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SESQUITERPENE LACTONES FROM *MONTANOA GIGAS* AND THE CRYSTAL STRUCTURE OF GIGANTANOLIDE A

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Key Word Index—*Montanoa gigas*; Asteraceae; Heliantheae; sesquiterpene lactones; 12,6β-germacrolides.

Abstract—Chemical analysis of *Montanoa gigas* afforded in addition to known kaurane-derivatives three new 12,6-*cis*-germacrolides named gigantanolides, A, B and C. The structures of the new compounds were established by spectral methods mainly ^{1}H NMR. The structure of gigantanolide A was confirmed by single crystal X-ray diffraction.

INTRODUCTION

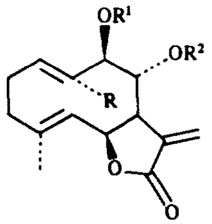
Montanoa gigas Rzedowski is one of the five arborescent species of the genus *Montanoa* which is found only in the state of Guerrero, México. This tree which grows up to 20 m tall and presents an amazing sight in flower was described in 1975 [1]. The same species was also described in 1976 [2] and more recently [3]. As part of our continuing study on the chemistry of *Montanoa* Cerv. [4–8], we have analysed the aerial parts of *M. gigas* Rzedowski. Besides the germacrolides **4** and **5** previously reported [3] and **6–8** which have also been reported from *M. tomentosa* subsp. *xanthiifolia* [9] and *M. hibiscifolia* [10], three new related 12,6-*cis*-germacrolides were isolated and named gigantanolide A(**1**), B(**2**) and C(**3**). The molecular structure of gigantanolide A(**1**) was determined by single crystal X-ray diffraction. The X-ray data demonstrated that the 10-member ring in **1** has [$_{15}D^5$, $^1D_{14}$] conformation [11] as do their analogues isolated from *M. hibiscifolia* [12].

RESULTS AND DISCUSSION

The petrol extract of aerial parts of *M. gigas* afforded common sterols, taraxasterol, taraxasteryl acetate and palmitate, *ent*-kaurenic acid, grandifloric acid, angeloylgrandifloric acid, cinnamoyl grandifloric acid, 17-hydroxy-*iso*-kaurenic acid, while the dichloro methane extract yielded the known lactones **4–8** in addition to three new ones which we named gigantanolides A(**1**), B(**2**) and C(**3**).

Gigantanolide (A(**1**), $C_{20}H_{26}O_6$ (CIMS$[M+1]^+$ at *m/z* 363), mp 118–122°, $[\alpha]_D$ −152° was an α-β-unsaturated γ-lactone, containing hydroxyl group(s) and an α,β-unsaturated ester (IR absorptions at 1760, 3400, 1695 cm^{-1}).

The nature of the ester group followed from the typical ^{1}H NMR (Table 1) signals, together with strong mass spectral peaks at *m/z* 83 and 55 which indicated the presence of an angelate moiety in the molecule. Other peaks at *m/z* 262 $[M-100]^+$ and 244 $[M-118]^+$ resulting from the loss of the side chain ester and water, were also present in the mass spectrum. The ^{1}H NMR spectrum of **1** (Table 1) exhibited the typical signals due to an exocyclic methylene conjugated with a γ-lactone as broadened singlets at δ5.52 (H-13a) and 6.22 (H-13b), and a broad triplet at δ3.43 ($J \sim 7.0$ Hz) which was assigned to H-7, since irradiation of this signal sharpened the H-13 signals to split doublets ($J \sim 1$ Hz) and collapsed the doublet of doublets at δ5.05 ($J = 11, 6$ Hz) to a doublet ($J = 11$ Hz) and the doublet of doublets at δ5.13 ($J = 9, 7$ Hz) to a doublet ($J = 9$ Hz). Therefore these signals had to be assigned to H-6 and H-8. The small allylic coupling constant $J_{7,13}$ (~ 1 Hz) together with $J_{6,7}$ (~6 Hz) value,



