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TRITERPENES AND SESQUITERPENE LACTONES FROM *CYCLOLEPIS GENISTOIDES*

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Key Word Index—*Cyclolepis genistoides*; Gochnatiinae; Mutisieae; Compositae; lupanes; oleananes; 12,13-epoxyoleanolic acid; 3β,28-dihydroxylup-20(29)-en-30-al; triterpenes; guaianolides; sesquiterpene lactones.

Abstract—Aerial parts of *Cyclolepis genistoides* afforded a number of oleananes and ursanes including the new 12α,13α-epoxyoleanolic acid, lupanes including 3β,30-dihydroxylup-20(29)-ene and the new 28-dihydroxylup-20(29)-en-30-al and the sesquiterpene lactones deacylcynaropicrin, dihydroeleganin and isolippidiol. ©1997 Published by Elsevier Science Ltd. All rights reserved

INTRODUCTION

Cyclolepis genistoides Don, the sole representative of a monotypic genus within Mutisieae, subtribe Gochnatiinae, occurs in salty soils ranging from southern Bolivia and Paraguay to southern Argentina [1]. Infusions of the aerial parts of this species, locally called 'palo azul' or 'matorro negro', are used in traditional medicine for the treatment of renal disease. The only reference to previous chemical work is a statement that unlike most species belonging to genera within other subtribes of Mutisiae some genera of the Gochnatiinae, including *Cyclolepis*, gave only triterpenes [2]. We have now examined a collection of this species from near Tucumán.

RESULTS AND DISCUSSION

In addition to oleanolic and ursolic acid, the main constituents of the extract, we isolated β-amyrin, dihydro-β-amyrin, oleanonic acid, taraxasterol, betulin, betulinic acid, methyl betulinate, the lupane **1a** previously reported from *Flourensia heterolepis* [3] and a *Gymnosperma* species [4], the new lupane **1b** and the new 12,13-epoxyoleanolic acid **2**.

The extract also furnished a complex mixture of sesquiterpene lactones. In an attempt to separate these, part of the mixture was acetylated and subjected to HPLC. This afforded the previously known **4b** [5], kandavanolide (**4c**) [6], 8α-acetoxyzaluzanin C (**4d**) [7] and the new derivatives **5b**, **5c**, **6b** and **6c**, while the unacetylated portion furnished deacylcynaropicrin (**4a**) [8], 11,13β-dihydrodeacylcynaropicrin (**5a**) [9] and isolippidiol (**6a**) [10]. Structures of the new derivatives are based on the ^{1}H NMR spectra (Table 1). The mono- and diacetates are presumably derived from the parent compounds **4a**, **5a** and **6a** originally present in the extract.

The structure of **1b** was clear from the mass spectrum and the ^{1}H NMR spectrum, which exhibited the usual signals of H-3 under an equatorial OH (*dd* at δ 3.17, *J*'s = 12.5 Hz), an aldehydic proton at δ 9.51 conjugated with two methylene protons (singlets at δ 6.28 and 5.93), a hydroxymethylene (mutually coupled doublets at δ 3.80 and 3.37) and five methyl singlets whose shifts indicated that the primary hydroxyl was located on C-28. The structure of **2** could also be deduced from the mass spectrum which indicated the molecular formula $C_{30}H_{48}O_4$ and the ^{1}H NMR spectrum which established the presence of axial H-3 under an OH (*dd* at δ 3.25, *J*'s = 11.5 and 4.5 Hz), an epoxidic proton at δ 3.03 ($W_{1/2}$ approx. 6 Hz) and seven methyl singlets whose chemical shifts indicated that the carboxyl group was attached to C-17. The chemical shift and half-height width of the epoxidic proton was typical of a 12α,13α- or 12β,13β-epoxyoleanane [11–13]. While the two isomeric series can apparently be distinguished by ^{13}C NMR spectrometry [12], the available amount of the new epoxide was not sufficient to permit distinction by this method. An attempt to settle the matter by perbenzoic oxidation of oleanolic acid resulted only in formation of **3a**, analogous to the action of various oxidizing agents, including perbenzoic acid on the acetate of

Table 1. ^{1}H NMR spectra of compounds **5b** and **c**, and **6b** and **c** ($CDCl_3$, 500 MH_2)

