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Diterpenes from *Laennecia sophiifolia*

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Abstract

From the aerial parts of *Laennecia sophiifolia* (Kunth) G.L. Nesom, a *neo*-clerodane and an acyclic furano diterpene were isolated, along with four known compounds, 2β-hydroxyhardwickiic acid, hawtriwaic acid, apigenin, and β-sitosterol. Their structures were established as 12-*epi*-bacchotricuneatin A and (2*E*,6*E*)-9-(3-furyl)-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid, by analysis of spectral evidence. The absolute structure of 12-*epi*-bacchotricuneatin A was determined by a circular dichroism spectral comparison with that of bacchotricuneatin A.

Keywords: *Laennecia sophiifolia*; Asteraceae; Asteroidae; 12-*epi*-Bacchotricuneatin A; (2*E*; 6*E*)-9-(3-furyl)-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid

1. Introduction

It is believed that several epithet of the genus *Conyza* Less. (Asteraceae, Asteroidae, tribe Astereae) have been transferred to the genus *Laennecia* Cass. (Nesom, 1990; Sancho and Ariza Espinar, 1999). Three species of the latter genus are distributed in Argentina and one of these, *Laennecia sophiifolia* (Kunth) G.L. Nesom, is growing in the central-western semiarid region of Cuyo. Several species of the *Conyza* genus have been chemically investigated and acyclic furano diterpene and *ent*-labdane diterpenes (Galal et al., 1998; Torrenegra et al., 1994), *neo*-clerodanes and rearranged clerodanes (Zdero et al., 1990a; Pandey et al., 1984; Bohlmann and Wegner, 1982), *seco*-clerodanes (Zdero et al., 1990b, 1991) and labdane glycosides (Ahmed, 1991; Torrenegra et al., 1994) have been reported as the principal diterpenes skeletons present. Some members of the *Conyza* genus have been used as a crude drug to treat a gastrointestinal ailment (Mata et al., 1997; Torrenegra et al., 1994).

As a continuation of our search for diterpenoids from the Asteraceae (Favier et al., 1997) and Lamiaceae (Nieto et al., 2000) families, we have now examined the aerial parts of *L. sophiifolia* for the purpose of comparing constituents between the genera of *Conyza* and *Laennecia*. From the acetone extract, a new *neo*-clerodane (**1**), epimer of **2** at C-12, and a new acyclic furano diterpene (**3**), configurational isomer of centipedic acid (**4**) (Bohlmann and Mahanta, 1979), were isolated together with four known compounds, 2β-hydroxyhardwickiic acid (**5**) (Jolad et al., 1988), as well as hawtriwaic acid (**6**) (Hsü et al., 1971), apigenin, and β-sitosterol. This paper deals with the structures of the new compounds.

2. Results and discussion

Compound **1** was isolated in crystalline form and assigned the molecular formula $C_{20}H_{22}O_5$, by elementary analysis. The UV spectrum absorption maxima at 205 and 239 nm, and IR absorptions at ν_{max} 1767 and 1731 cm^{-1}, pointed to the presence of two lactone carbonyl groups. The ^1H NMR spectral data (Table 1) showed characteristic signals of a β-substituted furan ring at δ 7.44 (*br s*, H-I5), 7.41 (*br s*, H-16) and 6.41 (*br*

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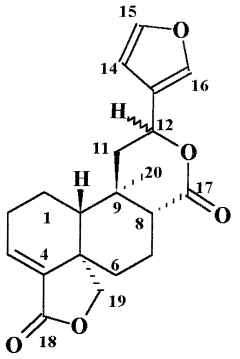
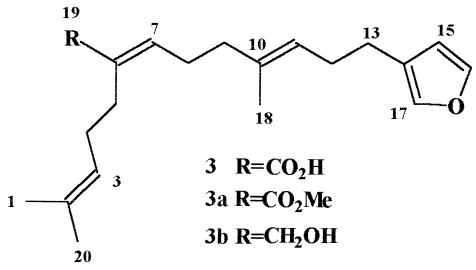
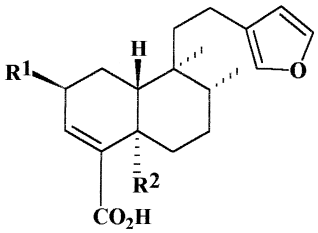


