

MINOR SESQUITERPENE LACTONES OF *HELIANTHUS PUMILUS**

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Key Word Index—*Helianthus pumilus*; Compositae; Heliantheae; sesquiterpene lactones; germacradienolides; heliangolides.

Abstract—The isolation of four known and two new germacradienolides and one known heliangolide from *Helianthus pumilus*, in addition to the previously reported major lactone constituent desacetylepaserrin and the flavone nevadensin, is reported.

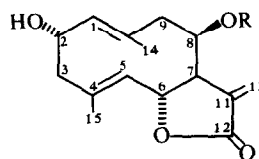
INTRODUCTION

In an earlier report [1] we identified the antileukaemic *trans,trans*-1(10),4,5-germacradienolide desacetylepaserrin (**1c**) as the major sesquiterpene lactone constituent of *Helianthus pumilus* L. The flavone nevadensin was also found. We now describe the isolation from this species of seven additional sesquiterpene lactones, two of which are new.

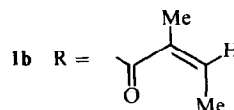
RESULTS AND DISCUSSION

Re-examination of the same collection studied previously [1] afforded, in addition to nevadensin and relatively large quantities of **1e**, smaller amounts of **1a**, **1b**, **1f**, **2** and an inseparable mixture of **1c** and **1d**. Compounds **1a**, **1c** and **1f** have been found previously in *Eupatorium mikanioides* [2]; **1d** was identical with mollisorin B from *Helianthus mollis* [3] which, we have suggested [2], is the 2'S,3'S diastereoisomer of **1c**. A detailed comparison of the ¹H NMR and ¹³C NMR spectra of **1c** and **1d** is given in Tables 1 and 2. Compound **1b** appeared to be new; its structure was evident from a comparison of the ¹H NMR and ¹³C NMR spectra (Tables 1 and 2) with those of known compounds of similar structure [1] and spin decoupling in the usual manner. Compound **2** was identical with acetylfruticin from *Tithonia frutescens* [4] and *Helianthus maximiliani* [5].

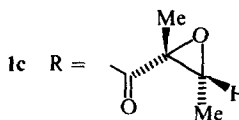
Analysis of the ¹H NMR spectrum of the remaining lactone **3a**, C₁₅H₂₂O₄, suggested that the lactone ring was closed to C-8 rather than C-6. Spin decoupling in CDCl₃ and C₆D₆ solution, when necessary to separate the relevant signals, established the sequences C-1 through C-3 and C-5 through C-9, with C-6 as the location of a free hydroxyl group as the H-6 signal exhibited a significant downfield shift on conversion to the diacetate **3b** (Table 1). The stereochemistry at C-6 and C-8 followed from the large values of *J*_{6,7} and *J*_{7,8}. In accordance with this conclusion, the substance did not undergo relactonization on treatment with base and subsequent acidification



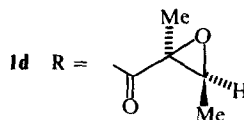
1a R = H



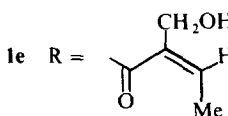
1b R =



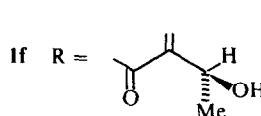
1c R =



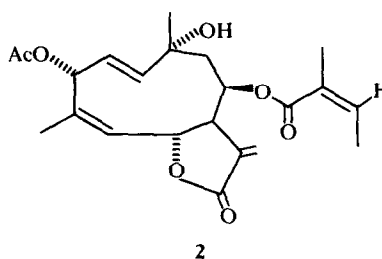
1d R =



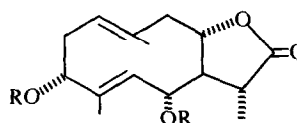
1e R =



1f R =



2



3a R = H

3b R = Ac

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Table 1. ¹H NMR spectra (270 MHz in CDCl₃ with TMS as internal standard)