	R	R¹	R²
1	CH_2OH	H	Ang
2	CH_2OH	Ang	H
3	CH_2OH	Mebut	H
4	Me	Ang	H
5	Me	Mebut	H
6	Me	H	Sen
7	Me	Sen	H
8	Me	Tig	H
9	CH_2OAc	Ac	Ang
10	CHO	H	Ang
11	CH_2OH	Tig	H
12	CHO	Ang	H
13	CHO	Mebut	H

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Table 1. ^1H NMR data of gigantanolide A (**1**) and derivatives **9** and **10** (80 MHz, $CDCl_3$, TMS as int. standard)

H	**1**	**1**(C_6D_6)	**1**(Me_2CO-d_6)	**9**	**9**(C_6D_6)	**10**
1	5.70 *br t*(8)*	5.25 *obs.*	5.68 *obs.*	5.80 *br t*(8)	5.30 *obs.*	6.93 *dd*(12, 6)
5	5.29 *br d*(11)	5.12 *br d*(11)	5.12†	5.25 *br d*(11)	5.02 *br d*(11)	5.20 *br d*(11)
6	5.05 *dd*(11, 6)	4.63 *dd*(11, 6)		5.06 *dd*(11, 6)	4.61 *dd*(11, 6)	4.88 *dd*(11, 6)
7	3.43 *br* t(~ 7)	3.11 *br t*(~ 7)	3.15 *m*	3.44 *br t*(7)	3.17 *m*	3.28 *brt*(7)
8	5.13 *dd*(9, 8)	5.26 *dd*(9, 7)	5.10 *dd*(9, 8)	5.30†	5.48†	4.94†
9	4.44 *d*(9)	4.28 *d*(9)	4.47 *dd*(9, 4)‡			
13a	5.52 *br s*	5.10 *dd*(~ 1, ~ 1)	5.53 *br s*	5.56 *br s*	5.17 *br s*	5.57 *br s*
13b	6.21 *br s*	6.18 *dd*(~ 1, ~ 1)	6.05 *brs*	6.25 *br s*	6.20 *br s*	6.20 *br s*
14a	3.90 *d*(12)	3.32 *d*(12)	4.16 *m*	4.42 *d*(12)	4.20 *d*(12)	9.83 *s*
14b	4.23 *dd*(12, 1.5)	3.62 *d*(12)	3.76 *m*	4.60 *d*(12)	4.52 *d*(12)	
15	1.63 *d*(1.5)	1.11 *d*(1.5)	1.67 *br s*	1.60 *d*(1.5)	1.04 *d*(1.5)	1.53 *d*(1.5)
OCOR	6.09 *qq*(7, 1.5)	5.67 *qq*(7, 1.5)	6.00 *br q*(7)	6.04 *qq*(7, 1.5)	5.68 *qq*(7, 1.5)	6.08 *qq*(7, 1.5)
	1.96 *dq*(7, 1.5)	1.96 *dq*(7, 1.5)	1.90 *br d*	1.83 *dq*(7, 1.5)	1.95 *dq*(7, 1.5)	1.93 *dq*(7, 1.5)
	1.98 *quint.* (1.5)	1.75 *quint.* (1.5)	1.85 *br s*	1.78 *quint.* (1.5)	1.78 *quint.* (1.5)	1.86 *quint.* (1.5)
OAc				2.10 *s*	1.76 *s*	
				1.97 *s*	1.65 *s*	

*Figures in parentheses are coupling constants or line separations in Hz.

†Two proton signals, not first order pattern.

‡Collapsed to a doublet ($J = 9$) on D_2O exchange.

§Collapsed to an AB quartet ($J = 12$) on D_2O exchange.

