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15-NORGUAIANOLIDES AND GERMACRANOLIDES FROM *MIKANIA MENDOCINA*

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Key Word Index—*Mikania mendocina*; Compositae; sesquiterpene lactones; 15-norguaianolides; guaianolides; germacranolides; heliangolides.

Abstract—Investigation of the aerial parts of *Mikania mendocina* yielded, in addition to known quadrangolide, two new 15-norguaianolides, a new guaianolide and three new germacranolides. The structure of a germacranolide isolated from *M. dusenii* has been revised.

INTRODUCTION

The genus *Mikania* with more than 400 species [1] is one of the largest and most easily recognized genera in the tribe Eupatorieae. However, species delimitations are often difficult owing to the existence of several highly polymorphic complexes. *Mikania mendocina* Philippi, a taxon found in Mendoza and Neuquén provinces, Argentina [2], is a member of the *M. scandens* complex [3] where, with a few exceptions [4–6], functionalized derivatives of the sesquiterpene dilactone isabelin are typical metabolites.

Continuing our work on this genus [7] we report here the isolation of two new 15-norguaianolides (**1** and **2**), a new guaianolide (**3**), the methyl ester **4**, the new germacranolides (**6–8**) and the known quadrangolide (**5**) from the aerial parts of *M. mendocina*. Quadrangolide (**5**) is a heliangolide with feeding deterrent activity against *Atta cephalotes* [8]. The structure **7** previously assigned to a lactone isolated from *M. dusenii* [9] has been revised to **8**.

RESULTS AND DISCUSSION

Compound **1** gave a $[M]^+$ peak at *m/z* 232, suggesting the molecular formula to be $C_{14}H_{16}O_3$. Its infrared spectrum showed bands for a γ-lactone at 1765 cm^{-1}, an α,β-unsaturated ketone at 1686 cm^{-1} and a double bond at 1639 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra indicated the structure clearly. A pair of doublets at δ6.22 (J = 3.3 Hz) and δ5.62 (J = 3.0 Hz) was typical for α-methylene-γ-lactone (H-13) protons. A signal centred at δ2.48 was assigned to H-7, whose allylic relationship with H-13 was evident from spin-decoupling experiments. A typical double double-doublet geminal to oxygen at δ4.30 (J = 12.0, 9.6 and 2.4 Hz) indicated an α-oriented oxygenated function at C-8. Irradiation of this signal collapsed the double triplets at δ2.38 (J = 13.2, 3.2 Hz) and δ1.97 (J = 4.4, 12.6 Hz) to double doublets, indicating a methylene group at C-9, which was coupled also with a multiplet at δ2.90 (H-10). Irradiation of this signal collapsed a doublet at δ1.26 (J = 7.4 Hz), which was assigned to the methyl on C-10. Similarly, decoupling of H-7 identified the signals of H-6 at δ3.17 (*dd*, J = 16.4 and 2.8 Hz) and δ1.88 (*ddt*, J = 16.4, 12.0 and 3.2 Hz). The absence of a signal for H-15 agreed with the molecular formula and the ^{13}C NMR spectrum, which showed only 14 signals. The DEPT spectrum showed the presence of one methyl, five methylene and three methine groups and five quaternary carbon atoms. The α-methylene-γ-lactone moiety was evident in the signals at δ169.6 for the carbonyl group, δ137.0 for C-13 and δ119.9 for C-11, as was the α,β-unsaturated ketone, with two quaternary olefinic carbons (δ208.7, 177.6 and 139.0). The UV absorption maximum at 236 nm also supported this conclusion. Heteronuclear multiple quantum correlation ^1H–^{13}C (HMQC) allowed us to assign unambiguously the signals of all the remaining carbons. Thus, the methine signals at δ80.9, 46.9 and 34.2 were assigned to C-8, C-7 and C-10, respectively, by their correlation with the corresponding proton signals. Similarly, the aliphatic methylene signals that appear at δ22.3, 31.3, 33.8 and 37.0 were assigned to C-6, C-2, C-3 and C-9, respectively, and the only methyl signal at δ18.6 was assigned to C-14. All these data are consistent with structure **1**, which is a new 15-norguaianolide. The configuration at C-10 was

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deduced from the observed NOE between the signals of H-8 and H-14.

