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GUAIANOLIDES AND GERMACRADIENOLIDES FROM *STEVIA SANGUINEA*

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Key Word Index—*Stevia sanguinea*; Eupatorieae; Compositae; guaianolides; germacradienolides; heliangolide; sesquiterpene lactones.

Abstract—Reinvestigation of aerial parts of *Stevia sanguinea* afforded twelve new and five known guaianolides, one previously known guaianolide whose structure was revised, one new and one known germacradienolide and one new heliangolide. © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION

Stevia sanguinea Hieron. (*Asteraceae, Eupatorieae*) is an endemic of northwestern Argentina found at altitudes of 1500–2500 m [1]. A report has described the isolation of the guaianolides **1a**, **2a**, a guaianolide tentatively ascribed formula **3** and a mixture of the latter with what was possibly **4** from a small collection from Salta province [2]. We have now studied a somewhat larger collection of the plant material from a slightly different location. HPLC of the extract furnished the guaianolides **1a** [2], **1b** earlier found in *Helianthus microcephalus* [3], **1c**, **2a** [2], **2b–d** the last previously isolated from *Trichogonia santosii* [4] as well as from *Helianthus microcephalus* [3, 5], **2e**, **5a** identical with the lactone tentatively ascribed formula **3** [2], **5b–d**, **6–9**, **10** [3] admixed with **11**, the germacradienolides **12a** and **12b**, the former previously reported from *Eupatorium scabridum* [6], and the heliangolide **13**.

RESULTS AND DISCUSSION

The structure of **1c** followed from the ^{1}H NMR and mass spectral data (Table 1) which compared with that of the known **1a** [2] except for a small upfield shift of the H-15 resonance and the additional signals of the epoxyangelate ester. Structures of **2b**, **c** and **2e** were also easily deduced from the ^{1}H NMR and mass spectra, the latter in Table 2, when compared with those of the known **2a** [2] and **2d** [3–5].

The ring-A stereochemistry in formula **3** was tentatively ascribed to a guaianolide isolated from the earlier collection of *Stevia sanguinea* on the basis of NOE data [2]. Reexamination has shown that these are equally compatible with the stereochemistry shown in formula **5a**; in fact the ring-A frequencies and coupling constants correspond in all respects to analogous 2-hydroxy-3,4-epoxyguaianolides assigned the 2α-hydroxy-3α,4α-epoxy-configuration (e.g. compound **3c** of ref. [7] and compound **7a** of ref. [8]) and not to the isomeric 2β-hydroxy-3β,4β-epoxyguaianolide **8a** of ref. [8]. ^{1}H NMR spectra of the new analogs **5b**, **c**, **d** carrying a second acyl group on C-2 are listed in Table 2. In the case of **5b** the chemical shifts of the protons associated with the second angelate attached to C-2 differ somewhat from those associated with the angelate attached to C-8 (compare **5b** with **2a–c**, **7**, **9**, **10** and **11**); consequently in **5c** where the angelate frequencies correspond to those of the second angelate of **5b**, the angelate is on C-2 and the epoxyangelate is on C-8. In the case of **5d** the epoxyangelate frequencies correspond to those of **2d** and **2e**; consequently we place the 2-methylbutyrate on C-2.

Structure assignment to a further guaianolide whose ^{1}H NMR spectrum (Table 1) resembled that of **1c** initially caused some difficulty; however, the upfield shift of the H-15 resonance, the mass spectrum which indicated the molecular formula $C_{20}H_{22}O_7$ and the presence in the ^{1}H NMR spectrum of a strong hydroxyl absorption at δ 5.55 eventually led to its formulation as **6**. The stereochemistry assigned to C-4 is based on the absence of a NOE between H-5 and H-15.

