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FURTHER DITERPENES FROM PLANTS OF THE COMPOSITAE, SUBTRIBE SOLIDAGININAE

J. JAKUPOVIC, R. N. BARUAH, C. ZDERO, F. EID, V. P. PATHAK, T. V. CHAU-THI, F. BOHLMANN, R. M. KING* and H. ROBINSON*

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, West Germany; *Smithsonian Institution, Department of Botany, Washington, DC 20560, U.S.A.

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Key Word Index—*Gutierrezia*; *Grindelia*; *Haplopappus*; *Solidago petradoria*; Compositae; diterpenes; *ent*-labdanes; *ent*-abietane; grindelic acid arabinoside, neoclerodanes; friedolabdane; absolute configuration.

Abstract—Six new *ent*-labdanes were isolated from the aerial parts of *Gutierrezia* species and nine from *Happlopappus pectinatus*. Four neoclerodanes and a friedolabdane were obtained from the aerial parts of *Haplopappus paucidentatus*. From the *Grindelia* species, in addition to known derivatives of grindelic acid, an arabinoside was isolated. The absolute configuration of the *ent*-labdanes was determined by transformation of grindelic acid to methyl-6-oxo-7,8-dihydrogrindelate where the configuration was established by the positive Cotton effect. From *Solidago petradoria* a new abietane derivative was isolated.

INTRODUCTION

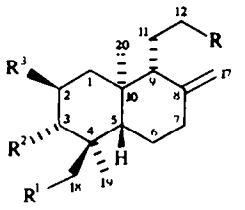
One of the main problems in the tribe Astereae is the delimitation of its subtribes [1]; chemical characters therefore might prove helpful here. Most of those genera which have been placed by Hoffman [2] in the Solidagininae are geographically restricted to South and North America. So far chemical investigations have shown that diterpenes of the labdane and clerodane type are widespread in this subtribe. However, several other natural compounds have also been reported. Thus special cadinene derivatives are typical of *Heterotheca* while the South African genera *Chrysopsis* and *Pteronia* differ characteristically in the absence of diterpenes and sesquiterpenes. We now have studied the constituents of two *Gutierrezia*, four *Grindelia*, three *Haplopappus* and one *Solidago* species from North and South America. The results are discussed in this paper.

RESULTS AND DISCUSSION

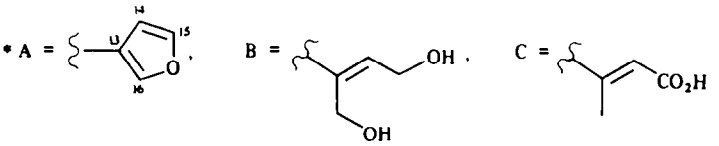
From the genus *Gutierrezia*, with about 20 species, flavones [3] and several labdanes have been reported [4–7]. Furthermore baccharis oxide [6] and acetylenes [8] are present. We now have studied the constituents of the aerial parts of *Gutierrezia gilliesii* Griseb. In addition to widespread compounds (see Table 4) the *ent*-labdanes **1** [7] and **3** [7] as well as the angelate **2** were obtained. The structure of **2** was clearly determined from the ^{1}H NMR data which were close to those of **3** [7]. The presence of the corresponding furan derivative followed from the typical signals of a β-substituted furan which replaced those of H-14 and H-16 in **3**.

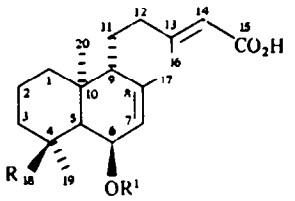
The aerial parts of *G. spathulata* (Phil.) Kurtz gave in addition to widespread compounds (see Table 4) the alicyclic diterpene 10*E*,17-hydroxygutiesolbriolide [7] and five new *ent*-labdanes, which were isolated as their methyl esters **4a**–**7a** and **9a**. The structure of **4a** followed from its ^{1}H NMR spectrum which was very close to that of the corresponding 16-hydroxy derivative [9]; however, the H-16 signal now was that of an olefinic methyl at δ2.19. The chemical shift indicated the *E*-configuration. The ^{1}H NMR spectrum of **5a** differed from that of **4a** by the presence of a pair of doublets at δ3.86 and 3.80 while the methyl singlet at δ0.68 was missing. Accordingly, a 18-hydroxy derivative of **4a** was present. The structure of **6a** also followed from the ^{1}H NMR spectrum. The presence of an aldehyde group was indicated by a singlet at δ9.29 while the position of the hydroxy group was established by spin decoupling. The configuration followed from the coupling $J_{5,6}$. The ^{1}H NMR spectrum of **7a** was in part close to that of **6a**. However, the aldehyde signal was replaced by a second methoxy signal and the H-6 signal was shifted downfield. The presence of an isovalerate was deduced from the typical NMR signals. The presence of an endoperoxide in the ester **9a** also followed from the mass spectrum where the typical fragment $[M-O_2]$ was visible; furthermore the ^{1}H NMR spectrum showed the expected signal. A pair of doublets at δ6.56 and 6.34 especially supported the proposed structure. The acid **9** must be formed by reaction of an isomer of **5** with oxygen. The roots of both species gave dehydrofalcarinol [10] and baccharis oxide.