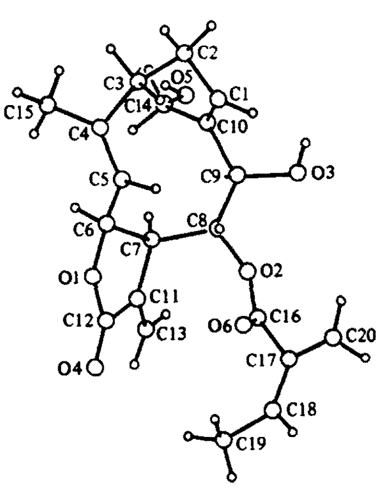
suggested the presence of a 6,12-*cis*-lactone. A doublet at δ4.44 ($J = 9$ Hz) and an AB quartet centred at δ4.07 ($J = 12$ Hz) were assigned to H-9 and H-14 on carbons bearing a secondary and a primary hydroxyl group respectively.

Acetylation of **1** confirmed the above assumption since these signals moved downfield to δ5.32 and 4.56 in **9**. Furthermore oxidation of **1** with manganese dioxide furnished the aldehyde **10** (1669 cm^{-1}), mp 118–120°, confirming the presence of the primary hydroxyl group at C-14. Accordingly, the H-1 doublet of doublets in the ^1H NMR spectrum of **10**, was shifted downfield to δ6.93 ($J = 12, 6$ Hz) and an aldehydic proton singlet appeared at δ9.85. The chemical shift of the last indicating the *trans* character of the 1(10) double bond [13]. A small signal at δ9.24 very likely due to the *cis*-isomer was also observed. Moreover after standing for 72 hr in $CDCl_3$ solution, the ^1H NMR profile of **10** changed. It displayed new aldehydic proton signals at *ca* δ9.3 (about four singlets) most likely due to a mixture of different conformers.

It is noteworthy that as in the case of closely related germacrolides from *M. atriplicifolia* [14], unusual *trans*-esterification together with isomerization of the angelate occurred when gigantanolide A (**1**) remained in $CDCl_3$ solution giving rise to compound **11**.

In order to verify the proposed structure and stereochemistry, single crystal X-ray data on gigantanolide A(**1**) were obtained. The results confirmed the *trans–trans* character of the double bonds in the cyclodecadiene and the *cis*-fusion of the lactone ring. The torsion angles demonstrated that the 10 membered-ring exists in the crystal in a chair-boat conformation [${}_{15}D^5$, ${}^1D_{14}$] [11] in which both groups at C-4 and C-10 are α-oriented, in contrast to the double-chair type [${}^{15}D_5$, ${}_1D^{14}$] typical of the 12,6-*trans*-germacrolides.

Gigantanolide B(**2**) and C(**3**) were isolated as a mixture of the isomeric angelate **2** and the corresponding methylbutyrate **3**, as followed from the typical ^1H NMR signals (Table 2). The relative position of the ester and the hydroxyl groups being indicated by the chemical shifts of



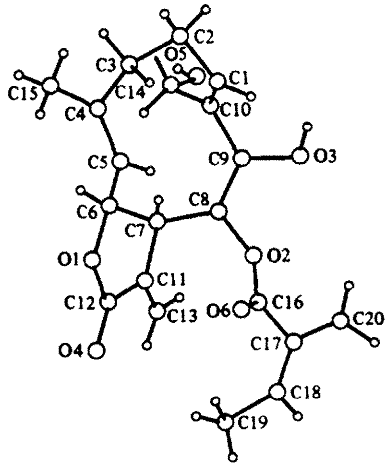


Table 2. ^{1}H NMR data of gigantanolide B (**2**), C(**3**) and derivatives **11**, **12**, **13**. (80 MHz, $CDCl_3$, TMS as internal standard)

