Phytochemistry, Vol. 30, No. 11, pp. 3669–3677, 1991
Printed in Great Britain.

0031-9422/91 $3.00+0.00

FRIEDOLABDANES AND OTHER CONSTITUENTS FROM CHILEAN *HAPLOPAPPUS* SPECIES

C. ZDERO, F. BOHLMANN and H. M. NIEMEYER*

Institute for Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, Germany; *Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

(*Received* 4 *April* 1991)

Key Word Index—*Haplopappus pulchellus, H. arbutoides, H. remyanus, H. rengifoanus, H. marginalis*; Compositae; diterpenes; labdanes; friedolabdanes; sesquiterpenes; monoterpenes.

Abstract—From the aerial parts of *Haplopappus pulchellus* two new labdanes and six friedolabdanes were isolated while *H. arbutoides* afforded in addition to known labdanes five new ones, two clerodanes and a cyperone derivative. *Haplopappus remyanus* gave two further labdanes, six monoterpene esters and three known flavanones while *H. rengifoanus* afforded large amounts of liguloxide. *Haplopappus marginalis* gave no characteristic compounds. The chemistry of the genus is discussed.

INTRODUCTION

The large genus *Haplopappus* (Compositae, tribe Astereae) is a complex one [1] and parts of it already have been placed in new genera (*Ericameria, Prionopsis, Isocoma*). Additionally the chemistry is not very uniform [2 and refs cited therein]. In continuation of our investigations of the chemistry of Chilean Compositae we have studied further *Haplopappus* species.

RESULTS AND DISCUSSION

The aerial parts of *H. pulchellus* afforded the labdanes **1** and **2** and the friedolabdanes **3**–**8**, all purified as their methyl esters. Compound **1**, isolated as its dimethyl ester **1a**, most likely is identical with a labdane isolated from an *Ericameria* species [3], previously a section of *Haplopappus* (Tables 1 and 2). A strong NOE between H-19 and H-20 established the stereochemistry at C-4. The positive sign of the optical rotation favours the presence of a normal labdane.

The ^{1}H NMR spectrum of **2a** (Table 1) required an allylic alcohol, because irradiation of the low field broadened triplet at δ4.31 sharpened a pair of exo-methylene proton signals at δ5.03 and 4.61. Further spin decoupling allowed the assignment of most signals. Inspection of a model indicated that the small vicinal coupling of H-7 agreed with an α-orientated hydroxy group. Presumably compound **1** is the precursor of **2**.

The ^{1}H NMR spectrum of **3** and its methyl ester **3a** (Table 1) indicated that a diterpene with an acetoxy group, a carbomethoxy group and a double bond was present. A pair of double doublets at δ2.34 and 2.10, as well as a doublet at δ0.94 showed that the side chain was the same as that in the acids **1** and **2**. However, the chemical shifts and splittings of the olefinic proton signals differed significantly. Spin decoupling showed that a 5,6-double bond was present; the resulting sequence required a friedolabdane derivative. The NOEs between H-18 and H-6 (17%) as well as between H-19′ and H-10 (4%) established the configuration at C-4 and C-10. Accordingly, the diterpene is the dihydro derivative of an acid isolated from *H. paucidentatum* [4]. The ^{13}C NMR spectrum also agreed with the structure (Table 2).

The ^{1}H NMR spectrum of **4a** (Table 1) differed from that of **3a** by some shift differences and especially by the absence of H-7 signals. Accordingly, H-6 showed only an allylic coupling with H-10, and H-8 was a clear quartet. In agreement with the molecular formula ($C_{23}H_{36}O_5$) and the ^{13}C NMR spectrum (Table 2), therefore, the 7-oxo derivative of **3** was present. A negative Cotton-effect at 320 nm supported the proposed absolute configuration as the conformation could be deduced from the observed NOEs (H-10 with H-8 (5%) and H-19 (4%) but no effect between H-20 and H-8).

The ^{1}H NMR spectra of **5a** and **6a** (Table 1) indicated that we were dealing with the corresponding free alcohols of the acetates **3a** and **4a**. As expected the H-18 signals were shifted upfield and some of the neighbouring protons also showed shift differences.

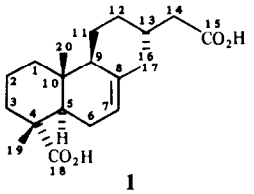
The molecular formula of **7a** ($C_{22}H_{36}O_4$) and its ^{1}H NMR spectrum (Table 1) showed the presence of a dimethyl ester of a dicarboxylic acid. This was further established by ^{13}C NMR data (Table 2). All data agreed only with the proposed structure.

The ^{1}H NMR spectrum of **8a** (Table 1) required the presence of the 15-hydroxy derivative of **7a**. The natural compound is present also in a *Koanophyllum* species where it was isolated as its 15-*O*-acetate [5].

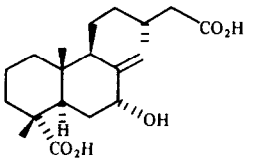
The aerial parts of *H. arbutoides* gave bisabolene, the labdanes **9** [6], **10** [7], **11** [8], **12** [9], **13** [10], **14** [11] and **15**–**19**, the clerodanes **20** and **21** as well as the β-cyperone derivative **22**.

The structure of **15** followed from its ^{1}H NMR spectrum (see Experimental) which was in part close to that of **13** and **14**. The presence of a dihydro derivative of the latter could be deduced from the typical pair of three-fold doublets at δ2.42 and 2.24 and the low field triplet at δ9.75.

