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DITERPENES FROM *CALCEOLARIA LEPIDA**

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Key Word Index—*Calceolaria lepida*; Scrophulariaceae; bis-diterpene; pimarane diterpenes; isopimaradiene derivatives; stemarane diterpenes.

Abstract—In addition to four new pimarane derivatives, the aerial parts of *Calceolaria lepida* yielded a new bis-diterpene and two novel stemarane diterpenes. The structure of the compounds were elucidated by spectroscopic methods and chemical transformations.

INTRODUCTION

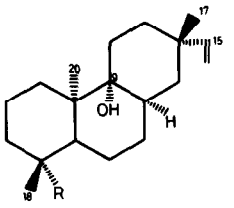
Several diterpenoids have been isolated from *Calceolaria* species in recent years [1–4]. Continuing our work on terpenoids from these species, we have now studied *C. lepida*, which also grows in the coastal hills of central Chile [5]. This paper describes the characterization of a new bis-diterpene which has been given the trivial name lepidate (**5**), four new pimarane derivatives (**1**–**4**), and two stemarane diterpenes, *ent*-stemar-13(14)-en-19-oic acid (**6**), and *ent*-stemar-13(14)-en-19-ol-(**7**), isolated from the aerial parts of the plant.

RESULTS AND DISCUSSION

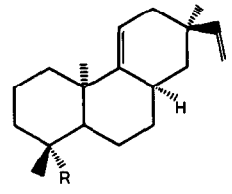
The petrol extract of the fresh aerial parts of *C. lepida* afforded 19-pentyloxy-*ent*-pimar-15-en-9α-ol (**1**), lepidate (**5**), *ent*-isopimara-9(11)-15-diene-19-ol (**4**), *ent*-pimar-15-en-9α,19-diol (**3**), *ent*-stemar-13(14)-en-19-ol (**7**) and some fractions enriched in diterpenic acids. These fractions were methylated with ethereal diazomethane and further chromatographed yielding methyl-*ent*-stemar-13(14)-en-19-oate (**6a**) and methyl 19-malonyloxy-*ent*-pimar-15-en-9α-ol (**2**).

The mass spectrum of the first diterpene revealed a molecular ion at *m/z* 390 corresponding to $C_{25}H_{42}O_3$, and its IR spectrum indicated the presence of hydroxyl, ester, and olefinic group absorptions. The ^{1}H NMR spectrum of **1** showed signals for a vinyl group (δ5.81, *dd*, H-15; 4.96 *dd*, H-16c; 4.90, *dd*, H-16t), a primary ester group (δ4.30, *d*, H-19; 3.87, *d*, H-19′) and three tertiary methyl groups. The remaining oxygen atom in the molecule was part of a tertiary hydroxyl group, because the ^{1}H NMR spectrum showed that **1** lacked the signals attributed to geminal protons of hydroxyl groups. The above evidence suggested that **1** possessed an *ent*-pimarane-type structure [1–3] and the other carbon atoms (C_5) in the molecule must be part of the acyl moiety. That the ester side chain of **1** is a pentoate residue was deduced from its molecular formula and by three triplets [δ2.27 (2H, H-2′), 1.25 (4H, H-3′ and H-4′), 0.94 (3H, H-5′)] in its ^{1}H NMR spectrum.

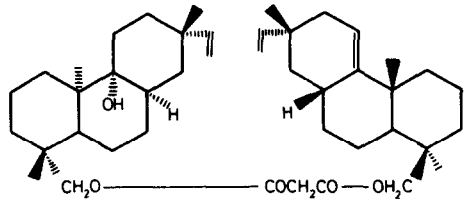
The ^{13}C NMR spectrum of **1** (Table 1) confirmed the presence of this residue by signals at δ173.9 (C-1′), 36.4



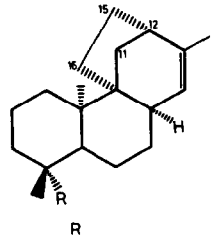
R
1 $CH_2OCO(CH_2)_3Me$
2 CH_2OCOCH_2COOMe
3 CH_2OH



R
4 CH_2OH
4a CH_2OAc



5



R
6 COOH
6a COOMe
7 CH_2OH
7a CH_2OAc

*Part 5 in the series 'Diterpenoids from *Calceolaria* species'. For Part 4 see ref. [1].

