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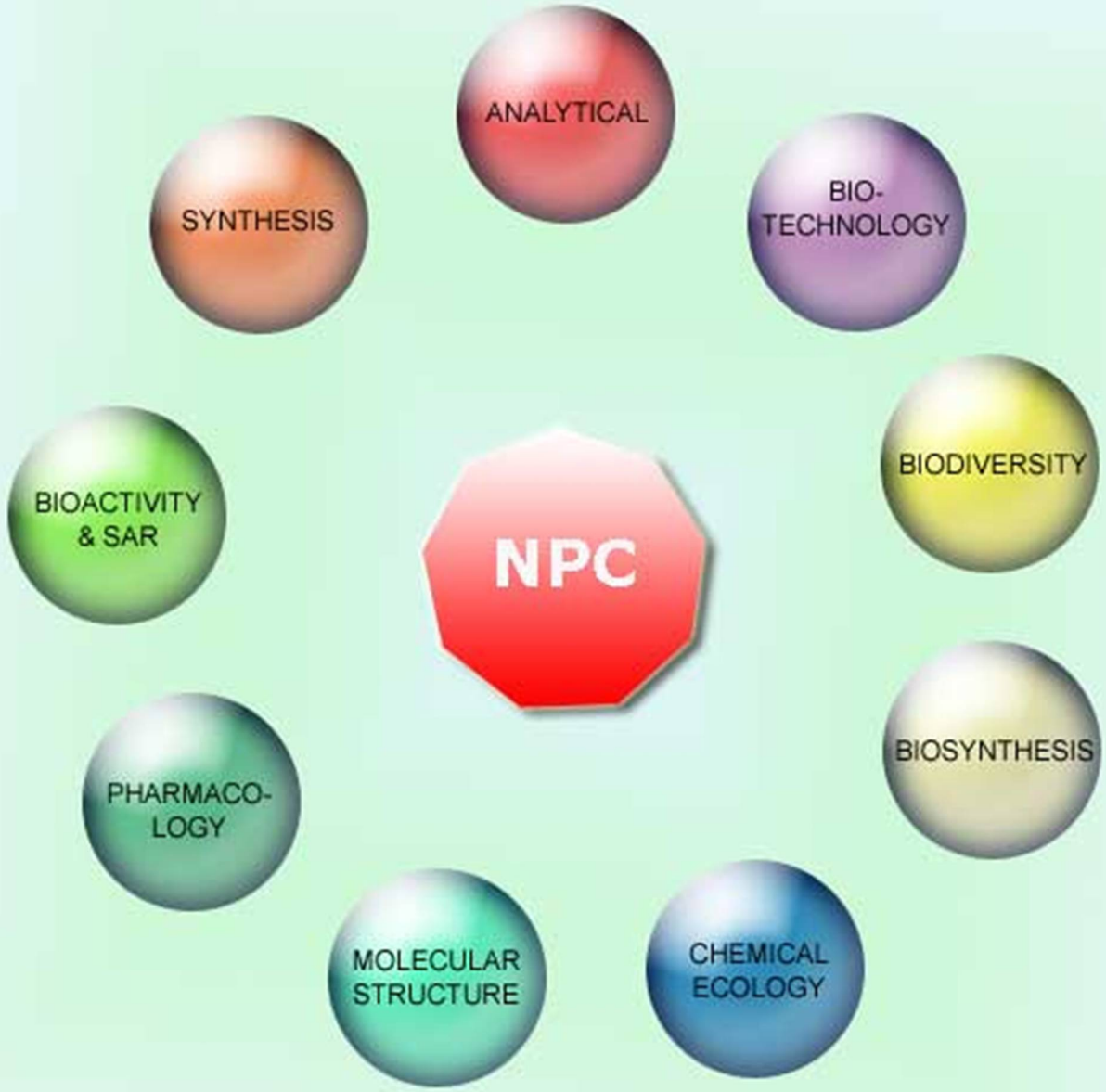

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New Acyclic Diterpenic Acids from Yacon (*Smallanthus sonchifolius*) Leaves

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Two new acyclic diterpenoids, smaditerpenic acid E (**1a**) and F (**2a**), along with nineteen melampolide-type sesquiterpene lactones, six of them not previously reported in yacon, were isolated from the methylene chloride leaf rinse extract. Their structures were elucidated from 1D and 2D NMR experiments and gas chromatography coupled to mass spectrometry.

