Phytochemistry, Vol. 26, No. 2, pp. 457–461, 1987.
Printed in Great Britain.

0031–9422/87 $3.00 + 0.00

MODIFIED HELENANOLIDES FROM *PSILOSTROPHE GNAPHALOIDES* AND *PSILOSTROPHE COOPERI*

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(*Received* 28 *May* 1986)

Key Word Index—*Psilostrophe gnaphaloides*; *Psilostrophe cooperi*; Compositae; Heliantheae; sesquiterpene lactones; modified helenanolides; flavones.

Abstract—Investigation of the aerial parts of *Psilostrophe gnaphaloides* and reinvestigation of *Psilostrophe cooperi* afforded in addition to known modified helenanolides several new representatives of this class, all closely related to hymenolide.

INTRODUCTION

Modified helenanolides of the type exemplified by psilotropin (floribundin, **1**) are characteristic secondary metabolites of certain *Hymenoxys* species (Compositae, tribe Heliantheae, subtribe Gaillardiinae) [1–5] and have also been found [6, 7] in the closely related genus *Psilostrophe* [8]. We now report isolation of several new representatives of this class from *Psilostrophe gnaphaloides* DC and *P. cooperi* (Gray) Greene.

RESULTS AND DISCUSSION

The chloroform extraction of *P. gnaphaloides* gave psilotropin (**1**) [1, 6], vermeerin (**2**) [1], hymenolide (**3a**) [1] and its previously unreported C-3 epimer **5a**, the mixture of epimeric hemiacetals which we have called [3] hymenovin (now shown to be mainly **3c** and **5b**), and the new hemiacetals **4a**, **6a** and **7a** as well as jaceidin (5,7,4′-trihydroxy-3,6,3′-trimethoxyflavone). Reinvestigation of *P. cooperi*, previously reported [6] to contain **1**, gave in addition **2**, **3a**, **5a** and the new hemiacetal **8a** as well as jaceidin, santin (5,7-dihydroxy-3,6,4′-trimethoxyflavone) [9] and vanillin.

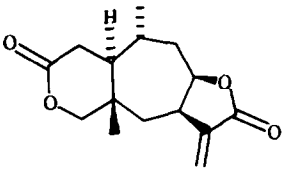
Hymenolide (**3a**) and **5a** were obtained as an inseparable mixture whose acetylation furnished only **3b**. Comparison of the ^{1}H NMR and ^{13}C NMR spectra of the mixture with those of authentic hymenolide (Tables 1 and 2) showed that the second component of the mixture was the C-3 epimer **5a**. Evidence for the different C-3 stereochemistry of the two components was provided by (a) the differing values of $J_{2a,b,3}$ and the chemical shift changes for the protons associated with the ethoxy group and (b) the diamagnetic shift of C-1 ($\Delta\delta$5.5) and the paramagnetic shift of C-3 ($\Delta\delta$2.4) of **5a** due to the α-orientated ethoxy group. These shift differences compare with the shift differences reported for 1α,3α- and 1α,3β-cholestanediol [10] which are analogously substituted in ring A.

Comparison of the ^{1}H NMR spectra of **3a** and **4a** and the corresponding acetates **3b** and **4b** (Table 1) showed that **4a** and **4b** had the stereochemistry of hymenolide. Confirmation was provided by the CD curve of **4b** which exhibited the expected negative Cotton effect at 253 nm and by NOE difference spectrometry; irradiation at the frequency of the H-4 signal (δ5.74) enhanced the signals of H-6a (δ1.44) and H-15 (δ1.02) by 16 and 9%, respectively. No NOE was observed for H-3. Comparison of the ^{13}C NMR spectra of **3a** and **4b** (Table 2) shows that the C-3 signal of **4b** displays the downfield shift ($\Delta\delta$6.6) associated with replacement of the hydroxyl on C-3 by an alkoxy group, whereas the C-4 signal is shifted upfield ($\Delta\delta$) due to exchange of an alkyl for an acyl residue. Hence **4a** carries the ethoxy group on C-3.

