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Spectral Assignments and Reference Data

^{1}H and ^{13}C NMR signal assignment of synthetic (-)-methyl thyrsiflorin B acetate, (-)-thyrsiflorin C and several scopadulane derivatives

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The ^{1}H and ^{13}C NMR signal assignment of the data of 13 scopadulane-type diterpenes is reported. It was based on one- and two- dimensional NMR techniques which included ^{1}H, ^{13}C, DEPT, HMQC and 1D NOE difference spectroscopy. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: ^{1}H NMR; ^{13}C NMR; scopadulcic acid derivatives; scopadulane terpenoids

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INTRODUCTION

Scopadulane diterpenes are a small group of structurally unique tetracyclic terpenoids isolated from medicinal plants of the Scrophulariaceae family. They were found for the first time in the plant *Scoparia dulcis* L. from Paraguay and later in different *Calceolaria* species from Chile.[1] These compounds and some derivatives have shown a broad range of bioactivities.[2]

In the course of our synthetic studies for the preparation of C7-functionalized scopadulane diterpenes, we reported the synthesis of the methyl ester of the natural (-)-thyrsiflorin B acetate (**8**) and also thyrsiflorin C (**9**).[3] More recently, we have synthesized several C6- and C7-functionalized scopadulane derivatives for their biological evaluation as antivirals.[4] During these syntheses, we have prepared a number of intermediates which have been characterized by NMR and physical data. We have realized that some NMR signal assignments found in the literature for **8** and **9** lack proof by 2D NMR correlation data and are different to our findings. Therefore, we describe in this paper the ^{1}H and ^{13}C NMR signal assignments based on 1D and 2D NMR techniques for the natural products **8** and **9**, and 11 structurally related scopadulane derivatives.

RESULTS AND DISCUSSION

The chemical structures and the numbering system of **1**–**13** are presented in Fig. 1. All compounds are based on the scopadulane carbon framework and are distinguished by their substitution pattern in the positions C-6, C-7, C-8, C-13, and C-14. For example, **1**–**4** present a double bond between C-8 and C-14 with modifications of oxygenation grade at positions C-6 and C-7. Compounds **5**–**11** only differ in the oxygenation pattern of positions C-7 and C-13 while compounds **12** and **13** differ only in the orientation of the

Table 1. ^{13}C NMR chemical shifts (δ, ppm) of 1–13

Carbon	1	2	3[c]	4[c]	5[c]	6	7[c]	8[c,d]	9	10	11[c]	12	13
1	32.82	32.89	31.21	30.82	32.33	32.27	32.11	32.25	32.45	32.22[a]	32.25	33.56	34.99
2	18.32	18.08	18.25	18.12	18.59	18.61	18.63	18.58	18.68	18.67	18.61	18.68	18.86
3	41.86	41.51	41.06	40.99	41.84	41.88	41.96	41.89	41.95	41.96	41.92	43.94	44.61
4	33.10	33.33	32.80	33.22	33.08	33.47	33.17	33.14	33.05	33.08	33.14	33.26	34.18
5	42.46	43.97	50.00	48.66	46.34	45.85	45.92	45.87	46.11	46.14	45.89	53.36	51.26
6	29.59[a]	37.03	127.25	56.15	32.02	27.94	28.05	27.98	31.85	32.11[a]	28.01	70.12	67.80
7	72.71	200.09	138.42	53.28	73.91	76.28[a]	76.58	75.97	73.80	74.20[b]	76.04	41.37	39.25
8	163.23	157.98	163.03	162.23	47.34	41.99	38.30	41.80	45.18	41.44	41.80	37.02	32.69
9	58.18	57.43	56.57	56.31	52.46	53.10	53.99	53.20	53.04	53.91	53.24	51.79	52.50
10	37.32	36.59	38.14	37.86	38.81	38.34	38.56	38.40	38.53	38.70	38.41	40.01	38.77
11	44.92	44.87	43.06	44.69	45.19	44.49	37.68	44.48	44.58	37.73	44.50	44.32	44.48
12	50.73	52.22	50.98	51.18	53.62	44.10	43.73	43.13	44.14	43.74	43.04	44.32	43.86
13	204.89	204.53	205.28	203.95	213.77	76.00[a]	74.49	79.31	76.22	74.65[b]	77.83	76.16	76.22
14	130.30	128.32	122.54	131.00	40.13	30.58[b]	33.10	30.30	30.66[a]	33.48	30.50	37.59	37.57
15	33.85	31.63[a]	33.11	33.82	36.73	33.99[b]	36.27	31.87	34.28[a]	36.34	31.94	30.50	30.51
16	29.69[a]	31.24[a]	29.14	30.05	25.57	25.83	24.24	25.82	25.97	24.32	25.85	24.75	23.86
17	20.11	19.54	20.34	20.33	19.69	23.08	23.85	22.90	23.13	23.91	23.03	23.26	23.23
18	33.40	32.62	33.05	32.87	33.50	33.12	33.51	33.47	33.50	33.52	33.48	36.95	33.85
19	22.44	21.50[b]	22.71	22.66	21.91	21.94	22.04	21.93	22.01	22.10	21.94	22.53	21.30
20	21.16	20.08[b]	18.40	20.10	17.47	17.49	17.71	17.50	17.58	17.80	17.50	18.59	25.15
R_1, R_2	133.01; 129.80	–	–	–	–	170.86; 21.30	171.07; 21.34	170.95; 21.34	–	–	170.99; 170.97	–	–
	129.53; 128.52	–	–	–	–				–	–	21.34; 21.23	–	–