Keywords: *Smallanthus sonchifolius*, yacon, acyclic diterpenes, geranylnerol derivatives, sesquiterpene lactones, epicuticular wax.

Yacon, *Smallanthus sonchifolius* (Poepp. & Endl.) H. Robinson (Asteraceae), is a perennial herb from the Andean region of South America. Yacon tuberous roots are rich in fructooligosacharides (FOS) and phenolic compounds, being consumed raw as 'fruits' since pre-Columbian times. In the past two decades yacon was introduced into several Asian and European countries. The Asian dispersal began in Japan, where the use of its leaves, emerged, apparently for the first time, as an anti-diabetic herbal tea. Potent antioxidant [1] and antidiabetic properties have been recently demonstrated for decoctions of yacon leaves [2-4] where enhydrin, its main sesquitepene lactone, along with several caffeic acid derivatives have been shown to be the active principles [5,6]. Therefore, yacon has recently become popular as a healthy herbal tea. It should be noted that in spite of its Andean origin, no evidence has been found for its use in traditional Andean medicine [7].

Melampolide-type sesquiterpene lactones (STL) [8-11], acyclic diterpenic acids [12] and *ent*-kaur-16-en-19-oic acid (kaurenoic acid) derivatives [13-16] have been isolated from *S. sonchifolius* leaves. Several of these compounds play a physiological role in pest-resistance and antimicrobial activities [9,13]. The melampolide enhydrin, a major constituent of the leaf rinse extract, shows anti-inflammatory [17,18] and antidiabetic properties [5].

In this work we report two new acyclic diterpenes along with nineteen melampolide-type STL and many other constituents isolated from dichloromethane leaf rinse extracts. The two new diterpenes reported here, named smaditerpenic acids E (**1a**) and F (**2a**), are closely related to smaditerpenic acids A-D (**3**-**6**) (Figure 1) recently isolated from a Chinese collection of yacon extracted with boiling water [12]. Possible artifacts formation during this process is briefly discussed below. Interestingly, diterpenes **3**-**6** exhibited a moderate inhibitory effect on α-glucosidase [19]. Additionally, a rapid and sensitive GC-MS method for analysis of STL in leaf rinse extracts is described, which permits identification and quantification of minor constituents.

Smaditerpenic acids E (**1a**) and F (**2a**) and sesquiterpene lactone **11** co-eluted as a 1:1:1 mixture from column chromatography over Si gel of dewaxed extract (see experimental). The mixture was treated with diazomethane to yield the corresponding methyl esters **1b**, **2b** and **12** (sonchifolin), respectively, which were cleanly separated by RP-HPLC.

Smaditerpenic acid E methyl ester (**1b**) showed IR absorptions for hydroxyl, saturated and α,β-unsaturated ester groups at 3350, 1735 and 1715 cm^{-1} respectively. The molecular formula $C_{23}H_{36}O_5$, followed from its HR-CIMS, which showed a quasimolecular ion peak

Table 1: ^{1}H and ^{13}C NMR spectroscopic data of **1b** (300 MHz, $CDCl_3$).

Position	δ_H (*J*)	COSY	δ_C (DEPT)	HMBC	NOE
1	4.11 brd (2H, 7.1)	2, 20	59.0		4, 2
2	5.45 brt (1H, 7.5)	1,20, 4	125.0	20	
3	-	-	138.9	1, 20	
4	2.14 brt (2H, 7.5)*		31.9	20	
5	2.24 brq (2H, 7.2)*		26.3		
6	5.42 brt (1H, 7.4)	19, 5	130.6	19, 8, 4	
7	-	-	133.7	19	
8	2.19 brt (2H, 7.1)*		34.8	10, 19	
9	2.54 brq (2H, 7.5)	8, 10	28.1		
10	5.84 brt (1H, 7.3)	9, 12	141.5	12	12, 9
11	-	-	131.9	9	
12	2.26 brt (2H, 7.5) *		34.7		
13	2.11 brq (2H, 7.1)*		27.8		
14	5.08 brt (1H, 7.0)	16, 17, 13	123.4	17, 16	16, 13
15	-	-	132.3	16, 17	
16	1.68 s (3H)	17, 13, 14	25.7	17	
17	1.58 s (3H)	16, 13, 14	17.7	16	
18	-	-	168.4	1’	
19	4.59 s (2H)	6, 5	61.7		9, 5
20	1.74 s (3H)	1, 2	23.4	4	
1’	3.73 s (3H)		51.2		
Ac	2.10 s (3H)		21.0		
	-	-	171.1	19	

Assignments based on HSQC, COSY, HMBC and NOE experiments; coupling constants are in Hz. *Overlapped signals.