Guaianolide **7** (Table 2) lacked the C-1 hydroxyl

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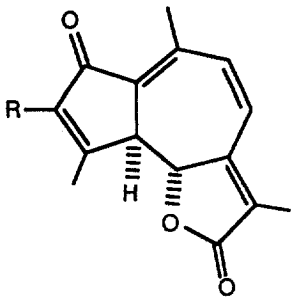
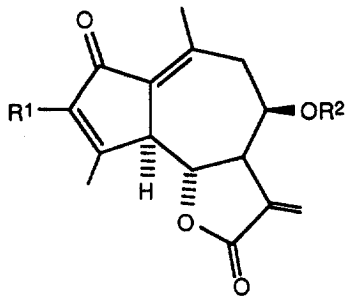
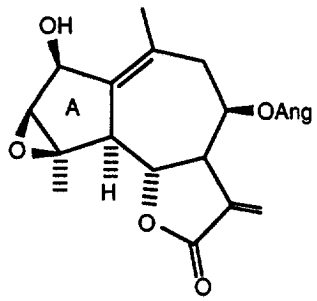


1 a R = Cl
b R = H
c R = OEpang



2 a R^1 = H, R^2 = Ang
b R^1 = Cl, R^2 = Ang
c R^1 = OH, R^2 = Ang
d R^1 = H, R^2 = Epang
e R^1 = Cl, R^2 = Epang



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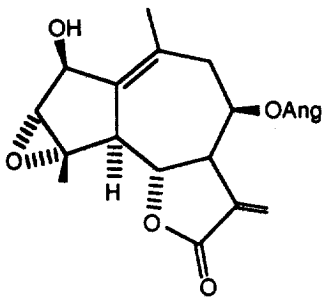

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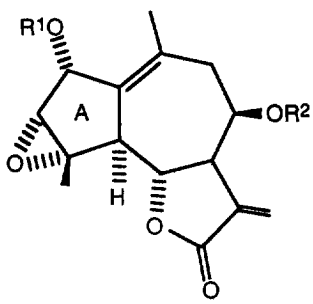
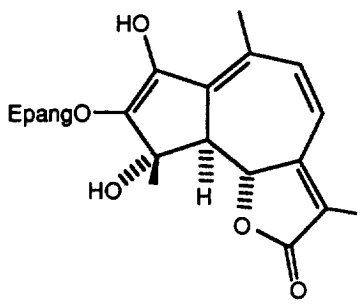


5 a R^1 = H, R^2 = Ang
b R^1, R^2 = Ang
c R^1 = Ang, R^2 = Epang
d R^1 = 2-MeBu, R^2 = Epang



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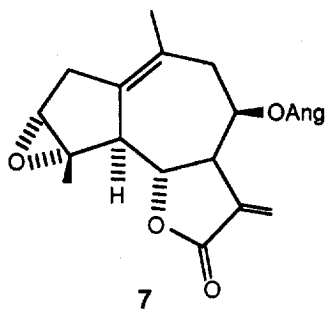
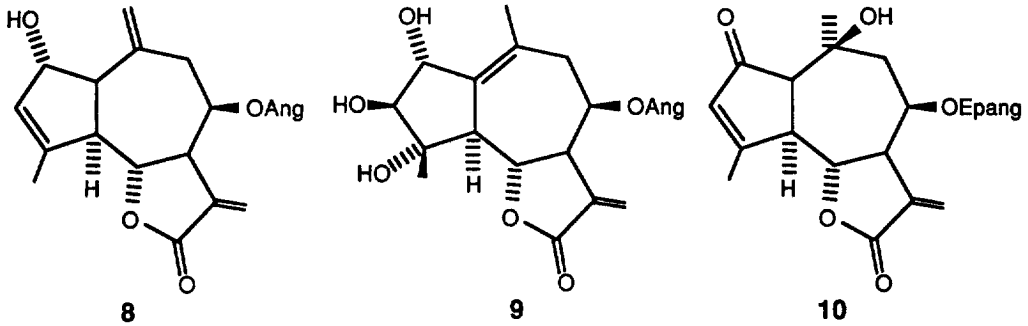


7

group of lactones **5a–d**. Its absence caused an upfield shift on the H-5 resonance which, however, remained long range coupled to H-3 and H-14 as in compounds **5a–d**, thus indicating that the stereochemistry of the epoxide was the same. Chemical shifts of the ring-A protons were essentially identical with those of 3,4-α-epoxy-8α-angelyloxy-9β-acetoxy-guaia-1(10),11(13)-dien-6,12-olide from *Helianthopsis helianthoides* [7] and with those of baccharilide B. For the latter a β-epoxide ring has been proposed [9] although the literature data do not exclude the α-configuration.