H	**2**	**3**	**12**	**13**	**11**	**11** ($C_6D_6/CDCl_3$,4:1)
1	5.45 *br t*(8)*	5.45 *br t*(8)	6.75 *dd*(12, 6)	6.75 *dd*(12, 6)	5.45 *br t*(8)	5.15 *obs*
5	5.15 *br d*(11)	5.15 *br d*(11)	4.95†	4.95†	5.02†	4.67†
6	5.00 *dd*(11, 6)	5.00 *dd*(11, 6)				
7	3.35 *br t*(7)	3.35 *br t*(7)	3.34 *m*	3.34 *m*	3.35 *br t*(7)	3.07 *m*
8	4.14 *dd*(9,8)	4.10 *dd*(9, 8)	3.99 *dd*(9, 8)	3.92 *dd*(9, 8)	4.14 *dd*(9, 8)	3.82 *dd*(9, 8)
9	5.02 *d*(9)	5.02 *d*(9)	5.57 *d*(9)	5.50 *d*(9)	4.99 *d*(9)	4.98 *d*(9)
13a	5.73 *br s*	5.73 *br s*	5.80 *br s*	5.80 *br s*	5.73 *br s*	5.42 *br s*
13b	6.38 *br s*	6.38 *br s*	6.38 *br s*	6.38 *br s*	6.39 *br s*	6.32 *br s*
14a	3.80 *d*(12)	3.80 *d*(12)	9.82 *s*	9.82 *s*	3.78 *d*(12)	3.52 *d*(12)
14b	4.32 *d*(12)	4.30 *d*(12)			4.30 *d*(12)	4.06 *d*(12)
15	1.60 *br s*	1.60 *br s*	1.52 *br s*	1.52 *br s*	1.60 *br s*	1.14 *br s*
OCOR	6.11 *qq*(7, 1.5)	1.12 *d*(7)	6.10 *qq*(7, 1.5)	1.10 *d*(7)	6.90 *qq*	6.83 *qq*(7, 1.5)
	1.97 *dq*(7, 1.5)	0.90 *t*(7)	1.97 *dq*(7, 1.5)	0.90 *t*(7)	1.80 *br d*(7)	1.45 *br d*(7)
	1.90 *quint.* (1.5)		1.90 *quint.*(1.5)		1.82 *br s*	1.68 *br s*

*Figures in parentheses are coupling constants or line separations in Hz.

†Two proton signals, not first order pattern.

H-8 and H-9. The EIMS of **2** and **3** showed only a weak molecular ion at m/z 362 in addition to peaks at m/z 83, 55 and 85, 57, characteristic of the angelate and methylbutyrate acylium ions. But the CIMS showed both $[M+]^+$ peaks at m/z 363 and 365 and common peaks at m/z 263 corresponding to the loss of angelic and methylbutyric acids and at m/z 245 to loss of water from m/z 263.

The ^{1}H NMR spectrum (Table 2) differed from that of **1** in the chemical shifts of H-8 (δ4.14) and H-9 (δ5.02), as expected, and the chemical shifts of H-1 and H-14.

As in the case of **1**, manganese dioxide oxidation of the mixture of **2** and **3** furnished the corresponding mixture of aldehydes (**12**, **13**) whose ^{1}H NMR clearly displayed the H-8 signal as a doublet of doublets at δ3.99 ($J = 9, 7$ Hz), since the (CH_2–OH) AB quartet which was overlapped with the H-8 signal in the spectrum of **2** and **3** disappeared in the aldehydes **12** **13**, and, instead an aldehydic proton singlet appeared at δ9.82.

The less polar fractions from the chromatography gave the isomeric lactones **6** and **7**. During the preparation of this paper the isolation of these lactones from *Montanoa tomentosa* subsp. *xanthiifolia* [9] was published. All IR, MS and ^{1}H NMR data for both lactones were quite similar with the reported data.

EXPERIMENTAL

The air-dried aerial parts (1400 g) of *M. gigas*, collected in Feb. 1984, near Filo de Caballo, in the state of Guerrero, México (E. Martinez S. 6147, voucher deposited at Herbario Nacional, UNAM (MEXU)), were extracted first, with petrol and then with CH_2Cl_2. The petrol extract (60 g) was separated by CC (silica gel) using petrol and petrol–EtOAc mixtures of increasing polarity to yield 95 fractions of 300 ml.

