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MINOR OPLOPANES FROM *SENECIO MEXICANUS*

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Key Word Index—*Senecio mexicanus*; Compositae; Senecioneae; sesquiterpenes; oplopane derivatives.

Abstract—Oplopenone and four new oplopane derivatives were isolated from the roots of *Senecio mexicanus*. Their structures follow from spectral data and the stereochemistry of three of these compounds was determined by single crystal X-ray diffraction studies.

INTRODUCTION

Most known oplopane [1] derivatives have been described during the last 12 years as metabolites from plants belonging to the tribe Senecioneae. Highly oxygenated oplopanes were isolated from *Rugelia nudicaulis* [2] and from *Arnoglossum atriplicifolium* [3]. In addition, oplopanes were isolated from *Acrisione denticulata* [4] and from *Ageratina ligustrina* [5]. Recently, we reported [6] the isolation of the oplopane derivative (**1**) from the roots of *Senecio mexicanus* M. Vaugh. Further exploration of the extracts resulted in the isolation of four new oplopane derivatives (**2**, **4**, **6** and **7**) and oplopenone **8** [7–9] as minor constituents. Their structures were elucidated by examination of spectral data and the stereochemistry followed from single crystal X-ray diffraction analyses of the 2,4-dinitrophenylhydrazone **3**, the *p*-nitrobenzoate **5** and the natural product **6**.

RESULTS AND DISCUSSION

Further chromatographic separations of the hexane extracts left-over after the isolation of **1** [6] gave, in addition to oplopenone **8** [7–9], the four new oplopane derivatives **2**, **4**, **6** and **7**.

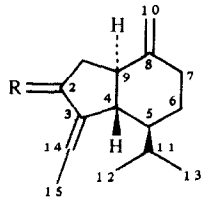
Compound **2** is a crystalline solid, mp 40–42°. Its spectral data are very similar to those of **1** [6], although the ^{1}H NMR spectrum shows the Me-15 double doublet of **1** at δ 2.10 shifted slightly downfield to 1.87, and the H-14 double quartet of **1** at 6.22 shifted up-field to 6.48. The ^{13}C NMR spectrum (Table 1) shows, as the more notable change, the C-14 signal shifted up-field. The above results indicate that **2** is a geometrical isomer of **1**. In order to corroborate the structure of **2** and to assess the stereochemistry, the 2,4-dinitrophenylhydrazone **3** was prepared as orange needles which were suitable for X-ray diffraction analysis. The molecular perspective (Fig. 1) shows the *E*-configuration for the 3,14-double bond and a *trans*-arrangement of H-4, H-5 and H-9 in agreement with the structure **2**.

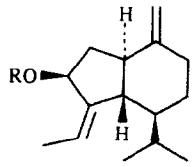
The ^{1}H NMR spectrum of **4** shows a triplet at δ 4.79 corresponding to a proton geminal to the hydroxyl group. The compound shows identical spectral properties as the alcohol prepared by sodium borohydride reduction of **1**. This is the first time that **4** has been found as a natural product. The H-1α, H-6α, H-6β and H-11 assignments were secured by irradiation experiments and the α-orientation of H-2 was determined from a single crystal X-ray diffraction analysis of the derived *p*-nitrobenzoate **5** (Fig. 2).

Compound **6** was isolated as a crystalline solid, mp 100–102°. The ^{1}H NMR spectrum shows two broad singlets at δ 4.50 and 4.77 due to an exocyclic methylene group and a quartet at 4.00 due to a proton coupled to a methyl group. Two doublets corresponding to an isopropyl group appear up-field. Homonuclear spin decoupling experiments allow the ^{1}H NMR assignments given in the experimental section. The ^{13}C NMR assignments were confirmed from a two dimensional ^{13}C–^{1}H chemical shifts correlation diagram and the assignments of C-4, C-5 and C-9 were established from a proton-coupled spectrum. The stereochemistry follows from the X-ray diffraction analysis. The molecular perspective (Fig. 3) shows the same *trans*-arrangement of H-4, H-5 and H-9 as the above compounds, the α-orientation of H-3 and the (*S*)-configuration of C-14.