In guaianolide **8** the 1(10)-double bond of preceding compounds was shifted to the 10(14)-position and the 3,4-epoxide of **5a–d** and **7** was absent as evidenced by the ^{1}H NMR spectrum (Table 3). Spin decoupling in the usual fashion located the angelate on C-8 and the hydroxyl group on C-2. However the chemical shifts of H-1, H-5, H-6 and H-9a,b and the coupling constants involving H-2, in particular $J_{1,2}$ = 3.5 Hz, were significantly different from similar guaianolides with a β-hydroxyl on C-2 [10, 11]. Consequently the 2-hydroxyl was α-orientated.

Lactone **9** was at first thought to be the 2β,3β-epoxy analog of **5a** since $J_{2,3}$ was 4.5 Hz compared with $J_{2,3}$ = 2 Hz in the **5a–d** series and since H-3 was not *W*-coupled to H-5 as in 3α,4α-epoxyguaianolides. However the mass spectrum indicated the presence of a ring-A triol, with the signals of H-2 and H-3 at somewhat lower and H-5 at somewhat higher field (δ 4.98, 3.75 and 2.97) than in **5a** (H-2, H-3 and H-5 at



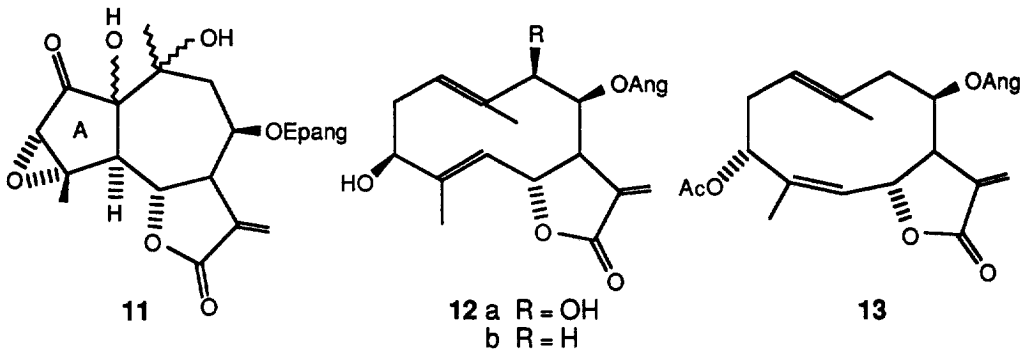


Table 1. ^{1}H NMR spectra of compounds **1c** and **6** (500 MHz, $CDCl_6$)

H	1c	6
5	3.41 *br d*	3.20 *br d*
6	4.87 *br d*	5.08 *br d*
8	6.23 *d*	6.19 *d*
9	6.60 *br d*	6.60 *br d*
13*	2.00 *d*	1.99 *d*
14*	2.46 *d*	2.38 *d*
15*	2.18 *br s*	1.66 *br s*
3′	3.14 *q*	3.10 *q*
4′*	1.51 *d*	1.46 *d*
5′*	1.70 *s*	1.46 *s*
–OH		5.55 *s*

* Intensity 3 protons.

J (Hz): 5, 6 = 11.5; 5, 14 = 6, 13 = 1.5; 5, 9 = 1; 8, 9 = 12, 3′, 4′ = 5.5.

δ 4.68, 3.58 and 3.22). Consequently we suggest the ring a stereochemistry shown in **9**.

The ^{1}H NMR data of guaianolide **11** listed in Table 3 were obtained from a mixture containing **10** [3] as the minor component. The mass spectrum of the mixture indicated that the empirical formula of the major component was $C_{20}H_{24}O_8$ with a facile loss of two molecules of water and one molecule of epoxy-angelic acid. Spin decoupling in the usual way located the signals of H-5 through H-9, established the location of the epoxidic proton at C-2 and showed that the two hydroxyls were attacked to C-1 and C-10 although their stereochemistry could not be established.

Structures of germacradienolide **12b** and heliangolide **13** were evident from the ^{1}H and NMR mass spectra (Table 3). In compound **12b** the chemical shifts and coupling constants involving H-3 and H-8 showed that the hydroxyl on C-3 was α- and the ester function on C-8 was β-orientated, whereas for compound **13** the coupling constants involving H-13 and the shifts of H-3 and H-8 showed that it was a heliangolide with an α-orientated ester on C-3 and a β-orientated ester on C-8. The angelate was sited on C-8 by analogy with the other lactones identified in the extract.