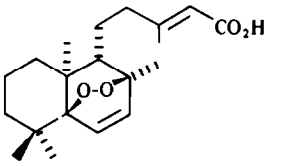
From the large genus *Haplopappus* several species have been investigated chemically. However, only a few characteristic compounds were reported. In addition to C_{10}-acetylenes [10, 11], coumarins [12, 13] and flavones [14–16], some clerodanes [17, 18] and labdanes [19] were isolated. Also some *p*-hydroxyacetophenone derivatives were present [19, 20]. We now have studied three further species from Argentina. The aerial parts of *Haplopappus glutinosus* Cass. gave 6,18-dihydroxy-*ent*-labda-7,13*E*-dien-15-oic acid (**8**); its structure clearly followed from the ^{1}H NMR of the corresponding methyl ester which was close to that of similar labdane derivatives. The *E*-



	1	2	3	4†	5†
R	A*	A	B*	C*	C
R^1	OH	OH	OH	H	OH
R^2	OAng	OAng	OAng	H	H
R^3	H	OH	OH	H	H
				Δ6	Δ6







	6†	7†	8†
R	CHO	CO_2H	CH_2OH
R^1	H	iVal	H

9†

configuration of the side chain followed from the chemical shift of H-16.

The aerial parts of *Haplopappus pectinatus* Phil. gave 8*Z*-matricarianol and its acetate [11] as well as a complex mixture of polar compounds. After reaction with diazomethane the *ent*-labdanes **10a**–**19a** were obtained. In all cases the ^{1}H NMR spectra indicated the presence of cativic acid derivatives by the typical signals of H-14 and H-16. Furthermore the absence of the olefinic methyl group (H-17) was obvious. The substitution at C-17 followed from the ^{1}H NMR data which clearly showed that **10a** and **13a** were 17-hydroxy, **11a**, **14a** and **19a** 17-acetoxy, **12a** and **15a** 17-oxo, **16a** and **17a** 17-methoxy and **18a** the corresponding carboxylate. Furthermore the position of additional oxygen functions could be observed from the low field signals. Thus **13a**–**15a** and **17a** had a 3-hydroxy group as followed from the double doublet at δ3.3. Comparison of the chemical shift of H-18 and H-19 with those of similar labdanes excluded 1-hydroxy derivatives. The relative position of the hydroxy group in **19a** could be deduced from the chemical shifts of H-19 which typically differ from those of 18-hydroxy derivatives. The aldehydes **12a** and **15a** also were prepared by manganese dioxide oxidation of **10a** and **13a** respectively. The absolute configuration was not determined. As however, that of the labdanes from *Grindelia* species could be established (see below) it was very likely that again *ent*-labdanes were present. The same is true for the *Gutierrezia* labdanes where the isolation of labdanes with known absolute configuration has shown that all diterpenes present are probably *ent*-labdanes [6].

The aerial parts of *Haplopappus paucidentatus* Phil. afforded in addition to widespread compounds five new diterpene acids, the neoclerodanes **23**–**26** and the friedolabdane **27**. The ^{1}H NMR spectrum of **23** and that of the methyl ester of **24** (Table 3) showed that a clerodane 15-acid was present with a function at C-18. Spin decoupling allowed the assignment of all signals though a few were overlapped multiplets. The resulting sequences indicated that the broadened doublet at δ1.36 was due to H-10. Accordingly, the presence of a new clerodane with a *cis*-decalin ring system was very likely. This was established by NOE difference spectroscopy since a clear effect was observed between H-19 and H-10. Further effects between H-17, H-20 and H-11, between H-8 and H-11, between H-20, H-11, H-3 and H-7 as well as between

Table 1. ^{1}H NMR spectral data of **2a**, **4a**, **5a** acetate and **6a–9a** (400 MHz, $CDCl_3$ TMS as internal standard)

	2a*	**4a**	**5a** acetate†	**6a**‡	**7a**§	**8a**	**9a**
H-6		6.15 *dd*	5.84 *dd*	4.09 *br d*	5.30 *br d*		6.34 *d*
H-7		5.72 *br d*	5.67 *br d*	5.39 *br s*	5.27 *br s*	5.35 *br s*	6.56 *d*
H-12	2.26 *m*	2.36 *ddd*	2.36 *ddd*	2.36 *ddd*	2.35 *m*	2.35 *m*	2.25 *m*
H-12	2.00 *m*	2.10 *m*	2.10 *m*	2.10 *m*	2.10 *m*	2.10 *m*	2.08 *m*
H-14	6.26 *br s*	5.70 *br s*	5.72 *br s*	5.67 *br s*	5.67 *br s*	5.68 *q*	5.65 *br s*
H-16	7.19 *br s*	2.18 *br s*	2.22 *br*	2.17 *d*	2.16 *d*	2.17 *d*	2.15 *s*
H-17	4.91 *br s*	4.90 *br s*	4.94 *br s*	1.75 *br s*	1.72 *br s*	1.69 *br s*	1.32 *s*
H-17	4.61 *br s*	4.80 *br s*	4.84 *br s*				
H-18	3.32 *d*	0.93 *s*	3.86 *d*	9.29 *s*	—	3.36 *d*	1.21 *s*
	2.90 *d*		3.80 *d*			3.13 *d*	
H-19	0.82 *s*	0.82 *s*	0.99 *s*	1.25 *s*	1.19 *s*	0.84 *s*	0.99 *s*
H-20	0.70 *s*	0.66 *s*	0.86 *s*	0.85 *s*	0.89 *s*	0.79 *s*	0.96 *s*
OMe	—	3.66 *s*	3.69 *s*	3.70 *s*	3.69 *s*	3.68 *s*	3.68 *s*
					3.65 *s*		