[a,b] Signals may be interchanged.
[c] Signal assignments based on HMQC experiments.
[d] Additional side-chain ester ^{13}C signals in **8** at δ 167.04 ppm (s), 166.23 ppm (s), 52.37 ppm (q) and 41.64 ppm (t).

Spectral Assignments and Reference Data

Table 2. ^{1}H NMR chemical shifts (δ, ppm) of 1–13

	1	2	3[c]	4[c]	5[c]	6	7[c]	8[c]	9	10	11[c]	12	13
H-1	1.50–1.60	1.50–1.60	~1.48	1.38	~1.47	~1.40	1.32–1.50	~1.40	~1.40	1.40	~1.41	~1.40	~1.40
H-2	1.50–1.70	1.50–1.65	1.50–1.75	1.54–1.75	1.30–1.55	1.30–1.60	1.38–1.60	1.34–1.61	1.30–1.60	1.30–1.60	1.30–1.52	1.30–1.60	1.30–1.60
H-3α	~1.20	~1.15	1.22	1.17	1.11	1.12	1.10	1.10	~1.10	~1.08	~1.10	– [d]	– [d]
H-3β	1.50–1.60	1.50–1.60	~1.50	~1.53	~1.41	~1.40	1.40	1.40	– [d]	– [d]	1.38	– [d]	– [d]
H-5	~1.25	~1.25	2.04	1.50	1.06	~1.01	1.03	1.02	~1.00	– [d]	1.04	– [d]	– [d]
H-6α	–	2.62	–	–	1.87	1.80–1.90	1.85	~1.85	– [d]	– [d]	~1.83	–	4.30
H-6β	1.90–2	2.51	6.23	3.38	~1.35	– [d]	~1.37	~1.33	– [d]	– [d]	~1.34	3.90	–
H-7α	–	–	–	–	3.53	4.68	4.67	4.71	3.41	3.36	4.72	– [d]	– [d]
H-7β	5.98	–	6.18	3.58	–	–	–	–	–	–	–	– [d]	– [d]
H-8	–	–	–	–	1.99	1.90	2.08	1.95	– [d]	– [d]	1.95	2.20	– [d]
H-11α	– [d]	1.70	1.76	1.52	1.69	1.46	1.54	1.52	1.42	– [d]	1.51	– [d]	– [d]
H-11β	~1.64	~1.80	1.58	1.71	1.40	– [d]	1.12	1.08	– [d]	– [d]	~1.06	– [d]	– [d]
H-13	–	–	–	–	–	3.35	3.43	4.67	3.38	3.48	4.60	3.40	3.42
H-14α	–	–	–	–	2.11	– [d]	~1.40	~1.12	– [d]	– [d]	~1.10	– [d]	– [d]
H-14β	6.14	6.64	5.68	6.27	2.72	~2.03	1.74	2.10	2.31	2.04	2.07	– [d]	– [d]
H-15	– [d]	– [d]	~1.68	~1.70	1.56–1.75	– [d]	~1.42	~1.20, 1.80	– [d]	– [d]	~1.20, 1.84	– [d]	– [d]
H-16	2.30	2.35	2.20	2.06	~2.01	– [d]	~1.73	~1.83	~1.80	~1.80	~1.79	– [d]	– [d]
H-16′	– [d]	– [d]	1.40	1.70	~1.67	– [d]	~1.42	~1.43	– [d]	– [d]	~1.42	– [d]	– [d]
H-17	1.19	1.24	1.22	1.20	1.04	0.99	1.01	0.94	0.99[a]	1.02[a]	0.92	1.01[a]	1.02
H-18	0.93	0.96	1.00	1.11	0.85	0.81[a]	0.84	0.83	0.82[b]	0.82	0.84	1.12	0.94
H-19	0.89	0.89	0.95	1.08	0.83	0.79[a]	0.83	0.81	0.81[b]	0.82	0.82	0.97	1.23[a]
H-20	1.00	1.00	0.95	1.02	1.00	0.99	1.06	1.02	0.97[a]	0.99[a]	1.02	1.03[a]	1.30[a]
R_1,R_2	7.40–8.00	–	–	–	–	2.02	2.05	2.04, 3.74, 3.36	–	–	2.03, 2.04	–	–