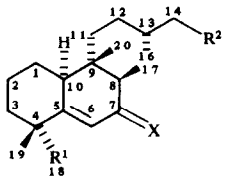
The aldehydes **16**, **17**, **20** and **21** could not be separated



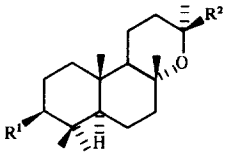
1



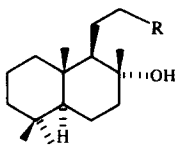
2



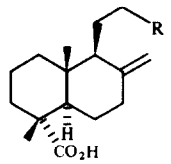
	3	4	5	6	7	8
R^1	CH_2OAc	CH_2OAc	CH_2OH	CH_2OH	CO_2H	CO_2H
R^2	CO_2H	CO_2H	CO_2H	CO_2H	CO_2H	CH_2OH
X	H_2	O	H_2	O	H_2	H_2



	9	10	11
R^1	H	OH	H
R^2	$CH{=}CH_2$	$CH{=}CH_2$	CH_2CHO



	R
12	$C(Me){=}CHCH_2OH$ (*E*)
13	$CH(Me)CH_2CH_2OH$
14	$C(Me){=}CHCHO$ (*E*)
15	$CH(Me)CH_2CHO$



	R
16	$C(Me){=}CHCHO$ (*E*)
17	$C(Me){=}CHCHO$ (*Z*)
18	$C(Me){=}CHCO_2Me$ (*E*)
19	$CH(Me)CH_2CH_2OH$

Table 1. ^{1}H NMR spectral data of compounds **1a–8a** (400 MHz, $CDCl_3$, δ-values)

H	1a	2a	3a	4a	5a	6a	7a	8a†
5	1.39 *br d*	2.44 *dd*	—	—	—	—	—	—
6 6′	1.94 *m*	1.35 *dq* 1.65 *dt*	5.53 *dt*	5.93 *d*	5.56 *dt*	5.99 *d*	5.58 *dt*	5.58 *dt*
7	5.29 *br d*	4.31 *t*	1.87 *m* 1.79 *m*	—	1.96 *m* 1.80 *ddt*	—	1.96 *m* 1.78 *ddt*	1.98 *m* 1.78 *ddt*
8	—	—	1.65 *m*	2.32 *q*	1.65 *m*	2.37 *q*	1.58 *m*	1.58 *m*
9	1.54 *m*	2.22 *br d*	—	—	—	—	—	—
10	—	—	2.10 *br d*	2.61 *ddd*	1.99 *br d*	2.51 *ddd*	2.19 *br d*	2.18 *br d*
13	1.95 *m*	1.93 *m*	1.87 *m*	1.87 *m*	1.87 *m*	1.88 *m*	1.85 *m*	1.46 *m*
14	2.29 *dd*	2.26 *dd*	2.34 *dd*	2.32 *dd*	2.34 *dd*	2.35 *dd*	2.33 *dd*	*
14′	2.13 *dd*	2.12 *dd*	2.10 *dd*	2.15 *dd*	2.12 *dd*	2.18 *dd*	2.10 *dd*	*
16	0.94 *d*	0.93 *d*	0.94 *d*	0.95 *d*	0.94 *d*	0.98 *d*	0.94 *d*	0.90 *d*
17	1.64 *br s*	5.03 *br s* 4.61 *br s*	0.77 *d*	0.96 *d*	0.97 *d*	1.00 *d*	0.82 *d*	0.82 *d*
18	—	—	3.97 *d*	4.33 *d*	3.59 *d*	3.57 *d*	—	—
18′	—	—	3.88 *d*	3.72 *d*	3.12 *d*	3.46 *d*	—	—
19	1.19 *s*	1.13 *s*	1.06 *s*	1.14 *s*	1.04 *s*	1.14 *s*	1.29 *s*	1.29 *a*
20	0.76 *s*	0.68 *s*	0.60 *s*	0.68 *s*	0.62 *s*	0.73 *s*	0.65 *s*	0.65 *s*
OMe	3.65 *s*	3.67 *s*	3.65 *s*	3.65 *s*	3.66 *s*	3.67 *s*	3.66 *s*	3.63 *s*
	3.62 *s*	3.65 *s*	—	—	—	—	3.64 *s*	—
OAc	—	—	2.02 *s*	1.92 *s*	—	—	—	—

*Obscured multiplets.

†H-15 3.66 *m*.

J [Hz]: 8,17 = 13,14 = 13,16 = 7; 14,14′ = 15; compound **1a**: 5,6 ~ 10; 6,7 = 4; compound **2a**: 5,6 = 6,7 = 6′,7 = 2,5; 5,6′ = 6,6′ = 13; compounds **3a**, **5a**, **7a** and **8a**: 1,10 = 12; 6,10 = 6,7′ ~ 2.5; 6,7 = 5; 7,7′ = 17; 7′,8 = 10; compounds **4a** and **6a**: 1,10 = 12; 1′,10 = 4; 6,10 = 2.

completely. However, an enrichment by HPLC and TLC allowed the assignment of the main ^{1}H NMR signals (see Experimental). The configurations of the Δ^{14} bond followed from the chemical shifts of H-16 and the presence of clerodanes in the case of **20** and **21** was indicated by the low field triplets at δ6.85 and 6.86, respectively. In the spectra of **16** and **17** the shift of the signals of the exomethylene protons were influenced by the configuration of the Δ^{14} bond.

Table 2. ^{13}C NMR spectral data of compounds **1a**, **3**, **4a** and **7a**

C	1a	3*	4a	7a
1	38.0	33.3	33.7	34.2
2	17.9	21.7	21.0	23.4
3	39.1	35.5	35.9	37.9
4	46.6	36.9	41.0	48.8
5	45.0	140.7	163.1	140.2
6	25.4	121.0	124.7	120.2
7	121.4	31.8	202.3	31.2
8	135.4	33.3	47.6	33.0
9	54.9	39.6	40.8	36.8
10	36.2	40.1	41.7	42.3
11	24.1	24.7	26.0	27.0
12	36.9	29.1	29.7	29.4
13	30.9	31.0	30.8	31.1
14	41.6	41.4	41.3	41.5
15	173.5	179.0	173.4	173.7
16	19.5	19.7	19.7	19.8
17	22.0	14.9	7.5	15.2
18	179.0	69.7	69.0	177.4
19	16.9	24.7	24.2	24.9
20	13.8	15.8	16.5	16.9
OMe	51.8	—	51.2	51.8
	51.3	—	—	51.3
OAc	—	171.2	170.7	—
		20.8	20.8	—

*Assigned by hetero 2D.

The structure of the methyl ester **18** followed from its ^{1}H NMR spectrum (see Experimental) which was very close to that of the isomeric 18-oic ester isolated from *H. deserticola* [2].

The ^{1}H NMR spectrum of **19** (see Experimental) was in part close to that of **18**. However, the changed situation of the side chain followed from the typical signals of the side chain being nearly identical with those of **13**. The optical rotations indicate that most likely normal-labdanes were present. Accordingly, normal clerodanes (**20** and **21**) are most probably present.