H	5b*	5c†		6c†	6b
1	2.95 *ddd* (10,8,8)		2.9 *m*		2.86 *ddd* (10,10,6.5)
2a	2.35 *ddd* (13.5,8,7)		2.3 *m*		2.33 *ddd* (13,6.5,6.5)
2b	1.79 *ddd* (14,8,7.5)		1.75 *m*		1.69 *ddd* (13,10,8.5)
3	5.55 *ttt* (7.5,1)	4.57 *br s* (7.5)		3.72 *ddd* (9,7.5,7.5)	4.68 *ddd* (8.5,8,7)
4	—		—		2.14 *ddq* (8.5,8,7)
5	2.83 *t* (10)	2.8 *m*		1.9 *m*	1.94 *ddd* (10,10,8)
6	4.04 *t* (10)	4.08 *t* (10)		3.98 *t* (10)	3.95 *t* (10)
7	2.25 *q* (10)	2.2 *m*		2.15 *m*	2.14 *ddd* (11,10,10)
8	4.91 *ddd* (10.5,8,5)	4.91 *ddd* (10.5,8,5)		4.81 *ddd* (10,10,45)	4.82 *ddd* (10,10,4.5)
9a	2.74 *dd* (14,5)		2.75 *m*		2.78 *dd* (12,4)
9b	2.20 *dd* (14,8)	2.2 *m*		2.1 *m*	2.8 *m*
13‡	1.30 *d* (7)		1.29 *d*, 1.28 *d*		1.28 *d* (7)
14	5.08 *br s* 5.05 *br s*		5.14 *br s*, 5.10 *br s* 5.08 *br s* 5.04 *br s*		5.11 *br s* 5.04 *br s*
15	5.44 *t* (1) 5.30 *t* (1)	5.40 *t* 5.32 *t*		1.20 *d*† (7)	1.15 *d*† (6.5)
Ac‡	2.10 *s*, 2.09 *s*		2.10 *s*, 2.09 *s*		2.09 *s*, 2.07 *s*

* From mixture with **4b**.
†From mixture with **4d**.
‡Intensity three protons.

oleanolic acid which produces **3b** [14–17]. However, one of the more polar constituents of the triterpene fraction proved to be identical with **3a** and was presumably formed by action of the silicic acid adsorbent on **2**. Consequently the epoxyoleanolic acid is the α-isomer.

Possible structures of several other triterpenes isolated in very small amounts from the triterpene fraction are mentioned in the Experimental.

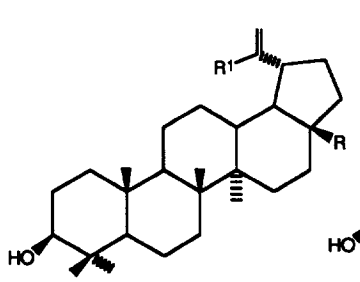
EXPERIMENTAL

General. For sepn of mixts HPLC with a differential refractometer was used. The columns employed were (A) a Beckman C18 (5μ, 10 × 250 mm and (B) a Beckman C8 (5μ, 10 × 250mm). R_fs were measured from the solvent peak.

Plant material. Aerial parts of *Cyclolepis genistoides* Don were collected at the flowering stage in January 1992 near Amaicha del Valle, Tucumán Province, Argentina. A voucher specimen (CANC 574) is deposited in the Instituto Miguel Lillo, Tucumán.

Extraction and isolation. Flowers and leaves (1.33 kg) were extracted with $CHCl_3$ (2 × 6 l) at room temp for 6 days to give 98.1 g of crude extract (yield 7.34%) which was suspended in EtOH (840 ml) at 60°, diluted with H_2O (630 ml) and extracted successively with hexane (3 × 400 ml) and $CHCl_3$ (3 × 500 ml). Evapn of the hexane extract at red. press. gave a residue (22 g) which was not studied further. Evapn of the $CHCl_3$ extract gave a residue (32 g), a portion of which (21 g) was chromatographed over silica gel (400 g) using $CHCl_3$ containing increasing amounts of MeOH (1–5%), 220 frs being collected, which were monitored by TLC.