EXPERIMENTAL

General. For sepn of mixts HPLC with a differential refractometer was used. The columns employed were (A) Beckman C-18 (5 μm, 10 × 250 mm) and (B) Beckman C-8 (5 μm, 10 × 250 mm). R_fs were measured from the solvent peak.

Plant material. Stevia sanguinea Hieron. was collected at the flowering stage on March 30, 1991 near Dique La Caldera, Salta province, Argentina. A voucher specimen (Catalán #203) is on deposit in the herbarium of the Instituto Miguel Lillo, Tucumán.

Extraction and Isolation. Flowers and leaves (207 g) were extracted with $CHCl_3$ (2 × 2 l) at room temp. for 4 days to give 18 g of crude extract which was suspended in EtOH (154 ml) at 60°, diluted with H_2O (116 ml) and extracted with petrol (3 × 300 ml) and

Table 2. ^{1}H NMR spectra of compounds **2b**, **c**, **e**, **5b–d** **7** and **9** ($CDCl_3$, 500 MHz)

H	**2b**	**2c***	**2e** (300 Mz)	**5b**‡	**5c** (300 Mz)§	**5d** (300 Mz)¶	**7**	**9**
2a	—	—	—	5.81 *quint* (1.5)	5.83 *quint* (1.5)	5.78 *quint* (1)	2.75 *dd* (18, 1)	4.98 *d* (4.5)
2b	—	—	—	—	—	—	2.49 *dd* (18, 1)	—
3	—	—	—	3.71 *dd* (1.5, 1)	3.73 *br d* (1.5)	3.68 *br d* (1.5)	3.41 *q* (1)	3.75 *d* (4.5)
5	3.57 *br d* (10)	3.50 *br d* (11)	3.56 *br d* (11)	3.32 *d quint* (10.5, 1)	3.33 *d quint* (11, 1)	3.33 *d quint* (11, 1)	3.06 *d quint* (11, 1)	2.97 *ddq* (10, 1.5, 1.5)
6	4.03 *t* (10)	4.05 *dd* (11, 10)	4.07 *t* (11)	4.06 *dd* (10.5, 10)	4.06 *dd* (11, 10.5)	4.09 *t* (11)	4.09 *dd* (11, 10)	4.41 *t* (10)
7	3.15 *dddd* (10, 3.5, 3, 2)	3.12 *dddd* (10, 3, 3, 2)	3.16 *dddd* (11, 3.5, 3.5, 2)	3.03 *dddd* (10, 3, 2.5, 2)	3.04 *dddd* (10.5, 3.5, 3, 2)	3.04 *dddd* (11, 3.5, 3.5, 2)	3.01 *dddd* (10, 3.5, 3, 2)	3.07 *dddd* (10, 3, 2.5, 1.5)
8	5.76 *ddd* (6.5, 2, 2)	5.74 *ddd* (6.5, 2, 1.5)	5.81 *ddd* (6.5, 2, 1.5)	5.61 *ddd* (6.5, 2, 2)	5.69 *ddd* (6.5, 2, 2)	5.69 *ddd* (6.5, 2, 2)	5.64 *ddd* (6, 2, 2)	5.67 *ddd* (6, 2, 1.5)
9a	2.93 *dd* (16, 6.5)	2.87 *dd* (15, 6.5)	2.92 *dd* (16, 6.5)	2.66 *dd* (15, 6.5)	2.64 *dd* (16, 6.5)	2.64 *dd* (16, 6.5)	2.59 *dd* (15, 6)	2.66 *dd* (15, 6)
9b	2.74 *br dd* (16, 2)	2.71 *br dd* (15, 1.5)	2.79 *br dd* (16, 1.5)	2.51 *br dd* (15, 2)	2.54 *br dd* (16, 2)	2.54 *br dd* (16, 2)	2.50 *br dd* (15, 2)	2.51 *ddqd* (15.5, 2, 1, 1)
13a	6.25 *d* (3)	6.23 *d* (3)	6.25 *d* (3.5)	6.21 *d* (3)	6.21 *d* (3.5)	6.21 *d* (3.5)	6.18 *d* (3.5)	6.25 *d* (3)
13b	5.54 *d* (3)	5.52 *d* (3)	5.51 *d* (3.5)	5.47 *d* (2.5)	5.42 *d* (3)	5.43 *d* (3.5)	5.39 *d* (3)	5.54 *d* (2.5)
14†	2.39 *br s*	2.33 *br s*	2.45 *br s*	1.62 *br s*	1.69 *br s*	1.69 *br s*	1.66 *br s*	1.91 *t* (1.5)
15†	2.36 *br s*	1.79 *br s*	2.39 *d* (1)	1.68 *s*	1.67 *s*	1.67 *s*	1.67 *s*	1.62 *s*
3′	6.09 *qq* (7, 1.5)	6.07 *qq* (7, 1.5)	2.98 *q* (6)	6.09 *qq* (7, 1.5)	3.00 *q* (6)	3.00 *q* (6)	2.99 *q* (5.5)	6.07 *qq* (7, 1.5)
4′†	1.88 *dq* (7, 1.5)	1.88 *dq* (7, 1.5)	1.19 *d* (6)	1.92 *dq* (7, 1.5)	1.22 *d* (6)	1.21 *d* (6)	1.21 *d* (5.5)	1.92 *dq* (7, 1.5)
5′†	1.73 *quint* (1.5)	1.75 *quint* (1.5)	1.42 *s*	1.78 *quint* (1.50)	1.45 *s*	1.45 *s*	1.44 *s*	1.81 *quint* (1.5)