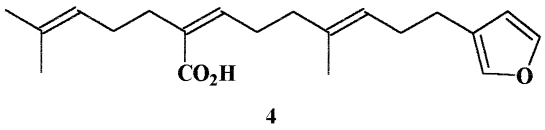
1= 12-S
2= 12-*R*



3 R=CO_2H
3a R=CO_2Me
3b R=CH_2OH



5 R^1= OH R^2= CH_3
6 R^1= H R^2= CH_2OH



4

s, H-14), which were in accordance with the IR absorption ν_{max} 3143, 1504, 874 cm^{-1} for a furan ring. A signal at 6.74 ppm (*dd*, *J*=6.5, 2.0 Hz) was ascribed to the olefinic H-3 on the β-carbon of a α,β-unsaturated carbonyl system. The one-proton resonance at δ 5.54 (*dd*, *J*=11.0, 5.9 Hz) together with signals as multiplets at 1.77 and 2.32 ppm, were consistent with an ABX system formed by H-12 and the C-11 methylene protons, respectively. The angular methyl at C-9 showed a resonance as a δ 0.9 singlet. On the other hand, three one-proton signals clearly coupled in the H/H COSY spectrum at δ 4.31 (*d*, *J*=7.9 Hz), 3.97 (*dd*, *J*=7.9, 1.0 Hz) and 1.25 (*br t*, *J*=12.0, 1.0 Hz), were assigned to H-19 *pro*-R, H-19 *pro*-S and H-6β protons, respectively in

Table 1
^{1}H NMR chemical shifts for compounds **1**, **3**, **3a**, and **3b** (*J*=Hz)

Proton	**1**[a]	Proton	**3**[b]	**3**[c]	**3a**[c]	**3b**[b]
2H-1	1.80 *m*	1	1.60 *br s*	1.63 *br s*	1.68 *br s*	1.69 *br s*
2A	2.45 *m*	3	5.20 *m*	5.19 *m*	5.19 *br t* (6.0)	5.11 *m*
2B	2.25 *m*	4	2.20–2.40[d]	2.27 *m*	2.10 *br t* (4.0)	2.25 *m*[d]
3	6.74 *dd* (6.5, 2.0)	5	2.20–2.40 *m*[d]	2.30 *m*	2.25 *m*[d]	
6α	1.80 *m*	7	6.90 t (7.3)	7.02 *t* (7.3)	6.72 *t* (7.3)	5.38 *br t* (7.4)
6β	1.25 *br t* (12.0, 1.0)	8	2.20–2.40 *m*[d]	2.07 *br q* (7.3)	2.35 *m*[d]	2.00–2.20 *m*[d]
8	2.30 *m*	9	2.00–2.20 *m*[d]	1.88 *br t* (7.3)	2.30 *m*[d]	2.00–2.20 *m*[d]
10	1.82 *m*	11	5.15 *br t* (8.2)	5.11 *ddd* (8.2, 1.0, 1.0)	5.20 *br t* (6.8)	5.18 *br t* (6.3)
11α	2.32 *m*	12	2.15 *m*	2.14 *m*	2.23 *m*[d]	2.00–2.20 *m*[d]
11β	1.77 *m*	13	2.45 *m*	2.39 *m*	2.45 *br q* (7.5)	2.47 *bt t* (7.3)
12	5.54 *dd* (11.0, 5.9)	15	6.30 *br s*	6.08 *br s*	6.28 *br s*	6.27 *br s*
14	6.41 *br s*	16	7.35 *br s*	7.15 *br s*	7.31 *br s*	7.31 *br s*
15	7.44 *br s*	17	7.20 *br s*	7.07 *br s*	7.20 *br s*	7.19 *br s*
16	7.41 *br s*	18	1.55 *br s*[d]	1.41 *br s*	1.60 *br s*	1.60 *br s*
19 *pro*-R	4.31 *d* (7.9)	19 (2H)				4.0 *br s*
19 *pro*-S	3.97 *dd* (7.9, 1.0)	20	1.55 *br s*[d]	1.55 *br s*	1.60 *br s*	1.60 *br s*
20	0.90 *s*	−OMe			3.72 *s*	

[a] Acquired at 400.0 MHz in $CDCl_3$.
[b] Acquired at 200.0 MHz in $CDCl_3$.
[c] Acquired at 200.0 MHz in C_6D_6.
[d] Overlap.

which H-6β showed the ^4J long range W coupling ($J = 1.0$ Hz) with the H-19 *pro*-S diasterotopic proton (Ceñal et al., 1997). Similarly, W coupling of the angular methyl group with both H-8 and H-11β, was observed.