The less polar fractions of the petrol extract afforded besides ubiquitous sterols, a mixture of triterpenes containing taraxasteryl acetate and palmitate. Fractions eluted with petrol-EtOAc (49:1) contained *ent*-kaurenic acid. From fractions eluted with petrol–EtOAc (19:1) angeloylgrandifloric acid was obtained. Fractions eluted with petrol-EtOAc (9:1) yielded a crystalline compound, mp 208–210°, spectroscopically identified as cinnamoylgrandifloric acid isolated before as an oil from *M. pteropoda* [15]. Fraction eluted with petrol–EtOAc (4:1) afforded a crystalline mixture of angeloylgrandifloric acid and 17-hydroxy-*iso*-kaurenoic acid, mp 228–232° [16]. Methylation of the mixture (98 mg) with CH_2N_2 in Et_2O gave the corresponding methyl esters, which were separated by TLC (petrol–EtOAc, 7:3, × 2) and identified by their spectral data. Oxidation of the methyl ester of 17-hydroxy-*iso*-kaurenoic acid (13 mg) with MnO_2 (126 mg) in the usual fashion, gave the corresponding aldehyde [17].

The CH_2Cl_2 extract (33 g) was separated by CC on silica gel (200 g) using petrol–CH_2Cl_2 (1:1) to yield 4 fractions and further by rechromatography of each fraction and repeated TLC purifications (silica gel) of combined fractions when necessary.

Rechromatography of fraction 1 over silica gel (150 g) using petrol–EtOAc mixtures of increasing polarity afforded a mixture of hydrocarbons, mainly hentriacontane, taraxasterol and ent-kaurenic acid. Fraction 2 yielded further amounts of *ent*-kaurenic acid and its 15α-angeloyloxy derivative. Fraction 3 was rechromatographed as mentioned above. Fractions eluted with petrol–EtOAc (49:1), yielded further amounts of the crystalline mixture of angeloylgrandifloric acid and 17-hydroxy-*iso*-kaurenoic acid. Fractions eluted with petrol–EtOAc (9:1) were further rechromatographed using CH_2Cl_2-Me_2CO mixtures as eluent. From fractions eluted with CH_2Cl_2–Me_2CO (49:1), **6** [9] was obtained. Fractions eluted with CH_2Cl_2–Me_2CO (49:1) afforded **7** [9] with small amounts of **4**, **5** [3] and **8** [10]. Fraction 4 was preadsorbed on silica gel (6 g) and rechromatographed over silica gel (20 g) using petrol–EtOAc mixtures as eluent. Fractions eluted with petrol–EtOAc (1:1) afforded **1**, while fractions eluted with petrol–EtOAc (1:1) afforded **1**, while fractions eluted with petrol–EtOAc (3:2) were combined and rechromatographed to yield a mixture of **2** and **3**.

Gigantanolide A (**1**). $C_{20}H_{26}O_6$, colourless crystals, mp 118–122°, $[\alpha]_D$ $-152°$ ($CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 209 (53950); IR ν_{max}^{KBr} cm^{-1}: 3400, 1760, 1695, 1150; EIMS (probe) 70 eV m/z (rel. int.): 362 $[M]^+$ (not observed), 262 $[M-C_5H_8O_2]^+$ (0.3), 244 $[M-C_5H_8O_2-H_2O]^+$ (1), 83 $[C_5H_7O]^+$ (100), 55 $[C_4H_7]^+$ (52). CIMS (*i*bu) m/z (rel. int.): 363 $[M+1]^+$ (89), 345 $[M+1-H_2O]^+$ (36), 263 $[M+1-C_5H_8O_2]^+$ (51), 245 $[M+1-C_5H_8O_2-H_2O]^+$ (100), 149 (37), 101 $[C_5H_8O_2+1]^+$ (85).