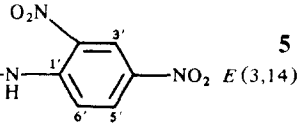
The ^{1}H NMR spectrum of **7** shows two doublets at δ 0.70 and 0.90, due to an isopropyl group, a double quartet at 6.12 and two methyl signals corresponding to an angelate group. A singlet due to an acetyl group at δ 2.20, and an AB system at 4.35 and 4.32 due to the C-10 methylene were also observed. The IR spectrum exhibited absorption for a carbonyl group (1706 cm^{-1}) and for a hydroxyl group (3600 and 3500 cm^{-1}). The ^{13}C NMR spectrum (Table 1) shows 20 signals, the one at δ 210.8 was assigned to the ketone carbonyl and two, at 73.4 and 65.3, to the carbons bearing the hydroxyl group and the ester group, respectively.

Oplopenone **8** was identified from the spectral data, which are in agreement with the reported values [7–9]. The H-3α, H-4β and H-5α-orientation was established from coupling constants values and inspection of a Dreiding model. The ^{1}H NMR data are given in the Experimental section and the ^{13}C NMR data in Table 1.



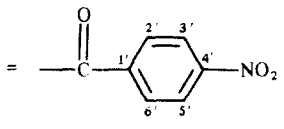


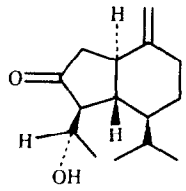
1 R = O *Z*(3,14)
2 R = O *E*(3,14)

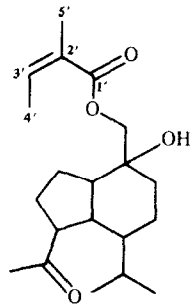


4 R = H

5 R =







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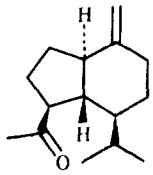

8

EXPERIMENTAL

General. Mps: uncorr. UV spectra were recorded in EtOH and in dioxane and IR spectra from films. The specific rotations were measured in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as int. standard. TLC were carried out on 0.25 mm layers of silica gel PF_{254} (Merck). The intensity data of the X-ray diffraction analyses were measured on a Nicolet R3m four-circle diffractometer with Cu-Kα monochromated radiation in the $\theta:2\theta$ scan mode. The structures were solved by direct methods using the software provided by the manufacturer and refined by full matrix least-squares assuming the anisotropic temperature factors for non-hydrogen atoms. Lists containing atomic coordinates and thermal parameters, bond distances, anisotropic temperature factors, hydrogen atom coordinates and comparison of the observed and calculated structure factors are deposited at the Cambridge Crystallographic Data Centre.

Plant material. Senecio mexicanus Mc. Vaugh was collected at Km 53 of the Morelia-Zacapu highway, in the State of Michoacán, México, during December 1986. A voucher specimen (JDH37) is deposited at the Herbarium of Departamento Botánico, ENCB-IPN, Mexico City, where Prof. Jerzy Rzedowski identified the plant material.

Extraction and isolation. Air-dried roots (700 g) of *Senecio mexicanus* were extracted with hexane and chromatographed on CC with silica gel 60 (70–230 mesh). Fractions eluted with hexane–$CHCl_3$ (4:1) yielded **2** (1 g) as colourless crystals, mp 40–42°; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1731, 1650 (C=C–CO), 1466, 1440, 1387, 1369 (isopropyl). UV λ_{max}^{EtOH} nm (log ε): 236 (3.97). ^1H NMR (300 MHz); δ0.82 and 1.00 (3H each, 2*d*, $J_{11,12}=J_{11,13}=7$ Hz, isopropyl), 1.30 (1H, complex signal, H-6β), 1.87 (3H, *dd*, $J_{15,14}=7.5$ Hz; $J_{15,4}=2.2$ Hz, Me-15) 4.58 (1H, *br s*, H-10), 4.79 (1H, *br s*, H-10′) and 6.47 (1H, *dq*, $J_{14,4}=2.2$ Hz, $J_{14,15}=7.5$ Hz, H-14). ^{13}C NMR, see Table 1.

$$[\alpha]=\frac{589\quad 578\quad 546\quad 436\quad 365\,nm}{-108\quad -115\quad -140\quad -370\quad -1685}\ (CHCl_3;\ c\ 0.13)$$