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Table 1. ^{13}C NMR spectral data of compounds **1–3**, **5**, **4a**, **6a** and **7a** ($CDCl_3$, TMS)

C	1*	2	3	5		4a†	6a	7a†
1	31.6	31.6	31.9	31.7	36.3	36.2	31.7	31.6
2	18.3	18.2	18.4	18.3	18.7	18.6	19.5	18.3
3	36.2	36.0	35.5	36.2	36.3	36.4	38.7	36.1
4	37.0	37.0	38.5	37.2	37.5	37.4	44.3	36.8
5	49.2	48.2	49.3	49.3	54.4	54.3	50.8	49.4
6	22.0	21.9	22.0	22.0	22.0	21.9	23.4	21.6
7	30.2	30.1	30.4	30.3	37.4	37.2	36.5	36.3
8	38.6	38.5	38.7	38.7	31.2	31.0	42.6	42.2
9	76.2	76.1	76.2	76.2	149.4	149.2	50.8	51.4
10	42.3	42.2	42.4	42.6	39.2	39.1	38.4	38.4
11	23.5	23.5	23.6	23.6	113.1	113.0	24.2	24.5
12	30.5	30.4	30.7	30.7	37.5	37.4	41.8	41.7
13	35.0	35.0	35.0	35.0	34.7	34.7	138.4	138.6
14	40.6	40.6	40.7	40.6	42.6	42.5	123.5	123.3
15	149.4	149.3	149.3	149.4	150.1	150.1	34.1	34.1
16	109.4	109.3	109.3	109.4	109.3	109.3	28.0	28.0
17	33.5	33.5	33.5	33.6	22.0	21.8	21.9	21.9
18	27.7	27.5	27.3	27.7	27.2	27.3	28.9	27.2
19	66.9	68.3	65.4	68.3	68.1	66.9	177.8	66.8
20	15.6	15.5	15.7	15.7	22.0	22.0	15.4	18.0
$\underline{CO}CH_2CO$		166.6		166.6				
$CO\underline{CH_2}CO$		41.4		41.8				
$COCH_2\underline{CO}$		166.7		166.6				
$\underline{MeO}$		52.3					51.0	

*Pentanoate carbons at 173.9 (*s*) C-1′; 36.4 (*t*) C-2′; 18.3 (*t*) C-3′; 29.7 (*t*) C-4′; 13.4 (*q*) C-5′.
†Acetate carbons at δ171.4 and 21.0.

(C-2′), 18.3 (C-3′), 29.7 (C-4′) and 13.4 (C-5′) [5]; it also established that the ester group was axially orientated (C-19, δ66.9) at C-4. The location of the tertiary hydroxyl group at C-9 was discerned from the ^{13}C NMR spectrum, which clearly showed a γ-effect on C-12 and the expected deshielding effect on C-10. The α-orientation of this group and the H-8 were deduced from the pronounced shielding effect on C-7 and the deshielding effect on C-8 (compare with a Dreiding molecular model). Finally, the configuration of C-13 was established by the chemical shift of C-17. On the basis of these data, compound **1** is shown to be 19-pentyloxy-*ent*-pimar-15-en-9α-ol.

Compound **2** was a crystalline product with molecular formula $C_{24}H_{39}O_5$. The ^{1}H NMR spectrum of **2** was very similar to that of **1**, but the signals due to the pentoate residue were missing. However **2** presents a singlet (δ3.38, 2H) corresponding to the methylene group of a malonate moiety [1–4]. The ^{13}C NMR spectrum of **2** (Table 1) confirmed this by the presence of signals at δ166, 6, 41, 4 and 166.7 which corresponded to the malonate carbons [1–4]. On the basis of this data, **2** is shown to be methyl 19-malonyloxy-*ent*-pimar-15-en-9α-ol.