Table 2: ^{1}H and ^{13}C NMR spectroscopic data of **2b** (300 MHz, $CDCl_3$).

Position	δ_H (*J*)	COSY	δ_C (DEPT)	HMBC	NOE
1	4.10 d (2H, 7.0)	2, 20	58.92		2, 4
2	5.45 brt (1H, 7.5)	1, 20	124.97	20	
3	-	-	138.84	1, 20	
4	2.14 m (2H)*		31.84	20	
5	2.19 m (2H)*		26.27		
6	5.43 brt (1H, 7.5)	5	130.63	19	
7	-	-	133.58	19, 5	
8	2.17 m (2H)*		34.76		
9	2.56 brq (2H, 7.5)	10, 8	28.08		
10	5.87 brt (1H, 7.5)	9	141.56	12	12, 9, 8
11	-	-	132.03	9	
12	2.37 dd (2H, 8.6, 7.3)	13	33.42		
13	2.12 m (2H)*		34.06		
14	-	-	155.06	16, 17	
15	2.22 m (1H)*	16,17	33.76	21a, 21b, 16, 17	
16	1.01 d (6H, 6.8)	15	21.72	15, 17	21b, 15, 13
17				15, 16	
18	-	-	168.29	1’	
19	4.59 s (2H)	5, 6	61.69		5, 9
20	1.74 brs (3H)	1, 2	23.34	2, 4	
21a	4.67 brs (1H)	21b, 13	106.85	15, 13	
21b	4.76 brs (1H)	21a, 15			
1’	3.75 s (3H)		51.24		
Ac	2.06 s (3H)		20.97		
	-	-	171.08	19	

Assignments based on HSQC, COSY, HMBC and NOE experiments; coupling constants are in Hz. *Overlapped signals.

$[M+H]^+$ at *m/z* 393.2644 (calcd 393.2640) accounting for six degrees of unsaturation (Figure 1). The ^{1}H NMR spectrum of **1b** (Table 1) displayed four olefinic protons at δ 5.45 and 5.42 (two overlapped brt, 2H, 7.5 Hz, H-2 and H-6 respectively), 5.84 (brt, 1H, 7.3 Hz, H-10) and 5.08 (brt, 1H, 7.0 Hz, H-14). In addition, signals at δ 4.11 (brd, 2H, 7.1 Hz, 1-H) and 4.59 (s, 2H, H-19) showing correlation with signals at δ 59.0 and 61.7 in the HSQC spectrum indicated that two -CH_2O- groups were present. Five methyl signals were also present at δ_H 3.73 (s, 3H, -CO_2Me), 2.10 (s, 3H, acetate), 1.74 (s, 3H, H-20), 1.68 (3H, s, H-16), and 1.58 (3H, s, H-17), which were correlated with signals at δ_C 51.2, 21.0, 23.4, 25.7, and 17.7, respectively, the overall spectrum clearly indicating that a geranyl nerol derivative containing a carboxymethyl group and an acetate residue was present. The deshielding of the protons at C-19 (δ_H 4.59) and their correlation with the acetate carbonyl at δ_C 171.1 in the HMBC experiment indicated that the acetate was located at C-19. Interpretation of the ^{13}C NMR, COSY, HSQC and HMBC spectra permitted assignment of all signals (Table 1). The configuration of the double bonds was deduced from NOE spectra.

The molecular formula $C_{24}H_{38}O_5$ was deduced from the HR-CIMS for smaditerpenic acid F methyl ester (**2b**), which showed a quasimolecular ion peak [M+H]+ at m/z 407.2799 (calcd for $C_{24}H_{39}O_5$ 407.2797) accounting for six degrees of unsaturation (Figure 1). The ^{1}H- and ^{13}C-NMR spectra of **2b** (Table 2) were similar to those of **1b** showing clearly that we were dealing with a homolog containing an additional =CH_2 group at C-14. Interpretation of the spectroscopic data permitted assignment of all signals and stereochemistry of **2b** (Table 2).