2,4-*Dinitrophenylhydrazone of compound* **2**. Orange needles: mp 212–214°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3312 (N-H), 1614 (C=N), 1591 (C=C) and 1332 (C-N). UV $\lambda_{max}^{dioxane}$ nm (log ε): 374 (3.96), 257 (3.67). ^1H NMR (300 MHz) δ0.82 and 1.03 (3H each, 2*d*, $J_{11,12}=J_{11,13}=7$ Hz, isopropyl), 1.92 (3H, *dd*, $J_{15,14}=7$ Hz; $J_{15,4}=2.5$ Hz Me-15), 2.40 (1H, *dd*, $J_{1\alpha,1\beta}=16$ Hz; $J_{1\beta,9\alpha}=11$ Hz, H-1β), 2.72 (1H, *dd*, $J_{1\alpha,9}=6.5$ Hz, H-1α), 4.70 (1H, *br s*, H-10), 4.86 (1H, *br s*, H-10′), 6.40 (1H, *dq*, $J_{14,4}=2$ Hz, H-14), 9.15, 8.30, 8.00 (1H each, aromatic ring) and 11.00 (1H, *s*, NH). ^{13}C NMR, see Table 1.

$$[\alpha]=\frac{589\quad 578\quad 546\,nm}{-59\quad -70\quad -119}\ (CHCl_3;\ c\ 0.15).$$

Table 1. ^{13}C NMR spectral data* (75.4 MHz, $CDCl_3$) of compounds **1–8**

C	1†	2	3	4	5	6	7‡	8
1	41.3	39.5	29.7	36.3	34.4	43.3	25.3[b]	27.3
2	206.5	204.5	161.8	69.5	74.0	217.7	28.6	28.5
3	141.5	142.3	140.3	147.4	143.0	59.8	55.4[c]	56.1
4	51.3	51.7	53.5	50.2	51.0	48.4	55.3[c]	52.1
5	44.9	41.6	41.6	44.2	44.4	49.6	46.0	49.2
6	26.0	25.0	25.5	26.2	26.3	26.6	22.5[b]	26.5
7	34.5	33.3	34.1	34.9	35.0	35.0	36.6	35.3
8	149.1	148.4	148.8	150.4	150.0	149.2	73.4	150.9
9	46.0	45.0	46.0	46.8	47.1	46.5	49.3	51.8
10	104.5	104.6	105.5	103.5	104.0	104.0	65.3	103.5
11	27.4	29.4	29.7	27.2	27.2	28.6	29.4[d]	29.9
12[a]	21.4	21.0	21.4	21.5	21.7	21.9	21.9	21.9
13[a]	15.6	15.9	16.4	15.7	16.0	16.0	15.6	15.7
14	131.7	127.0	121.6	117.1	120.1	67.9	210.8	211.7
15	14.5	14.1	14.6	13.6	14.1	22.6	29.5[d]	28.8
1′			145.1		135.9		168.1	
2′			129.4		130.7		127.5	
3′			123.7		123.4		138.8	
4′			137.9		150.5		15.8	
5′			130.1		123.4		20.6	
6′			116.6		130.7			
–COO					164.4			

*In ppm from TMS as the internal standard.
†From ref. [6].
‡The assignment of the angelate residue follows from the signals of angelic acid [10].
[a–d]Assignments having the same label may be interchanged.

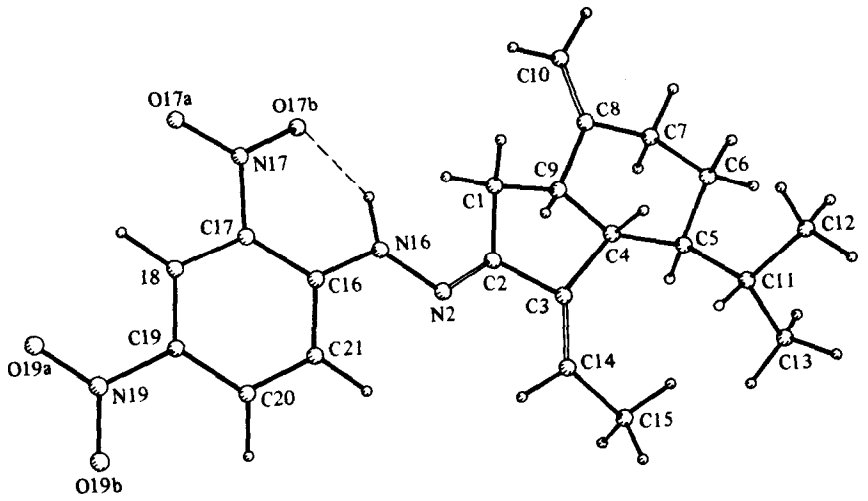

Fig. 1. Molecular perspective of compound **3**.

