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Spectral Assignments and Reference Data

Assignment of ^{1}H and ^{13}C NMR data for (−)-methyl thyrsiflorin A and some scopadulan precursors

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The ^{1}H and ^{13}C NMR spectral analysis of synthetic (−)-methylthyrsiflorin A and 10 scopadulan precursors is reported. Resonance assignments were based on one- and two-dimensional NMR techniques, which included ^{1}H, ^{13}C, DEPT and HMQC and also 1D NOE difference spectroscopy. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; scopadulan diterpenes; scopadulan precursors

INTRODUCTION

A number of structurally unique tetracyclic terpenoids have been isolated from the medicinal plants *Scoparia dulcis* L. and *Calceolaria thyrsiflora* (both belonging to the Scrophulariaceae family).[1] These compounds and some semisynthetic analogues have been shown to be potentially useful for treating disorders such as peptic ulcers, osteoporosis, cancer and some viral infections.[2]

We recently reported the first diastereoselective synthesis of the methyl ester of the scopadulan diterpene (−)-methylthyrsiflorin A (**11**).[3] During this synthesis, we prepared several intermediates whose structures were confirmed by both NMR spectroscopy and physical data. Among these scopadulan precursors, we noted that several tricyclic intermediates possessing a podocarpene skeleton can exist in two different conformations. A complete conformational study using their ^{1}H NMR data together with molecular mechanics calculations was published separately.[4]

In this paper, we report the ^{1}H and ^{13}C NMR chemical shift assignments obtained from one- and two-dimensional NMR techniques for synthetic **11** and the rest of the scopadulan intermediates (**1**–**10**) of our synthesis. The ^{13}C NMR data for synthetic **11** were identical with those previously reported, whereas the ^{1}H NMR, HMQC and 1D NOE difference data showed that the assignments of protons H-17 and H-20 were reversed in the literature.[1d]

RESULTS AND DISCUSSION

The structures and numbering system for compounds **1**–**11** are presented in Fig. 1. Assignments of ^{1}H and ^{13}C NMR chemical shifts for **1**–**11** are listed in Tables 1 and 3, respectively, and the multiplicity and coupling constants of some characteristic ^{1}H NMR signals are shown in Table 2. The obvious signal assignments were made from ^{1}H and ^{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, and some 1D NOE difference experiments (NOED). When it is indicated, the α and β orientations of protons H-6, H-7, H-11 and H-14 were determined unequivocally by NOED experiments.

From the ^{1}H NMR data, it is interesting to note the chemical shift of proton H-5 in **4**–**6** (0.65–0.77 ppm). The high shielding of this proton may be attributed to the magnetic anisotropy induced by the cyclopropane ring between C-8 and C-9.

From the ^{13}C NMR data, the γ-effect observed between C-1 and C-16 in **7**–**11** is also of interest. This effect is transmitted through proton H-1α, so the distance between this proton and C-16 determines the intensity of the effect, the greatest effect being with the shortest distance. Therefore, the signal due to C-1 in **7**–**11** is upfield (about 3–5 ppm to lower frequency) with respect to **1**–**6** with longer distances between H-1α and C-16, where the latter exists. The ^{13}C NMR spectral data for synthetic **11** were found to be identical with those reported for the methyl ester of the natural (−)-methylthyrsiflorin A,[1d] whereas the HMQC spectrum and NOED experiments indicated that the assignments of protons H-17 and H-20 were originally reversed. In particular, the NOE enhancement of the signal located at 0.92 ppm when proton H-13 was irradiated proved that this signal was due to protons H-17.

Using our synthetic route for the synthesis of **11**, we prepared several intermediates with no precedents in the literature, in particular **4**–**6** which have a novel pentacyclic carbon framework. We think that the ^{1}H and ^{13}C NMR data of these compounds will be useful as reference data for the assignment and characterization of similar compounds.