Smaditerpenic acids E (**1a**) and F (**2a**) are closely related to acyclic diterpenes **3**-**6** previously extracted from yacon leaves using water under reflux [12]. As can be seen in Figure 1, smaditerpenic acids A (**3**), B (**4**), C (**5**) and D (**6**) could be artifacts formed by hydrolysis of the acetate residue at C-19, followed by allylic rearrangement of the primary carbinol group at C-1 of **1a** and **2a**, respectively. To test this hypothesis, 20 mg of smaditerpenic acid F (**2a**) dissolved in 10 mL of water was refluxed for 24 h and extracted with chloroform. ^{1}H NMR analysis of the reaction product showed that very little rearrangement (ca. 4%) had occurred as deduced by integration of the signals corresponding to the vinyl moiety of **6** (Figure 1). Similar results were obtained when **1a** was subjected to the same treatment. These results suggest that smaditerpenic acids A-D (**3**-**6**) are also true natural products, which is supported by the quirality observed for **4** and **6** [12]. The difference between the diterpenes isolated by us and those previously reported by Chinese workers [12] could be due to agroecological growing conditions or most probably to a different cultivar (clone).

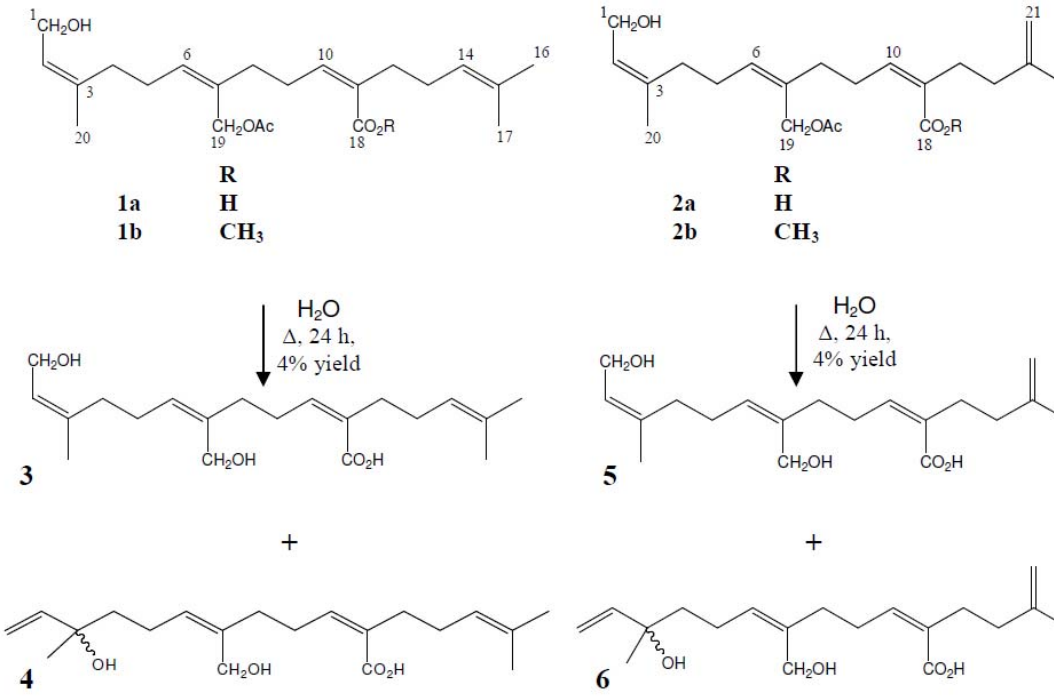
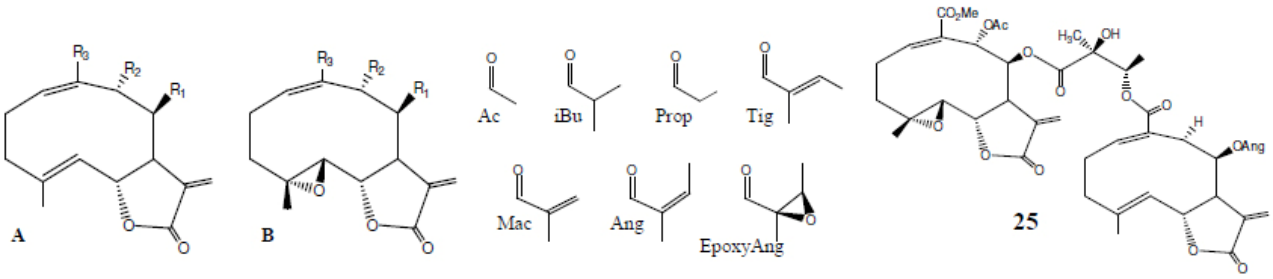


Figure 1: Smaditerpenic acids E (**1a**) and F (**2a**) and products (smaditerpenic acids A-D, **3**-**6**) obtained after refluxing for 24 h with water.