The IR spectrum of **3** $C_{20}H_{34}O_2$ ([M]$^+$ 306) indicated the presence of a vinyl and a hydroxyl group (1625 and 3300 cm^{-1}). Comparison of ^{1}H NMR spectrum of **3** with that of **2** showed only minor differences for the skeletal proton signals. In particular, the malonyl protons singlet was missing and the H-19 and H-19′ signals shifted upfield from δ4.38 and 3.94 to 3.65 and 3.25 respectively. These differences indicated that **3** must be the demalonyl derivative of **2**. The ^{13}C NMR spectrum of **3** (Table 1) confirmed all the above results and defined the proposed structure as *ent*-pimar-15-en-9α,19-diol. In agreement with this, alkaline hydrolysis of **2** yielded **3**.

Compound **4**, $C_{20}H_{32}O$, was purified and characterized as its acetate derivative **4a**. As could be deduced from its ^{1}H NMR spectrum, **4a** had a isopimarane skeleton with a trisubstituted double bond. The ^{13}C NMR spectrum of **4a** agreed with this assumption. The double bond position $\Delta^{9(11)}$ was confirmed by ^{13}C NMR data (Table 1) and by the mass fragmentation pattern which showed a peak attributable to an elimination of 2-methylbutadiene by a retro-Diels–Alder process of the C ring (262, 68) [6]. The configuration at C-13 was confirmed by the chemical shift of C.17 (δ21.8) which was only compatible with an equatorial methyl group having one γ gauche interaction [7], this interaction only being due to C-8. Thus, C-8 had to be located on the same side of the molecule as the methyl group at C-13. The *trans* localization of H-8 and H-5 was inferred by the chemical shifts of C-8 and C-5 (δ30.8 and 50.8 respectively) [8].

Lepidate **5** isolated as a gum, had a molecular formula $C_{43}H_{66}O_5$ ([M]$^+$ at *m/z* 662) and its IR spectrum revealed absorptions attributable to ester (1720 cm^{-1}), olefinic (3060, 1640 cm^{-1}), and hydroxyl (3400 cm^{-1}) groups. The ^{1}H NMR spectrum exhibited the characteristics of a isopimarane nucleus and a malonate unit (δ3.37). However, the integral due to the terpene moiety was twice that of the malonate residue which suggested that two diterpene units must be linked by malonic acid [1]. Comparison of the ^{13}C NMR data (Table 1) with those of **2** and **4** indicated that lepidate **5** was a dimeric compound formed by *ent*-isopimar-15-en-9α-19-diol and 19-malonyloxy-*ent*-pimar-15-en-9α-ol acid. The struc-

ture was further supported by acid catalysed methanolysis [9] which led to **2** and **4**.

Compound **6** was purified and characterized as its methyl ester derivative **6a**. The mass spectrum of **6a** revealed a molecular ion at *m/z* 316 corresponding to $C_{21}H_{32}O_2$ and its IR spectrum indicated the presence of an ester function (1710 cm^{-1}) and a trisubstituted olefin (1690 cm^{-1}). The ^1H NMR spectrum showed signals for a proton on a trisubstituted double bond (δ4.72, *br s*, H-14), an olefinic methyl group (δ1.64 *d*, Me-17) and two tertiary methyl groups. A characteristic feature is the absence of a vinyl group signal.

The ^{13}C NMR spectrum revealed the presence of 21 carbon atoms, a trisubstituted bond, and also established that the ester group was axially orientated at C-4 (C-18 appeared at δ27.8 ppm); therefore, a tetracyclic structure for this compound was assumed. The nature of the bicyclo[3, 2, 1]octane moiety constituting the C/D ring system relates compound **6a** to the stemodane and stemarane skeletons [10, 11]. On the basis of these data and by comparison with the spectral data of stemarin [12, 13] and tetracyclic hydrocarbons isolated by Taran *et al.* [14], the new substance is shown to be *ent*-stemar-13(14)-en-19-oic acid.