The ^{1}H NMR and ^{13}C NMR spectra of **2** were very similar to those of **1**. The signals of a new methyl group (doublet at δ1.25, J = 6.8 Hz) in ^{1}H NMR and δ12.7 in ^{13}C NMR and the absence of the exomethylene group along with a molecular weight two units higher than that of **1**, indicated that **2** was the 11,13-dihydro derivative of **1**. The configuration at C-10 and C-11 was deduced from the observed NOE of H-8 with H-14 and H-11.

The infrared (1725 cm^{-1}), ^{1}H NMR (δ2.15) and ^{13}C NMR (δ170.3 and 20.4) spectra of compound **3** indicated the existence of an acetoxyl group. The observed differences were in agreement with the existence in compound **3** of an acetylated hydroxymethylene group at the C-4 position (δ4.58 in ^{1}H NMR and 67.9 in ^{13}C NMR) and an epoxyl group at C-4/C-5 rather than a tetrasubstituted double bond. The mass spectrum displayed fragment ions at m/z 264 (4.3) $[M - C_2H_2O$ (ketene)$]^+$ characteristic of an acetoxyl group and m/z 249 (100) $[M - C_2H_2O - CH_3]^+$, which were in agreement with a molecular formula $C_{17}H_{22}O_5$ and allowed us to assign structure **3** to this third metabolite. The stereochemistry of **3** at C-1, C-4 and C-10 was deduced by the observed NOEs of H-7 with H-1, of H-15 with H-6β and H-8 with H-14. It is interesting to note that from the biogenetic point of view the new 15-norguaianolides, **1** and **2**, are probably formed from guaianolide (**3**) by cleavage of the 4,5-epoxide followed by oxidative decarboxylation of an intermediate hydroxy acid.

The ^{1}H NMR spectrum of **4** exhibited signals similar to those of **1**. However, a methoxyl singlet at δ3.78, and slightly broadened singlets for exomethylene protons (δ6.44 and 5.83) indicated the presence of a methyl ester rather than a lactone. Consequently, the structure of the methyl ester of the hydroxyacid corresponding to **1** was assigned to compound **4**. Although such hydroxy esters are frequent in *Onopordon* species [10–14] and most likely are the biosynthetic precursors of the sesquiterpene lactones [12], compound **4** is probably an artefact formed during the extraction and isolation process.

Table 2. ^{13}C NMR data for compounds **1**, **2** and **3** (100 MHz, $CDCl_3$, δ values)

C	1	2	3
1	177.6	177.8	53.6
2	31.3	31.2	24.2
3	33.8	33.8	36.2
4	208.7	208.6	—
5	139.0	137.6	—
6	22.3	23.2	43.7
7	46.9	50.4	42.4
8	80.9	80.7	79.6
9	37.0	36.6	40.6
10	34.2	34.2	33.4
11	137.0	42.0	138.4
12	169.6	178.2	169.1
13	119.9	12.7	120.4
14	18.6	18.3	14.4
15	—	—	67.9