*H-2 4.04 *ddd*, H-3 4.81 *d*, H-7 2.80 *ddd*, H-7′ 2.55 *ddd*, H-15 7.34 *t*, OAng 6.18 *qq*, 2.02 *dq*, 1.92 *dq*.
†OAc: 2.06 *s*.
‡H-5 1.73 *d*.
§OiVal: 2.17 *m*, 2.06 *m*, 0.94 *d*, 0.95 *d*.
J (Hz): 11,12 = 11′,12′ = 13; 11′,12 = 12′,11 = 5; 14,16 = 1; compound **2a**: 1α,2 = 4.5; 1β,2 = 12; 2,3 = 10; 6,7 = 6; 6′,7 = 6; 6,7′ = 4; 6′,7′ = 10; 7,7′ = 14; 14,15 = 15,16 = 1; 18,18′ = 12; OAng: 3′,4′ = 7; 3′,5′ = 4′,5′ = 1.5; compounds **4a** and **5a** acetate: 5,6 = 3; 6,7 = 9.5; (**5a** acetate: 18,18′ = 11); compounds **6a** and **7a**: 5,6 = 9; 6,7 ~ 3; compound **8a**: 14,16 = 1; 18,18′ = 11; compound **9a**: 6,7 = 8.

H-10, H-1β, H-11 and H-14 indicated the configurations of the chiral centres and from the chemical shift of H-16 the presence of a 13*E*-double bond was deduced. The downfield shift of H-18 in compound **23** showed that this diterpene was the 19-*O*-acetate of **24**. The spectral data of the methyl esters of **25** and **26** (Table 3) indicated that these compounds were isomeric diterpenes which only differed in the position of the hydroxy group. The differences in the chemical shifts and the couplings of the corresponding signal of the hydroxymethylene clearly showed that **25a** was an 18-hydroxy and **26a** a 19-hydroxy derivative. The nature of the side chain followed from the typical ^{1}H NMR signals. Compound **25** was therefore most likely the 13,14-dihydro derivative of **24** which was supported by the similarity of all data.

The ^{1}H NMR spectrum of the methyl ester of **27** showed more pronounced differences from those of the other diterpenes though the molecular formula indicated that it was again an isomer of **25a** and **26a**. While the signals of the side chain were nearly the same as in the spectra of **25a** and **26a** the splitting of the olefinic signal was different. Furthermore there was no signal for an olefinic methyl or hydroxymethylene group. Spin decoupling clearly showed that a 5,6-double bond was present. As an allylic coupling with H-10 also was observed the sequences of rings A and B could be combined. NOE difference spectroscopy allowed the assignment of the stereochemistry. Thus clear effects were obtained between H-20, H-17, H-1α, H-7α and H-11, between H-17, H-20, H-7α and H-7β, between H-18 and H-6, as well as between H-19, H-10 and H-2β. Neoclerodanes such as haplopappic acid are present in *Happlopappus foliosus* [17] and *H. ciliatus* [17].

The genus *Grindelia* is represented by about 60 species in North America and in South America, South of the tropics. While the roots contain many C_{10}-acetylenes [11] the aerial parts mostly afforded labdane derivatives [21–28], especially grindelic acid and its derivatives [21–24, 28]. Also the aerial parts of *G. boliviana* Rusby gave large amounts of grindelic acid and also 3- and 17-hydroxy derivatives. Furthermore 6β-hydroxy-8(17)-dehydrodihydrogrindelic acid [23] and an arabinoside (**20**) were present. The latter was purified as its triacetate. The ^{1}H NMR spectrum was close to that of grindelic acid. The presence of an arabinoside directly followed from the typical ^{1}H NMR signals [29] while the position of the diterpene residue was deduced from the downfield shift of the H-1′ signal. In the mass spectrum of the triacetate a clear molecular ion as well as the fragments, corresponding to the diterpene acyl cation and the oxonium ion of the sugar moiety, were visible. The aerial parts of *G. chiloensis* (Corub.) Cabrera also gave large amounts of grindelic acid which also was the main compound from the aerial parts of *G. aphanactis* Rydb., collected in Colorado. This species also gave 17-hydroxygrindelic acid and germacrene D.