Finally, compound **7** was purified and characterized as its acetyl derivative **7a**. The structure of compound **7a**, $C_{22}H_{34}O_2$ was determined on the basis of the similarity of its ^1H and ^{13}C spectral data of **6a**: instead of the carboxy function on C-19, there appears an acetoxymethylene group as the only difference (δ4.25 *d*, 3.84, *d*, H-19; 2.03 *s* OAc). This compound was also identified in another species of this genus *C. latifolia* [16]. According to these results, this would be the second species of the Scrophulariaceae which shows rather uncommon arrangement of the C/D ring system, the first one being *Stemodia maritima* [10–15].

EXPERIMENTAL

Mps: uncorr. ^1H NMR: 60, 100 and 400 MHz in $CDCl_3$ with TMS; ^{13}C NMR: 100 MHz, $CDCl_3$ with TMS. Assignments of ^{13}C NMR chemical shifts were made with the aid of APT and SFORD. IR: film on NaCl or KBr pellets; MS: direct inlet, 70 eV.

Calceolaria lepida Phil. was collected in Cuesta "El Melón", V Región, Chile, in September 1987. A voucher specimen is deposited at Universidad Santa María.

The aerial parts of *C. lepida* (2 kg) were extracted at room temp. with petrol for 24 hr, affording 60 g of a syrup. This crude material (25 g) was chromatographed on a silica gel column (600 g, HF_{254} for TLC) and eluted with mixtures of petrol and EtOAc of increasing polarity. Fractions (125 ml) were combined, based upon TLC and ^1H NMR (60 MHz) monitoring to give in order of elution: a mixture containing 19-pentyloxy-*ent*-pimar-15-en-9α-ol (**1**) and lepidate (**5**), *ent*-isopimara-9(11)-15-diene-19-ol (**4**), a mixture containing *ent*-pimara-15-en-9α,19-diol (**3**) and *ent*-stemara-13(14)-en-19-acetoxy, and a fraction enriched in diterpenic acids. This last fraction, after addition of ethereal CH_2N_2, was subjected to silica gel CC (100 g, HF_{254} for TLC) using petrol–EtOAc (9:1, 2 l) as eluant, yielding methyl-*ent*-stema-13(14)-en-19-oate (**6a**) and methyl 19-malonyloxy-*ent*-pimar-15-en-9α-ol (**2**).

ent-*Pimar*-15-*en*-9α,19-*diol* (**3**). Mp: 107–109°. $[\alpha]_D^{25}$ 0° ($CHCl_3$; *c* 1.0). IR ν_{max}^{KBr} cm^{-1}: 3300, 2930, 1625, 1080, 1020, 845, 810, 760. ^1H NMR (100 MHz): δ5.70 (1H, *dd*, *J* = 11, 17 Hz, H-15), 4.82 (1H, *dd*, *J* = 17, 1.0 Hz, H-16t), 4.76 (1H, *dd*, *J* = 1.0, 11 Hz, H-16c), 3.65 (1H, *d*, *J* = 11 Hz, H-19), 3.25 (1H, *d*, *J* = 11 Hz, H-19'), 1.0 (3H, *s*, Me-17), 0.87 (3H, *s*, Me-18), 0.79 (3H, *s*, Me-20); ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 306 $[C_{20}H_{34}O_2, M]^+$, (82.9), 288 $[M-H_2O]^+$ (4.4), 276 (74), 275 (78.4), 258 (71.5), 257 (66.6), 164 (89.4), 150 (81.4), 149 (74.2), 138 (66.1), 107 (100), 97 (92.3), 95 (90.4), 93 (72.9), 81 (80.7), 55 (80.5), 43 (48.6).