Six methylene carbons including one oxygenated methylene at δ_c 71.1, three methine sp^3 carbons including one oxygenated methine at δ_c 71.8 and two sp^3 quaternary carbons were observed from the ^{13}C NMR spectrum. All the NMR signals of **1** were assigned by analyzing the DEPT, H/H-COSY, HMQC, and HMBC experiments. The HMBC correlation shown in Table 3 proved **1** to have all the expected connectivities for the proposed clerodane skeleton. Taking into account the above discussed spectral data the framework of compound **1** was similar to bacchotricuneatin A (**2**), a *neo*-clerodane diterpene isolated from several species of the genus *Baccharis* (Asteraceae) (Wagner et al., 1978; Merrit and Ley, 1992). When the ^1H NMR spectrum of **1** was subjected to a direct comparison with the spectral data of an authentic sample of **2** isolated from *Boccharis spicata* (Lam.) Beill (Gallardo et al., 1996) a close resemblance was observed. Thus only 0.2 ppm down-field H-12 chemical shift, 0.11 up-field for H-20 difference respect to **2**, and minor disagreement in the methylene protons regions, were observed as relevant features. However, both the melting point and optical rotation values were different. Now, taking in mind the sensitivity of the ^{13}C NMR spectroscopy in order to detect configurational changes, spectral comparison between compounds **1** and **2** showed significant gaps in the chemical shifts of some carbon atoms (Table 2), namely an up-field shift for C-17 ($\Delta\delta_C = -4.7$ ppm), and C-20 ($\Delta\delta_C = -5.7$ ppm) as well as the down-field shift of C-12 ($\Delta\delta_C = +1.9$ ppm). With the aforementioned exceptions the remaining ^{13}C NMR signals were very close to those observed for **2**. The detected ^{13}C NMR chemical shift differences between compounds **1** and **2**, together with the different ^1H NMR coupling constants obtained for H-12, suggest opposite configuration for the C-12 stereogenic center. In order to confirm the relative stereochemistry depicted for compound **1**, the ROESY experiments were carried out using **1** and **2**. Thus, while a significant NOE cross-peak was observed between H-12 and H-20 in **1**, no cross-peak was detected between these protons in the corresponding ROESY spectrum of compound **2**. In addition, the observed cross-peaks between H-20 and both H-19 *pro*-S and H-19 *pro*-R were in agreement with the proposed relative stereochemistry for compound **1**.

The absolute structure of **1** was determined by comparing the CD curve with that of **2** which had been determined unequivocally by X-ray diffraction analysis (Wagner et al., 1978). The CD spectrum of **1** in CH_3CN exhibited two negative Cotton effects, at 238 ($\Delta\varepsilon = -8.1$) and 205 nm ($\Delta\varepsilon = -2.8$) (Fig. 1). The first Cotton effect, assigned to a transition of the α,β-unsaturated lactone, showed the same sign and almost identical intensity with the corresponding Cotton effect obtained from compound **2** (241 nm, $\Delta\varepsilon = -8.5$), therefore leading to the conclusion that both compounds have the same steric environment. In addition, the second Cotton effect corresponding to the transition of the furan ring, exhibited remarkably decreased the intensity than **2** (197 nm, $\Delta\varepsilon = -7.3$), indicating **1** to be the 12 S-epimer of **2** (Ciardelli and Salvadori, 1973; Nakanishi et al., 1994). Thus, compound **1** was proved to be 12-*epi*-bacchotricuneatin A.

Table 2
^{13}C NMR spectral data for compounds **1**, **3**, **3a**, and **3b**[a]