The ^{1}H NMR spectrum of **22** (see Experimental) was close to that of the corresponding 8-keto derivative isolated from *H. fremonti* [12]. All signals could be assigned by spin decoupling.

The aerial parts of *H. remyanus* afforded the known flavanones **31**–**33**, the labdane acids **23** and **24** as well as the monoterpene ester **25**–**30**.

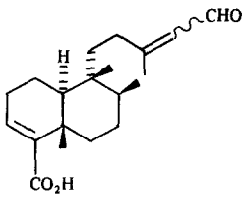
The ^{1}H NMR spectrum of **23** (see Experimental) was close to that of labda-7,13*E*-dien-15-oic acid [13]. The replacement of a methyl singlet by a pair of doublets at δ3.37 and 3.13 indicated the presence of a 18-hydroxy derivative. The chemical shift and the absence of a *W*-coupling excluded a 19-hydroxy derivative. The ^{1}H NMR data of **24** required a dihydrocinnamate of **23**. As expected the H-18 doublets were shifted downfield.

The ^{1}H NMR spectra of **25** and **26** (Table 3) differed mainly by the signals of the ester groups which are typical for a cinnamate and a dihydrocinnamate, respectively. A pair of doublets showed slightly different chemical shifts

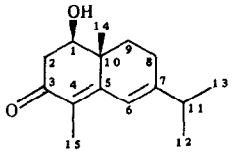
Table 3. ^{1}H NMR spectral data of compounds **25**–**30** (400 MHz, $CDCl_3$, δ-values)

H	25*	26†	27‡	28§	29‖	30¶
2	5.41 *br s*	5.39 *br s*	5.94 *br d*	7.17 *br d*	7.15 *br d*	6.38 *dd*
3 3′	2.00 *m*	2.04 *br d* 1.88 *br dd*	6.27 *br dd*	7.35 *br d*	7.31 *br d*	—
4	1.76 *dddd*	1.60 *dddd*	2.47 *m*	—	—	—
5 5′	1.85 *dddd* 1.33 *dddd*	1.76 *dddd* 1.26 *dddd*	1.83 *ddt* 1.36 *dddd*	7.35 *br d*	7.31 *br d*	2.30 *m*
6 6′	2.00 *m*	1.95 *m*	2.47 *dt* 2.30 *br dd*	7.17 *br d*	7.15 *br d*	5.47 *br t*
7	1.65 *br s*	1.65 *br s*	4.81 *br s* 4.78 *br s*	2.35 *br s*	2.34 *br s*	—
9 9′	4.25 *d* 4.17 *d*	4.09 *d* 4.00 *d*	4.08 *d* 4.02 *d*	4.29 *d* 4.20 *d*	4.28 *d* 4.18 *d*	4.71 *br s*
10	1.22 *s*	1.09 *s*	1.11 *s*	1.55 *s*	1.49 *s*	5.04 *br s* 5.00 *br s*

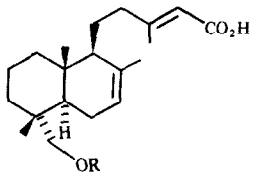
*OCOR 6.50 *d*, 7.72 *d*, 7.54 *m*, 7.40 *m*.
†OCOR 2.71 *t*, 2.97 *br t*, 7.28 *m* (2H), 7.20 *m* (3H).
‡OAc 2.12 *s*.
§OAC 2.06 *s*.
‖OCOR 2.64 *t*, 2.90 *br t*, 7.28 *m*, 7.17 *m*.
¶H-1c 5.07 *d*, H-1t 5.24 *d*, H-8 1.81 *br s*.
J [Hz]: $OCOCH_2CH_2Ph$: 7′,8′ = 7.5; 9,9′ = 11; compounds **25** and **26**: 2,3 = 2; 2,3′ = 4, 3,3′ = 15; 3,4 ~ 2; 3′,4 = 4,5′ = 12; 4,5 = 5; 5,5′ = 13; 5,6 ~ 3; 5,6′ ~ 3; 5′,6 = 12; 5′,6′ = 6; OCinn: 7′,8′ = 16; compound **27**: 2,3 = 10, 3,4 = 2.5; 4,5 = 4; 4,5′ = 12; 5,5′ = 13; 5,6 = 4; 5,6′ = 3.5; 5′,6 = 3.5; 5′,6′ = 3.5; 6,6′ = 14; compounds **28** and **29**: 2,3 = 5,6 = 8; compound **30**: 1c,2 = 10; 1t,2 = 17.



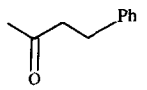
20 14*E*
21 14*Z*

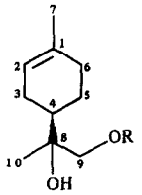


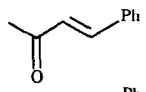
22

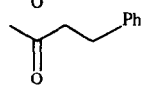


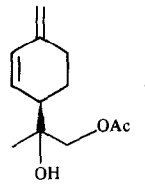
23 R = H

24 R = 

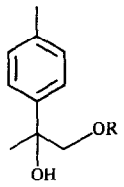


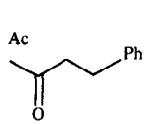
25 R = 

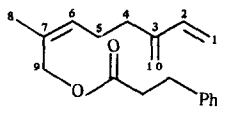
26 R = 



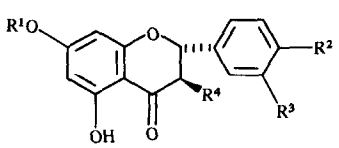
27



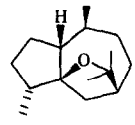
28 R = Ac
29 R = 



30



	31	**32**	**33**
R^1	Me	Me	H
R^2	H	H	OH
R^3	H	H	OH
R^4	H	OAc	H



34

indicating that the ester groups had to be placed at the corresponding carbon. Spin decoupling allowed the assignment of all signals which agreed well with the presence of α-terpineol derivatives with a 9-acyloxy group.

The ^{1}H NMR spectrum of **27** (Table 3) requires an acetoxy derivative of a monoterpene. Again a pair of doublets at *ca* δ4 indicated that we were dealing with an acetate related to **26**. However, as followed from the low field signals, a derivative of 8-hydroxy-β-phellandrene had to be proposed. Spin decoupling established that a 9-acetoxy-8-hydroxy-β-phellandrene was present.