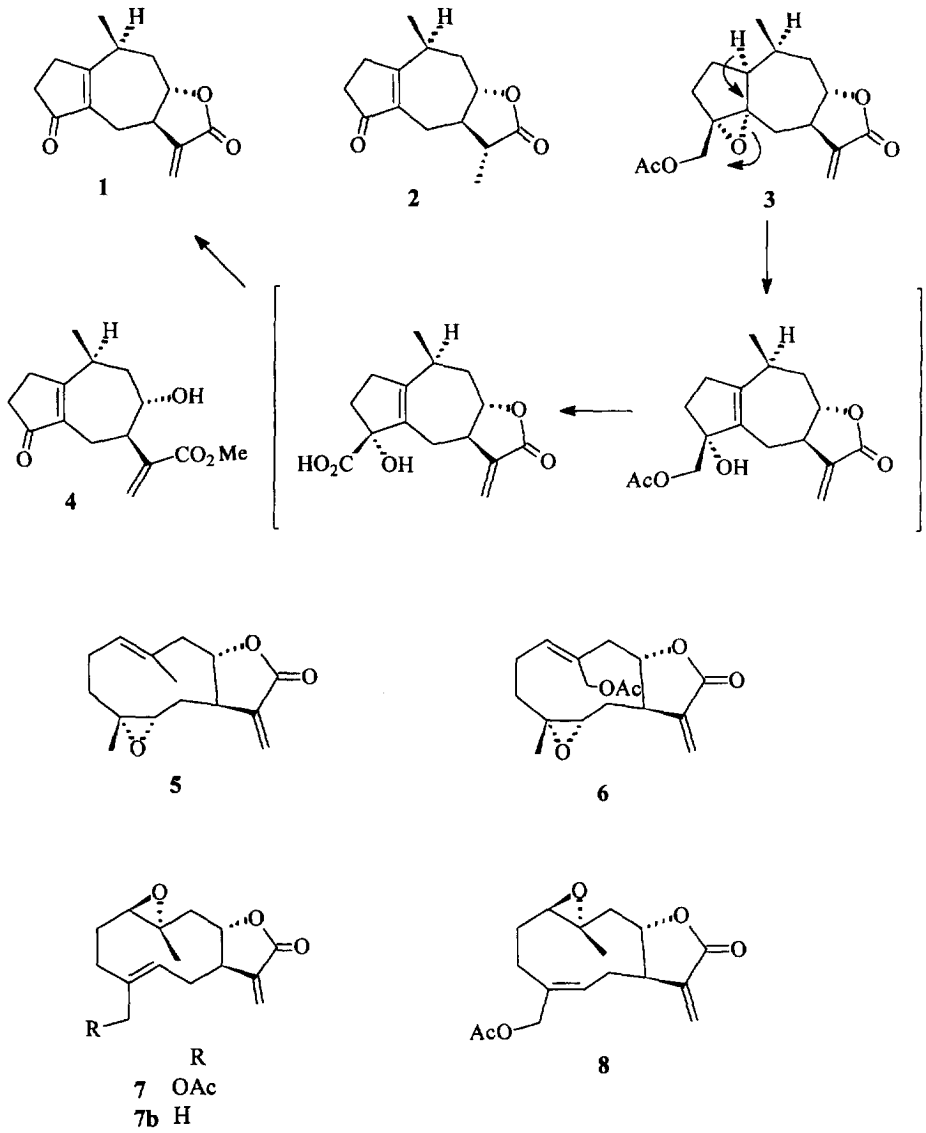
Other signals: 20.4 and 170.3 for CH_3COO.

Compound **5** displayed infrared bands at 1766 and 1664 cm^{-1} which suggested the presence of γ-lactone and olefinic groups. The mass spectrum showed a molecular peak at m/z 248, which agrees with the molecular formula $C_{15}H_{20}O_3$. The features of the ^{1}H NMR spectrum suggested a germacrane ring with a double bond at $\Delta^{1(10)}$ (a broad triplet at δ5.44 was assigned to H-1 and a singlet at δ1.71 to H-14), an α-methylene-γ-lactone closed to C-8

Table 1. ^{1}H NMR data for compounds **1–4** (400 MHz, $CDCl_3$, δvalues, J in Hz)

H	1	2	3	4
1	—	—	3.03 *br d* (8.0)	—
2	2.72 *dm* (14.0)	2.70 *dm* (14.0)	2.15–2.25	2.68 *dm* (14.0)
2′	2.52 *dm* (14.0)	2.50 *dm* (14.0)	1.60 *m*	2.49 *dm* (14.0)
3	2.43 *m*	2.42 *m*	2.44 *dt* (16.8, 6.4)	2.41 *m*
3′	2.43 *m*	2.42 *m*	2.25–2.40	2.41 *m*
6	3.17 *dd* (16.4, 2.8)	2.98 *dd* (16.4, 3.2)	2.95 *dd* (17.6, 5.0)	2.99 *dd* (16.0, 2.8)
6′	1.88 *ddt* (16.4, 12.0, 3.2)	1.79 *ddt* (16.4, 12.4, 3.2)	2.30–2.40	1.80 *ddt* (16.4, 12.0, 3.2)
7	2.48 *m*	2.42 *m*	3.22 *m*	2.46 *m*
8	4.30 *ddd* (12.0, 9.6, 2.4)	4.32 *ddd* (11.6, 10.0, 2.8)	4.04 *ddd* (12.4, 9.6, 2.8)	4.32 *ddd* (11.6, 10.0, 2.8)
9	1.97 *dt* (4.4, 12.6)	1.84 *dt* (4.4, 12.8)	2.04 *dt* (5.0; 12.4)	1.84 *dt* (4.0, 12.8)
9′	2.38 *dt* (13.2, 3.2)	2.35 *dt* (13.2, 3.2)	2.25–2.40	2.37 *dt* (13.2, 3.2)
10	2.90 *tq* (4.0, 7.4)	2.86 *tq* (3.8, 7.6)	2.20	2.86 *tq* (4.0, 7.4)
11	—	2.38 *m*	—	—
13	6.22 *d* (3.3)	1.25 *d* (6.8)	6.25 *d* (3.2)	6.44 *s*
13′	5.62 *d* (3.0)	—	5.48 *d* (3.0)	5.83 *s*
14	1.26 *d* (7.4)	1.26 *d* (7.6)	0.85 *d* (7.2)	1.26 *d* (7.2)
15	—	—	4.58 *s*	—

Other signals: 2.15 *s* for CH_3COO of compound **3** and 3.78 for CH_3O– of compound **4**.