X-ray analysis of compound **3**. Single crystals of **3** were grown by slow crystallization from $CHCl_3$–EtOH. They were orthorhombic, space group $P2_12_12_1$ with $a=6.7136(26)$, $b=9.9097(85)$, $c=30.9527(218)$ Å and $d_{calc}=1.28$ g/cm^3 for $Z=4$ (M, 398.4). The size of the crystal used for data collection was *ca* $0.50\times0.10\times0.02$ mm. No absorption correction was necessary ($\mu=7.5$ cm^{-1}). A total of 1568 reflections were measured for $3°\leq\theta\leq110°$ of which 1191 reflections were considered to be observed [$I\geq2.5\sigma(I)$]. The final discrepancy indices were $R=5.70\%$ using 1171 reflections in the final refinement. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.29 e/Å^3.

Compound **4**. Fractions eluted with hexane–$CHCl_3$ (4:1) yielded **4** (20 mg) as colourless crystals, mp 54–56°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3440 (OH), 1720, 1660 (C=C), 1468, 1443, 1381, 1356 (isopropyl). ^1H NMR (300 MHz): δ 0.78, 0.96 (3 each, 2*d*, $J_{12,11}=J_{13,11}=7$ Hz, isopropyl), 1.17 (1H, *dq*, $J_{6\beta,6\alpha}=J_{6\beta,5\alpha}=J_{6\beta,7\alpha}=13$ Hz; $J_{6\beta,7\beta}=4.5$ Hz, H-6β), 1.76 (3H, *dd*, $J_{15,14}=7$ Hz; $J_{15,4}=2$ Hz, Me-15), 4.56 (1H, *br s*, H-10), 4.68 (1H, *br s*, H-10′), 4.79 (1H, *br t*, $J=6.8$ Hz, H-2) and 5.63 (1H, *tq*, $J_{14,4}$

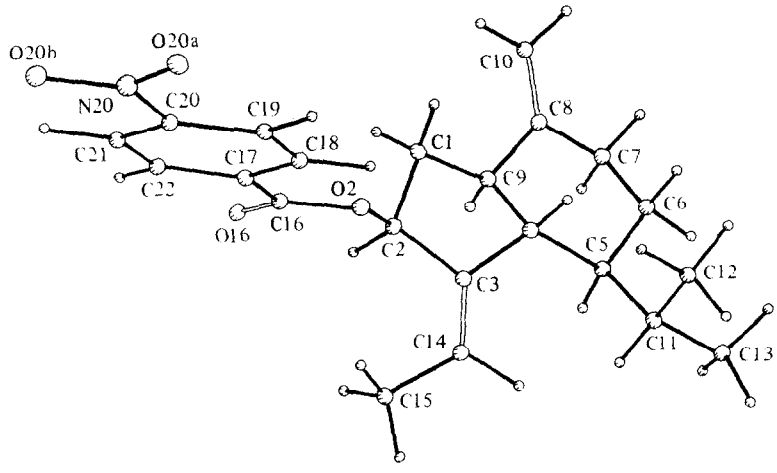

Fig. 2. Molecular perspective of compound **5**.

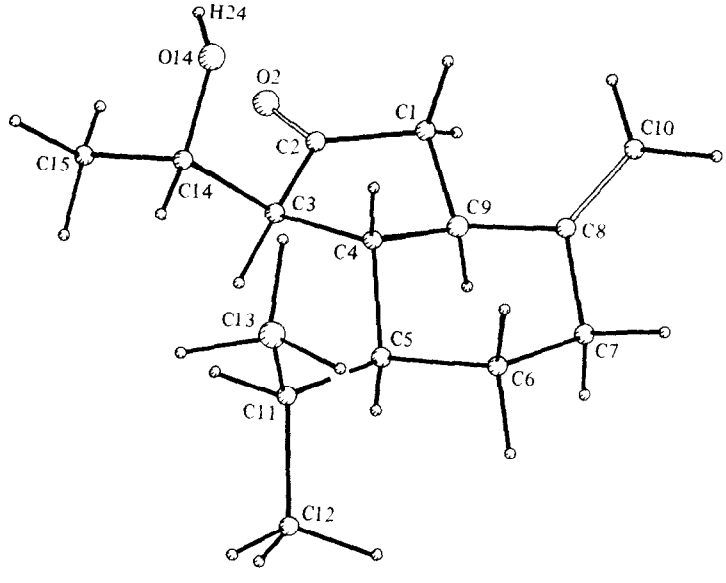

Fig. 3. Molecular perspective of compound **6**.