	Compound	Skeleton	R_1	R_2	R_3	M+	RT	KI	RRI	%
7		A	OProp	H	CO_2Me	348	25.93	2534	0.891	trace*
8		A	OiBu	H	CO_2Me	362	26.88	2563	0.900	trace*
9		A	OMac	H	CO_2Me	360	28.13	2609	0.916	trace*
10		A	OMac	OAc	CO_2Me	418	29.73	2654	0.932	trace*
11		A	OAng	H	CO_2H	360	31.71	2711	0.952	trace*
12	Sonchifolin	A	OAng	H	CO_2Me	374	31.85	2716	0.953	1.2
13		A	OAng	H	CHO	344	32.34	2724	0.958	trace*
14		A	OTig	H	CO_2Me	374	33.28	2761	0.969	trace*
15	Polymatin B	A	OAng	OAc	CO_2Me	432	33.80	2775	0.974	5.5
16		A	OAng	OAc	CHO	402	34.30	2781	0.976	4.2
17	Fluctuadin } Ratio	B	OMac	OAc	CO_2Me	434	34.53	2788	0.978	4.0
18	Polymatin A } 4:1	A	OAng	OH	CO_2Me	390				
19		A	OTig	OAc	CO_2Me	432	34.96	2800	0.983	trace*
20	Uvedalin	A	OEpoxyAng	OAc	CO_2Me	448	36.45	2847	1.000	16.8
21		A	OEpoxyAng	OAc	CHO	418	36.65	2863	1.005	3.7
22	Fluctuanin	B	OAng	OAc	CO_2Me	448	38.27	2914	1.023	8.4
23	Polymatin C	B	OAc	OEpoxyAng	CO_2Me	464	39.20	2942	1.033	5.6
24	Enhydrin	B	OEpoxyAng	OAc	CO_2Me	464	40.58	2977	1.045	48.7

Table 3: Melampolides isolated from leaf rinse extract of *Smallanthus sonchifolius*. *Trace <0.5%.

So far, sixteen melampolide-type STL have been identified in yacon leaves [8-11], enhydrin being the main lactone constituent. In this work we report a capillary GC-MS method to analyze STL from yacon which permitted quantification and identification of very minor and trace constituents (see experimental). Quantification is relevant since enhydrin (**24**) has recently been characterized as one of the antidiabetic principles of yacon [5]. Eighteen melampolides were identified in the dewaxed leaf rinse extract and are listed in Table 3. Enhydrin (**24**) is the main constituent representing almost a half of the total STL mixture, followed by uvedalin (**20**) (16.8%) and fluctuanin (**22**) (8.4%). Lactones **7**, **8**, **17** [20], **19**, **21** and **23** [21] are reported in yacon for the first time. Dimeric melampolide **25** [10], which is not volatile enough to be analyzed by GC, was isolated from the more polar fractions of the dewaxed extract.

Experimental

General experimental procedures: Melting points were determined on a Ernst Leitz 350 microscope. Infra-red spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. NMR measurements were recorded on a Bruker 300 AVANCE. Two dimensional homonuclear (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOE) and heteronuclear experiments (^{1}H-^{13}C $^1J_{CH}$ HSQC, ^{1}H-^{13}C $^{2\text{-}3}J_{CH}$ HMBC) were acquired and processed with TopSpin-NMR software provided by Bruker. For GC-MS analysis, a 5973 Hewlett-Packard selective mass detector (quadrupole) coupled to a Hewlett-Packard 6890 GC fitted with an Elite-5MS Perkin-Elmer column (5% phenylmethylsiloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness); ionization energy 70 eV, was used. The following conditions were employed to analyze STL: injector, GC-MS interphase, ion source and selective mass detector temperatures were maintained at 220ºC, 280ºC, 230ºC and 150ºC, respectively; ionization energy, 70 eV; injection size: 1 μL (split mode 80:1); carrier gas, helium at a flow rate of 1.2 mL min^{-1}. The oven was programmed as follows: from 180°C to 300°C at 2°C min^{-1} and then held at 300ºC for 10 min. Solvent delay 4 min. In order to be injected, the samples were dissolved in methylene chloride using 25 μL of solvent per mg of STL mixture. Percentages are reported as the means of at least 3 runs and were calculated from the TIC (Total Ion Chromatogram) by the computer. Waxes were analyzed using an injector temperature of 280ºC and the following oven temperature program: from 140°C to 300°C at 2°C min^{-1} and then held at 300ºC for 10 min; the remaining conditions were the same as for STL.