(two doublets at δ6.34 and 5.59 were assigned to H-13 and a double triplet at δ4.42, J = 7.6 and 4.3 Hz was assigned to H-8) and an epoxyl group at C-4/C-5 (a double doublet at δ2.52, J = 10.0 and 4.4 Hz was assigned to H-5 and a singlet at δ1.28 to H-15). A full analysis of the spectrum and the results of decoupling experiments, together with NOE and ^{13}C NMR data, led to structure **5**. This compound, named quadrangolide, has been isolated from *Eupatorium quadrangulare* DC.[8] (= *Critonia quadrangularis* (DC) R. M. King and H. Robinson [1]) and it is a potent feeding deterrent for *A. cephalotes* [8]. Further characterization of this compound was obtained by heteronuclear multiple quantum correlation ^{1}H–^{13}C (HMQC), which allowed us to assign unambiguously the signals of all the carbons and to complete the assignment of the ^{1}H NMR spectrum.

The spectral features of **6** were very similar to those **5**. Its mass spectrum showed a molecular ion at m/z 306 differing by 58 amu from that of **5**. The IR band at 1735 cm^{-1}, a sharp singlet at δ2.07 in its ^{1}H NMR and signals at δ170.6 and 20.8 in its ^{13}C NMR spectrum indicated an acetoxyl group, which was attached to C-14 (replacement of the signal corresponding to the C-10 methyl by a $-CH_2O-$ signal (AB system at δ4.65 and 4.55, J = 12.4 Hz in the ^{1}H NMR and a signal at 62.4 (t) in the ^{13}C NMR spectrum). Consequently, compound **6** is the new 14-*O*-acetylquadrangolide. The HMQC and NOE experiments also agreed with the proposed structure.

The spectral features of **7** and **8** showed some similarities to those of **6**. As in **6**, the infrared bands of γ-lactone, acetate and the double bond were also (1760, 1730 and 1655 cm^{-1} in compound **7** and 1759, 1736 and 1657 cm^{-1} in compound **8**). The molecular formulas of **7** and **8** are identical to that of **6** ($C_{17}H_{22}O_5$) and, furthermore, the ^{1}H NMR spectra are very similar. However, some differences in the chemical shifts and couplings are observed in the signals of characteristic protons (H-8, H-1 and H-5). In agreement with all these data we assigned structures with an epoxyl group at C-1/C-10,

Table 3. ^{1}H NMR data for compounds **5**–**7** (400 MHz, $CDCl_3$, δ values, J in Hz)

H	5	6	7
1	5.44 *br t*	5.66 *br t*	2.67 *dd* (11.0, 2.6)
2	2.41 *m*	2.49 *m*	2.10–2.20
2′	2.15 *m*	2.15 *m*	1.45 *m*
3	1.27 *m*	1.19 *m*	2.30–2.45
3′	2.15 *m*	2.20 *m*	2.30–2.45
5	2.52 *dd* (10.0, 4.4)	2.59 *dd* (10.0, 4.4)	5.44 *dd* (10.6, 5.0)
6	2.12 *m*	2.13 *td* (12.8, 4.3)	2.30–2.45
6′	1.65 *ddd* (13.7, 10.4, 4.3)	1.63 *ddd* (13.8, 10.4, 4.4)	2.65–2.70
7	2.87 *m*	2.98 *m*	2.75–2.80
8	4.42 *dt* (7.6, 4.3)	4.54 *m*	4.14 *dd* (10.4, 6.0)
9	2.74 *br d* (11.6)	2.92 *dd* (13.2, 3.6)	2.75 *d* (14.0)
9′	2.10 *m*	2.10 *m*	1.45 *dd* (13.6, 10.0)
13	6.34 *d* (3.2)	6.35 *d* (3.2)	6.31 *d* (3.3)
13′	5.59 *d* (2.8)	5.60 *d* (2.8)	5.63 *d* (3.0)
14	1.71 *s*	4.65 *d* (12.4)	1.26 *s*
		4.55 *d* (12.4)	—
15	1.28 *s*	1.29 *s*	4.72 *d* (12.4)
			4.48 *d* (12.4)
AcO–		2.07 *s*	2.08 *s*