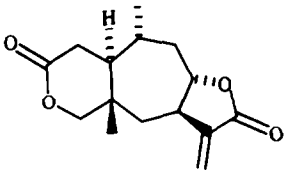
Another fraction was identical with hymenovin, the toxic principle of *Hymenoxys odorata* [3], *H. richardsonii* [4] and *Dugaldia hoopesii* [4], which we have shown to be a mixture of C-2 and/or C-4 epimeric hydrolysis products of hymenolide [3]. One of these (hymenoxon, **3c**) has been isolated in pure form from *H. odorata* [5], *Dugaldia hoopesii* [11, 12] and *D. integrifolia* [13]. Analysis of the ^{1}H NMR and ^{13}C NMR spectra of the mixture (see Experimental and Table 2) showed that the only epimers present in significant quantities were **3c** and **5b** (ratio *ca* 4:1). Evidence for the presence of a small amount of dialdehyde **9** was provided by two signals at δ9.82 and 9.68. Diagnostic for the stereochemistry of the two hemiacetals are the differences in the coupling constants involving H-2 and H-3 and, in the ^{13}C NMR spectra, the upfield shift of C-1 and the downfield shift of C-3 of **5b** associated with inversion of the stereochemistry of the ethoxy group.

Separation of the 4:1 mixture of **6a** and **7a** was effected through the acetates **6b** and **7b** whose structure and stereochemistry was established by NMR and CD spectrometry. Each compound exhibited the negative Cotton effect characteristic of a *cis*-lactone closed to C-8. In the case of **6b**, the shifts listed in Tables 1 and 2 showed that the ethoxy group was on C-3 and the coupling constants involving H-2 and H-3 showed that it was α-orientated. Evidence for the stereochemistry at C-4 was provided by the NOE data listed in Table 3.

Compound **7a** was an analogue of **4a** containing an additional α-orientated hydroxyl group on C-1. This was evident on comparing the ^{1}H NMR spectra of **4a** and **4b** with those of **7a** and **7b**, from the values of $J_{1,2}$ (10 Hz) and



1



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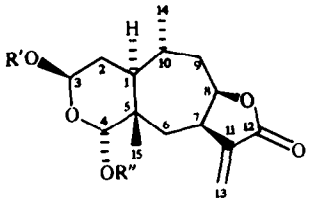
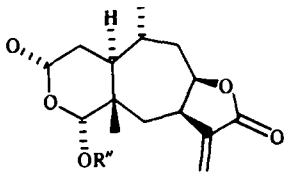
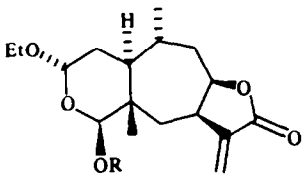


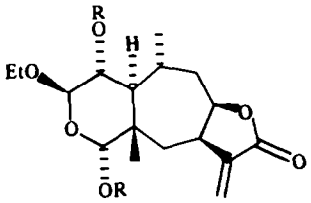
3a R' = H, R'' = Et
3b R' = Ac, R'' = Et
3c R', R'' = H
4a R' = Et, R'' = H
4b R' = Et, R'' = Ac



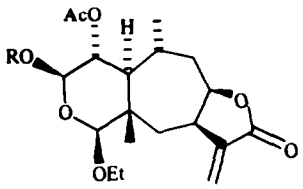
5a R' = H, R'' = Et
5b R, R'' = H



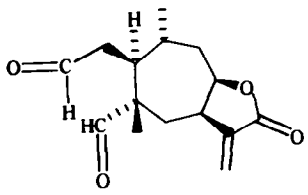
6a R = H
6b R = Ac



7a R = H
7b R = Ac



8a R = H
8b R = Ac



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$J_{2,3}$ (8 Hz) of **7b** and from the NOE data in Table 3. By contrast, in the only new compound from *P. cooperi*, the isomeric modified helenanolide **8a** which exhibited values of $J_{1,2}$ and $J_{2,3}$ identical with those of **7a**, the C-4 hydroxyl was α-orientated as shown by the NOE measurements (Table 3). Compounds **7b** and **8b** are stereoisomers of substances isolated from *P. villosa* [7].

The chemistry of the three *Psilostrophe* species investigated so far thus presents a rather uniform picture and also illustrates the close relationship to *Hymenoxys* posited previously on other grounds.