* From mixture with **2a**.

† Intensity three protons.

‡ 3″ 6.08 *qq*, 4″ 1.99 *dq*, 5″ 1.89 *quint*.

§ 3″ 6.10 *qq*, 4″ 1.99 *dq*, 5″ 1.89 *quint*.

¶ 2″ 2.45 *sext* (7), 3″ a 1.98 *m*, 3″b 1.88 *m*, 4″ 0.93 *t* (7)†, 5″ 1.16 *d* (7)†.

Table 3. ^{1}H NMR spectra of compounds **8**, **11**, **12b** and **13** (500 MHz, CDl_3)

H	**8***	**11**†	**12b**	**13**
1	2.92 *br dd* (8, 3.5, 1)	—	4.91 *ddd* (13, 4.5, 1)	5.06 *br t* (8)
2a	4.78 *dq* (3.5, 1.5)	—	2.48 *ddd* (14, 6, 4.5)	2.75 *m*
2b	—	—	2.31 *ddd* (14, 6, 4.5)	obsc.
3	5.70 *sext* (1.5)	2.99 *br d* (1.5)	4.33 *dd* (10, 6)	5.57 *br dd* (11, 5)
5	3.04 *ddquint* (11, 8, 1.5)	2.91 *dd* (2, 1.5)	4.84 *dq* (10, 1)	5.19 *dquint* (10.5, 1.5)
6	4.42 *dd* (11, 9)	4.88 *dd* (11, 2)	5.18 *dd* (10, 8.5)	5.23 *br d* (10.5)
7	3.16 *ddd* (9, 3.5, 3.5, 2.5)	3.07 *ddd* (5.5, 1.5, 1.5)	2.89 *ddd* (8.5, 3.5, 3.5, 1.5)	2.97 *br s*
8	5.62 *ddd* (5.5, 5.5, 2.5)	5.69 *ddd* (5.5, 1.5, 1.5)	5.76 *ddd* (6, 2, 1.5)	5.27 *br t* (3)
9a	2.68 *br dd* (14, 6)	2.25 *br dd* (17, 1.5)	2.86 *ddd* (15, 6, 1)	2.71 *dd* (14.5, 3.5)
9b	2.49 *br dd* (14, 5.5)	1.93 *dd* (17, 1.5)	2.31 *dd* (15, 2)	2.37 *dd* (14.5, 3.5)
13a	6.30 *d* (3.5)	6.27 *d* (3)	6.31 *d* (3.5)	6.35 *d* (2)
13b	5.55 *d* (3.5)	5.49 *d* (3)	5.61 *d* (3.5)	5.73 *d* (2)
14a	4.95 *br s*	1.24 *s*‡	1.53 *br s*‡	1.89 *br s*‡
14b	4.92 *br s*			
15‡	1.93 *q* (1)	1.56 *s*	1.78 *d* (1)	1.78 *d* (1.5)
H-3′	6.04 *qq* (7, 1.5)	3.04 *q* (5.5)	6.09 *qq* (7, 1.5)	6.07 *qq* (7, 1.5)
H-4′‡	1.89 *dq* (7, 1.5)	1.30 *d* (5.5)	1.98 *dq* (7, 1.5)	1.94 *dq* (7, 1.5)
H-5′‡	1.77 *quint* (1.5)	1.54 *s*	1.87 *quint* (1.5)	1.85 *quint* (1.5)
Ac‡				2.07 *s*