Table 4. ^{13}C NMR data of compounds **5**–**7** (100 MHz, $CDCl_3$, δ values)

C	5	6	7
1	126.9	133.2	65.6
2	22.5	22.7	24.6
3	36.3	37.7	31.6
4	59.8	59.2	133.8
5	61.7	62.3	130.7
6	34.6	34.5	31.0
7	40.9	40.5	49.2
8	80.2	80.3	81.8
9	45.3	40.0	46.0
10	131.2	129.4	57.6
11	138.7	138.6	138.6
12	169.4	169.2	168.8
13	123.2	123.4	121.9
14	18.3	62.4	17.6
15	15.4	15.3	61.2

Other signals: CH_3COO at 20.8 and 170.6 for **6** and 20.9 and 170.8 for **7**.

a double bond at C-4/C-5 and an acetoxy group at C-15. In most respects the ^{1}H NMR spectrum of **7** was essentially identical to that of a germacranolide isolated from *Inula helenium* [15] whose structure was corrected later to **7b** [16]. A full analysis of the ^{1}H NMR spectrum (including decoupling experiments), together with ^{13}C NMR data (including DEPT and HMQC) agreed well with the proposed structure **7**. The results obtained from NOE experiments, with the aid of Dreiding models, confirmed the position of the epoxide and allowed a clear assignment of the relative stereochemistry of this compound. Irradiation at the H-5 frequency enhanced the H-1 as well as the H-7 signal, indicating the proximity of these protons on one face of the molecule. Furthermore, irradiation of the resonance of H-14 enhanced the H-8 and H-15 signals, suggesting that these groups are positioned on the face of the molecule opposite from H-5/H-1/H-7 set. Consequently, the structure of 15-acetoxy-1β,10α-epoxy-8-epi-inunolide was assigned to compound **7**. This structure is that assigned to a substance (**4a** in ref. [9]) isolated very recently from *M. dusenii*, although the ^{1}H and ^{13}C NMR spectra of our **7** and that from *M. dusenii* do not agree.

Fortunately, *M. mendocina* also provided a compound **8** with spectral features in perfect agreement with those of the supposed **7** from *M. dusenii* [9], whose full spectroscopic analysis (^{1}H, ^{13}C, DEPT and NOE) showed that its structure differed from **7** in the geometry of the Δ^4 double bond. Thus, NOEs were observed between H-1 to H-7 and H-8 to H-14 as well as between H-5 to H-15. Therefore, compound **7** from *M. mendocina* is the new 15-acetoxy-1β,10α-epoxy-8-epi-inunolide and compound **8** from *M. mendocina* is identical with a compound previously assigned structure **7** from *M. dusenii* [9].

Among the *ca* 45 *Mikania* species that have been studied to date, *M. mendocina* is the only one to have yielded the very rare 15-norguaianolides. However, all lactones isolated are closed toward C-8, a typical feature in members of the *M. scandens* complex.

EXPERIMENTAL

General. For separation of mixtures a KONIK HPLC (KNK 500 A, Rheodyne injector with a 2 ml loop and ERC-7522 differential refractometer) equipment was used. The columns employed were (A) Phenomenex Maxsil 10 C8 (10 μm, 10 × 500 mm) and (B) Phenomenex Ultremex C18 (5 μm, 10 × 250 mm). Retention times were measured from the solvent peak.

Plant material. Aerial parts of *M. mendocina* were collected at the flowering stage in Departamento Guaymallén,

Mendoza province, Argentina, in the summer of 1991 (a voucher specimen, LIL N° 598198, is deposited at Herbario de la Fundación Miguel Lillo, Tucumán province, Argentina.)

Extraction of M. mendocina. Flowers and leaves (328 g) were extracted with $CHCl_3$ (2 × 3 l) at room temp. for 7 days to give 39.3 g of residue (yield 12%) which was suspended in 350 ml of EtOH at 55°, diluted with 250 ml of H_2O and extracted successively with hexane (3 × 400 ml) and $CHCl_3$ (3 × 400 ml). Evapn of the $CHCl_3$ extract gave 15.6 g of residue which was chromatographed on silica gel using $CHCl_3$ and increasing amounts of MeOH (0–20%) to give 141 frs. Frs containing γ-lactones (IR absorption at 1760 cm^{-1}) were further purified.