Assignment	1b	1c	1d	3a	3a*	3b	3b*
H-1	5.04 <i>d</i> (<i>br</i>)	5.03 <i>d</i> (<i>br</i>)	5.03 <i>d</i> (<i>br</i>)	5.11 <i>dd</i> (<i>br</i>)	4.95	5.08 <i>d</i> (<i>br</i>)	5.32‡
H-2a	4.75 <i>dt</i>	4.77 <i>dt</i>	4.77 <i>t</i>	2.43‡	2.0‡	2.48‡	2.0
H-2b				2.28 <i>dt</i>	2.0‡	2.37‡	2.05§
H-3a	2.74 <i>dd</i>	2.75 <i>dd</i>	2.75 <i>dd</i>	4.38 <i>t</i>	3.85	5.30 <i>t</i>	5.21
H-3b	2.09 <i>t</i>	2.14 <i>t</i>	2.14 <i>t</i>				
H-5	5.00 <i>d</i> (<i>br</i>)	4.99 <i>d</i> (<i>br</i>)	4.99 <i>d</i> (<i>br</i>)	5.25 <i>d</i> (<i>br</i>)	4.90	4.98 <i>d</i> (<i>br</i>)	5.34‡
H-6	5.11 <i>dd</i>	5.08 <i>dd</i>	5.11 <i>dd</i>	4.35 <i>t</i>	3.70	5.55 <i>t</i>	5.21
H-7	2.97 <i>m</i>	2.98 <i>m</i>	2.98 <i>m</i>	2.09 <i>ddd</i>	1.62	2.30 <i>ddd</i>	1.82
H-8	5.81 <i>dd</i> (<i>br</i>)	5.85 <i>dd</i> (<i>br</i>)	5.82 <i>dd</i> (<i>br</i>)	4.05 <i>ddd</i>	3.43	4.18 <i>ddd</i>	3.45
H-9a	2.87 <i>dd</i>	2.84 <i>dd</i>	2.84 <i>dd</i>	2.72 <i>dd</i>	2.58	2.83 <i>dd</i>	2.59
H-9b	2.35 <i>dd</i>	2.36 <i>dd</i>	2.36 <i>dd</i>	2.43‡	2.07	2.48‡	2.05§
H-11				2.80 <i>dq</i>	2.50	2.59 <i>dq</i>	2.15
H-13a	6.32 <i>d</i>	6.31 <i>d</i>	6.32 <i>d</i>	1.43 <i>d</i> ¶	1.53¶	1.42 <i>d</i> ¶	1.31¶
H-13b	5.63 <i>d</i>	5.58 <i>d</i>	5.63 <i>d</i>				
H-14¶	1.54 (<i>br</i>)	1.61 (<i>br</i>)	1.59 <i>q</i> (<i>br</i>)	1.55§	1.04	1.59	1.10
H-15¶	1.80 (<i>br</i>)	1.83 (<i>br</i>)	1.83 (<i>br</i>)	1.55§	1.15	1.72	1.49
H-3'	6.13 <i>dq</i>	3.02 <i>q</i>	3.07 <i>q</i>				
H-4' ¶	1.99 <i>d</i> (<i>br</i>)	1.23 <i>d</i>	1.27 <i>d</i>				
H-5' ¶	1.87 (<i>br</i>)	1.54	1.53				
Miscellaneous				2.95 (OH)		2.07	1.52
						2.11	1.64
						(Ac)	(Ac)

Coupling constants (in Hz) for 1b: $J_{1,10} = 1.5$, $J_{1,2} = 10$, $J_{2,3a} = 6$, $J_{2,3b} = 10$, $J_{3a,3b} = J_{5,6} = 10.5$, $J_{5,15} = 1.5$, $J_{6,7} = 8.5$, $J_{7,8} = 1.5$, $J_{7,13a} = 3.5$, $J_{7,13b} = 3$, $J_{8,9a} = 6$, $J_{8,9b} = 3$, $J_{9a,9b} = 14$; for 3a, b: $J_{1,10} = 1$, $J_{1,2a} = 10$, $J_{1,2b} = 3$, $J_{2a,2b} = 13.5$, $J_{2a,3} = J_{2b,3} = 3$, $J_{5,6} = J_{6,7} = 10$, $J_{5,15} = 1.5$, $J_{7,8} = 8.5$, $J_{7,11} = 9$, $J_{8,9a} = 2$, $J_{8,9b} = 10.5$, $J_{9a,9b} = 13$, $J_{11,13} = 7$.