EXPERIMENTAL

Extraction of Psilostrophe gnaphaloides. Above ground parts of *P. gnaphaloides* DC, collected by Mr. J. Norris in May 1984, 13 miles south of Catavina, Baja California Norte, Mexico (voucher J. Norris 433 deposited in the herbarium of the University of Texas), wt 0.5 kg, were extracted with $CHCl_3$ and worked up in the usual fashion [14]. The crude gum (21 g) was absorbed on 40 g of silicic acid (Mallinckrodt, 100 mesh) and chromatographed over 500 g of the same adsorbent packed in hexane, 375 ml fractions being collected as follows: fr. 1–4 (hexane), 5–8 (hexane–EtOAc, 9:1), 9–12 (hexane–EtOAc, 4:1), 13–16 (hexane–EtOAc, 2:1), 17–20 (hexane–EtOAc, 1:1), 21–24 (hexane–EtOAc, 2:3), 25–28 (hexane–EtOAc, 1:4), 29–32 (EtOAc) and 33–36 (EtOAc–MeOH 9:1).

Rechromatography of fr. 11–13 (2.2 g) gave 170 mg of a 4:1 mixture of hymenolide (**3a**) and its C-3 epimer **5a**. ^{1}H NMR and ^{13}C NMR spectra are listed in Tables 1 and 2. Acetylation of 20 mg of the mixture (Ac_2O–pyridine) gave 19 mg of **3b**, ^{1}H NMR spectrum in Table 1. Column rechromatography (C_6H_6–EtOAc, 17:3) of fr. 14 and 15 (2.7 g) and TLC (C_6H_6–EtOAc, 9:1, two developments) of the first few fractions of the eluate gave 40 mg