To Frs 37–41 (combined weight 380 mg) 19 ml of pure MeOH were added to separate nonsoluble material. The supernatant contained sesquiterpene lactones. After filtration and solvent evapn the residue was processed by HPLC (Column A, MeOH–H_2O 4:3, 2 ml min^{-1}) to give compound **1** (12 mg, R_t 24 min) and compound **5** (54 mg, R_t 20 min).

Frs 42–47 (combined weight 295 mg) were separated by HPLC (Column B, MeOH–H_2O 9:11, 2 ml min^{-1}) giving **2** (3 mg, R_t 20 min), **1** (5 mg, R_t 22 min), **6** (5.5 mg, R_t 24 min) and **8** (15 mg, R_t 28 min).

Frs 48–59 (combined weight 190 mg) were processed by HPLC (Column B, MeOH–H_2O 1:1, 2 ml min^{-1}) to give **7** (4.4 mg, R_t 20 min).

Frs 60–80 (combined weight 850 mg) were processed by HPLC (Column B, MeOH–H_2O 1:1, 1 ml min^{-1}) to give three peaks that were further rechromatographed (Column A, MeOH–H_2O 1:1) to yield **4** (1 mg, R_t 10 min), scopoletin (1 mg, R_t 19 min) and **3** (5 mg, R_t 12 min).

Frs 81–141 showed complex mixtures from which no pure compounds could be isolated.

Compound **1**. Oil, $[\alpha]_D^{20}$ + 49.1° ($CHCl_3$; *c* 3.83); IR ν_{max} cm^{-1}: 1765, 1686, 1639, 1150, 1124, 986, 963; UV λ_{max}^{MeOH} nm: 236; MS *m/z* (rel. int.): 232 (100), 217 (3.8), 214 (7.3), 204 (6.0), 189 (7.9), 176 (3.6), 161 (7.8).

Compound **2**. Oil, $[\alpha]_D^{20}$ + 250.6° ($CHCl_3$; *c* 0.76); IR ν_{max} cm^{-1}: 1770, 1695, 1625, 1220, 1155, 1045, 985; UV λ_{max}^{MeOH} nm: 236; MS *m/z* (rel. int.): 234 (100), 219 (2.7), 206 (14.0), 191 (12.6), 178 (10.1), 163 (14.3).

Compound **3**. Oil, $[\alpha]_D^{20}$ + 60.8° ($CHCl_3$; *c* 3.64); IR ν_{max} cm^{-1}: 1755, 1725, 1695; MS *m/z* (rel. int.): 264 (4.3), 249 (100), 231 (9.7), 221 (45.0), 203 (11.0), 189 (14.7).

Compound **5**. mp 117–119° (methanol), $[\alpha]_D^{20}$ + 134.6° ($CHCl_3$; *c* 5.75); IR ν_{max} cm^{-1}: 1766, 1664, 1234, 1154, 1002, 926; MS *m/z* (rel. int.): 248 (16.6), 233 (14.2), 230 (15.9), 215 (29.9).

Compound **6**. Oil, $[\alpha]_D^{20}$ + 90.3° ($CHCl_3$; *c* 5.66); IR ν_{max} cm^{-1}: 1759, 1735, 1657, 1143, 1027, 999; MS *m/z* (rel. int.): 307 (11.7) $[M + 1]^+$, 306 (1.0) $[M]^+$, 264 (6.3), 247 (29.6), 246 (21.8), 229 (60.5), 228 (16.9).

Compound **7**. Oil, $[\alpha]_D^{20}$ − 3.21° ($CHCl_3$; *c* 1.77); IR ν_{max} cm^{-1}: 1760, 1730, 1655; MS *m/z* (rel. int.): 306 (5.6) $[M]^+$, 264 (32.8), 251 (90.8), 246 (57.1), 233 (36.6), 228 (28.5).

Compound **8**. Oil, IR ν_{max} cm^{-1}: 1759, 1736, 1657, 1025, 991, 815; MS *m/z* (rel. int.): 306 (4.3) $[M]^+$, 264 (24.8), 251 (56.2), 246 (40.4), 233 (24.5), 228 (17.2).

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