ent-*Isopimar*-9(11)-15-*diene*-19-*ol* (**4**). Acetylation of **4** (60 mg) with Ac_2O–pyridine (overnight, room temp.) gave the corresponding acetate (40 mg) **4a**. Mp: 88–90°; $[\alpha]_D^{25}$: +20 ($CHCl_3$; *c* 1.0). IR ν_{max}^{KBr} cm^{-1}: 2920, 1730, 1630, 1250, 1040, 1000. ^1H NMR (360 MHz): δ5.81 (1H, *dd*, *J* = 8, 13 Hz, H-15), 5.32 (1H, *m*, H-11), 4.92 (1H, *dd*, *J* = 1, 13 Hz, H-16t), 4.88 (1H, *dd*, *J* = 10, 8 Hz, H-16c), 4.3 (1H, *d*, *J* = 8 Hz, H-19), 3.9 (1H, *d*, *J* = 8 Hz, H-19'), 2.1 (3H, *s*, –OAc), 1.05 (3H, *s*, Me-17), 0.96 (3H, *s*, Me-18), 0.92 (3H, *s*, Me-20); ^{13}C NMR: see Table 1. MS *m/z* (rel. int.): 330 $[C_{22}H_{34}O_2, M]^+$ (1.5), 315 $[M-Me]^+$ (1.7), 270 $[M-HOAc]^+$ (4.0), 257 $([M-CH_2OAc]^+$ (1.20), 262 (3.0), 187 (17.4), 173 (11.2), 159 (10.6), 147 (12.7), 145 (17.3), 134 (12.6), 131 (24.6), 121 (17.4), 119 (33.9), 107 (41.5), 105 (51.0), 93 (49.1), 81 (100), 77 (40.2), 68 (37.2), 55 (82), 45 (29).

Lepidate (**5**). Viscous oil, $[\alpha]_D^{20}$ ±18.5 ($CHCl_3$; *c* 1.0). IR ν_{max}^{film} cm^{-1}: 3400–3200°, 2960, 1730, 1640, 1460, 1250, 1150, 1020. ^1H NMR (400 MHz) δ: 5.80 (2H, *dd*, *J* = 11, 17 Hz, H-15 and H-15'), 5.28 (1H, *br d*, H-11'), 4.88 (2H, *m*, H-16 and H-16'), 4.32 (2H, *t*, H-19e and H-19'e), 3.92 (2H, *t*, H-19a and H-19'a), 3.36 (2H, *s*, H-2-malonyl), 1.05 (6H, *s*, Me-17 and Me-17'), 0.90 (6H, *s*, Me-18 and Me-18'), 0.89 (6H, *s*, Me-20 and Me-20'). ^{13}C NMR: see Table 1. MS *m/z* (rel. int.): 662 $[C_{43}H_{66}O_5, M]^+$ (25), 647 $[M-Me]^+$ (16), 306 $[C_{20}H_{34}O_2]^+$ (20), 290 $[C_{20}H_{34}O]^+$ (25), 288 (6), 275 (10), 150 (75), 107 (100), 105 (40), 93 (60), 81 (90), 77 (40).

Methylent-stemar-13(14)-*en*-19-*oate* (**6a**). Mp 95–97°, $[\alpha]_D^{25}$ +23.6 ($CHCl_3$; *c* 1.0); IR ν_{max}^{KBr} cm^{-1}: 2880, 2800, 1720, 1415, 1430, 1370, 1330, 1280, 1230, 1170, 1145, 1080, 1060, 1020, 880. ^1H NMR (250 MHz): δ4.79 (1H, *br s*, H-14), 3.63 (3H, *s*, OMe), 1.62 (3H, *s*, Me-17), 1.15 (3H, *s*, Me-18), 0.82 (3H, *s*, Me-20). ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 316 $[C_{21}H_{32}O_2, M]^+$ (53.3), 301 $[M-Me]^+$ (50.5), 288 $[M-OMe]^+$ (4.2), 273 $[M-43]^+$ (27.5), 257 (44.9), 241 (100), 213 (22.9), 187 (16.2), 185 (22.1), 159 (26), 147 (15.5), 133 (20.9), 131 (33.8), 105 (62), 93 (35.4), 91 (49.0), 81 (45.5), 69 (39).