Carbon	**1**[b]	Δδ (**1**–**2**)	**3**[c]	**3**[d]	**3a**[c]	**3b**[c]
1	18.9 *t*	−0.3	25.6 *q*	25.7 *q*	27.0 *q*	25.9 *q*
2	27.3 *t*	−0.2	132.3 *s*	132.1 *s*	131.7 *s*	131.8 *s*
3	135.8 *d*	−0.1	123.6 *d*	124.1 *d*	123.7 *d*	124.0 *d*[e]
4	137.4 *s*	−0.1	27.5 *t*[e]	28.0 *t*	27.0 *t*[e]	27.0 *t*[e]
5	44.2 *s*	+0.3	28.4 *t*[e]	28.7 *t*	28.3 *t*[e]	28.1 *t*[e]
6	33.1 *t*	−0.4	131.3 *s*	131.7 *s*	132.1 *s*	135.2 *s*
7	18.9 *t*	−1.1	145.3 *d*	145.6 *d*	142.6 *d*[e]	124.1 *d*[e]
8	53.1 *d*	−0.8	26.7 *t*[e]	27.0 *t*	27.6 *t*[e]	28.3 *t*[e]
9	36.9 *s*	+0.1	38.3 *t*	38.5 *t*	38.4 *t*	39.5 *t*
10	50.8 *d*	+3.3	134.4 *s*	134.4 *s*	134.5 *s*	137.8 *s*
11	42.5 *t*	−0.9	124.7 *d*[e]	125.1 *d*	124.5 *d*	126.7 *d*
12	71.8 *d*	+1.9	27.3 *t*[e]	27.4 *t*	25.6 *t*[e]	25.6 *t*[e]
13	125.4 *s*	+1.1	24.9 *t*[e]	25.1 *t*	24.8 *t*[e]	24.9 *t*[e]
14	108.3 *d*	−0.1	124.7 *s*[e]	128.2 *s*	124.7 *s*	124.8 *s*
15	143.7 *d*	−0.1	111.0 *d*	111.2 *d*	110.9 *d*	111.0 *d*
16	139.3 *d*	−0.2	142.5 *d*	142.8 *d*	142.5 *d*[e]	142.4 *d*
17	168.4 *s*	−4.7	138.3 *d*	139.2 *d*	138.7 *d*	138.7 *d*
18	171.1 *s*	+2.6	15.9 *q*[e]	15.8 *q*	15.9 *q*	15.9 *q*
19	71.1 *t*	0.0	173.5 *s*	174.3 *s*	168.3 *s*	67.1 *t*
20	13.4 *q*	−5.7	17.6 *q*[e]	17.6 *q*	17.5 *q*	17.6 *q*
−OMe					51.5 *q*	

[a] Multiplicities were determined by a DEPT experiment.
[b] Acquired at 127.7 MHz in $CDCl_3$.
[c] Acquired at 50.2 MHz in $CDCl_3$.
[d] Acquired at 50.2 MHz in C_6D_6.
[e] Interchangeable in each column.

Table 3
Two and three bond HMBC correlations for compound **1**[a]

Proton	Correlated carbons
H-2	C-4
H-3	C-1, C-2, C-4, C-5, C-18
2H-11	C-9, C-12, C-13
H-12	C-11, C-13, C-14, C-16, C-17
H-14	C-13, C-15, C-16
H-15	C-13, C-14
H-16	C-13, C-14
2H-19	C-4, C-5, C-6, C-10, C-18
H-20	C-8, C-9, C-10, C-11

[a] Determined in $CDCl_3$ at 400 MHz.

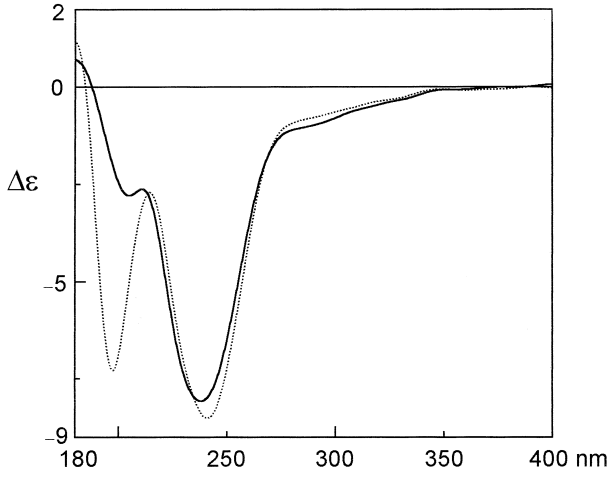


Fig. 1. CD spectra of compounds **1** (solid line) and **2** (dotted line) in CH_3CN.

Compound **3** was estimated by the molecular formula $C_{20}H_{28}O_3$ by EIMS ($[M]^+$, m/z 316), ^1H NMR and ^{13}C NMR spectral data. A base peak at m/z 81$[C_5H_5O]^+$ in the EIMS spectrum as well as IR absorption at 873 and 1502 cm^{-1}, together with the broad singlet low-field signals at δ 6.30, 7.35 and 7.20 in the ^1H NMR spectrum (Table 1), indicated the existence of a β-substituted furan ring. The ^1H NMR spectra in $CDCl_3$ also showed the presence of three vinyl methyl groups, two of them overlapped at δ 1.55 and the other one at 1.60 ppm. These signals were clearly allylically coupled from the H/H COSY spectrum with the olefinic protons at δ 5.15 (*br t*) and 5.20 (*m*), respectively. Complex patterns of methylene-proton signals at δ 2.00–2.50 were also observed. The ^1H NMR spectral data of **3** was fully interpreted through the use of C_6D_6 as solvent. In this case the high-field methyl and methylene proton signals were shifted significantly (see Table 1), due to the different magnetic environment provided by the solvent. Using this condition the 2D NMR spectral data were obtained.