Table 1. ^{1}H NMR spectra of compounds

	3a	5a*	3a†	5a*†	4a	4b	6a‡	6b	6b†	7a‡	7b	8a	8a‖	8b
H-1	1.66 *m*		1.42 *ddd* (11, 11, 3)		1.72 *m*	1.69 *m*		1.70 *m*	1.60 *m*		1.98 (10)	2.05 *t* (10)	1.87 *t*	2.12 *m*
H-2α	1.94 *ddd* (14, 3, 3)		1.74 *ddd*		1.90 *ddd*	1.93 *ddd*		1.8 *br dd* (13, 3)	1.51 *br dd*	—	—	—	—	—
H-4β	1.24 *m*		0.98 *ddd* (14, 11, 10)		1.34 *ddd* (12, 10, 10)	1.49 *ddd*		1.53 *ddd* (13, 13, 3.5)	1.09 *ddd*	4.03 *m*	5.10 *dd* (10, 8)	4.91 *dd*	4.88 *dd*	5.17 *dd*
H-3	5.07 *dd* (10, 3)	5.11 *br d* (3.5)	4.88 *dd* (10, 3)	5.02 *br d* (3.5)	5.02 *dd* (10, 3)	4.83 *dd*	4.89 *br d* (3.5)	4.90 *br d*	4.68 *br d*	4.52 *d* (7.5)	4.66 *d* (8)	4.83 *t* (8)	4.78 *t*	5.85 *d* (8)
H-4	4.23	4.22	4.03		4.72 *br*	5.74	4.73 *d* (3)	5.92	6.07	4.78 *br*	5.76	4.21	3.98	4.22
H-6a	1.47 *dd* (15, 3.5)		1.20 *dd*		1.63 *m*	1.44 *dd*		1.50 *dd*	1.29 *m*		1.39 *dd*	1.48 *dd*	1.28 *dd*	1.64 *dd*
H-6b	1.63 *dd* (15, 13)		1.38 *dd*		1.63 *m*	1.71 *dd*		1.68 *dd*	1.29 *m*		1.70 *dd*	1.63 *dd*	1.38 *dd*	1.64 *dd*
H-7	3.47 *m*		3.24 *m*		3.53 *m*	3.28 *m*	3.53 *m*	3.27 *m*	2.56 *m*	3.40 *m*	3.19 *m*	3.40 *m*	3.12 *m*	3.41 *m*
H-8	4.72 *ddd* (12, 9, 3.5)		4.37 *ddd*	4.41 *dd*	4.78 *ddd*	4.76 *ddd*	4.80 *ddd*	4.79 *ddd*	3.99 *ddd*	4.76 *ddd*	4.74 *ddd*	4.73 *ddd*	4.41 *ddd*	4.74 *ddd*
H-9a	1.83 *br dd* (14, 3.5)		1.65 *br dd*	1.64 *br dd*	1.83 *br dd*	1.87 *br dd*		1.87 *br dd*	1.47 *br dd*		1.85 *br dd*	1.82 *br dd*	1.62 *br dd*	1.82 *br dd*
H-9b	2.0 *m*		1.78 *m*		2.02 *m*	2.05 *m*		2.10 *m*	1.65 *m*		2.10 *m*	2.10 *m*	1.84 *m*	2.05 *m*
H-10	1.66 *m*		1.30 *m*		1.74 *m*	1.72 *m*		1.70 *m*	1.14 *m*		2.05 *m*	1.96 *m*	1.73 *m*	2.04 *m*
H-13a	6.20 *d* (2.2)	6.21 *d* (2.2)	6.17 *d*	6.17 *d*	6.21 *d*	6.23 *d*	6.24 *d* (2.5)	6.25 *d*	6.15 *d*	6.23 *d*	6.22 *d*	6.21 *d* (2)	6.18 *d*	6.22 *d*
H-13b	5.49 *d* (2)	5.49 *d* (2)	5.28 *d*	5.26 *d*	5.59 *d* (1.9)	5.41 *d*	5.46 *d*	5.53 *d*	5.03 *d*	5.61 *d*	5.40 *d*	5.53 *d* (2)	5.31 *d*	5.53 *d*
H-14§	1.08 *d* (7)		0.79 *d*	0.83 *d*	1.08 *d*	1.18 *d*	1.07 *d*	1.10 *d*	0.63 *d*	1.04 *d*	1.18 *d*	1.16 *d*	0.97 *d*	1.12 *d*
H-14§	1.01	0.98	0.81	0.73	1.02	1.11	0.98	1.02	0.85	0.95	1.22	1.16	0.96	1.17
OEt	3.83 *dq* (10, 7)	4.02 *dq* (10, 7)	3.68 *dq*	3.88 *dq*	3.85 *dq*	3.86 *dq*	3.93 *dq*	3.91 *dq*	4.11 *dq*	3.78 *dq*	3.79 *dq*	3.90 *dq*	3.74 *dq*	4.01 *dq*
	3.49 *dq* (10, 7)	3.58 *dq* (10, 7)	3.30 *dq*	3.30 *dq*	3.50 *dq*	3.46 *dq*	3.52 *dq*	3.50 *dq*	3.39 *dq*	3.52 *dq*	3.47 *dq*	3.55 *dq*	3.32 *dq*	3.54 *dq*
	1.22 *t* (7)§	1.22 *t* (7)§	1.09 *t*§	1.06 *t*§	1.24 *t*§	1.20 *t*§	1.22 *t*§	1.24 *t*§	1.20 *t*§	1.22 *t*§	1.19 *t*§	1.28 *t*	1.11 *t*	1.30 *t*
OH	3.20 *br*		3.08 *br*		2.96 *br*	—	2.65 d (3)	—	—	—	—	3.12 *d* (8)	2.94 *d*	—
OAc§						2.15		2.15	1.65		2.20 2.07	2.10	1.92	2.07 2.04

*From mixture with **3a**.
† In C_6D_6.
‡From mixture of **6a** and **7a**.
§Intensity three protons.

Table 2. ^{13}C NMR spectra of compounds **3a**, **3c**, **4b**, **5a**, **5b**, **6b** (67.89 MHz, $CDCl_3$)