*In C₆D₆. Multiplicities identical with multiplicities in preceding column.

‡, §, ||Overlapping or obscured signals.

¶Intensity three protons.

Table 2. ¹³C NMR spectra (67.9 MHz in CDCl₃ with TMS as internal standard)*

Carbon	1b	1c	1d	3a†
1	134.04 <i>d</i>	134.44 <i>d</i>	134.60 <i>d</i>	126.63 <i>d</i> ‡
2	69.13 <i>d</i>	68.04 <i>d</i>	68.82 <i>d</i>	32.79 <i>t</i>
3	48.75 <i>t</i>	48.67 <i>t</i>	48.67 <i>t</i>	73.99 <i>d</i>
4	142.69	143.05	143.10	137.63
5	129.29 <i>d</i>	129.04 <i>d</i>	128.80 <i>d</i>	129.19 <i>d</i> ‡
6	75.71 <i>d</i>	75.36 <i>d</i>	75.49 <i>d</i>	70.70 <i>d</i>
7	53.13 <i>d</i>	52.56 <i>d</i>	52.56 <i>d</i>	59.42 <i>d</i>
8	71.17 <i>d</i>	72.81 <i>d</i>	72.75 <i>d</i>	80.00 <i>d</i>
9	43.98 <i>t</i>	44.08 <i>d</i>	43.80 <i>t</i>	47.96 <i>t</i>
10	134.79	133.94	133.88	131.97
11	136.59	136.34	136.53	41.14 <i>d</i>
12	169.52	169.81	169.00	179.48
13	121.17 <i>t</i>	121.25 <i>t</i>	121.25 <i>t</i>	17.92 <i>q</i> §
14	19.74 <i>q</i>	20.53 <i>q</i>	19.87 <i>q</i>	16.18 <i>q</i> §
15	18.62 <i>q</i>	18.68 <i>q</i> §	18.55 <i>q</i> §	15.82 <i>q</i> §
1'	166.36	168.49	168.49	
2'	126.73	59.40	59.54	
3'	140.03 <i>d</i>	59.98 <i>d</i>	59.72 <i>d</i>	
4'	20.53 <i>q</i>	13.64 <i>q</i>	13.78 <i>q</i>	
5'	15.85 <i>q</i>	19.09 <i>q</i> §	19.30 <i>q</i> §	

*Unmarked signals are singlets.

†Run at 55° to improve solubility.

‡, §Assignments interchangeable.

||Assignments made by single frequency resonance decoupling.

[6]. The value of $J_{2,3}$ (3 Hz) required an α -orientation of the hydroxyl on C-3 and the magnitude of $J_{7,11}$ (9 Hz) indicated α (or pseudoequatorial) orientation of the C-11 methyl group (model). This was supported by the solvent shifts ($\Delta\delta_{\text{CDCl}_3-\text{C}_6\text{D}_6} = 0.10$ ppm for **3a**, -0.11 ppm for **3b**) [7].† Hence the new lactone was 11 β H-dihydrochamissonin. 11,13-Dihydrochamissonin diacetates of unspecified C-11 stereochemistry have been prepared by catalytic hydrogenation of chamissonin diacetate [10, 11] and NaBH_4 reduction of chihuahuin acetate [12].

EXPERIMENTAL

The crude gum (60 g) remaining from the previous work [1] was adsorbed on 80 g of silicic acid (Mallinckrodt 100 mesh) and chromatographed over 700 g of silicic acid, 500 ml fractions being collected as follows: fractions 1–6 CHCl_3 -toluene (1:1), 7–11 CHCl_3 , 12–17 CHCl_3 -MeOH (90:1), 18–33 CHCl_3 -MeOH (97:3), 24–29 CHCl_3 -MeOH (19:1) and 30–35 CHCl_3 -MeOH (9:1). Fractions 3–6 after recrystallization from CHCl_3 -MeOH gave 120 mg of nevadensin, mp 185°. Fractions 7–11 showed the presence of one major constituent. Further purification by prep. TLC afforded 150 mg of the mollissorin B (**1d**)-**1c** mixture in the ratio 2:1.