The ^{13}C NMR of compound **3** (Table 2) showed signals for one acid carbonyl group, six sp^2 methines, six methylenes, four sp^2 quaternary carbons and three methyl groups. The multiplicities were assigned by DEPT and extensive 2D experiments (HETCOR and COLOC).

All the above discussed spectral data, as well as the seven degrees of unsaturation from the molecular formula, suggested for compound **3** a structure closely related with that reported for centipedic acid, **4** (Bohlmann and Mahanta, 1979). This kind of acyclic diterpene has been reported from other members of the *Conyza* genus (Galal et al., 1988; Zdero et al., 1990a,b, 1991; Bohlmann and Wegner, 1982).

The stereochemistry at the C-6-C-7 double bond was proposed taking into account the ^1H NMR spectral data of **3** and the values reported for **4**. In the same solvent ($CDCl_3$) the H-7 resonance of compound **3** was shifted to 0.9 ppm lower field, this result agrees well with a 6*E* configuration, similar to that shown by related diterpenes (Saad et al., 1987), and opposite to the centipedic acid **4**. Furthermore, the NOESY experiment of **3** in C_6D_6 showing no overlapped signals for the methylene region, revealed a characteristic cross-peak between H-9 and H-11, this result was in concordance with the proposed *E* stereochemistry.

The methyl ester **3a** was prepared from **3** using diazomethane and its spectral data were consistent with the presence of one carboxyl group in the molecule under study. The ^1H NMR spectrum of **3a** (Table 1) showed close resemblance to that of **3**; the methoxyl group appeared as a singlet at δ 3.72 and the H-7 proton resonance was shifted 0.30 ppm to the upper field in C_6D_6 solution (Saad et al., 1987). Reduction of **3a** with DIBAL-H in THF at −20°C, gave the allylic alcohol **3b**. Its ^1H NMR spectrum (Table 1) displayed signals for an hydroxymethylene group as a broad two-proton singlet at 4.0 ppm. On the other hand the chemical shift of H-7 (δ 5.38, *t*, J=7.4 Hz), indicated reduction of the ester function without Michael addition of the hydride ion to C-7. The remaining signals appeared to be similar to those of the starting material. The ^{13}C NMR spectral data (Table 2) were in agreement with the proposed structure for **3b**. Hence, the structure of compound **3** was established as (2*E*,6*E*)-9-(3-furyl)-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid, the 6*E* isomer of **4**.

Four known compounds, 2β-hydroxyhardwickiic acid (**5**), hawtriwaic acid (**6**), apigenine, and β-sitosterol were also isolated from this plant material and identified by comparing their spectral data with those of authentic samples, respectively.

We now found out that the main constituents of *L. sophiifolia* here reported had a chemotaxonomically close resemblance to those isolated from several species of *Conyza* plants (Zdero et al., 1991), although this plant had been classified again from the *Conyza* to *Laennecia* genus (Nesom, 1990).

3. Experimental

3.1. General

Mp: uncorr.; optical rotation: $CHCl_3$; ^1H NMR (400 and 200 MHz) and ^{13}C NMR (100.60 and 50.23 MHz): $CDCl_3$ or C_6D_6 with TMS as int. standard; HMBC, HMQC, ROESY, COSY, HETCOR, NOESY, and COLOC experiments: resolved using standard software. EIMS (probe) 70 eV; UV: CH_3CN; IR: KBr. Combustion analysis was carried out using a programmed instrument. CD: CH_3CN; prior to measurement of CD spectra, all compounds were purified by HPLC (μ-Porasil

column 300×7.8 mm i.d.) with *n*-hexane–EtOAc as eluents. Column chromatography was performed on silica gel G 70-230 mesh and Kieselgel 60 H; TLC was carried out on silica gel 60 F_{254} (0.2 thick). Preparative HPLC: silica gel (25–40 μm, 15 mm i.d.×50 cm) and refractive index detector with *n*-hexane–EtOAc (65:35) as solvent, flow 0.6 ml/min, fraction: each 1.0 ml.