The ^{1}H NMR spectra of **28** and **29** (Table 3) showed that we were dealing with *p*-cymene derivatives, again differing only in the nature of the ester groups. In agreement with the molecular formulae 9-acyloxy derivatives of 8-hydroxy-*p*-cymene were present. The ^{13}C NMR data of **28** are in good agreement with the structure (see Experimental).

The ^{1}H NMR data of **30** (Table 3) differed completely from those of **25–29**. Spin decoupling showed that a derivative of myrcene with a dihydrocinnamoyloxy group at C-8 or C-9 was present. Clear NOEs between H-8 and H-6 (8%) as well as between H-9 and H-5 (4%) require a *Z*-configuration of the Δ^6 bond. The absolute configuration is supported by the sign of the optical rotation of **26**. The aerial parts of *H. marginalis* gave no characteristic compound and *H. rengifoanus* afforded in high concentration liguloxide (**34**) so far only isolated from *Ligularia* species [14].

CONCLUSIONS

The genus *Haplopappus* belongs to the homochromous group in the tribe Astereae [15] and is one of the most highly developed genera. Relationships are proposed to *Chrysothamnus* and *Grindelia* [15] which is supported by the chemistry. The ancestral home may be Mexico but phytogenetic connections between the North American (Sections 1–16) and the South American species (Sections 17–21) are more or less absent [15]. Following the

classification into sections of Hall [15] the results on the chemistry of *Haplopappus* is summarized in Table 4. Most reports are concerned with the occurrence of flavanoids. But the accumulation of diterpenes, especially in the South America sections, is also obvious. However, a clear relationship between the chemistry and the various sections is not visible. Most likely in many cases the presence or absence of diterpenes has not been studied properly. The question whether the sections *Ericamaria*, *Hazardia*, *Isocoma* and *Prionopsis* should have the rank of genera cannot be answered from the available chemical data. Clearly more work has to be done on the chemistry and taxonomy of this complicated genus.

EXPERIMENTAL

Air-dried aerial parts were extracted with MeOH–Et_2O–petrol (1:1:1). After defatting with MeOH at −20°, extracts were sepd by CC, TLC and HPLC as reported previously [16]. Vouchers are deposited in the Herbarium of the University of Chile, Santiago. An extract of the aerial parts (266 g) of *H. pulchellus* DC. (voucher Niemeyer 89148, collected in September 1989 in the Region de Valparaiso, Chile) gave by CC 2 frs (Et_2O–petrol, 1:3 and Et_2O). One-tenth of CC fr. 1 gave by HPLC (MeOH–H_2O, 9:1, always RP 8, flow rate 3 ml min^{-1}) 80 mg **3** (R_t 7.8 min). The acids for CC fr. 2 were extracted with Na_2CO_3 soln and the acidic part sepd by HPLC as above affording 400 mg **1** (R_t 2.5 min), 200 mg **3** (R_t 7.2 min), 230 mg crude **7** (R_t 3.8 min) and two mixts: 2/1 (R_t 1.5 min) and 2/2 (R_t 4.5 min). To fr. 2/1 CH_2N_2 in Et_2O was added. HPLC (MeOH–H_2O, 9:1) gave 5 mg **6a** (R_t 2.5 min), 30 mg **4a** (R_t 3.0 min), and 20 mg **2a** (R_t 4.2 min). After addition of CH_2N_2 to crude **7**, HPLC (MeOH–H_2O, 19:1) gave 200 mg **7a** (R_t 7.2 min) and 20 mg **1a** (R_t 8.2 min). After addition of CH_2N_2 fr. 2/2 gave by HPLC (MeOH–H_2O, 19:1) 15 mg **8a** (R_t 4.2 min), 15 mg **5a** (R_t 4.7 min) and 20 mg **3a** (R_t 9.0 min).

An extract of air-dried aerial parts (520 g) of *H. arbutoides* Remy (voucher Niemeyer 8906, collected in February 1989 in the Region Liberator Bernardo O'Higgins, Chile) gave by CC 3 frs. The first one contained 100 mg *bis*abolene. TLC of fr. 2 gave 900 mg **9** and 200 mg **11**. Fr. 3 was sepd by HPLC (MeOH–H_2O, 9:1) affording 100 mg *p*-hydroxyacetophenone, 500 mg **12** (R_t 4.3 min), 600 mg **13** (R_t 5.7 min) and four mixts (3/1–3/4, R_t 1.7, 2.7, 3.8 and 5.0 min). TLC of fr. 3/1 (Et_2O–petrol, 3:1) gave 5 mg **22** (R_f 0.30). HPLC of 3/2 (MeOH–H_2O, 17:3) gave 2 mg **19** (R_t 8.1 min) and a mixt. of **16**/**17** and **20**/**21** which gave by TLC (EtOAc–petrol, 3:7) 2 mg **21** (R_f 0.6), 2 mg **17** (containing still **16** and **20**) and 2 mg of a mixt. of **16** and **20** (*ca* 3:4). TLC of fr. 3/3 (Et_2O–petrol, 3:1) gave 20 mg **10** (R_f 0.65). TLC of fr. 3/4 (Et_2O–petrol, 3:1) gave 5 mg **18** (R_f 0.85), 3 mg **14** (R_f 0.70) and 5 mg **15** (R_f 0.65).

An extract of aerial parts (235 g) of *H. remyanus* Wedd. (voucher Niemeyer 89146, collected in September 1990 in the Region de Valparaiso, Chile) was sepd by CC into 3 frs (1: Et_2O–petrol, 1:3 and 1:1; 2: Et_2O and 3: Et_2O–MeOH, 9:1). Fr. 2 contained 600 mg **31** and fr. 3, 6 g **32**. TLC (Et_2O–petrol, 1:1) of fr. 1 gave 3 bands (1/1–1/3). HPLC (MeOH–H_2O, 17:3) of 1/1 gave 30 mg **28** (R_t 1.2 min), 10 mg **27** (R_t 1.5 min), 10 mg **29** (R_t 3.3 min), 30 mg **26** (R_t 5.2 min), 15 mg **25** (R_t 6.1 min) and a mixt. (R_t 7.8 min) which gave by TLC (Et_2O–petrol, 1:1) 3 mg **30** (R_f 0.62). HPLC of 1/2 (MeOH–H_2O, 3:1) gave 3 mg **28** (R_t 2.4 min), 10 mg **33** (R_t 3.3 min), 2 mg **27** (R_t 3.7 min), 5 mg **31** (R_t 7.3 min) and two mixts (1/2/5 and 1/2/6). Fr. 1/2/6 gave by repeated HPLC (MeOH–H_2O, 17:3) 5 mg **24** (R_t 26.3 min) and 2 mg **26** (R_t 4.7 min) while TLC (Et_2O–petrol, 1:1) of fr. 1/2/5 afforded 10 mg **23** (R_f 0.35).