Merck Silica gel (230-400 mesh, ASTM) was used for column chromatography (CC). For thin layer chromatography, TLC aluminum sheets of silica gel 60 F_{254} from Merck were used. Detection was achieved by spraying the plates with *p*-anisaldehyde-sulfuric acid reagent followed by heating.

For separation of methylated diterpenes and STL mixtures, Gilson 322 HPLC equipment with a differential refractive index detector was used. The following semipreparative columns were employed: i) a Beckman Ultrasphere C8 (5 μm, 10 × 250 mm) and ii) a Beckman Ultrasphere C18 (5 μm, 10 × 250 mm).

Plant material: Leaves of *S. sonchifolius* (clone LIEY 97-1) were collected in August 2008 from experimental plots cultivated at the Centro Universitario Horco Molle, Tucumán, Argentina (26° 47'S, 65° 19'W, 547 m a.s.l.). Voucher specimens are deposited in the herbarium of Instituto Miguel Lillo, San Miguel de Tucumán, Tucumán, Argentina (LIL 607173).

Extraction and isolation of waxes, sesquiterpene lactones and acyclic diterpenes: Leaves of yacon were extracted by soaking air-dried leaves in CH_2Cl_2 following the procedure described by Schorr *et al*. [10], with modifications. Whole air-dried leaves (200 g) were soaked individually in CH_2Cl_2 (2.35 L), and placed in a rectangular TLC developing tank 22 x 23 x 7 cm made of common glass. Each leaf was soaked in the solvent for 20 secs at room temperature with a continuous and gentle swinging motion using large chromium-plated steel forceps. The solution was filtered through a filter paper and the solvent evaporated to yield 2.47 g of crude residue, which was dissolved in MeOH (35 mL) at 50ºC to facilitate disolution. After cooling, distilled water (15 mL) was added dropwise to precipitate waxes. Epicuticular waxes were concentrated in this precipitate. After filtering and drying in a vacuum dessicator, 1.15 g of waxes was obtained. The hydromethanolic filtrate was evaporated at reduced pressure to yield 1.25 g of dewaxed extract containing sesquiterpene lactones and diterpenes.

Waxes (1.10 g) were column chromatographed over Si gel 230-400 mesh (45 g) using *n*-hexane with increasing amounts of EtOAc (0-20%); 25 fractions were collected, which were analyzed by capillary GC-MS. The following compounds were identified: neophytadiene, γ-tocopherol, 6,10,14-trimethyl-2-pentadecanone, *n*-alkanes within the C_{25}-C_{31} range (odd carbons predominating), 1-tetracosanol, 1-hexacosanol, 1-octacosanol, α- and β-amyrin, the phytosterols sitosterol (major) and stigmasterol (minor) and the diterpene *ent*-kaur-16-en-19-oic acid (kaurenoic acid). These compounds were characterized by comparison of their MS with those in the computer and NIST98

GC–MS libraries, and by co-injection with authentic samples, whenever available.

The dewaxed extract (1.25 g) was column chromatographed over Si gel (50 g; 230-400 mesh) using $CHCl_3$ with increasing amounts of EtOAc (10-40%); 152 fractions were collected, which were monitored and grouped into 17 fractions (A-Q) on the basis of their TLC profiles. After solvent evaporation, all the fractions were analyzed by FT-IR, GC-MS and ^{1}H NMR.