[a,b] Signals may be interchanged.
[c] Signal assignments based on HMQC experiments.
[d] Signal not assigned.

Table 3. Selected ^{1}H NMR signals of 1–13: multiplicities and coupling constants (J, Hz)

	1	2	3[a]	4[a]	5[a]	6	7[a]	8[a]	9	10	11[a]	12	13
H-5	–	–	dd; 2.5, 1.5	br s	dd; 12, 2.5	–	dd; 12.5, 2.5	dd; 12.5, 2.5	–	–	dd; 12, 2.5	–	–
H-6α	–	dd; 19, 7	–	–	ddd; 12.5, 5.5, 2.5	–	ddd; 12.5, 5.5, 2.5	–	–	–	–	–	br s; $W_{h/2} = 8$
H-6β	–	dd; 19, 12.5	dd; 10, 2.5	dd; 4, 2.5	–	–	–	–	–	–	–	ddd; 11, 10.5, 5.5	–
H-7α	–	–	dd; 10, 1.5	–	ddd; 11, 10.5, 5.5	ddd; 11, 10.5, 5.5	ddd; 11, 11, 5.5	ddd; 11, 11, 5.5	ddd; 11, 9, 5.5	ddd; 11, 10, 5.5	ddd; 11, 10.5, 5.5	–	–
H-7β	dd; 3, 3	–	–	d;4	–	–	–	–	–	–	–	–	–
H-8	–	–	–	–	–	–	ddd; 11, 11, 5	ddd; 11, 11, 5	–	–	ddd; 11.5, 10.5, 5	–	–
H-11α	–	d; 11.5	d; 11.5	d; 11.5	d; 12	d; 12	br d; 11.5	d; 11	d;11.5	–	d; 11.5	–	–
H-11β	–	–	br d; 11.5	br d; 11.5	br d; 12	–	br d; 11.5	br d; 11	–	–	–	–	–
H-13	–	–	–	–	–	dd; 10, 6	br s; $W_{h/2} = 8$	dd; 10.5, 6	dd; 10.5, 6	br s; $W_{h/2} = 8$	ddd; 10.5, 6, 1	dd; 10.5, 5.5	dd; 10, 6.5
H-14α	br s	s	s	s	dd; 15.5, 11.5	–	–	–	–	–	–	–	–
H-14β	–	–	–	–	dd; 15.5, 6	–	ddd; 15, 5, 2	ddd; 13, 6, 5	ddd; 13, 6, 5	ddd; 14, 5, 2	ddd; 13, 6, 5	–	–
H-16	ddd; 12.5, 10, 7	ddd; 12.5, 12.5, 7	ddd; 12.5, 10, 6.5	–	–	–	–	–	–	–	–	–	–

[a] Signal assignments based on HMQC experiments.