The aerial parts of *Grindelia perennis* A. Nels. gave also grindelic acid and large amounts of the 17-hydroxy derivative [30] as well as the corresponding acetate [22], isobutyrate [22] and 2-methylbutyrate [22]. As the absolute configuration of grindelic acid seemed to be unknown, we have transformed the methyl ester by chromic acid in pyridine to the corresponding 6-keto derivative [21]. Hydrogenation gave **21** which showed a positive Cotton effect. As in this case the octant rule should be applicable therefore grindelic acid belongs to the *ent*-labdane series. Accordingly, most likely all labdanes from *Grindelia* species also have the same absolute configuration.

The aerial parts of *Solidago petradoria* Blake gave a diterpene, a succinate **22**, as deduced from its molecular

Table 2. ^{1}H NMR spectral data of **10a**–**19a** (400 MHz, $CDCl_3$, TMS as internal standard)

	10a	**11a**	**12a**	**13a**	**14a**	**15a**	**16a**	**17a**	**18a**	**19a**
H-3				3.25 *dd*	3.24 *dd*	3.24 *dd*		3.24 *dd*		
H-7	5.74 *br ddd*	5.79 *br ddd*	6.78 *ddd*	5.71 *br ddd*	5.70 *br ddd*	6.76 *ddd*	5.75 *br ddd*	5.75 *br ddd*	6.63 *ddd*	5.77 *br ddd*
H-14	2.33 *dd*	2.30 *dd*	2.38 *dd*	2.32 *dd*	2.30 *dd*	2.36 *dd*	2.36 *dd*	2.34 *dd*	2.30 *dd*	2.31 *dd*
H-14′	2.15 *dd*	2.10 *dd*	2.12 *dd*	2.16 *dd*	2.11 *dd*	2.12 *dd*	2.11 *dd*	2.12 *dd*	2.08 *dd*	2.11 *dd*
H-16	0.97 *d*	0.94 *d*	0.95 *d*	0.95 *d*	0.94 *d*	0.94 *d*	0.96 *d*	0.96 *d*	0.92 *d*	0.96 *d*
H-17	4.13 *br d*	4.53 *br d*	9.37 *s*	4.12 *br d*	4.52 *br d*	9.37 *s*	3.92 *br d*	3.92 *br d*	—	4.53 *br d*
H-17′	3.96 *br d*	4.40 *br d*		3.97 *br d*	4.41 *br d*		3.63 *br d*	3.64 *br d*	—	4.43 *br d*
H-18	0.89 *s*	0.89 *s*	0.93 *s*	0.98 *s*	0.99 *s*	1.00 *s*	0.88 *s*	0.97 *s*	0.90 *s*	3.37 *br d* 3.14 *br d*
H-19	0.86 *s*	0.86 *s*	0.88 *s*	0.86 *s*	0.86 *s*	0.91 *s*	0.85 *s*	0.86 *s*	0.86 *s*	0.86 *s*
H-20	0.76 *s*	0.75 *s*	0.79 *s*	0.75 *s*	0.76 *s*	0.80 *s*	0.74 *s*	0.76 *s*	0.81 *s*	0.80 *s*
OMe	3.66 *s*	3.65 *s*	3.66 *s*	3.66 *s*	3.65 *s*	3.65 *s*	3.66 *s*	3.65 *s*	3.65 *s* 3.70 *s*	3.65 *s*
							3.28 *s*	3.28 *s*		
OAc	—	2.06 *s*	—	—	2.06 *s*	—	—	—		2.06 *s*

J (Hz): 6,7 = 5;6′,7 = 7,9 ~ 2;13,14 = 6.5;13,14′ = 7.5;14,14′ = 15;17,17′ = 12; compounds **13a**–**15a** and **17a**: 2,3 = 11;2′,3 = 4; compound **18a**: 18,18′ = 11.

formula ($C_{24}H_{36}O_4$) and the ^{1}H NMR spectral data (Table 3). In the spectrum of the methyl ester **22a** in deuteriochloroform most of the signals overlapped whereas in deuteriobenzene all signals could be assigned by spin decoupling together with a 2D J-resolved spectrum. The stereochemistry at C-4 was deduced from the observed W-coupling between H-3β and H-19′. Furthermore NOE difference spectroscopy established the configurations at C-5, C-9 and C-10 as clear effects were observed between H-3β and H-5, between H-5, H-9 and H-18 between H-18, H-5, H-6β and H-19 as well as between H-20, H-2α, H-11α and H-19. The absolute configuration of **22** was not determined. So far only *ent*-abietanes have been found in *Solidago* species [31, 32].

From the aerial parts of *Hysterionica jasionoides* Willd. no diterpenes could be isolated. The roots gave lachnophyllum and matricaria ester which was also present in the roots of *H. pinifolia* Benth. et Hook. [11].

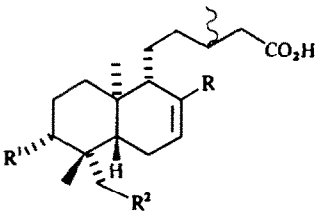
The overall picture of the chemistry of the subtribe Solidagininae is in part very uniform as *ent*-labdanes together with C_{10}-acetylenes accumulate in the major genera. Clerodanes are also common and *Haplopappus* contains diterpenes which are intermediates between labdanes and clerodanes. The *Grindelia* species examined are very uniform in accumulating grindelic acid and its derivatives. However, some genera like *Heterotheca*, *Pteronia*, *Chrysopsis* and *Hysterionica* differ remarkably from the above pattern.