Frs 66–69 (410 mg) were combined. A portion (100 mg) was processed by HPLC (col. A. MeOH, 3.5 ml min^{-1}) to give 15.3 mg of lupeol (R_t 17.7 min) and a number of poorly resolved peaks which were rechromatographed on the same column using MeCN–EtOAc (3:1, 3 ml min^{-1}) to yield 1 mg taraxasterol (R_t 29 min), 2.0 mg of β-amyrin (R_t 31 min) both identified by MS and ^{1}H NMR, and small amounts of diterpene mixts in the subsequent frs. Frs 88–110 (303 mg) were recrystallized twice from heptane–EtOAc (2:1) to give 28 mg of betulin identified by MS, ^{1}H and ^{13}C NMR. More betulin could be recovered from the mother liquors. Frs 111–113 (40 mg) on HPLC (column A, MeOH–H_2O, 96.5:3.5, 2 ml min^{-1}) gave 1.1 mg of a mixture (R_t 4.5 min) and 2 mg of betulin (R_t 7 min). Frs 114–120 (124 mg) were combined and processed by HPLC as before to give 1.4 mg of **2** (R_t 5.5 min), 1.4 mg of methyl betulinate (R_t 7.5 min) identified by MS and ^{1}H NMR, 1.4 mg of a mixt. of two ursenes (R_t 9.2 min), probably 12,13-dihydromicromeric acid (**7**) and its $\Delta^{19,29}$-isomer (**8**) as a gum, MS CI (NH_3) *m/z* (rel int.): 474 ($[M+NH_4]^+$(100), 456 (46.9), 358 (29.9); MS PCI (isobutane): 457 [M + H$^+$], 437 (88); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.99 and 4.59 (*br s*, H-29a, b of **8**), 4.64 and 4.61 (both *t*, *J* = 2 Hz, H-30a, b of **7**), 3.20 (*dd*, *J* = 11.5, 5 Hz, H-3α of both), 1.08 and 1.07 (both *d* and 3p, *J* = 7 Hz, H-29 of **7** and H-30 of **8**), 1.05, 1.00, 0.99, 0.97, 0.95, 0.93, 0.86, 0.77, 0.77 (all *s* and 3*p*). Further HPLC of these fractions gave 1.4 mg of oleanonic acid (R_t 12 min), identified by MS and ^{1}H NMR, and 2 mg of the unknown 3β,19-dihydroxyursane or more likely one of the two epimeric ψ-taraxastane-3β,20-diols [19–21] as a gum (R_t 12 min), MS PCI (isobutane) *m/z* (rel. int.): 445 $[M+H]^+$ (35.9), 427 (100), 410 (51.2); MS EI *m/z*: 444 (13.7), 426 (41.6, 411 (16.5), 373 (100), 355 (64.1), 207 (49.2), 191 (41.7), 189 (52.4); ^{1}H NMR: δ 3.20 (*dd*, *J* = 11.5, 4.5 Hz, H-3α), 1.06 (*d*, *J* = 6 Hz, H-30 of the dihy-



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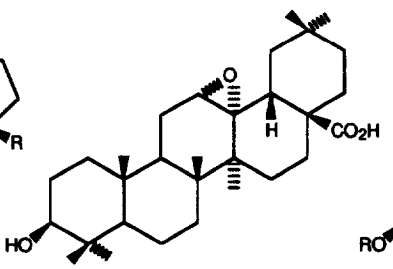
b R = CH_2OH, R^1 = CHO



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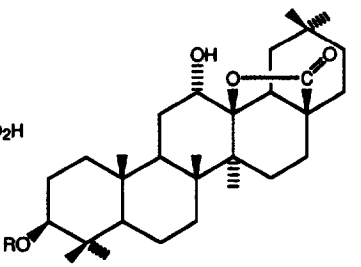

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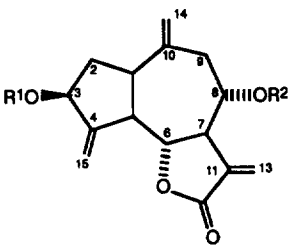

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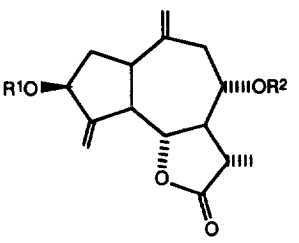
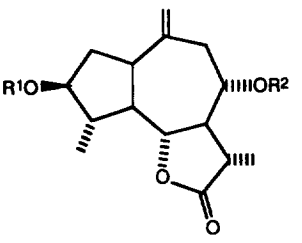
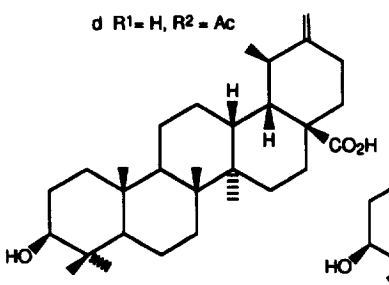
b R^1, R^2 = Ac
c R^1 = Ac, R^2 = H
d R^1 = H, R^2 = Ac