$=2$ Hz; $J_{14,2}=2$ Hz, H-14). The H-1α, H-6α, and H-11 signals are overlapping at δ2.35. ^{13}C NMR, see Table 1.

$$[\alpha]=\frac{\begin{matrix}589 & 578 & 546 & 436 & 365\text{ nm}\end{matrix}}{\begin{matrix}+29 & +31 & +36 & +70 & +127\end{matrix}}(CHCl_3;\ c\ 0.1)$$

p-*Nitrobenzoate of compound* **4**. A sample of **4** (50 mg) was added to a soln containing 50 mg *p*-nitrobenzoyl chloride and 1 ml pyridine. The soln was heated on a steam bath for 1 hr. The product was extracted with EtOAc and chromatographed on CC with silica gel. Compound **5** was obtained as lightly yellow crystals which were recrystallized from $CHCl_3$–hexane, mp 110–112°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1719 (C=O), 1600 (aromatic), 1532 (NO_2). UV λ_{max}^{EtOH} nm (log ε): 261 (3.58). ^{1}H NMR (300 MHz): δ0.84, 1.00 (3H each, 2*d*, $J_{12,11}=J_{13,11}=7$ Hz, isopropyl), 1.21 (H, *dq*, $J_{6\beta,6\alpha}=J_{6\beta,5}=J_{6\beta,7\alpha}=13$ Hz; $J_{6\beta,7\beta}=4.5$ Hz, H-6β), 1.67 (3H, *dd*, $J_{15,14}=7$ Hz; $J_{15,2}=2$ Hz, Me-15), 2.64 (1H, *ddd*, $J_{1\alpha,1\beta}=12.6$ Hz; $J_{1\alpha,2}=7.3$ Hz; $J_{1\alpha,9}=5.3$ Hz, H-1α), 4.54 (1H, *br s*, H-10), 4.71 (1H, *br s*, H-10'), 5.78 (1H, *tq*, $J_{14,4}=J_{14,2}=2$ Hz; $J_{14,15}=7$ Hz, H-14), 5.95 (1H, *t*, $J=6$ Hz, H-2) and 8.50 (4H, AA' BB', $J_{ortho}=8.8$ Hz, H-aromatic). ^{13}C NMR, see Table 1.

$$[\alpha]=\frac{\begin{matrix}589 & 578 & 546 & 436\text{ nm}\end{matrix}}{\begin{matrix}+87 & +93 & +107 & +198\end{matrix}}(CHCl_3;\ c\ 0.2)$$

X-ray analysis of compound **5**. Single crystals of **5** were grown by slow crystallization from $CHCl_3$–hexane. They were monoclinic, space group $P2_1$, with $a=11.3314(52)$, $b=7.5408(29)$, $c=13.1701(83)$, $\beta=111.885(41)$, $\alpha=\gamma=90.00(00)$ and $d_{calc}=1.17$ g/cm^3 for $Z=2$ (M, 369.4). The size of the crystal used for data collection was *ca* $0.60\times0.20\times0.02$ mm. No absorption correction was necessary ($\mu=6.2$ cm^{-1}). A total of 1510 reflections were measured for $3°\leq\theta\leq110°$ of which 1085 reflections were

considered to be observed [$1 \geq 2.5\sigma(I)$]. The final discrepancy indices were $R = 6.68\%$ using 1082 reflections in the final refinement. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.18 e/Å^3.

Compound **6**. Chromatography of the hexane extracts of the roots (700 g) yielded 80 mg of **6** as colourless crystals, mp 100–102°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (C=O), 3587, 3448 (OH), 1652 (C=C), 1458, 1382 (isopropyl). ^{1}H NMR (300 MHz): δ0.84, 0.98 (3H each, 2*d*, $J_{12,11} = J_{13,11} = 7$ Hz, isopropyl), 1.24 (1H, *dq*, $J_{6\beta,6\alpha} = J_{6\beta,7\alpha} = J_{6\beta,5\alpha} = 13$ Hz; $J_{6\beta,7\beta} = 4.5$ Hz, H-6β), 1.50 (3H, *d*, $J_{15,14} = 7$ Hz, Me-15), 2.46 (1H, *dq*, $J_{7\alpha,7\beta} = 13.5$ Hz; $J_{7\beta,6\beta} = 4$ Hz; $J_{7\beta,6\alpha} = 4.4$ Hz, H-7β), 4.00 (1H, *q*, $J = 7$ Hz, H-14), 4.51 (1H, *br s*, H-10) and 4.72 (1H, *br s*, H-10′). ^{13}C NMR, see Table 1.