* $J_{1,3} = J_{2,5} = J_{3,5} = J_{3,15} = J_{5,15} = 1.5$ Hz; $J_{1,14a} = J_{9a,14a} = J_{9a,14b} = 1$ Hz.
† From mixture of **10** and **11**.
‡ Intensity three protons.

then with $CHCl_3$ (3 × 300 ml). Evapn of the $CHCl_3$ extracts at red. pres. furnished 7.8 g of residue which was chromatographed over silica gel (180 g) using $CHCl_3$ containing increasing amounts of MeOH (0–20%), 192 frs being collected and monitored by TLC.

Frs 122–140 (75 mg) were combined and processed by HPLC (column A, MeOH–H_2O 2:1, 2 ml min^{-1}) to give 4 mg of **1a** (solid, mp not determined, R_t 10.8 min), 12 mg of a mixt. of **2a** and **2c** (mp 162–165°, R_t 12.5 min), 2 mg of **13** (R_t 21.5 min), 5 mg of **2b** (solid, mp not determined, R_t 24.5 min), 3 mg of **5b** (R_t 60.5 min) and 12.2 mg from a broad peak (R_t 6 min) which was rechromatographed on column B (MeOH–H_2O 3:2, 1.5 ml min^{-1}) to give 1.6 mg of a sesquiterpene lactone mixt. (R_t 14.7 min), 3.4 mg of **1b** (solid, mp not determined, R_t 16 min), 1.9 mg of an acetate $C_{14}H_{22}O_2$ (R_t 19 min), MS PCI (*i*-butane) *m/z* (rel. int.) 223 (100) and 2 mg of a sesquiterpene lactone mixt. The ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the acetate exhibited mutually coupled signals of a methylene group at δ 2.52 *ddd* (J = 16, 9.5, 6.5 Hz) and 2.47 *ddd* (J = 16, 9.5, 6.5 Hz), 2.15 *s* (3H, Ac), 2.12 *m*, 2.03–1.97 *c* (3H), 1.83 *ddd* (J = 5, 5, 4.5 Hz) coupled to signals at δ 2.12 *m*, 1.72 *c* and 1.01 *ddd*, mutually coupled signals at δ 1.77 *c* and 1.72 *c*, the latter coupled to two superimposed methyl doublets at δ 0.91 *d* (J = 7 Hz, 6H), 1.67–1.62 *c* (2H), 1.01 *ddd* (J = 9.5, 4.5, 3 Hz) coupled to the δ 1.83 multiplet by 4.5 Hz to 1.62 *m* by 3 Hz and to 0.69 *dddd* (J = 9.5, 8.5, 5.5 and 4.5 Hz) by 4.5 Hz. The 0.69 *dddd* was also coupled to 1.77 *c*, 1.72 *c* and 1.62 *c*.

Frs 141–143 (316 mg) were combined. A portion (170 mg) was processed by HPLC (column A, MeOH–H_2O 2:1, 2 ml min^{-1}) to give 32.1 mg of **2d** (R_t 3.8 min), 3 mg of **7** (R_t 5.5 min), 2 mg of **1b** (solid, R_t 6.5 min), 28 mg of **2a** (solid, mp 186–194° without

recrystallization, R_f 14 min), 4 mg of **5c** (R_f 18.5 mg), 3 mg of **5d** (R_f 19.5 min) and 17.5 mg of a mixt. (R_f 7.5–9.5 min) which was rechromatographed on the same column (MeOH–H_2O 3:2, 1.5 ml min^{-1}) to yield 2.3 mg of **5a** (R_f 20.5 min), 5.5 mg of **2e** (solid, mp not determined, R_f 23.2 min) and 4.9 mg of **1c** (R_f 26.2 min).