19-*Pentyloxyent-pimar*-15-*en*-9α-*ol* (**1**). Mp 110–112°. $[\alpha]_D^{25}$ −7.5 ($CHCl_3$; *c* 1.0). IR ν_{max}^{KBr} cm^{-1}: 3565, 2860, 1720, 1630, 1050. ^1H NMR (360 MHz): δ5.81 (1H, *dd*, *J* = 11.0, 17.7 Hz, H-15), 4.96 (1H, *dd*, *J* = 17.7, 1.0 Hz, H-16t), 4.90 (1H, *dd*, *J* = 11, 1.0 Hz, H-16c), 4.30 (1H, *d*, *J* = 10.8 Hz, H-19), 3.87 (1H, *d*, *J* = 10.8 Hz, H-19'), 2.27 (2H, *t*, H-2'), 1.25 (4H, *t*, H-3' and H-4'), 0.94 (3H, *t*, H-5'), 1.02 (3H, *s*, Me-17), 0.93 (3H, *s*, Me-18), 0.89 (3H, *s*, Me-20); ^{13}C NMR: see Table 1. MS *m/z* (rel. int): 390 $[C_{25}H_{42}O_3, M]^+$ (1.73), 343 $[M-H_2O]^+$ (0.5), 3.06 $[M-C_5H_9O]^+$ (0.5), 288 [306 $-H_2O$] (4.8), 275 (4.33), 257 (15.9), 164 (10.7), 150 (22.4), 138 (23.0), 105 (14.5), 95 (44.1), 81 (79.9), 71 (74.9), 55 (64.9), 43 (100).

Methyl-19-*malonyloxy*-ent-*pimar*-15-*en*-9α-*ol* (**2**). Mp 56–57°. $[\alpha]_D^{25}$ +12.36 ($CHCl_3$; *c* 1.2). IR ν_{max}^{KBr} cm^{-1}: 3500, 2960, 1750, 1730, 1630, 1150, 1030. ^1H NMR (360 MHz): δ5.82 (1H, *dd*, *J* = 8, 12 Hz, H-15), 4.97 (1H, *dd*, *J* = 12, 1.0 Hz, H-16t), 4.90 (1H, *dd*, *J* = 8, 1.0 Hz, H-16c), 4.39 (1H, *d*, *J* = 8 Hz, H-19), 3.94 (1H, *d*, *J* = 8 Hz, H-19'), 3.74 (3H, *s*, $-CO_2Me$), 3.38 (2H, *s*, H_2-malonyl), 1.05 (3H, *s*, Me-17), 0.92 (3H, *s*, Me-18), 0.88 (3H, *s*, Me-20). ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 406 $[C_{24}H_{38}O_5, M]^+$ (2.1), 318 $[M-HO_2CCH_2CO_2Me]^+$ (0.5), 135 (12.6), 123 (17.37), 121 (16.5), 101 (42.3), 94 (16.2), 81 (76.3), 69 (60.6), 55 (99.3), 43 (84.2), 41 (100).

ent-*Stemar*-13(14)-*en*-19-*acetoxy* (**7a**). Acetylation of **7** (100 mg) with Ac_2O–pyridine (overnight, room temp. give the corresponding acetate (80 mg) **7a**. Mp: 95–97°, $[\alpha]_D^{25}$: −16.8

($CHCl_3$; *c* 1.0). IR ν_{max}^{KBr} cm^{-1}: 2960, 2880, 1720, 1640, 1460, 1370, 1250, 1030. ^1H NMR (250 MHz): 4.77 (1H, *br s*, H-14), 4.25 (1H, *d*, *J*: 11 Hz, H-19), 3.84 (1H, *d*, *J* = 11 Hz, H-19'), 2.03 (3H, *s*, OAc), 1.61 (3H, *s*, Me-17), 1.0 (3H, *s*, Me-18), 091 (3H, *s*, Me-20). ^{13}C NMR: see Table 1. MS *m/z* (rel. int.): 330 $[C_{22}H_{34}O_2, M]^+$ (24.7), 315 $[M-Me]^+$ (26.3), 270 $[M-MeCO_2H]^+$ (6.2), 255 $[270-Me]^+$ (39), 159 (19.5), 145 (33.5), 133 (23.7), 131 (45.6), 119 (42.7), 117 (34.4), 107 (43.9), 105 (100), 95 (34.5), 93 (62.5), 91 (97.0), 81 (66.7), 79 (65), 77 (51.4).

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