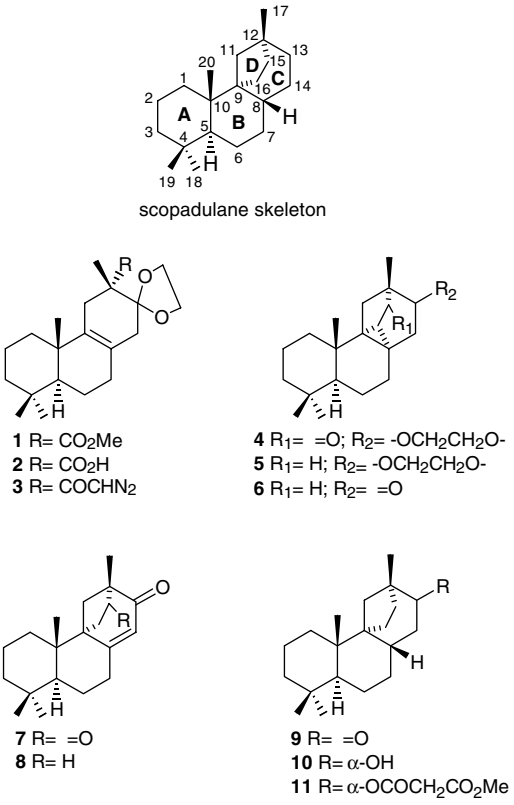

Figure 1. Structures and numbering of the compounds investigated.

EXPERIMENTAL

Compounds

All the compounds were prepared as reported previously.[4]

Spectra

^{1}H, ^{13}C NMR and DEPT spectra were measured on a Varian XL-300 spectrometer (299.95 MHz for ^{1}H and 75.43 MHz for ^{13}C) operating at a probe temperature of 298 K using a dual $^{1}H/^{13}C$ 5 mm probe. The ^{1}H measurement conditions were spectral width 4000 Hz, 90° pulse with 18 μs, acquisition time 3.7 s, number of transients 16–64 and 0.1 Hz digital resolution.

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Spectral Assignments and Reference Data

Table 1. ^{1}H NMR chemical shifts (δ, ppm) for compounds **1–11**

Proton	1	2	3	4	5	6	7	8	9	10	11[a]
1α	1.19	~1.19	—[c]	1.00	1.05	1.14	1.33	1.50	~1.47	1.30–1.50	~1.40
1β	1.78	1.76	1.80	1.69	1.77	1.82	1.52				
2α	~1.45	1.40–1.50	—[c]	1.38–1.50	1.20–1.28	1.52	1.51	1.50	~1.30–1.55	1.36–1.64	1.40–1.60
2β	1.58	1.58	1.55		1.54	1.56					
3α	~1.15	1.16	—[c]	1.06	1.12	1.15	1.16	1.18	1.14	1.09	~1.08
3β	~1.40	1.35–1.45	—[c]	1.38	1.40	1.43	1.47	1.46	~1.40	~1.37	~1.36
5	1.26	1.23	~1.25	0.65	0.70	0.77	1.14	1.26	1.00	0.90	0.88
6α	~1.65	~1.68	—[c]	1.25–1.40	1.20–1.28[b]	1.27–1.36	1.69	1.64[b]	~1.56[b]	~1.51[b]	~1.48
6β	1.42	1.38–1.46	—[c]		1.32–1.44[b]		1.55	~1.55[b]	~1.32[b]	~1.20[b]	1.30
7α	1.80–1.95	1.84–1.94	—[c]	1.65–1.83	1.35–1.75	1.64–1.76	2.39	2.48	1.60[b]	~1.50[b]	~1.50[b]
7β			—[c]				2.64	2.59	~1.26[b]	~1.26[b]	~1.13[b]
8	—	—	—	—	—	—	—	—	2.12	1.80	1.84
11α	2.81	2.66	2.76	1.68	1.41	1.65[b]	1.94	1.54	1.70[b]	1.46[b]	1.50[b]
11β	2.02	2.16	~1.90	2.11	1.78	1.79[b]	2.30	1.63	1.39[b]	0.95[b]	1.03[b]
13	—	—	—	—	—	—	—	—	—	3.38	4.66
14α	2.02	2.10	2.00	2.04[b]	1.92[b]	2.45	5.76	5.74	1.96	~0.91[b]	~1.00
14β	2.15		2.10	2.28[b]	1.99[b]		—	—	2.23	1.82[b]	1.90
15	—	—	—	—	1.36	1.77	—	1.64	~1.56	~1.19	~1.18
15′	—	—	—	—	1.96		—	1.71	~1.74	~1.73	~1.73
16	3.68	—	5.78	1.80	0.98	1.22	2.22	2.19	2.02	~1.38	~1.41
16′	—	—	—	—	—	—	2.61	1.44	~1.72	~1.73	~1.73
17	1.21	1.25	1.16	0.90	0.88	1.02	1.20	1.18	1.05	1.00	0.92
18	0.87	0.87	0.88	0.79	0.80	0.83	0.92	0.92	0.85	0.82	0.81
19	0.83	0.83	0.84	0.81	0.81	0.83	0.91	0.90	0.82	0.80	0.80
20	0.93	0.94	0.94	1.07	1.05	1.08	1.00	0.95	1.00	0.97	0.96
Ketal	3.75–4.00	4.07	3.80–4.00	3.68–4.00	3.75–3.92	—	—	—	—	—	—