Frs 144–151 (1.3 g) were combined and a portion (240 mg) was processed by HPLC (column A, MeOH–H_2O 2:1, 1 ml min^{-1}) to give 6 mg of **2d** (R_f 8 min), 3 mg of **6** (R_f 10.5 min), 3 mg of **8** (R_f 29.2 min) and two broadened peaks, R_f 7 min and 14.5 min, which were rechromatographed on column A and column B, respectively, MeOH–H_2O 3:2, 1.5 ml min^{-1}) to give 2.5 mg of a mixt. and 12.9 mg of **2d** from column A and 1.8 mg of a mixt. 15.5 mg of **5a** (solid, mp 74–76°) and 5.7 mg of **2e** from column B.

Frs 152–161 (752 mg) were combined and a portion (200 mg) was processed by HPLC (column A, MeOH–H_2O 2:1, 1 ml min^{-1}) to yield 5.6 mg of **12b** (R_f 27.2 min) and a mixt. (R_f 3 min) which was rechromatographed on column B (MeOH–H_2O 1:1, 1.5 ml min^{-1}) to give 6.1 mg of a mixt. (R_f 8.8 min) of **10** (minor constituent) and **11** (major constituent) and 2.3 mg of unidentified material (R_f 13.2 min). HPLC (column B, MeOH–H_2O 3:2, 2 ml min^{-1}) of frs 172–175 (25 mg) gave 2.5 mg of **9** (R_f 8.5 min) HPLC (column B, MeOH–H_2O 3:2, 1.5 ml min^{-1}) of a portion (170 mg) of frs 176–192 (2.7 g) furnished 22 mg of **12a** (R_f 9.5 min).

(5S*,6R*)-3-*Epoxyangelyloxy*-2-*oxoguaia*-1(10),3,7(11),8-*tetraen*-6,12-*olide* (**1c**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.): 357 (100 [$C_{20}H_{20}O_6+H^+$]), ^1H NMR in Table 1.

(5S*,6R*,7R*,8R*)-8-*Angelyloxy*-3-*chloro*-2-*oxoguaia*-1(10),3,11(13)-*trien*-6,12-*olide* (**2b**). Solid, mp not determined; MS PCI (*i*-butane) *m/z* (rel. intensity): 379 (33.5 [$C_{20}H_{21}O_5Cl^{37}+H^+$]), 377 (100[$C_{20}H_{21}O_5Cl^{35}+H^+$]); ^1H NMR in Table 2.

Mixture of (5S*,6R*,7R*,8R*)-8-*Angelyloxy*-2-*oxo-guaia*-1(10),3,11(13)-*trien*-6,12-*olide and* 8-*angeloxy* - 3 - *hydroxy* - 2 - *oxo* - 1(10),3,11(13) - *trien*-6,12-*olide* (**2a** [2] and **2c**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.); 359 (46.8 [M of **2c**+H^+]), 343 (100 [M+H^+ of **2a**]), 259 (43.2 [M+H^+-$C_5H_8O_2$ of **2c**]), 243 (24.1 [M+H^+-$C_5H_8O_2$ of **2a**]) 101 (18.3 [$C_5H_8O_2$]), ^1H NMR of **2c** in Table 2).

(5S*,6R*,7R*,8R*)-3-*Chloro*-8-*epoxyangelyloxy*-2-*oxoguaia*-1(10),3,11(13)-*trien*-6,12-*olide* (**2e**). Solid; mp not determined; MS PCI (*i*-butane) *m/z* (rel. int.): 395 (34.9 [$C_{20}H_{21}O_6Cl^{37}+H^+$]), 393 (100 [$C_{20}H_{21}O_6Cl^{35}+H^+$]); ^1H NMR in Table 2.

(2R*,3R*,4S*,5S*,6S*,7R*,8R*)-2,8-*Diangelyloxy*-3,4-*epoxyguia*-1(10),11(13)-*dien*-6,12-*olide* (**5b**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.) 443 (12.7 [M+H^+]), 343 (100 [M+H^+-$C_5H_8O_2$]), 243 (7.2 [M+H^+]-2x $C_5H_8O_2$]), ^1H NMR in Table 2.

(2R*,3R*,4S*,5S*,6S*,7R*,8R*)-2-*Angelyloxy*-8-*epoxyangelyloxy*-3,4-*epoxyguia*-1(10),11(13)-*dien*-6,12-*olide* (**5c**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.) 459 (5.8 [M+H^+]), 117 (7.6 [$C_5H_8O_3+H^+$]), 101 (37.7 [$C_5H_8O_2+H^+$]), 73 (100); ^1H NMR in Table 2.