3.2. Plant material

L. sophiifolia (Kunth) G.L. Nesom, was collected in El Volcan, Dpto. La Capital, San Luis, Argentina, in February 1998. A herbarium sample was deposited in the Herbario of the Universidad Nacional de San Luis (L.A. Del Vitto, E.M. Petenatti and O.S. Giordano, voucher DPG 6758-UNSL).

3.3. Extraction and isolation

The air-dried aerial part of *L. sophiifolia* (2.9 kg) was extracted with Me_2CO (×3) at room temperature for 2 days. The extract was concentrated in vacuo and the resulting dark brown syrup (837 g) was dissolved in a mixture of MeOH–H_2O (9:1), filtered, and extracted with *n*-hexane in order to remove pigment and fatty materials. The aqueous-alcohol solution was diluted with H_2O to give a MeOH–H_2O ratio of 7:3, and this was then extracted with $CHCl_3$. After evaporation of the solvent, the resulting residue was fractionated by repeated Si gel flash chromatography, CC and HPLC to yield compounds **1** (310 mg), **3** (480 mg), **5** (28 mg), **6** (150 mg). The known compounds apigenin (65 mg) and β-sitosterol (32 mg) were identified by comparison with authentic samples, respectively.

3.4. 12-epi-Bacchotricuneatin A (*1*)

Crystals, mp 173–5°C; $[\alpha]_D^{25}$ −110° ($CHCl_3$, *c* 1.1); UV (CH_3CN) λ_{max}: 239 (1600) and 205 nm (8800); CD (CH_3CN) λ_{ext} 238 (Δε−8.1) and 205 nm (Δε−2.8); IR ν_{max}^{KBr}: cm^{-1}: 3143, 2800, 1767, 1731, 1660, 1504, 1201 and 874. ^1H and ^{13}C NMR: Tables 1 and 2. Elemental analysis: Found C, 70.12; H, 6.52 ($C_{20}H_{22}O_5$ requires: C, 70.16; H, 6.48), EIMS, (probe, 70 eV) *m/z* (rel. int.): 342 (8) $[M]^+$, 312 (100), 217 (8), 189 (16), 145 (25), 131 (14), 94 (26), 95 (22) and 81(9).

3.5. (2E,6E)-9-(3-Furyl)-6-methyl-2-(4-methylpent-3-enyl)-nona-2,6-dienoic acid (*3*)

Oil. IR ν_{max}^{KBr}: cm^{-1}: 3500–2500 (*br*, COOH), 1680, 1620, 1502, 1400, 1301, 873 and 701. ^1H and ^{13}C NMR: Tables 1 and 2. EIMS, (probe, 70 eV) *m/z* (rel. int.): 316 (3) $[M]^+$, 301 (8) $[M\text{-}15]^+$, 247 (57), 235 (4) $[M\text{-}81]^+$, 229 (28), 201 (20), 175 (21), 135 (46), 121 (13), 105 (26), 91 (39), 81 (100) and 69 (42).

3.6. Compound *3a*

Compound **3** (100 mg, 0.316 mmol) was dissolved in Et_2O and treated with diazomethane. Purification of the methylated product by CC afforded the methyl ester (**3a**) (98 mg, 94.2% yield). IR ν_{max}^{KBr}: cm^{-1}: 2930, 1718, 1439, 1244, 1163, 1120, 1005 and 873. ^1H and ^{13}C NMR: Tables 1 and 2. EIMS, (probe, 70 eV) *m/z* (rel. int.): 330 (3) $[M]^+$, 315 (7), 261 (70), 229 (100), 201 (70), 183 (28), 175 (47), 135 (57), 105 (34), 91(39), 81 (78) and 67 (34).

3.7. Compound *3b*

DIBAL-H (1.1 eq.) was added to a stirred soln. of **3a** (50 mg, 0.15-mmol) in dry THF (10 ml) under a stream of argon at −20°C. After 4 h, the reaction mixture was quenched by addition of brine, and the mixture was extracted twice with Et_2O. The combined Et_2O solubles were washed, dried (Na_2SO_4) and concentrated in vacuo to give a residue. The latter was purified by flash chromatography to afford alcohol **3b** (36 mg, 78.6% yield). Oil. IR ν_{max}^{KBr}: cm^{-1}: 3400 (*br*), 3340, 2924, 2856, 1502, 1380, 1164, 1025 and 873. ^1H and ^{13}C NMR: Tables 1 and 2. EIMS, (probe, 70 eV) *m/z* (rel. int.): 302 (2) $[M]^+$, 287 (3), 233 (12), 215 (13), 202 (13), 187 (19), 147 (31), 135 (46), 91 (55), 81 (100) and 67 (46).

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