$$[\alpha] = \frac{\begin{matrix}589 & 578 & 546 & 436 & 365\ \text{nm}\end{matrix}}{\begin{matrix}-108 & -114 & -136 & -320 & -898\end{matrix}} (CHCl_3;\ c\ 0.14)$$

X-ray analysis of compound **6**. Single crystals of **6** were grown by slow crystallization from cold hexane. They were monoclinic, space group $P2_1$ with $a = 8.9059(55)$, $b = 6.1872(28)$, $c = 13.3447(69)$, $\beta = 97.353(46)$, $\alpha = \gamma = 90.00(00)$ and $d_{calc} = 1.07$ g/cm^3 for $Z = 2$ (M, 236.3). The size of the crystal used for data collection was *ca* $0.40 \times 0.16 \times 0.14$ mm. No absorption correction was necessary ($\mu = 5.5$ cm^{-1}). A total of 1109 reflections were measured for $3° \leq \theta \leq 110°$ of which 980 reflections were considered to be observed [$I \geq 2.5\sigma(I)$]. The final discrepancy indices were $R = 3.45\%$ using 970 reflections in the final refinement. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.12 e/Å^3.

Compound **7**. Fractions eluted with hexane–Me_2CO (9:1) from the chromatography of the hexane extracts of the roots (700 g) yielded 50 mg of **7** as colourless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1706 (C=O), 3600, 3500 (OH). ^{1}H NMR, D_2O, (300 MHz, $CDCl_3$): δ0.70, 0.90 (3H each, 2*d*, $J_{11,12} = J_{11,13} = 7$ Hz, isopropyl), 2.20 (3H, *s*, Me-15), 2.66 (1H, *m*, H-3), 4.32, 4.35 (2H, AB, $J = 11.7$ Hz, H-10) and 6.12 *dq*, 2.03 *d*, 1.92 *d*, (H-angelate). ^{13}C NMR, see Table 1.

$$[\alpha] = \frac{\begin{matrix}589 & 578 & 546 & 436 & 365\ \text{nm}\end{matrix}}{\begin{matrix}-22 & -24 & -29 & -71 & -213\end{matrix}} (CHCl_3;\ c\ 0.17)$$

Oplopenone **8**. Fractions eluted with hexane–Me_2CO (9:1) from the chromatography of the hexane extracts of the roots (700 g) yielded 15 mg of **8** mp 52–54° (no recrystallized) ($mp_{lit.}$ 67–69° [8]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1707 (C=O), 1649 (C=C), 1463, 1358 (isopropyl). ^{1}H NMR (300 MHz, $CDCl_3$); δ0.90, 0.65 (3H each, 2*d*, $J_{11,12} = J_{11,13} = 7$ Hz, Me-12, 13), 2.18 (3H, *s*, Me-15), 2.37 (1H, *dq*, $J_{7\beta,7\alpha} = 13$ Hz; $J_{7\beta,6\alpha} = 2.5$ Hz; $J_{7\beta,6\beta} = 4$ Hz, H-7β), 2.71 (1H, *ddd*, $J_{3,4} = 11$ Hz; $J_{3,2\beta} = 5$ Hz; $J_{3,2\alpha} = 10$ Hz, H-3), 4.56 (1H, *q*, $J = 2$ Hz, H-10), 4.68 (1H, *q*, $J = 2$ Hz, H-10′) and 1.10 (1H, *dq*, $J_{6\alpha,\ 6\beta} = J_{6\beta,5} = J_{6\beta,7\alpha} = 13$ Hz; $J_{6\beta,7\beta} = 4$ Hz, H-6β). ^{13}C NMR, see Table 1.

$$[\alpha] = \frac{\begin{matrix}589 & 578 & 546 & 436 & 365\ \text{nm}\end{matrix}}{\begin{matrix}-11 & -15 & -25 & -67 & -225\end{matrix}} (CHCl_3;\ c\ 0.07)$$

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