EXPERIMENTAL

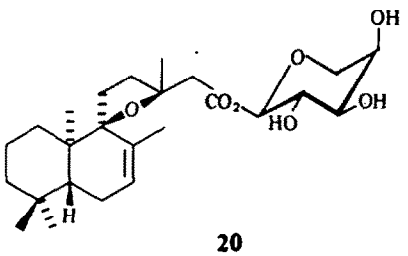
The air dried plant material was extracted at room temp. with MeOH–Et_2O–petrol (1:1:1) and the extracts obtained were worked-up and separated as reported previously [33]. For CC, silica gel, for TLC, silica gel PF 254 and for HPLC, RP columns (flow rate *ca* 3 ml/min, 100 bar) were used. In Table 4 the isolated compounds and in Table 5 the physical data are summarized. Known compounds were identified by comparing their 400 MHz ^{1}H NMR spectra with those of authentic materials.

Oxidation of **10a** *and* **13a**. 5 mg of **10a** and **13a** respectively were stirred for 2 hr with 50 mg MnO_2. After filtration TLC gave **12a** and **15a** respectively, identical with the esters of the natural compounds (^{1}H NMR, TLC).

Grindelic acid 15-O-*arabinoside* (**20**). Colourless oil; ^{1}H NMR ($CDCl_3$): δ5.48 (*br s*, H-7), 2.79 and 2.67 (*d*, H-14), 1.31 (*s*, H-16), 1.71 (*br s*, H-17), 0.85 (*s*, H-18), 0.81 (*s*, H-19), 0.75 (*s*, H-20), 5.40 (*d*, H-1′), 3.79 (*dd*, H-2′), 3.67 (*dd*, H-3′), 3.93 (*br s*, H-4′), 3.98 (*dd*) and 3.63 (*br d*, H-5′). Compound **20** (50 mg) in 3 ml $CHCl_3$ was heated with 20 mg *p*-dimethylaminopyridine and 0.1 ml Ac_2O for 2 hr at 60°. After addition of MeOH and evaporation the residue was purified by TLC (Et_2O–petrol, 3:1, R_f 0.70) affording 40 mg **20** triacetate; colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1755 (OAc); MS *m/z* (rel. int.): 578.309 $[M]^+$ (13) (calc. for $C_{31}H_{46}O_{10}$: 578.309), 518 (0.2) $[M - HOAc]$, 454 (78) $[M - C_9H_{16}]^+$, 303 (15) $[RCO]^+$, 261 (17) $[303 - CH_2CO]^+$, 259 (90) [arabinosyl triacetate residue]$^+$, 199 (35) $[259 - HOAc]^+$, 139 (100) $[199 - HOAc]^+$; ^{1}H NMR ($CDCl_3$): δ5.50 (*br s*, H-7), 2.80 and 2.64 (*d*, H-14), 1.33 (*s*, H-16), 1.75 (*br s*, H-17), 0.89 (*s*, H-18), 0.86 (*s*, H-19), 0.80 (*s*, H-20), 5.68 (*d*, H-1′), 5.25 (*dd*, H-2′), 5.11 (*dd*, H-3′), 5.29 (*ddd*, H-4′), 4.02 and 3.75 (*dd*, H-5′), 2.12, 2.04, 2.03 (*s*, OAc); [*J* (Hz): 14,14′ = 14; 1′,2′ = 6.5; 2′,3′ = 8; 3′,4′ = 3.5; 4′,5$_1$′ = 4; 4′,5$_2$′ = 2]; $[\alpha]_D^{24°} - 65$ ($CHCl_3$; *c* 1.6).



	10†	11†	12†	13†	14†	15†	16†	17†	18†	19†
R	CH_2OH	CH_2OAc	CHO	CH_2OH	CH_2OAc	CHO	CH_2OMe	CH_2OMe	CO_2H	CH_2OAc
R^1	H	H	H	OH	OH	OH	H	OH	H	H
R^2	H	H	H	H	H	H	H	H	H	OH



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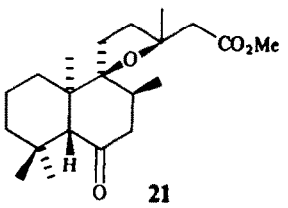

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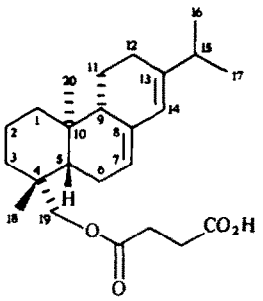
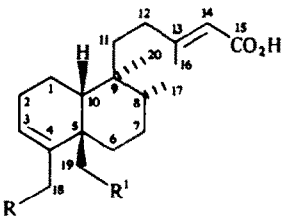
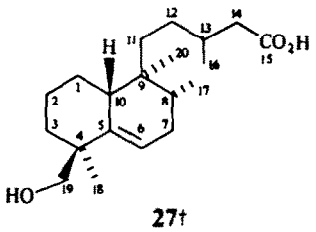