5 a R^1, R^2 = H
b R^1, R^2 = Ac
c R^1 = H, R^2 = Ac



6 a R^1, R^2 = H
b R^1, R^2 = Ac
c R^1 = H, R^2 = Ac



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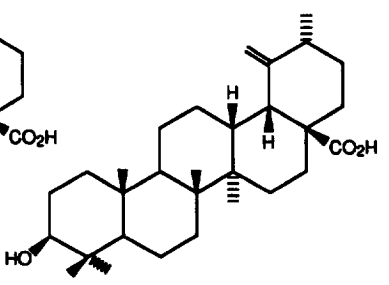

8

droxyursane or H-29 of ψ-taraxastanediol), Me singlets at δ 1.08, 1.04, 0.97, 0.94, 0.90, 0.84, 0.77, Me doublet at δ 1.06 (J = 6 Hz). A peak in the EI MS at m/z 373, in our case the base peak, may be diagnostic of the ψ-taraxastanediols [20]. In the literature [20, 21], the methyl signals in the ^{1}H NMR spectra of the purportedly isomeric ψ-taraxastanediols are all described as singlets, rather than as one doublet and seven singlets, with essentially identical chemical shifts in both isomers whereas one would expect significant differences in the shifts of the H-29 and H-30 signals of the two. Finally, HPLC of these frs gave 35 mg of dihydro-β amyrin (R_t 23.7 min), mp 230°, identified by MS and ^{1}H NMR.

Frs 121–125 (80 mg) were combined and processed by HPLC in the same manner to give 1.2 mg of a 19- or 20-hydroxyursolic acid derivative with an additional equatorial hydroxyl as a gum (R_t 4 min), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.32 (*t*, $J \sim 3$ Hz, H-12), 3.6 (*m*, H under -OH), 3.20 (*dd*, J = 12, 5 Hz, H-3α), Me singlets at δ 1.23, 1.10, 0.97, 0.91, 0.77 and 0.76, Me doublet at δ 0.84, 21.7 mg of betulinic acid (R_t 7 min), identified by MS and ^{1}H NMR, triterpene mixtures and 2.4 mg of dihydro-β-amyrin (R_t 20.5 min).

Frs 126–133 (125 mg) were combined and processed by HPLC as before to give 3.1 mg of **1b** (R_t 3.2 min), 23.8 mg of betulinic acid (R_t 7.5 min), 13 mg of oleanolic acid (R_t 9.7 min) and 2.4 mg of **1a** (R_t 20 min) [3, 4] whose ^{1}H NMR spectrum exhibited signals at δ 4.93 *br s* and 4.91 *br s* (H-29a,b), 4.13 and 4.09 (both *d*, *J*-9 Hz, H-28 a,b), 3.19 (*dd*, J = 7, 3 Hz, H-3α), 2.28 (*td*, J = 7,3 Hz, H-19), 2.06 (*tt*, J = 7 and 6 Hz), 1.03, 0.97, 0.83, 0.78, 0.76 (Me singlets). Frs 134–159 (3 g) contained mainly oleanolic and ursolic acid in a 3:2 ratio (HPLC analysis). A portion (400 mg) was recrystallized from heptane–HOAc (2:1). The crystalline material was processed by HPLC (column A, MeOH–H_2O, 19:1, 1 ml min^{-1}) to give 40 mg of pure oleanolic and 35 mg of pure ursolic acid.

Frs 160–192 (378 mg) were combined and rechromatographed ($CHCl_3$–EtOAc, 9:1) over silica gel, 60 subfrs being collected. Subfrs 26–32 (44 mg) on recrystallization from MeOH–H_2O (14:5) afforded 32 mg of ursolic acid. Subfrs 33–44 (51 mg) were com-