Gigantanolide B and C (**2** *and* **3**). Colourless gum, UV λ_{max}^{MeOH} nm (ε): 205 (50100); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1765, 1710; EIMS (probe) 70 eV m/z (rel. int.): 364 $[M(\mathbf{2b})]^+$ (not observed), 362 [M(**2a**)]$^+$ (0.2), 344 [M(**2a**)-H_2O]$^+$ (0.2), 262 [M(**2a**) $-C_5H_8O_2$]$^+$, [M(**2b**)-$C_5H_{10}O_2$]$^+$ (1.2), 244 [262 $-H_2O$]$^+$ (2.4), 85 [C_5H_9O(**2b**)]$^+$ (12), 83 [C_5H_7O(**2a**)]$^+$ (95), 57 [C_4H_9 (**2b**)]$^+$ (37), 55 [C_4H_7(**2a**)]$^+$ (100); CIMS (*i*bu) *m/z* (rel. int.): 365[M(**2b**) + 1]$^+$ (21), 363 [M(**2a**) + 1]$^+$ (53), 347 [M(**2b**) $-H_2O$]$^+$ (7), 345 [M(**2a**) $-H_2O$]$^+$ (12), 263 [M(**2b**) + 1 $-C_5H_{10}O_2$]$^+$, [M(**2a**) + 1 $-C_5H_8O_2$]$^+$ (26), 245 [263 $-H_2O$]$^+$ (52), 149 (28), 103 [$C_5H_{10}O_2$(**2b**) + 1]$^+$ (31), 101 [$C_5H_8O_2$(**2a**) + 1]$^+$ (100).

Gigantanolide A diacetate (**9**). Acetylation of **1a** (17 mg) with Ac_2O/Py as usual, gave after TLC purification (petrol–EtOAc, 3:2, × 2) the diacetate **9** as a colourless gum. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1760, 1740; EIMS (probe) 70 eV *m/z* (rel. int.): 446 [M]$^+$ (0.8), 387 [M $-$ AcO]$^+$ (0.8), 346 [M $-C_5H_8O_2$]$^+$ (0.1), 287 [M $-$ AcO $-C_5H_8O_2$]$^+$ (0.4), 226 [M $-$ 2AcO $-C_5H_8O_2$]$^+$ (10), 83 [C_5H_7O]$^+$ (100), 55 [C_4H_7]$^+$ (44), 43 [Ac]$^+$ (38).

Oxidation of gigantanolide A (**1**). A 50 mg sample of **1** was treated with MnO_2 (500 mg) in CH_2Cl_2 at room temp. for 1 hr, worked up as usual and purified by CC on silica gel (1.5 g). **10** was eluted with petrol–EtOAc (7:3), colourless crystals, mp 118–20°. UV $\lambda_{\max}^{MeOH}$ nm (ε): 206 (10,800); IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3600, 1769, 1718, 1669, 1147; EIMS (probe) 70 eV *m/z* (rel. int.): 360 [M]$^+$ (0.1), 260 [M $-C_5H_8O_2$]$^+$ (2.4), 242 [M $-C_5H_8O_2-H_2O$]$^+$ (0.2), 91 (9), 83 [C_5H_7O]$^+$ (100), 55 [C_4H_7]$^+$ (63).

Oxidation of gigantanolide B and C (**2** and **3**). Oxidation of the mixture of **2** and **3** (70 mg) with MnO_2 as described above gave after TLC purification ($CH_2Cl_2-Me_2CO$, 9:1) the corresponding aldehydes **12**, **13** as a colourless gum. UV $\lambda_{\max}^{MeOH}$ nm (ε): 209 (30,200); IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3478, 1765, 1717, 1670, 1551; EIMS (probe) 70 eV *m/z* (rel. int.): 360 [M(**2c**)]$^+$ (0.3), 260 [M(**2c**) $-C_5H_8O_2$]$^+$, [M(**2d**) $-C_5H_{10}O_2$]$^+$ (1), 242 [260 $-H_2O$]$^+$ (4), 85 [C_5H_9O(**2d**)]$^+$ (13), 83 [C_5H_7O(**2c**)]$^+$ (93), 57 [C_5H_9(**2d**)]$^+$ (54), 55 [C_5H_7(**2c**)]$^+$ (100).

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