22†



	23†	24†	25†	26†
R	OAc	OH	OH	H
R^1	H	H	H	OH
			(13.14H)	(13.14H)



27†

† **4a – 19a** and **22a – 27a** are the corresponding methyl esters

Preparation of **21**. Oxidation of 18 mg methyl grindelate in 2 ml CH_2Cl_2 with excess of CrO_3 in pyridine for 7 hr at room temp. gave after TLC (Et_2O–petrol, 1:1) 7 mg methyl-6-oxogrindelate, which was hydrogenated in 10 ml Et_2O in the presence of 50 mg Pd/C (10%) for 14 hr. TLC (Et_2O–petrol, 1:2) gave 3 mg **21**; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (CO_2R, C=O); MS *m/z* (rel. int.): 350.246 $[M]^+$ (9) (calc. for $C_{21}H_{34}O_4$: 350.246), 335 (3) $[M-Me]^+$, 277 (10) $[M-CH_2CO_2Me]^+$, 197 (100) $[C_{11}H_{17}O_3]^+$, 165 (18) $[197-MeOH]^+$; ^1H NMR ($CDCl_3$): δ5.67 (*q*, H-7), 0.97 (*d*, H-17), 2.74 and 2.67 (*d*, H-14), 2.43 (*t*, H-7), 1.98 (*dd*, H-7'), 2.11 (*m*, H-8), 1.45 (*s*, H-16), 1.20 (*s*, H-18), 0.97 (*s*, H-19), 0.87 (*s*, H-20), 3.68 (*s*, OMe); [*J* (Hz): 7,7' = 7,8 = 13; 7',8 = 4; 8,17 = 6.5; 14,14' = 14]; CD (MeCN): $\Delta\varepsilon_{295} = +0.61$.

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Table 3. ^{1}H NMR spectral data of **22a–27a** (400 MHz, $CDCl_3$ TMS as internal standard)

H	**22a***	**23a**	**24a**(C_6D_6)	**25a**†	**26a**†	**27a**‡
1α	1.75 *ddd*	2.03 *m*	1.90 *m*	1.88 *m*	1.85 *m*	1.10 *dddd*
1β	0.92 *dddd*	1.81 *br dd*	1.64 *br dd*	1.79 *br dd*	1.78 *m*	1.74 *br d*
2α	1.58 *ddddd*	2.19 *m*	2.02 *m*	2.06 *m*	2.00 *m*	1.60 *m*
2β	1.41 *dddd*					1.43 *m*
3	1.92 *ddd*	5.69 *br t*	5.53 *br t*	5.62 *br t*	5.60 *br t*	1.33 *ddd*
	0.95 *dddd*					1.56 *m*
6α	1.90 *ddd*	1.97 *br d*	2.13 *br d*			5.57 *ddd*
6β	2.12 *ddd*	1.18 *m*	1.06 *ddd*			
7α	5.43 *br dd*	1.28 *m*	1.22 *m*			1.82 *ddd*
7β						1.97 *m*
8	—	1.42 *dd*	1.90 *m*			1.50 *m*
10	—	1.36 *br d*	1.22 *m*			2.00 *m*
11	1.23 *ddd*	1.63 *ddd*	1.50 *ddd*			1.56 *m*
11′	1.67 *ddd*	1.38 *m*	1.30 *ddd*			1.43 *m*
12	2.01 *br d*	2.03 *m*	1.82 *br dd*			2.00 *br dd*
13	—	—	—	2.00 *m*	1.96 *m*	—
14	5.98 *br s*	5.71 *br s*	5.94 *br s*	2.35 *dd*	2.34 *dd*	5.68 *q*
				2.14 *dd*	2.12 *dd*	
16	1.07 *d*	2.19 *d*	2.31 *s*	0.96 *d*	0.95 *d*	2.17 *d*
17	1.06 *d*	0.79 *d*	0.70 *d*	0.74 *d*	0.76 *d*	0.84 *d*
18	1.01 *d*	4.58 *br s*	4.08 *br d*	4.23 *br d*	1.70 *dt*	1.05 *s*
			3.94 *br d*	4.11 *br d*		
19	4.95 *d*	1.12 *s*	1.16 *s*	1.12 *s*	3.36 *d*	3.58 *d*
					3.23 *br d*	3.15 *br d*
20	0.79 *br s*	0.80 *s*	0.76 *s*	0.76 *s*	0.77 *s*	0.65 *s*
OAc		2.07 *s*	—	—	—	—
OMe	—	—	3.52 *s*	3.67 *s*	3.67 *s*	3.68 *s*

*H-5 1.36 *dd*, H-9 1.83 *ddd*, H-15 2.23 *br qq*, $OCOCH_2CH_2CO_2Me$ 2.41 A_2B_2 and 3.36 *s*.

†Remaining signals overlapped multiplets.

‡OH 1.15 *br d*.