[a] Additional side-chain ester ^{1}H signals in **11** at δ 3.74 (s) and 3.35 (s).

[b] α and β may be interchanged.

[c] Signal not assigned.

Table 2. Selected ^{1}H NMR signals for compounds **1–11**: multiplicity and coupling constants (Hz)[a]

Proton	1	2	3	4	5	6	7	8	9	10	11
H-5	dd; 11, 2	dd; 11, 2	dd; 11, 2	dd; 12, 4	dd; 9, 6	dd; 11, 4	dd; 13, 3	dd; 13, 3	dd; 12, 3	dd; 12, 3	dd; 12, 3
H-7α	m	m	m	m	m	m	dddd; 17.5, 13, 6.5, 2.5	dddd; 17.5, 12, 7, 2	m	m	m
H-7β	m	m	m	m	m	m	ddd; 17.5, 5, 1.5	dddd; 17.5, 6, 2.5, 0.5	m	m	m
H-11α	br d; 16.5	br d; 16.5	br d; 16.5	d; 12	d; 12	d[b]; 12	d; 12	d; 11.5	d[b]; 12	d[b]; 11.5	d[b]; 11.5
H-11β	d; 16.5	d; 16.5	d; 16.5	d; 12	d; 12	dd[b]; 12, 2	dd; 12, 3.5	br d; 11.5	br d[b]; 12	br d[b]; 11.5	br d[b]; 11.5
H-13	—	—	—	—	—	—	—	—	—	dd; 10.5, 5.5	ddd; 11, 6, 1
H-14α	d; 16.5	br s	d; 16.5	d; 15	d; 15	s	d; 2.5	dd; 2, 0.5	dd; 15, 12	m	m
H-14β	br d; 16.5	br s	br d; 16.5	d; 15	d; 15	s	—	—	dd; 15, 5.5	m	ddd; 12.5, 6, 6
H-15	—	—	—	—	dd; 12, 3	m	—	m	m	m	m
H-15′	—	—	—	—	d; 12	m	—	m	m	m	m
H-16	—	—	—	s	d; 3	d; 3	dd; 17.5, 3.5	ddd; 12.5, 10, 6	m	m	m
H-16′	—	—	—	—	—	—	d; 17.5	m	m	m	m

[a] Some coupling constants were determined by analysis of the multiplet in an NOE difference spectrum and double resonance experiments.

[b] α and β may be interchanged.

