1360. ^1H NMR: δ 5.14 (1H, *t*, $J = 7.1$ Hz), 1.55 (3H, *s*), 0.94 (3H, *s*), 0.91 (3H, *d*, $J = 6.5$ Hz), 0.89 (6H, *d*, $J = 6.5$ Hz). **10**. Colourless oil. IR ν_{max}^{film} cm^{-1}: 3080, 1645, 1465, 1390, 1370, 890. ^1H NMR: δ 4.88 (1H, *m*), 4.79 (1H, *m*), 2.81 (1H, *m*), 0.90 (3H, *s*), 0.81 (6H, *d*, $J = 6.8$ Hz), 0.87 (3H, *d*, $J = 6.8$ Hz).

Ozonolysis of **8**. **8** (65 mg) was dissolved in 10 ml of CH_2Cl_2 and after cooling to – 78°, O_3 was bubbled through the soln for 4 min. The reaction product was then poured over HOAc (1 ml),

CH_2Cl_2 (5 ml) and powdered Zn (500 mg). The mixt. was 7 stirred for 2 hr, after which the CH_2Cl_2 was evapd and the residue obtained dissolved in Et_2O. The Et_2O soln was washed with 5% $NaHCO_3$ and H_2O until neutral, dried (Na_2SO_4) and concd *in vacuo*. CC of the reaction product on silica gel, eluting with (*n*-hexane–Et_2O, 49:1) yielded **11** (12 mg). Colourless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1745, 1465, 1380; ^{1}H NMR (see Table 3); CD (*n*-hexane): $\Delta\varepsilon_{296} = -1.57$.

Ozonolysis of **9**. Upon subjecting 55 mg of **9** to the above treatment, 22 mg of **12** were obtained. Colourless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1710, 1230, 1170, 1150, 870, ^{1}H NMR: δ 3.26 (1H, *m*), 2.12 (3H, *s*), 0.91 (3H, *s*), 0.86 (3H, *d*, $J = 6.8$ Hz). EIMS 70 eV *m/z* (rel. int.): 208 $[M]^+$ (37), 192 (25), 190 (42), 175 (22), 165 (31), 163 (80), 150 (86), 138 (37), 137 (51), 135 (38), 123 (54), 109 (99), 95 (100), 93 (37), 81 (74), 79 (40), 71 (4).

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