J(Hz): 8, 17 = 7; 14, 16 = 1; compound **22a**: 1α, 1β = 1β, 2α = 2α, 2β = 13; 1α, 2α = 3; 1α, 2β = 1β, 2β = 4; 1β, 20 = 1; 2α, 3α = 2β, 3α = 2β, 3β = 3.5; 3α, 3β = 14; 3β, 19′ = 1.5; 5, 6α = 12; 5, 6β = 6β, 7 = 4; 6α, 6β = 18; 6α, 7 = 2; 7, 9 = 1; 9, 11α = 9, 11β = 6; 11α, 11β = 12; 11α, 12 = 11β, 12 ~ 7; 15, 16 = 15, 17 = 7; 19, 19′ = 11; compounds **23** and **24a**: 1α, 1β = 14; 1β, 2β = 7.5; 1β, 10 = 5; 2, 3 = 3; 6α, 6β = 14; 7α, 8 = 13; 7β, 8 = 6; 11, 11′ = 15; 11, 12 = 8; (compound **24a**: 18, 18′ = 14); compounds **25a** and **26a**: 2, 3 = 3; 13, 14 = 6; 13, 14′ = 8; 13, 16 = 7; 14, 14′ = 14.5; (compound **25a**: 1α, 1β = 14; 1β, 2β = 7; 18, 18′ = 14; compound **26a**: 19, 19′ = 11); compound **27a**: 1α, 1β = 1α, 2β = 1α, 10 = 13; 1α, 2α = 3.5; 2α, 3α = 4; 2β, 3α = 3α, 3β = 1; 6, 7α = 2; 6, 7β = 5; 6, 10 ~ 2; 7α, 7β = 7α, 8 = 13; 11, 12 ~ 8; 19, 19′ = 11.

Table 4. Investigated species and isolated constituents

Species (voucher*, origin)	Grams of aerial parts	Constituents
Grindelia aphanactis Rydb. (RMK 9084, Colorado)	320	260 mg germacrene D, 800 mg grindelic acid, 9 mg 17-hydroxygrindelic acid
G. boliviana Rusby (RMK 9464, Argentina Catamarca)	600	15 g grindelic acid, 2.3 g 17-hydroxygrindelic acid, 20 mg 3α-hydroxygrindelic acid, 50 mg 7β-hydroxy-8(17)-dehydro-7,8-dihydrogrindelic acid, 500 mg **20**
G. chiloensis (Corub.) Cabrera (RMK 9370, Argentina, Neuquen)	1600	4 mg germacrene D, 5 mg caryophyllene, 3 mg α-humulene, 4 mg isocomene, 22 g grindelic acid
G. perennis A. Nels, (RMK 9501, Colorado)	450	400 mg germacrene D, 500 mg grindelic acid, 4.5 g 17-hydroxy-, 4 g 17-acetoxy-, 2.5 g 17-isobutyryloxy-, 1.5 g 17-2-methylbutyryloxy-grindelic acid
Gutierrezia gilliesii Griseb. (RMK 9346, Argentina, Rio Negro)	200	3 mg bisabolene-1-one, 3 mg 6-hydroxybisabolene-1-one, 15 mg **1**, 15 mg **2**, 10 mg **3**
G. spathulata (Phil.) Kurtz (RMK 9411, Argentina, Neuquen)	300	4 mg β-selinene, 5 mg β-farnesene, 5 mg squalene, 3 mg dehydrofalcarinol, 5 mg spathulenol, 15 mg **4**, 4 mg **5**, 12 mg **6**, 2 mg **7**, 12 mg **9**, 5 mg 3-prenyl-*p*-acetoxyacetophenone
Haplopappus paucidentatus Phil. (RMK 9400, Argentina, Neuquen)	200	280 mg germacrene D, 100 mg caryophyllene epoxide, 420 mg *p*-hydroxyacetophenone, 6.5 mg 3,8-di-oxo-selina-4,6-diene, 8 mg **23**, 7 mg **24**, 2 mg **25**, 2 mg **26**, 2 mg **27**
H. pectinatus Phil. (RMK 9375, Argentina, Neuquen)	500	20 mg 4-*E*-matricarianol, 40 mg 8*E*-matricarianol acetate, 100 mg **10**, 45 mg **11**, 30 mg **12**, 300 mg **13**, 10 mg **14**, 15 mg **15**, 25 mg **16**, 6 mg **17**, 5 mg **18**, 10 mg **19**
H. glutinosus Cass. (RMK 9373, Argentina, Neuquen)	300	20 mg germacrene D, 10 mg β-farnesene, 20 mg *p*-hydroxyacetophenone, 20 mg **8**
Solidago petradoria Blake (RMK 9496, Colorado)	550	50 mg germacrene D, 200 mg **22**

*Deposited in the US National Herbarium, Washington DC, U.S.A.