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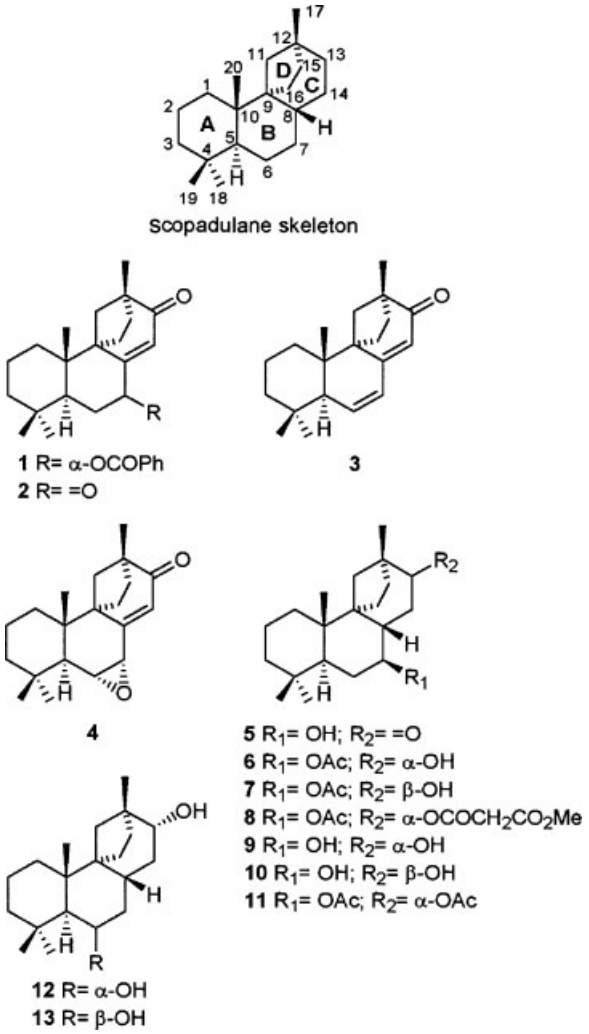

Figure 1. Structures and numbering of the compounds investigated.

C-6 hydroxy group. Signal assignments of ^{13}C NMR chemical shifts are listed in Table 1. The ^{1}H NMR chemical shifts are presented in Table 2; multiplicities and coupling constants of the most relevant ^{1}H NMR signals are shown in Table 3. The obvious assignments were deduced from the corresponding ^{1}H NMR, ^{13}C NMR and DEPT spectra according to their chemical shifts and multiplicities. The remaining signals were assigned with the aid of double resonance experiments, one-bond heteronuclear (^{1}H,^{13}C) multiple quantum correlation (HMQC) spectra, some 1D NOE difference experiments, and by comparison with literature data.[5]

The stereochemistry of the substituents located at positions C-6, C-7 and C-13 (**1**, **6**–**13**) can be deduced from the coupling constant of the corresponding proton. For example, proton H-6 in **12** presents coupling constants (J = 11, 10.5 and 5.5 Hz) in agreement with an axial disposition (α) of this proton, whereas in **13** that proton signal appears as a broad singlet with a $W_{1/2}$ of 8 Hz indicating an equatorial orientation (β). In a similar manner, the stereochemistry of the protons H-7 and/or H-13 can be deduced in **1** and **6**–**11**. The stereochemistry of the epoxide in **4** was assigned by NOE difference experiments, in particular, irradiation of the C-20 methyl signal gave NOE enhancements of the H-6, H-7 and H-19 signals, thereby confirming the α-orientation of the oxirane ring. From the ^{13}C NMR data, we can observe a γ-effect on C-8 when there is an axial substituent on C-6 or C-13. For example, the signal due to C-8 in **7** and **10** is upfield (about 3.7 ppm to lower frequency) with respect to **6** and **9** respectively.

The ^{1}H NMR and ^{13}C NMR data of the synthetic derivatives **8** and **9** were similar to those reported for the methyl ester of thyrsiflorin B acetate and thyrsiflorin C respectively.[1d,e] However, our ^{1}H NMR data of **8**, specially the HMQC spectrum and NOE difference experiments, indicated that the assignments of H-17 and H-20 as well as some ^{13}C signal assignments had to be reversed. We believe that this contribution could be useful as a reference for the assignment and characterization of similar compounds.

EXPERIMENTAL

Compounds

All the compounds were prepared as described previously.[3,4]

NMR spectroscopy

All NMR experiments **1**–**13** dissolved in $CDCl_3$ were performed with Varian XL-300 and Varian 400 spectrometers operating at a proton frequency of 299.95 MHz and 399.95 MHz respectively. Detailed experimental parameters have been presented previously.[5]

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