(2R*,3R*,4S*,5S*,6S*,7R*,8R*)-2-(2-*methylbutanoxyloxy*-8-*epoxyangelyloxy*-3,4-*epoxyguaia*-1(10),11(13)-*dien*-6,12-*olide* (**5d**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.) 461 (26.2 [M+H^+]), 359 (100 [M+H^+-$C_5H_{10}O_2$]), 345 (38.8 [M+H^+-$C_5H_8O_3$]), 243 (8.8 [M+H^+-$C_5H_{10}O_2$-$C_5H_8O_3$]), 103 (2.2); ^1H NMR in Table 2.

(4R*,5S*,6R*)2,4-*Dihydroxy*-3-*epoxyangelyloxy guaia*-1(10),2,7(11),8-*tetraen*-6,12-*olide* (**6**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.) 375 (22.7 [$C_{20}H_{22}O_7+H^+$]), 357 (100 [M+H^+-H_2O]), ^1H NMR in Table 1.

(3R*,4S*,5S*,6S*,7R*,8R*)-8-*Angelyloxy*-2,3,4-*trihydroxyguaia*-1(10),11(13)-*dien*-6,12-*olide* (**7**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.): 361 (38.3 [$C_{20}H_{24}O_6+H^+$]), 245 (100 [M-$C_5H_8O_3+H^+$]); ^1H NMR in Table 2.

(1R*,2R*,5R*,6R*,7R*,8R*)-8-*Angelyloxy*-2-*hydroxyguaia*-3,10(14),11(13)-*trien*-6,12-*olide* (**8**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.): 345 (41 [$C_{20}H_{24}O_5+H^+$]), 327 (100); ^1H NMR in Table 3.

(2R*,3R*,4R*,5S*,6S*,7R*,8R*)-8-*Angelyloxy*-3,4-*epoxy*-2-*hydroxyguaia*-1(10),11(13)-*dien*-6,12-*olide* (**9**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.): 379 (100 [$C_{20}H_{26}O_7+H^+$]), 361 (57.2), 342 (42.0); ^1H NMR in Table 2.

Mixture of (1R*,5R*,6R*,7R*,8R*,10S*)-8-*Epoxyangelyloxy*-10-*hydroxy*-2-*oxoguai*-11(13)-*en*-6,12-*olide* (**6f** [3] and 1?,3S*,4S*,5S*,6S*,7R*,8R*,10?)-1,10-*dihydroxy*-8-*epoxyangelyloxy*-3,4-*epoxy*-2-*oxoguai*-11(13)*en*-6,12-*olide* (**11**). Gum; MS PCI (*i*-butane) *m/z* (rel. int.): 393 (100 [M+H^+ of **11**]), 377 (61.5 [M+H^+ of **10**]), 375 (63.8 [M+H^+ of **11**-H_2O]), 359 (83.8 [M+H^+ of **10**-H_2O]), 277 (37.6, M+H^+ of **11**-$C_5H_8O_3$), 261 (30.8 [M+H^+ of **10**-$C_5H_8O_2$]), 259 (25.6 [M+H^+ of **11**-$C_5H_8O_3$-H_2O]). ^1H NMR of **11** from mixt. in Table 3.

(3S*,6S*,7R*,8R*)-8-*Angelyloxy*-3-*hydroxygermacra*-1(10),4,11(13)-*dien*-6,12-*olide* (**12b**). Gum which gradually decomposed on standing; MS PCI *m/z* (rel. int.): 347 (35.3, [$C_{20}H_{26}O_5+H^+$]), 329 (100 [M+H^+-H_2O]),^1H NMR in Table 3.

(3R*,6S,7R*,8R*)-3-*Acetoxy*-8-*angelyloxyheliangа*-1(10),4,11(13)-*trien*-6,12-*olide* (**13**). Gum, MS PCI (*i*-butane) *m/z* (rel. int.): 389 (12.7 [$C_{22}H_{28}O_6+H^+$]), 329 (45.0 [M+H^+-HOAc]), 289 (17.8 [M+H^+-$C_5H_8O_2$]), 229 (100, [M+H^+-HOAc-$C_5H_8O_2$]); ^1H NMR in Table 3.

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