Table 5. Data of **2**, **4a**, **5a** acetate, **6a–19a**, **22a**, **23** and **24a–27a**

	R_f or R_t (min)	IR bands (ν_{max} cm^{-1})	$[M]^+$	Fragments (%)
2	R_f 0.37	3620 (OH)	416.256 (13)	316 (7), 286 (21), 271 (23), 83 (100)
	A, 1:1	1710 (C=O)	($C_{25}H_{36}O_5$)	
4a	R_f 0.76	1715 (C=O)	316.240 (2.5)	270 (19), 87 (100)
	A, 1:9		($C_{21}H_{32}O_2$)	
5a-acetate	R_f 0.23	1720 (C=O)	374.246 (4)	314 (12), 299 (22), 201 (71), 187 (80), 185 (90), 149 (100)
	B, 1:1:1		($C_{23}H_{34}O_4$)	
6a	R_f 0.30	3600 (OH)	348.230 (4)	234 (9.5), 217 (5), 188 (100)
	B, 1:1:5	1720 (C=O)	($C_{21}H_{32}O_4$)	
7a	R_f 0.10	1720 (C=O)	462 (1)	377.223 (62) ($C_{22}H_{33}O_5$, [M − C_5H_9O]), 317 (56), 285 (48), 85 (78), 57 (100)
	A, 1:9			
8a	R_f 0.6	3620 (OH)	334.251 (0.2)	220 (80), 109 (100)
	A, 1:0	1730 (C=O)	($C_{21}H_{34}O_3$)	
9a	R_f 0.16	1720 (C=O)	348.230 (1.3)	316 (22), 202 (100), 133 (88)
	A, 1:9		($C_{21}H_{32}O_4$)	
10a	R_f 0.5	3610 (OH)	336.266 (6)	318 (6), 196 (48), 165 (56), 109 (100)
	A, 1:1	1730 (C=O)	($C_{21}H_{36}O_3$)	
11a	R_f 0.2	1740 (C=O)	—	318.256 (8) ($C_{21}H_{34}O_2$, [M − HOAC]), 189 (50), 175 (96), 109 (100)
	A, 1:2			
12a	R_f 0.6	1740 (C=O)	334.251 (4)	302 (4.5), 274 (2.5), 109 (100)
	A, 1:1	1690 (C=C–C=O)	($C_{21}H_{34}O_3$)	
13a	R_f 0.5	3600 (OH)	—	334.251 (65) ($C_{21}H_{34}O_3$, [M − H_2O]), 316 (4), 303 (6), 301 (6), 187 (100)
	A, 1.0	1730 (C=O)		
14a	R_t 12.0	3600 (OH)	—	334.251 (5.5) ($C_{21}H_{34}O_3$, [M − AcOH]), 316 (4), 303 (6), 301 (7), 187 (100)
	C, 4:1	1730 (C=O)		
15a	R_t 9.0	3610 (OH)	350.246 (4)	300 (6), 231 (6.5), 96 (62), 86 (63), 84 (100)
	C, 4:1	1740, 1700 (C=O)	($C_{21}H_{34}O_4$)	
16a	R_f 0.4	1745 (C=O)	—	318 (22), 303 (20), 189 (100), 109 (96)
	A, 1:1			
17a	R_t 14.0	1730 (C=O)	366.277 (4)	334 (19), 301 (10), 187 (100)
	C, 4:1		($C_{22}H_{38}O_4$)	
18a	R_t 16.5	1745, 1725	364.261 (3)	332 (66), 300 (26), 189 (60), 109 (100)
	C, 4:1	(C=O)	($C_{22}H_{36}O_4$)	
19a	R_f 0.3	3610 (OH)	394.272 (0.2)	334 (6), 303 (12), 187 (100), 106 (66)
	A, 1:2	1740 (C=O)	($C_{23}H_{38}O_5$)	
22a	R_f 0.60	1730 (C=O)	402.277 (18)	270 (64), 255 (27), 187 (48), 115 (62), 97 (36), 69 (68), 57 (100)
	A, 1:9		($C_{25}H_{38}O_4$)	
23	R_t 22.5	3500–2600 (OH)	362 (0.2)	302.225 (18) ($C_{20}H_{30}O_2$, [M − HOAc]), 287 (18), 189 (100), 105 (96)
	C, 4:1	1740, 1720 (C=O)		
24a	R_t 16.5	3615 (OH)	334 (0.1)	316.240 (16) ($C_{21}H_{32}O_2$, [M − H_2O]), 189 (100), 107 (88), 105 (76)
	C, 17:3	1715 (C=O)		
25a	R_t 15.5	3620 (OH)	336 (0.9)	318.256 (9) ($C_{21}H_{34}O_2$, [M − H_2O]), 305 (12), 189 (100), 107 (48), 105 (48)
	C, 17:3	1730 (C=O)		
26a	R_t 8.75	3600 (OH)	336.266 (0.2)	318 (22), 305 (44), 207 (8), 189 (64), 177 (100), 107 (42)
	C, 9:1	1730 (C=O)	($C_{21}H_{36}O_3$)	
27a	R_t 0.2	3600 (OH)	—	316.236 (2) ($C_{21}H_{32}O_2$, [M − H_2O]), 305 (36), 207 (32), 189 (44), 177 (100), 121 (64)
	C, 9:1	1715 (C=O)		

A, Et_2O–petrol; B, Et_2O–CH_2Cl_2–C_6H_6; C, MeOH–H_2O.

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