Fractions B (9 mg), C (39 mg), D (135 mg), E (49 mg), F (63 mg), G (93 mg), H (109 mg) and I (110) showing a γ-lactone carbonyl absorption at 1755-1780 cm^{-1} in their IR spectra were analyzed by GC-MS. Lactones **7**, **8**, **10**, sonchifolin (**12**) and polymatin B (**15**) were identified in fraction B; lactones **8**, **9**, **10**, **12**, **14** and **15** were identified in Fraction C; lactones **12**, **13**, **14**, **15**, **16**, **19**, uvedalin (**20**) and fluctuanin (**22**) were present in fraction D; **16**, **20** and **22** in fraction E; **20**, **21**, **22**, polymatin C (**23**) and enhydrin (**24**) in fractions E and F; and fluctuadin (**17**), polymatin A (**18**), **21**, **23** and **24** in fractions H and I. Analytical samples of the lactones were obtained by semipreparative RP-HPLC of the above fractions using a C8 (octyl) column with MeOH-H_2O 60 : 40 at a flow rate of 2.0 mL min^{-1} (injection: 1.2 mL of a solution containing 4.1 mg of STL mixture per mL) and re-chromatography on a C18 (octadecyl) column with MeOH-H_2O (1 : 1) at 1.8 mL min^{-1}, if necessary. Thus, 165 mg of enhydrin (**24**), 54 mg of uvedalin (**20**), 34 mg of fluctuanin (**22**), 19 mg of polymatin B (**15**), 3.5 mg of sonchifolin (**12**), 10 mg of 8β-epoxyangeloyloxy-9α-acetyloxy-14-oxo-1(10)*E*,4*E*,11(13)-germacratrien-6α, 12-olide (**21**) and small amounts of several minor lactones, all of them listed in Table 3, were isolated. The isolated lactones were identified by MS and ^{1}H, ^{13}C NMR, HMBC and HSQC spectroscopic data.

Fractions J (18 mg) and K (32 mg) did not show γ-lactone carbonyl absorption and yielded no identifiable material. Fraction L (119 mg) was washed several times with diethyl ether to afford a white solid that was crystallized from EtOH-EtOAc 2:1 to yield 20 mg of dimeric lactone **25** [10] as white crystals, mp 263-265ºC. The ^{1}H and ^{13}C NMR spectra were identical to those reported [10].

Fractions M (26 mg), N (47 mg) and O (59 mg) from CC of dewaxed extract were complex mixtures and gave no identifiable material.

Fraction P (143 mg) showed the presence of a carboxyl group in the IR spectrum and was shown to be a mixture of **1a**, **2a** and **11** by ^{1}H and ^{13}C NMR. A portion of this fraction (70 mg) was dissolved in diethyl ether and treated with an ethereal solution of diazomethane. After solvent evaporation, the residue was processed by RP-HPLC (C8 column; MeOH-H_2O 7:3 at 2.0 mL min^{-1}) to afford sonchifolin (**12**) (5 mg), smaditerpenic acid E methyl ester (**1b**) (15 mg) and smaditerpenic acid F methyl ester (**2b**) (19 mg).

Fraction Q (144 mg) was shown to be a complex mixture of polar compounds and pigments which yielded no identifiable material.

Smaditerpenic acid E, methyl ester (**1b**)
Gum.
^{1}H and ^{13}C NMR: Table 1.
MS (EI, 70 eV): *m/z* (%.): 314 (1) [M -AcOH, -H_2O]$^{\cdot+}$, 299 (1) [314 -CH_3]$^+$, 281 (1), 267 (3), 255 (4), 245 (8), 231 (2), 213 (6), 199 (7), 185 (18), 171 (8), 159 (19), 145 (20), 133 (33), 119 (39), 105 (42), 95 (20), 91 (43), 84 (14), 81 (31), 79 (30), 77 (15), 69 (100), 67 (26), 59 (11), 55 (29), 53 (21), 43 (62), 41 (85).
HR-CIMS (isobutane): calcd for [$C_{23}H_{36}O_5$ + H]$^+$ *m/z* 393.2640; found: 393.2644.

Smaditerpenic acid F methyl ester (**2b**)
Gum.
^{1}H and ^{13}C NMR: Table 2.
MS (EI, 70 eV): *m/z* (%.): 328 (1) [M -AcOH, -H_2O]$^{\cdot+}$, 313 (1) [328 -CH_3]$^+$, 299 (1), 285 (3), 269 (6), 253 (4), 245 (5), 229 (4), 213 (6), 201 (9), 196 (9), 185 (17), 168 (11), 159 (30), 151 (25), 145 (25), 133 (47), 119 (44), 107 (41), 105 (62), 93 (69), 91 (66), 81 (38), 79 (50), 67 (37), 55 (76), 43 (100), 41 (70).
HR-CIMS (isobutane): calcd for [$C_{24}H_{38}O_5$ + H]$^+$ *m/z* 407.2797; found: 407.2799.

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