Fractions 12–17 contained two compounds which were separated by prep. TLC (CHCl_3 -MeOH, 19:1, double development). The upper band was a gum (**1b**), yield 50 mg; $[\alpha]_D^{25} + 60^\circ$ (c 0.2, CHCl_3); ^1H NMR and ^{13}C NMR signals in Tables 1 and 2. The low resolution MS did not exhibit the molecular ion, but had strong peaks at m/z 263 ($\text{M}^+ - \text{C}_5\text{H}_7\text{O}$), 246 ($\text{M}^+ - \text{C}_5\text{H}_8\text{O}_2$), 228, 218, 163, 135, 95 and 83. CIMS (CH_2Cl_2) exhibited two prominent peaks at 397 ($\text{M}^+ + \text{Cl}$) $^-$ and 381 ($\text{M}^+ - 18 + \text{Cl}$) $^-$. The lower band gave 100 mg of acetylfruticin (**2**).

Fractions 18–23 which contained one major constituent afforded 8 g of desacetylupaserrin (**1e**), mp 135–136°, after recrystallization from EtOAc-hexane. Fractions 24–29 contained two substances which were separated by prep. TLC

(EtOAc-hexane, 3:1). The upper band (**1a**) was recrystallized from CHCl_3 -MeOH, yield 50 mg, mp 184–185°, identical with authentic material. The lower band, yield 50 mg, which could not be induced to crystallize, was identical with authentic **1f** [1].

Fractions 30–32 contained one major compound (**3a**) which was purified by prep. TLC, but could not be induced to crystallize, yield 80 mg; IR bands at 3400 and 1770 cm^{-1} ; ^1H NMR and ^{13}C NMR signals in Tables 1 and 2. (Calc. for $\text{C}_{15}\text{H}_{22}\text{O}_4$: MW, 266.1517. Found: MW (MS), 266.1494 (4.4%).) Other significant peaks in the high resolution MS were at m/z (composition, rel. int.) 248 ($\text{C}_{15}\text{H}_{20}\text{O}_3$, 11.3), 247 ($\text{C}_{15}\text{H}_{19}\text{O}_3$, 9.8), 230 ($\text{C}_{13}\text{H}_{18}\text{O}_2$, 4.6), 221 ($\text{C}_{13}\text{H}_{17}\text{O}_3$, 6.7), 218 ($\text{C}_{14}\text{H}_{18}\text{O}_2$, 4.7), 217 ($\text{C}_{14}\text{H}_{17}\text{O}_2$, 3.7), 175 ($\text{C}_{13}\text{H}_{15}\text{O}$, 16.9), 166 ($\text{C}_{10}\text{H}_{14}\text{O}_2$, 10.4), 151 ($\text{C}_9\text{H}_{11}\text{O}_2$, 28.2), 149 ($\text{C}_{10}\text{H}_{13}\text{O}$, 21.2), 124 ($\text{C}_8\text{H}_{12}\text{O}$, 39.3), 123 ($\text{C}_8\text{H}_{11}\text{O}$, 79.3), 122 ($\text{C}_8\text{H}_{10}\text{O}$, 35.4), 121 (C_9H_{13} , 45.4), 107 (C_8H_{11} , 71.8), 100 ($\text{C}_5\text{H}_8\text{O}_2$, 100). Acetylation of 20 mg of **3a** furnished 21 mg of gummy **3b** which had IR bands at 1770, 1740 and 1258 cm^{-1} . The ^1H NMR spectrum is listed in Table 1; MS m/z : 350 (M^+), 308, 290, 248, 230, 202, 93 and 84. Exposure of **3a** to aq. 15% KOH for 1 hr and subsequent acidification resulted in the recovery of unchanged starting material.

REFERENCES

†The solvent shift for **3a** falls between the values reported for the 11-epimeric dihydrolaurenobiolides [8, 9] but is considerably below the average value for sesquiterpene lactones with pseudoaxial methyl groups [7]. The negative value for **3b** seems unusual, but clearly points to pseudoequatorial orientation of the methyl group.

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