bined and processed by HPLC (column A, MeOH–H_2O, 19:1, 2 ml min^{-1}) to give 1.2 mg (R_f 4.7 min) of a uvaol derivative $C_{30}H_{50}O_3$ containing an additional equatorial hydroxyl group in rings D or E, as shown by mass spectral fragmentation, probably in the same location as the ursolic acid derivative from frs 121–125, CI(NH_3)-MS *m/z* (rel. int.): 476 $[M+NH_4]^+$, 457 (40.3), 441 (100), 423 (85.6), 409 (20.8), 232 (19.5), 207 (30.7) 191 (24.9), 189 (12.5; MS PCI (isobutane) *m/z* (rel. int.): 441 $[M+H-H_2O]^+$ (73.0), 423 (100); ^1H NMR: δ 5.08 (*t*, $J \sim 3$ Hz, H) 3.87 (*d*, $J = 11$ Hz, H-28a), 3.69 (*dd*, $J = 11.5$, 4.8 Hz, H under eq. -OH), 3.30d ($J = 11$ Hz, H-28b), 3.21 (*dd*, $J = 10.5$, 5.3 Hz, H-3α), 1.10, 0.98, 0.97, 0.92, 0.77 (all Me singlets), 0.97 and 0.76 (both *d* and 3p, $J = 6.3$ resp. 6 Hz, H-29 and H-30). Subfrs 33–44 mg further gave 3.0 mg of an isomeric ursenetriol $C_{30}H_{50}O_3$ (R_f 5 min) with one equatorial hydroxyl at C-3 and two equatorial hydroxyl in rings D and E as shown by strong mass spectral peaks at *m/z* 250 and 232, and the typical peaks at *m/z* 207 and 189, mp 266–268° without recrystallization, MS EI *m/z* (rel. int.): 458 $[M]^+$ (9.0), 440 (14.6), 422 (17.6), 250 (86.0), 232 (100), 207 (48.2), 203 (24.5), 201 (28.0), 190 (21.2), 189 (22.2); MS PCI (isobutane) *m/z*: 441 $[M+H-H_2O]^+$ (100), 423 (88.7); ^1H NMR ($CDCl_3$, 300 MHz); δ 5.03 (*t*, $J = 3$ Hz), 4.53 (*dd*, $J = 12$, 5.5 Hz, axial H under OH at C-15 or C-16 ?), 3.50 *dd*, $J = 13.5$, 4.5 Hz, axial H under OH at C-22 ?), 3.20 (*dd*, $J = 11.5$, 5 Hz, H-3a), 1.13, 1.04, 1.02, 0.98, 0.94, 0.78 (six Me singlets), 0.98 and 0.75 (both *d* and 3p, $J = 6$ resp. 7 Hz, H-29 and H-30). This was followed by 5.2 mg of ursolic acid (R_f 9.5 min). Subfrs 45–60 (90 mg) were combined and processed by HPLC as before to give 2.9 mg of **3a** (R_f 5.5 min) identical in all respects with synthetic **3a** and 11.7 mg of ursolic acid (R_f 10.7 min).

Frs 193–194 (900 mg) were combined. A portion (500 mg) was acetylated (Ac_2O–Py, RT, 24 hr) to give 311 mg of acetylated material. Chromatography of the latter (silica gel, 15 g, eluent hexane–EtOAc, 7:1) furnished 150 frs. Frs 30–38 (23 mg) were combined and processed by HPLC (column A, MeO–H_2O, 2 ml min^{-1}) to give 2 mg of a mixture (R_f 14.5 min) of **4b** (major constituent) and **5b** (minor constituent) and 13 mg of **6b** (R_f 19.5 min). Frs 39–51 of the rechromatogram (38 mg) were combined and subjected to HPLC (column A, MeOH–H_2O, 2:1, 2 ml min^{-1}) to give 7 mg of a mixture (R_f 14.5 min) of **4b** (minor constituent) and **5b** (major constituent). Frs 95–138 of the rechromatogram (33 mg) were combined; HPLC (column A, MeOH–H_2O, 2:1, 2 ml min^{-1}) afforded 11 mg of kandavanolide (**4c**) (R_f 9 min) identified by MS and ^1H NMR and 7 mg of a mixture of **4d**, **5c** and **6c**.

Frs 195–199 (300 mg) of the main chromatogram were combined. HPLC (column A, MeOH–H_2O, 5:6, 2 ml min^{-1}) gave 5.4 mg of **5a** and **6a** (R_f 6 min) identified by MS and ^1H NMR, 36.7 mg of **5a** (R_f 6.7 min) and 17.2 mg of **4a** (R_f 8.7 min). Frs 200–209 (160 mg) of the main chromatogram were combined; HPLC (column A, MeOH–H_2O, 1:1, 1.5 ml min^{-1}) gave 14 mg of a mixture of **5a** and **6a** (R_f 4.2 min) and 2 mg of impure **4a** (R_f 5 min).