An extract of aerial parts (416 g) of *H. rengifoanus* Remy (voucher Niemeyer 89121, collected in September 1990 in the Region de Coquimbo, Chile) gave by CC 500 mg **34**, identified by comparison of 400 MHz ^1H NMR and ^{13}C NMR data ($CDCl_3$, δ-values, C-1–C-15): 92.6 *s*, 80.7 *s*, 55.8 *d*, 45.1 *d*, 42.4 *d*, 39.4 *d*, 33.5 *t*, 31.5 *q*, 30.8 *t*, 29.7 *t*, 29.0 *t*, 28.1 *t*, 23.0 *q*, 22.9 *q*, 13.5 *q*.

An extract of 770 g aerial parts of *H. marginalis* Phil. (voucher Niemeyer 8945, collected in February 1989 in the Region del Bio-Bio, Chile) gave by CC and TLC 10 mg germacrene D and large amounts of fatty acids.

Labd-7-en-15,18-dioic acid (**1**). Isolated as its diMeester **1a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (CO_2R). MS *m/z* (rel. int.): 364.261 $[M]^+$ (32) (calc. for $C_{22}H_{36}O_4$: 364.261), 349 $[M-Me]^+$ (28), 305 $[M-CO_2Me]^+$ (67), 304 $[M-HCO_2Me]^+$ (74), 289 $[304-Me]^+$ (30), 235 $[M-CH_2CH_2CH(Me)CH_2CO_2Me]^+$ (100), 175 $[235-HCO_2Me]^+$ (92), 122 (98), 121 (87), 95 (74), 81 (70), 69 (55). $[\alpha]_D^{24°}$ +25 ($CHCl_3$; *c* 5.18).

7α-Hydroxy-labd-8(17)-en-15,18-dioc acid (**2**). Isolated as its diMeester **2a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3625 (OH), 3100, 1650, 925 ($C{=}CH_2$), 1740 (CO_2R). MS *m/z* (rel. int.): 380.256 $[M]^+$ (10) (calc. for $C_{22}H_{36}O_5$: 380.256), 362 $[M-H_2O]^+$ (48), 303 $[362-CO_2Me]^+$ (57), 243 $[362-CH_2CH_2CH(Me)CH_2CO_2Me]^+$ (43), 173 (70), 123 (100), 81 (66), 69 (65). $[\alpha]_D^{24°}$ −8 ($CHCl_3$; *c* 1.86).

18-Acetoxy-friedolabd-5-en-15-oic acid (**3**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500–2500, 1720 (CO_2H) 1750 (OAc). MS *m/z* (rel. int.): 364.252 $[M]^+$ (0.5) (calc. for $C_{22}H_{36}O_4$: 364.252), 304 $[M-HOAc]^+$ (43), 291 $[M-CH_2OAc]^+$ (64), 249 (38), 189 (100), 134 (68), 121 (78), 69 (36). Meester **3a**: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1750 (OAc), 1735 (CO_2Me). MS *m/z* (rel. int.): 378.277 $[M]^+$ (1.5) (calc. for $C_{23}H_{38}O_4$: 378.277), 347 $[M-OMe]^+$ (3.5), 318 $[M-HOAc]^+$ (52), 305 $[M-CH_2OAc]^+$ (54), 287 $[347-HCO_2Me]^+$ (30), 243 (53), 235 (40), 189 (100), 121 (62), 69 (48).

18-Acetoxy-friedolabd-5-en-7-one-15-oic acid (**4**). Isolated as its Meester **4a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (OAc, CO_2R), 1690 (C=CC=O). MS *m/z* (rel. int.): 392.256 $[M]^+$ (32) (calc. for $C_{23}H_{36}O_5$: 392.256), 361 $[M-OMe]^+$ (11), 301 $[361-HOAc]^+$ (14), 277 (26), 203 (100), 189 (44), 166 (52), 135 (41), 69 (38). CD (MeOH): $\Delta\varepsilon_{320}$ −1.9.

18-Hydroxy-friedolabd-5-en-15-oic acid (**5**). Isolated as its Meester **5a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640 (OH), 1740 (CO_2R). MS *m/z* (rel. int.): 336.266 $[M]^+$ (1.5) (calc. for $C_{21}H_{36}O_3$: 336.266), 305 $[M-CH_2OH]^+$ (100), 235 (31), 207 $[M-CH_2CH_2CH(Me)CH_2CO_2Me]^+$ (43), 177 $[207-CH_2O]^+$ (80), 121 (81).

18-Hydroxy-7-oxo-friedolabd-5-en-15-oic acid (**6**). Isolated as its Meester **6a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1740 (CO_2R), 1690 (C=CC=O). MS *m/z* (rel. int.): 350.246 $[M]^+$ (10) (calc. for $C_{21}H_{34}O_4$: 350.246), 320 $[M-CH_2O]^+$ (42), 249 (20), 221 $[M-CH_2CH_2CH(Me)CH_2CO_2Me]^+$ (18), 203 $[221-H_2O]^+$ (62), 109 (68), 81 (66), 55 (100).

Friedolabd-5-en-15,18-dioic acid (**7**). Purified as its diMeester **7a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (CO_2R). MS *m/z* (rel. int.): 364.261 $[M]^+$ (14) (calc. for $C_{22}H_{36}O_4$: 364.261), 253 $[M-OMe]^+$ (6), 305 $[M-CO_2Me]^+$ (38), 273 $[305-MeOH]^+$ (10), 235 $[M-CH_2CH_2CH(Me)CH_2CO_2Me]^+$ (100), 175 $[235-HCO_2Me]^+$ (82), 121 (57), 93 (37), 69 (34). $[\alpha]_D^{24°}$ −9 ($CHCl_3$; *c* 3.20).