MRC

Spectral Assignments and Reference Data

Table 3. ^{13}C NMR chemical shifts (δ, ppm) for compounds **1–11**

Carbon	1	2	3[a]	4	5	6	7	8	9	10	11[b]
1	35.94	35.91	36.28	36.56	36.84	37.05	33.03	32.79	32.55	32.57	32.49
2	18.71	18.71	18.99	18.41	18.79	18.71	18.23	18.40	18.70	18.79	18.72
3	41.55	41.55	41.89	41.59	41.98	41.87	41.64	41.91	42.12	42.20	42.16
4	33.17	33.25	33.36	33.05	33.07	33.08	33.47	33.43	33.13	33.12	33.10
5	51.07	51.12	51.31	47.48	48.16	48.11	47.95	47.22	47.98	47.97	47.94
6	18.49	18.51	19.14	17.75	18.26	18.04	20.62	20.97	21.70	21.83	21.77
7	31.15	31.26	31.67	29.19	30.53	29.53	31.03	30.80	30.29	30.14	29.94
8	122.91	122.41	122.54	32.20	19.68	19.97	171.42	171.12	40.01	37.39	37.14
9	135.75	135.93	136.96	52.29	43.84	42.05	52.57	58.94	52.44	52.47	52.49
10	37.28	37.44	37.73	34.06	33.63	33.56	37.33	37.46	38.83	38.52	38.52
11	33.40	33.56	33.32	31.89	35.30	36.40	42.83	44.12	45.38	44.50	44.47
12	48.41	47.64	52.30	47.89	41.69	49.79	63.69	50.39	53.10	44.11	43.05
13	110.13	110.75	110.85	112.24	111.34	213.36	192.26	204.50	214.64	76.38	80.00
14	39.31	37.33	39.67	41.82	42.56	41.67	125.70	124.37	43.68	38.17	34.19
15	—	—	—	210.99	36.14	36.92	211.82	35.29	36.88	30.69	31.94
16	—	—	—	39.47	26.51	26.49	41.33	29.27	24.09	24.43	24.36
17	18.73	19.02	19.28	10.97	17.72	17.32	14.46	20.22	19.81	23.30	23.11
18	33.05	33.11	33.28	33.71	33.91	33.87	33.71	33.76	33.61	33.62	33.60
19	21.51	21.58	21.77	21.37	21.50	21.46	22.69	22.66	21.96	22.05	22.02
20	18.93	19.11	19.36	17.53	19.76	19.86	19.10	20.86	17.24	17.34	17.31
R	175.07; 51.88	176.13	196.10; 53.52	—	—	—	—	—	—	—	—
Ketal	64.98; 64.90	64.59; 64.50	64.66; 64.66	65.24; 64.94	64.72; 64.62	—	—	—	—	—	—

[a] In C_6D_6.

[b] Additional side-chain ester ^{13}C signals in **11** at δ 167.17 (s), 166.21 (s), 52.34 (q) and 41.70 (t).

^1H–^{13}C HMQC and NOED spectra were measured on a Varian 400 spectrometer (399.95 MHz for ^1H and 100 MHz for ^{13}C) equipped with a 5 mm indirect detection probe operating at 298 K. Sample concentrations were typically in the range 5–20 mg per 0.5 ml of $CDCl_3$. The signal of TMS was taken as the reference. All these experiments were performed either using standard pulse sequences supplied by the spectrometer manufacturer or slightly modified pulse sequences. NOED experiments were typically acquired with 8 K data points covering a spectral width of 3200 Hz and with a 1.5 s presaturation time. Spectra at each presaturation position were interleaved in groups of four scans to minimize artefacts due to instrument inconsistencies and processed with a 1 Hz exponential line broadening to reduce subtraction artefacts. The HMQC spectrum was obtained using a spectral width of 3200 Hz in the ^1H dimension and 16 000 Hz in the ^{13}C dimension. A total of 256 increments were collected with eight transients per increment and an acquisition time of 0.1 s.

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