3β, 28-*Dihydroxylup*-20(29)-*en*-30-*al* (**1b**). Mp 248–249° (without recrystallization); MS PCI (isobutane) *m/z* (rel. int.): 457 $[M+H]^+$ (47.8) $C_{30}H_{48}O_3$), 439 (100) 421 (48.6); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.51 (*s*, H-30), 6.28 and 5.93 (both *d*, H-29a,b), 3.37 and 3.08 (both *s*, $J = 11$ Hz, H-28 a,b), 3.17 (*dd*, $J = 12,5$ Hz, H-3), 1.01, 0.97, 0.96, 0.81 and 0.76 (all *s* and 3*p*, H-24, 25, 26, 27 and 28).

12α,13α-*Epoxyoleanolic acid* (**2**). Amorphous solid; MS PCI (isobutane) *m/z* (rel. int.): 473 $[M+H]^+$ (49.6) $C_{30}H_{48}O_4$) 455 (100), 427 (37.7); MS CI (NH_3): 490 $[M+NH_4]^+$ (100); ^1H NMR (500 MHz, $CDCl_3$): δ 3.25 (*dd*, $J = 11.5$, 4.5 Hz, H-3), 3.03 *br s* ($J = 3.5$ Hz, H-12), 2.3? (*dd*, $J = 14$, 3 Hz, H-18), 2.13 (*ddd*, $J = 13.5$, 13.5, 5.5 Hz), 1.92 (*ddd*, $J =$ 13, 3.5, 3.5 Hz), 1.87 ($J = 14$ Hz) 1.75–1.48*c*, 1.37 (*ddd*, $J = 14$, 14, 4.5 Hz), 1.33–126*c*, 1.22–1.15*c*, 1.10*s*, 1.07*s*, 1.03*s*, 1.00*s*, 1.00*s*, 0.92*s*, 0.80 (each 3p, H-24, H-25, H-26, H-27, H-29, H-30).

Peracid oxidation of oleanolic acid. A soln of *m*-chloroperbenzoic acid (53 mg) in $CHCl_3$ (7 ml) was added dropwise to a soln of oleanolic acid in $CHCl_3$ (9 ml). The mixt. was stirred overnight, washed with Na_2SO_3 (3 × 5 ml), 5% aq $NaHCO_3$ (2 × 3 ml) and H_2O (2 × 4 ml). The residue (43 mg) obtained after evapn of the organic layer was purified by HPLC (col. A, MeOH–H_2O, 46:1, 2 ml min^{-1}) to give 26.3 mg of **3a**, mp 239–242° (heptane–EtOAc), lit. [17] mp of material prepd by hydrolysis of the acetate 274–278° (MeOH), ^1H NMR (500 MHz, $CDCl_3$): δ 3.87 (*br s*), $W_{1/2}$ 7 Hz, H-12), 3.21 (*dd*, $J = 11.5$ Hz, H-3), 2.12 (*ddd*, $J = 13$, 13, 6 Hz), 2.05–1.98 (*m*, 2p), 1.98 (*dd*, $J = 14$, 14 Hz), 1.92–1.84 (*c*, 2p), 1.71 (*ddd*, $J = 13$, 3.5, 3.5 Hz), 1.67–1.51 (*c*, 7p), 1.48–1.34 (*m*, 2p), 1.29–1.22 (*c*, 4p), 1.15 (*br dd*, $J = 14$, 6 Hz), 1.30*s*, 1.15, 0.98, 0.97, 0.89, 0.88, 0.71 (7 methyl singlets); ^{13}C NMR ($CDCl_3$) 179.8 (C-28), 90.6 (C-13), 78.8 (C-3), 76.4 (C-12), 55.2 (C-5), 51.1 (C-9), 44.7 (C-17), 44.6 (C-18), 42.3 and 42.1 (C-8, C-14), 39.4 and 38.9 (C-1, C-19), 38.8 (C-10), 34.2 and 34.0 (C-7, C-21), 33.3 (C-29), 31.6 (C-20), 28.8 (C-15), 28.1 (C-2), 28.0 (C-23), 27.5 and 27.3 (C-16, C-22), 23.9 (C-30), 21.2 (C-11), 18.6 (C-6), 18.5 and 17.9 (C-26, C-27), 16.3 (C-25), 15.3 (C-24).

Diacetoxyisolippidiol (**5b**). Gum; MS PCI (isobutane) *m/z*: 351 (100) $[M+H]^+$ ($C_{19}H_{26}O_6$), 291 (90.5), 231 (41.9); ^1H NMR: Table 1.

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