15-Hydroxy-friedolabd-5-en-18-oic acid (**8**). Isolated as its Meester **8a**. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3650 (OH), 1740 (CO_2R). MS *m/z* (rel. int.): 336.266 $[M]^+$ (8) (calc. for $C_{22}H_{36}O_3$: 336.266), 277 $[M-CO_2Me]^+$ (22), 235 $[M-CH_2CH_2CH(Me)CH_2CH_2OH]^+$ (100), 175 $[235-HCO_2Me]^+$ (83), 121 (58), 69 (41).

8α-Hydroxy-labdan-15-al (**15**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 2720, 1730 (CHO). MS *m/z* (rel. int.): 308.272 $[M]^+$ (17) (calc. for $C_{20}H_{36}O_2$: 308.272), 290 $[M-H_2O]^+$ (17), 275 $[290-Me]^+$ (21), 251 (30), 219 $[M-\text{side chain}]^+$ (38), 195 (63), 177 (82), 137 (84), 123 (84), 109 (87), 95 (83), 81 (90), 71 (100). ^1H NMR

Table 4. Distribution of compounds in *Haplopappus* species (sections following Hall)

	Labdanes	Friedolabdanes	Clerodanes	Cyperone derivatives	Flavanoids	C_{10}-Acetylenes	*p*-Hydroxy acetophenone derivatives	Coumarins	Diverse
Sect. 1									
H. brandegei	—	—	—	—	—	+	—	—	—
Sect. 2									
H. gracilis	—	—	—	—	+	—	—	—	—
Sect. 3									
H. ciliatus	—	—	+	—	+	—	—	—	—
Sect. 4									
H. fremonti	—	—	—	+	—	—	—	+	—
Sect. 5									
H. croceus	—	—	—	—	—	+	—	—	—
H. clematis	—	—	—	—	—	+	—	—	—
Sect. 6									
H. linearifolius	+	—	—	—	+	—	—	—	—
Sect. 13									
H. acradenia	—	—	—	—	+	—	—	—	—
H. drummondi	—	—	—	—	+	—	—	—	—
H. hartwegii	+	—	—	—	+	—	+	—	α-Cedrene deriv.
H. pluriflorus	—	—	—	+	—	—	—	—	—
H. tenuisecta	+	—	—	—	—	—	+	—	—
H. venetus	+	—	—		+	+	—	—	
Sect. 14									
H. squarrosus	—	—	—	—	+	—	—	—	—
Sect. 15									
H. cooperi	—	—	—	—	+	—	—	—	—
H. laricifolius	+	—	—	—	+	—	—	—	—
H. parrasana	—	—	—	—	+	—	—	—	—
H. sanoviensis	—	—	—	—	+	—	—	—	—

Sect. 17									
H. anthylloides	—	—	—	—	—	—	+	—	—
H. arbutoides	+	+	+	—	—	—	—	—	—
H. baylahuen	—	—	—	—	+	—	—	—	—
H. canescens	—	—	—	—	+	—	—	—	—
H. glutinosus	+	—	—	—	+	—	+	+	—
H. marginalis	—	—	—	—	—	—	—	—	—
H. paucidentatus	—	+	+	+	+	—	+	—	—
H. pectinctus	+	—	—	—	+	+	—	—	—
H. pulchellus	+	+	—	—	+	—	—	—	—
H. scrobiculatus	—	—	—	—	+	—	—	—	—
Sect. 18									
H. intergerrimus		—	—	—	+	+	—	—	—
H. sericeus		—	—	—	+	—	—	—	—
Sect. 19									
H. deserticolus	+	—	—	—	—	—	—	+	—
H. foliosus	—	—	—	—	+	—	—	+	—
H. multifolius	—	—	—	—	—	—	—	+	—
H. remyanus	+	—	—	—	+	—	—	—	Monoterpene esters
H. rengifoanus	—	—	—	—	—	—	—	—	Liguloxide
Sect. 20.									
H. parvifolius	+	—	—	—	—	—	—	—	—
H. angustifolius	—	—	+	—	—	—	—	—	Seco, nor, re-arranged labdanes

($CDCl_3$): δ2.04 (*m*, H-13), 2.42 and 2.24 (*ddd*, H-14), 9.75 (*t*, H-15), 0.98 (*d*, H-16), 1.14 (*s*, H-17), 0.86 (*s*, H-18), 0.79 (*s*, H-19, H-20); *J* [Hz]: 13,14 = 5.5; 13,14′ = 8; 13,16 = 6.5; 14,14′ = 16; 14,15 = 2.3. $[\alpha]_D^{24°}$ +9 ($CHCl_3$; *c* 0.95).

15-*Oxo-labda*-8(17),14E + *Z*-*diene*-18-*oic acid* (**16** and **17**). MS *m/z* (rel. int.): 318.219 $[M]^+$ (2) (calc. for $C_{20}H_{30}O_3$: 318.219), 303 $[M-Me]^+$ (6), 300 $[M-H_2O]^+$ (9), 285 $[300-Me]^+$ (24), 274 $[M-CO_2]^+$ (23), 235 $[M-C_5H_7O]^+$ (21), 149 (50), 81 (90), 55 (100). ^{1}H NMR ($CDCl_3$): **16**: δ5.88 (*br d*, H-14), 9.98 (*d*, H-15), 2.17 (*d*, H-16), 4.88 and 4.51 (*br s*, H-17), 1.16 (*s*, H-19), 0.73 (*s*, H-20). **17**: δ5.89 (*br d*, H-14), 9.85 (*d*, H-15), 1.98 (*d*, H-16), 4.92 and 4.58 (*br s*, H-17), 1.15 (*s*, H-19), 0.77 (*s*, H-20); *J* [Hz]: 14,15 = 8.5; 14,16 = 1.

Labda-8(17),13E-*dien*-15,18-*dioic acid*-15-*methylester* (**18**). MS *m/z* (rel. int.): 348.230 $[M]^+$ (1) (calc. for $C_{21}H_{32}O_4$: 348.230), 330 $[M-H_2O]^+$ (2), 299 $[330-OMe]^+$ (3), 121 (100). ^{1}H NMR ($CDCl_3$): δ2.04 (*br dt*, H-7), 1.95 (*m*, H-7′), 2.39 (*m*, H-12), 2.29 (*m*, H-12′), 5.65 (*tq*, H-14), 2.16 (*d*, H-16), 4.86 and 4.52 (*br s*, H-17), 1.15 (*s*, H-19), 0.72 (*s*, H-20), 3.69 (*s*, OMe); *J* [Hz]: 6,7 = 7,7′ = 13; 6′,7 = 5; 12,14 = 14,16 ~ 1.5.

