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A NEO-CLERODANE DITERPENOID FROM *SCUTELLARIA BAICALENSIS*

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Key Word Index—*Scutellaria baicalensis*; Labiatae; neo-clerodane diterpene; scutebaicalin; absolute configuration; CD exciton chirality method.

Abstract—An acetone extract of the aerial parts of *Scutellaria baicalensis* provided a new neo-clerodane, scutebaicalin, the structure of which was established as 6α,7β-dibenzoyloxy-8β-hydroxy-neo-cleroda-4(18),13-dien-15,16-olide by spectroscopic means. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

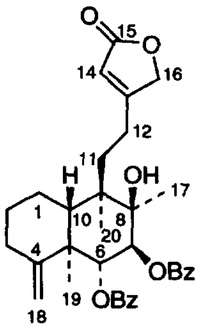
The neo-clerodane diterpenes isolated from *Scutellaria* species possess several interesting biological activities [1–4], in particular as insect antifeedants and agents against plant pathogenic fungi. In continuation of our studies on *Scutellaria* plants [4–7], we have now investigated the aerial parts of *S. baicalensis*. We report here on the isolation and structural elucidation of a new neo-clerodane derivative, scutebaicalin (**1**), found in this plant.

RESULTS AND DISCUSSION

An acetone extract of the aerial parts of *S. baicalensis* yielded compound **1** as the sole detectable diterpene constituent. Combustion analysis and low-resolution mass spectrometry indicated the molecular formula $C_{34}H_{38}O_7$ for this new diterpenoid. Its IR spectrum was consistent with the presence of hydroxyl (3520 and 3480 cm^{-1}), exocyclic methylene (3080, 1640 and 895 cm^{-1}), α,β-unsaturated γ-lactone (1780, 1750 and 1630 cm^{-1}) and benzoate (3040, 1735 vs, 1600, 1580, 1280, 710 and 690 cm^{-1}) groups. The ^{1}H and ^{13}C NMR spectra of **1** (Tables 1 and 2, respectively) were very similar to those of scutalpin L (**2**), a neo-clerodane derivative previously found in *S. alpina* [5], and the observed differences were consistent with the existence in **1** of an exocyclic methylene group at C-4, C-18 [δ_H 4.58 and 4.76, 1H each, both *br s*, $W_{1/2}$ 4 and 1.5 Hz, respectively; δ_C 153.95 *s* (C-4) and 104.65 *t* (C-18)] and a methyl group at C-19 (δ_H 1.48, 3H, *s*; δ_C 16.92 *q*) instead of the 4α,18-oxirane [δ_H 2.32, 1H, *d*, $J = 3.9$ Hz, and 3.36, 1H, *dd*, $J = 3.9$ and 2.2 Hz; δ_C 65.1 *s* (C-4) and 49.6 *t* (C-18)] and the 19-acetoxymethylene group [δ_H 4.75 *d* and 4.81 *br d*, 1H each, $J = 12.2$ Hz; 2.01, 3H, *s*; δ_C 62.5 *t* (C-19), 171.0 *s* and 21.0 *q* (OAc)] of **2** [5].

The relative stereochemistry of all the asymmetric centres of **1** was firmly established from its NOESY spectrum. The H-7α axial proton showed NOE cross-peaks with the Me-17, Me-19 and Me-20 protons, and H-6β (axial) exhibited NOE correlations with H-10β and H$_B$-18, thus establishing that H-7α, Me-17, Me-19 and Me-20 are on the same side of the plane of the decalin, and H-6β and H-10β are on the opposite one. The NOESY spectrum of **1** also provided information for distinguishing both methylene protons at C-18, because H-6β showed a NOE with H$_B$-18 (pro *Z* hydrogen of the exocyclic methylene) and H$_A$-18 (pro *E* hydrogen) with H-3β.

A careful analysis of the coupling values between the decalin protons of scutebaicalin (see Table 1) also supported the relative stereochemistry depicted in **1** and established that both rings A and B are in a chair conformation ($^4C_1$ and $^6C_9$, respectively).



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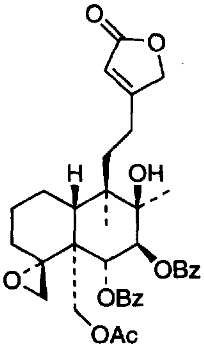

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Table 1. ^{1}H NMR spectral data for compound **1** [500 MHz, CDCl$_3$, δ values relative to residual CHCl$_3$ (δ 7.25)]*