	3a	**3c***	**4b**	**5a†**	**5b***	**6b**
C-1	38.3 *d*	37.6 *d*	38.7 *d*	32.8 *d*	32.1 *d*	39.6 *d*
C-2	41.6 *t*	41.5 *t*	40.5 *t*	42.3 *t*	42.1 *t*	38.7 *t*
C-3	90.8 *t*	90.7 *d*	97.4 *d*	93.2 *d*	93.1 *d*	97.2 *d*
C-4	107.6 *d*	102.0 *d*	100.6 *d*	107.4 *d*	102.0 *d*	91.5 *d*
C-5	37.8 *s*	37.9 *s*	37.8 *s*	36.8 *s*	36.6 *s*	39.1 *s*
C-6	34.2 *t*	33.9 *t*	31.8 *t*	33.1 *t*	32.4 *t*	31.0 *t*
C-7	38.8 *d*	38.6 *t*	38.6 *d*	38.3 *d*	38.6 *d*	37.7 *d*
C-8	76.7 *d*	76.9 *d*	76.2 *d*	76.7 *d*	76.9 *d*	76.3 *d*
C-9	34.9 *t*	34.9 *t*	34.8 *t*	35.0 *t*	35.1 *t*	35.2 *t*
C-10	30.4 *d*	30.3 *d*	30.5 *d*	30.7 *d*	30.3 *d*	30.3 *d*
C-11	140.4 *s*	140.6 *s*	140.1 *s*	140.8 *s*	140.5 *s*	139.9 *s*
C-12	170.0 *s*	170.3 *s*	169.3 *s*	170.1 *s*	170.3 *s*	169.5 *s*
C-13	122.2 *t*	122.6 *t*	122.5 *t*	122.2 *t*	122.8 *t*	123.0 *t*
C-14	20.0 *q*	20.1 *q*	20.1 *q*	20.0 *q*	20.1 *q*	20.7 *q*
C-15	20.0 *q*	20.1 *q*	20.1 *q*	19.6 *q*	19.6 *q*	13.8 *q*
OEt	63.5 *t*		64.5 *t*	64.9 *q*		63.0 *t*
	15.1 *q*		15.0 *q*	15.1 *q*		14.9 *q*
OAc			170.3 *s*			170.1 *s*
			21.0 *q*			21.0 *q*

*From mixture.
†From mixture with **3a**.

Table 3. NOE difference spectra of compounds **6b**, **7b** and **8b**

Irradiated	Observed **6b**	**7b**	**8b**
H-3	$-OC\underline{H}_2CH_3$ at δ3.39 (16)	$-OC\underline{H}_2CH_3$ at δ3.47 (14)	H-1 (8)
	None for H-4	None for H-4	H-4 (5)
		H-1 (16)	
H-4	H-1 (20)	H-6 at δ1.39 (12)	H-1 (4)
	H-6 at δ1.50 (14)	H-15 (17)	H-3 (5)
	H-7 (7)	None for H-3	H-6 at δ1.47 (7)
	$-OCH_2C\underline{H}_3$ (8)		H-7 (6)
	None for H-3		$-OC\underline{H}_2CH_3$ at δ3.54 (15)
H-15	H-2β (13)		
	H-6β (30)		
	H-9β (7)		
	H-10 (15)		
	OAc (11)		

of jaceidin. The later fractions furnished 80 mg of vermeerin (**2**). Column chromatography (C_6H_6–EtOAc, 4:1) of fr. 17 (1 g) gave 80 mg of psilotropin (floribundin) (**1**).

Rechromatography (C_6H_6–EtOAc, 4:1) of fr. 18 and 19 gave two fractions. Radial chromatography (hexane–Et_2O 3:2) of fr. 1 gave 80 mg of somewhat impure gummy **4a** (^1H NMR spectrum in Table 1) which was converted to the non-crystalline acetate **4b** (70 mg), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1745; CD curve (MeOH) $[\theta]_{253}$ −3050 (min), $[\theta]_{233}$ 0, $[\theta]_{210}$ + 20000 (last reading); ^1H NMR and ^{13}C NMR spectra in Tables 1 and 2. The positive CIMS exhibited peaks at *m/z* (rel. int.): 353 (M^+ + H, 100), 307 (5), 293 (71), 265 (4), 247 (2), 219 (2), 192 (2). The second fraction was an inseparable mixture of **6a** and **7a** (^1H NMR spectra in Table 1). Acetylation of 130 mg of the mixture and CC of the crude product (hexane–Et_2O, 7:3) gave 90 mg of **6b** and 15 mg of **7b**. Compound **6b** was an amorphous solid, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1750; CD curve (MeOH) $[\theta]_{253}$ −3580, $[\theta]_{233}$ = 0; $[\theta]_{215}$ + 18700; ^1H NMR and ^{13}C NMR spectra in Tables 1 and 2. The positive CIMS exhibited peaks at *m/z* (rel. int.): 353 (M^+ + H, 100), 307 (5–8), 293 (66), 265 (4), 247 (2), 219 (1), 192 (2). Compound **7b** was a gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1750, 1745; CD curve (MeOH) $[\theta]_{308}$ + 140, $[\theta]_{292}$ 0, $[\theta]_{253}$ −3420; $[\theta]_{232}$ 0, $[\theta]_{215}$ + 17600; ^1H NMR and ^{13}C NMR spectra in Tables 1 and 2; MS (pos. CI) *m/z* (rel. int.): 411 (M^+ + H, 100), 367 (41), 365 (30), 351 (75), 311 (9), 307 (25), 293 (7), 291 (6), 265 (10), 247 (4).