15-*Hydroxy-labd*-8(17)-*en*-18-*oic aicd* (**19**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 3500–2700, 1720 (CO_2H). MS *m/z* (rel. int.): 322.251 $[M]^+$ (12) (calc. for $C_{20}H_{34}O_3$: 322.251), 304 $[M-H_2O]^+$ (8), 276 $[M-HCO_2H]^+$ (52), 261 $[276-Me]^+$ (23), 221 $[M-$side chain$]^+$ (40), 121 (100), 95 (78), 81 (84), 69 (61). ^{1}H NMR ($CDCl_3$): δ1.95 (*dd*, H-5), 1.49 and 1.35 (*m*, H-6), 2.35 (*br d*, H-7), 2.05 (*br dt*, H-7′), 1.55 (*m*, H-13), 3.68 (*m*, H-15), 0.90 (*d*, H-16), 4.82 and 4.51 (*br s*, H-17), 1.14 (*s*, H-19), 0.70 (*s*, H-20); *J* [Hz]: 5,6 = 12; 5,6′ = 2.5; 6,7′ = 7,7′ = 13; 6′,7′ = 4; 13,16 = 7.

15-*Oxo-cleroda*-3,13E-*dien*-18-*oic acid* (**20**). Not free from **16**. MS *m/z* (rel. int.): 318.219 $[M]^+$ (2) (calc. for $C_{20}H_{30}O_3$: 318.219), 303 $[M-Me]^+$ (8), 300 $[M-H_2O]^+$ (24), 285 $[300-Me]^+$ (66), 221 $[M-$side chain$]^+$ (24), 203 $[221-H_2O]^+$ (32), 133 (52), 125 (100). ^{1}H NMR ($CDCl_3$): δ6.86 (*t*, H-3), 5.87 (*br d*, H-14), 10.0 (*d*, H-15), 2.18 (*d*, H-16), 0.82 (*d*, H-17), 1.25 (*s*, H-19), 0.73 (*s*, H-20); *J* [Hz]: 2,3 = 3; 14,15 = 8.5; 14,16 = 1.

15-*Oxo-cleroda*-3,13*Z*-*dien*-18-*oic acid* (**21**). MS *m/z* (rel. int.): 318.219 $[M]^+$ (2) (calc. for $C_{20}H_{30}O_3$: 318.219), 303 $[M-Me]^+$ (7), 300 $[M-H_2O]^+$ (25), 285 $[300-Me]^+$ (60), 221 $[M-$side chain$]^+$ (27), 133 (50), 125 (100). ^{1}H NMR ($CDCl_3$): δ6.85 (*t*, H-3), 5.86 (*br d*, H-14), 9.90 (*d*, H-15), 1.98 (*d*, H-16), 0.85 (*d*, H-17), 1.26 (*s*, H-19), 0.77 (*s*, H-20); *J* [Hz]: 2,3 = 3; 14,15 = 8.5; 14,16 = 1.

1β-*Hydroxy*-β-*cyperone* (**22**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1665, 1620 ($[C{=}C]_2C{=}O$). MS *m/z* (rel. int.): 234.162 $[M]^+$ (100) (calc. for $C_{15}H_{22}O_2$: 234.162), 219 $[M-Me]^+$ (14), 216 $[M-H_2O]^+$ (6), 190 $[M-C_2H_4O]^+$ (75), 147 (63), 119 (42), 81 (66). ^{1}H NMR ($CDCl_3$): δ3.83 (*dd*, H-1), 2.72 and 2.63 (*dd*, H-2), 6.33 (*dd*, H-6), 2.33 and 2.23 (*br dd*, H-8), 2.13 and 1.39 (*ddd*, H-9), 2.46 (*br qq*, H-11), 1.12 (*d*, H-12, H-13), 1.05 (*s*, H-14), 1.84 (*s*, H-15); *J* [Hz]: 1,2 = 6; 1,2′ = 12; 2,2′ = 17; 6,7 = 6,8 ~ 1.5; 8,8′ = 18; 8,9 = 5; 8,9′ = 9,9′ = 12.5; 8′,9 = 5; 8′,9′ = 6. $[\alpha]_D^{24°}$ +151 ($CHCl_3$; *c* 0.4).

18-*Hydroxy-labda*-7,13E-*dien*-15-*oic acid* (**23**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: MS *m/z* (rel. int.): 320.235 $[M]^+$ (1) (calc. for $C_{20}H_{32}O_3$: 320.235), 220 $[M-Me_2C{=}CHCO_2H$, McLafferty$]^+$ (54), 155 (94), 133 (60), 110 (100), 94 (94), 81 (97). ^{1}H NMR ($CDCl_3$): δ1.87 (*m*, H-6), 5.39 (*br s*, H-7), 2.38 and 2.12 (*ddd*, H-12), 5.71 (*br s*, H-14), 2.19 (*d*, H-16), 1.69 (*br s*, H-17), 3.37 and 3.13 (*d*, H-18), 0.84 (*s*, H-19), 0.80 (*s*, H-20); *J* [Hz]: 11,12 = 11′,12′ = 12,12′ ~ 13; 11,12′ = 11′,12 = 5; 18,18′ = 11. $[\alpha]_D^{24°}$ +44 ($CHCl_3$; *c* 0.41).

18-*Dihydrocinnamoyloxy-labda*-7,13E-*dien*-15-*oic acid* (**24**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: MS *m/z* (rel. int.): 452.293 $[M]^+$ (1) (calc. for $C_{29}H_{40}O_4$: 452.293), 353 $[M-CH_2C(Me){=}CHCO_2H]^+$ (44), 352 $[M-Me_2C{=}CHCO_2H]^+$ (86), 220 $[352-O{=}C{=}CHCH_2Ph]^+$ (24), 203 $[352-OCOR]^+$ (82), 202 $[352-RCO_2H]^+$ (93), 187 (47), 133 $[RCO]^+$ (78), 109 (100), 105 (80), 91 (82), 81 (81). ^{1}H NMR ($CDCl_3$): δ1.85 (*m*, H-6), 5.37 (*br s*, H-7), 2.39 and 2.12 (*ddd*, H-12), 5.71 (*br s*, H-14), 2.19 (*d*, H-16), 1.70 (*br s*, H-17), 3.78 and 3.67 (*d*, H-18), 0.88 (*s*, H-19), 0.78 (*s*, H-20), 7.28 (*m*, H-3′, H-5′), 7.20 (*m*, H-2′, H-4′, H-6′), 2.95 (*br t*, H-7′), 2.66 (*t*, H-8′); *J* [Hz]: 11,12 = 11′,12′ = 12,12′ ~ 13; 11,12′ = 11′,12 = 5; 18,18′ = 11; 7′,8′ = 7.5.

9-*Cinnamoyloxy*-α-*terpineol* (**25**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1725, 1645, 1580 ($PhC{=}CCO_2R$). MS *m/z* (rel. int.): 300.172 $[M]^+$ (1) (calc. for $C_{19}H_{24}O_3$: 300.172), 282 $[M-H_2O]^+$ (6), 134 $[C_{10}H_{14}]^+$ (100), 131 $[RCO]^+$ (56), 105 (80), 91 (92).

9-*Dihydrocinnamoyloxy*-α-*terpineol* (**26**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610 (OH), 1745 (CO_2R). MS *m/z* (rel. int.): 284.178 $[M-H_2O]^+$ (8) (calc. for $C_{19}H_{24}O_2$: 284.178). 134 $[C_{10}H_{14}]^+$ (100), 133 $[RCO]^+$ (42), 105 (84), 91 (83). ^{13}C NMR ($CDCl_3$, C-1–C-10): δ 143.8, 120.4, 30.9, 40.9, 25.8, 30.8, 23.3, 73.4, 69.8, 21.0; OCOR (C-1′ C-9′): 140.2, 128.2, 128.5, 126.4, 128.5, 128.2, 24.0, 35.7, 173.0. $[\alpha]_D^{24°}$ +51 ($CHCl_3$; *c* 4.79).

8-*Hydroxy*-9-*acetoxy*-β-*phellandrene* (**27**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1753, 1250 (OAc), 3090, 1645, 895 ($C{=}CH_2$). MS *m/z* (rel. int.): 192.115 $[M-H_2O]^+$ (19) (calc. for $C_{12}H_{16}O_2$: 192.115), 150 $[M-HOAc]^+$ (5), 135 $[150-Me]^+$ (88), 117 $[135-H_2O]^+$ (100), 94 (88), 93 (82), 91 (66), 79 (80), 75 (95). $[\alpha]_D^{24°}$ −9 ($CHCl_3$; *c* 1.23).

8-*Hydroxy*-9-*acetoxy*-p-*cymene* (**28**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610 (OH), 1755, 1245 (OAc). MS *m/z* (rel. int.): 208.110 $[M]^+$ (12) (calc. for $C_{12}H_{16}O_3$: 210.110), 148 $[M-HOAc]^+$ (23), 135 $[M-CH_2OAc]^+$ (100), 119 (40), 105 (37), 91 (50).

8-*Hydroxy*-9-*dihydrocinnamoyloxy*-p-*cymene* (**29**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1735 (CO_2R). MS *m/z* (rel. int.): 298.157 $[M]^+$ (2) (calc. for $C_{19}H_{22}O_3$: 298.157), 135 $[M-CH_2OCOR]^+$ (100), 119 (35), 105 (40), 91 (45).

9-(p-*cumaroyloxy*)-*Myrcene* (**30**). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1715, 1640, 1610 ($PhC{=}CCO_2R$). MS *m/z* (rel. int.): 298.157 $[M]^+$ (10) (calc. for $C_{19}H_{22}O_3$: 298.157), 147 $[RCO]^+$ (100), 134 $[M-RCO_2H]^+$ (36), 119 (35), 91 (41).

REFERENCES

1. Grau, J. (1977) *The Biology and Chemistry of the Compositae* (Heywood, V. H., Harborne, J. B. and Turner, B. L., eds), p. 539. Academic Press, London.
2. Zdero, C., Bohlmann, F. and Niemeyer, H. M. (1990) *Phytochemistry* **29**, 326.
3. Dentali, S. J., Hoffmann, J. J., Jolad, S. D. and Timmermann, B. N. (1987) *Phytochemistry* **26**, 3025.
4. Jakupovic, J., Baruah, R. N., Zdero, C., Eid, F., Pathak, V. P., Chau-Thi, T. V., Bohlmann, F., King, R. M. and Robinson, H. (1986) *Phytochemistry* **25**, 1873.
5. Bohlmann, F., Abraham, W. R., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 1903.
6. Hosking, J. R. and Brandt, C. W. (1935) *Chem. Ber.* **68**, 1311.
7. Bohlmann, F. and Czerson, H. (1979) *Phytochemistry* **18**, 115.
8. Bohlmann, F., Banerjee, S., Jakupovic, J., Grenz, M., Misra, L. N., Schmeda-Hirschmann, G., King, R. M. and Robinson, H. (1985) *Phytochemistry* **24**, 511.
9. Jakupovic, J., Schuster, A., Ganzer, U., Bohlmann, F. and Boldt, P. E. (1990) *Phytochemistry* **29**, 2217.
10. Amaro, J. M. L. and Adrian, M. R. (1982) *Rev. Latinoam. Quim.* **13**, 110.
11. Bohlmann, F., Gupta, R. K., Robinson, H. and King, R. M. (1981) *Phytochemistry* **20**, 275.

12. Jakupovic, J., Boeker, R. and King, R. M. (1986) *Planta Med.* **52**, 441.
13. Bevan, C. W. L., Ekong, D. E. V. and Okogun, J. L. (1968) *J. Chem. Soc.* C, 1067.
14. Ishii, H., Tozyo, T., Nakamura, M. and Minato, H. (1970) *Tetrahedron* **26**, 2911.
15. Hall, H. M. (1928) *Carnegie Instn. Publs.* **389**, 1–391.
16. Bohlmann, F., Zdero, C., King, R. M. and Robinson, H. (1984) *Phytochemistry* **23**, 1979.