Fractions 20–21 (2.4 g) on CC (hexane–EtOAc, 1:1) gave 1 g of a gum whose ^1H NMR spectrum showed it to be a mixture of the

various hymenovin epimers. The main constituents were hymenoxon (**3c**) and its C-3 epimer **5b**; the former exhibited ^{1}H NMR peaks at δ6.24 (*d*, J = 2.2 Hz) and 5.56 (*d*, J = 2 Hz, H-13a, b), 5.27 (*dd*, J = 8.5, 3.5 Hz, H-3), 4.76 (*m*, H-8), 4.72 (*br s*, H-4), 3.52 (*m*, H-7), 1.10 (*d*, J = 7 Hz, H-14) and 1.04 (H-15); the latter had peaks at δ6.23 (*d*, J = 2.2 Hz) and 5.60 *d*, J = 2 Hz, 13a, b), 5.33 (*br d*, J = 3.5 Hz, H-3), 4.73 (*m*, H-8), 4.72 (*br*, H-4) 3.52 (*m*, H-7) 1.10 (*d*, J = 7 Hz, H-14) and 0.99 (H-15). The ^{13}C NMR spectra are listed in Table 2.

Extraction of Psilostrophe cooperi. Above ground parts of *P. cooperi* (Gray) Greene, collected by Mr. R. J. Barr on May 7, 1963 at the intersection of the Spanish Trail and Harrison Road, Tucson, Pima Co., Arizona (Barr voucher 63181 on deposit in herbarium of Florida State University), wt 1.7 kg, was extracted with $CHCl_3$ and worked up in the usual fashion. The crude gum (18 g) was adsorbed on 30 g of silicic acid and chromatographed over 300 g of the same adsorbent packed in hexane, 250 ml fractions being collected as follows; 1–4 (hexane), 5–8 (hexane–EtOAc, 3:1), 9–12 (hexane–EtOAc, 4:1), 13–16 (hexane–EtOAc, 2:1), 17–20 (hexane–EtOAc, 1:1), 21–24 (hexane–EtOAc, 2:3), 25–28 (hexane–EtOAc, 1:4), 29–32 (EtOAc), 33–36 (EtOAc–MeOH, 9:1).

Fraction 9 (200 mg) on column rechromatography (C_6H_6–EtOAc, 17:3) gave 15 mg of vanillin and 20 mg of santin, mp 161°, lit. mp 164–166° [9], identified by MS and comparison of the ^{1}H NMR spectrum with that reported in lit. [9]. Fraction 11 (1.2 g) on rechromatography (C_6H_6–EtOAc, 4:1) gave 0.8 g of the 4:1 mixture of **3a** and **5a**. Fraction 12 (0.5 g) on rechromatography (hexane–Et_2O, 3:2) gave 15 mg of slightly impure **8a**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1760, 1740; CD curve (MeOH) θ_{310} + 200 (max), $[\theta]_{290}$ 0, $[\theta]_{253}$ − 3630 (min), $[\theta]_{233}$ 0, $[\theta]_{214}$ + 21 700 (last reading); ^{1}H NMR spectrum in Table 1; positive CIMS *m/z* (rel. int.): 369 (M^+ + H, 100), 351 (59), 323 (21), 311 (68), 296 (36), 293 (13), 265 (25), 263 (14), 197 (36). Acetylation of 8 mg of **8a** (Ac_2O–pyridine) furnished 5 mg of gummy **8b**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1750, 1735; ^{1}H NMR spectrum in Table 1. Rechromatography of fr. 13 (4 g) (hexane–Et_2O, 3:7) furnished 0.1 g of jaceidin, 0.2 g of vermeerin and 1.5 g of psilotropin. Rechromatography of fr. 14 (1.1 g) gave another 1 g of psilotropin.

Acknowledgements—We thank Mr. J. Norris and Prof. B. S. Turner, University of Texas at Austin, for providing the *P. gnaphaloides* collection.

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