H	1	H	1	*J* (Hz)	1	*J* (Hz)	1
1α	1.77 *dddd*	16B	4.72 *dd*	1α,1β	13.1	11A,12A	12.5
1β	1.45 *m*†	Me-17	1.18 *s*	1α, 2α	4.0	11A, 12B	4.1
2α	1.96 *m*‡	18A	4.58 *br s*§	1α, 2β	12.4	11B, 12A	4.5
2β	1.39 *ddddd*	18B	4.76 *br s*‖	1α, 10β	12.4	11B, 12B	12.4
3α	2.30 *td*	Me-19	1.48 *s*	1β, 2α	¶	12A, 12B	16.8
3β	2.12 *ddd*	Me-20	1.06 *s*	1β, 2β	4.4	12A, 14	1.2
6β	6.10 *d*	OH (8β)	1.62 *br s***	1β, 10β	2.7	12B, 14	1.2
7α	5.72 *d*	OBz (6α)		2α, 2β	13.5	14, 16A	1.6
10β	2.10 *dd*	2′, 6′	7.87 *dd*	2α, 3α	4.6	14, 16B	1.6
11A	1.56 *ddd*	3′, 5′	7.32 *br t*	2α, 3β	4.3	16A, 16B	17.3
11B	1.89 *ddd*	4′	7.47 *tt*	2β, 3α	13.3	18A, 18B	<0.4
12A	2.25 *dddd*	OBz (7β)		2β, 3β	1.4	18A, 3α	0.6
12B	3.08 *dddd*	2″, 6″	7.73 *dd*	3α, 3β	13.3	OBz	
14	5.80 *br quint*	3″, 5″	7.22 *br t*	6β, 7α	10.1	*ortho*	8.5–7.9
16A	4.71 *dd*	4″	7.37 *tt*	11A, 11B	14.9	*meta*	1.4
						para	*ca* 0

*Spectral parameters were obtained by first-order approximation. All these assignments were in agreement with COSY, TOCSY, HMQC and HMBC spectra.

†$W_{1/2}$ = 12 Hz.

‡$W_{1/2}$ = 22 Hz.

§$W_{1/2}$ = 4 Hz; pro *E* hydrogen, distinguished by NOE experiments.

‖$W_{1/2}$ = 1.5 Hz; pro *Z* hydrogen, distinguished by NOE experiments.

¶Not measured.

**Disappeared after addition of D$_2$O.

Finally, the absolute stereochemistry of **1** was established by using the CD exciton chirality method [8]. The 6α,7β-dibenzoyloxy binary system showed a negative first and a positive second Cotton effect ($\Delta\varepsilon_{240}$ − 147.7, $\Delta\varepsilon_{226}$ + 76.8), thus defining a negative chirality and, consequently, a neo-clerodane absolute configuration [9] for this diterpenoid.

Table 2. ^{13}C NMR spectral data for compound **1** (125.7 MHz, CDCl$_3$, δ values relative to the solvent signal, δ_{CDCl_3} 77.00)*

C	1	C	1
1	22.25 *t*	OBz (C-6)	
2	28.36 *t*	Ph$\underline{C}$O$_2$	165.96 *s*
3	33.10 *t*	1′	130.10 *s*
4	153.95 *s*	2′, 6′	129.78 *d*
5	45.98 *s*	3′, 5′	128.24 *d*
6	74.42 *d*	4′	133.15 *d*
7	76.14 *d*		
8	79.49 *s*	OBz (C-7)	
9	43.24 *s*	Ph$\underline{C}$O$_2$	166.11 *s*
10	43.81 *d*	1″	129.02 *s*
11	35.03 *t*	2″, 6″	129.41 *d*
12	25.02 *t*	3″, 5″	128.05 *d*
13	171.66 *s*	4″	132.66 *d*
14	114.39 *d*		
15	174.13 *s*		
16	73.21 *t*		
17	21.67 *q*		
18	104.65 *t*		
19	16.92 *q*		
20	21.61 *q*		

*Multiplicities were determined by DEPT and HMQC spectra. All these assignments were in agreement with HMQC and HMBC spectra.

EXPERIMENTAL

General. Mps: uncorr. The plant was cultivated in the Orto Botanico dell'Università di Milano at Tuscolano (Brescia, Italy). Seeds of the species were provided by the 'Botanischer Garten der Justus Liebig Universität', Giessen, and 'Botanischer Garten der Johannes Gutenberg Universität', Mainz (Germany). The plant material was collected in August 1994 and voucher specimens are deposited in the Herbarium of the Dipartimento di Biologia, University of Milan, Italy.

Extraction and isolation of the diterpenoid. Dried and finely powdered aerial parts of *S. baicalensis* Georgi (1.14 kg) were extracted with Me$_2$CO (2 × 8 l) at room temp. for 1 week. After filtration, the solvent was evapd to dryness under red. pres. and low temp. (40°) yielding a residue (34 g), which was subjected to CC (silica gel Merck No. 7734, deactivated with 10% H$_2$O, w/v, 700 g) eluting with a hexane–EtOAc gradient. The fr. eluted with hexane–EtOAc (2:1) (790 mg) was decolorized by filtration through a pad of a mixt. (1:1) of activated C and celite, eluting with EtOAc. Evapn of the solvent and crystallization of the residue (580 mg) from EtOAc–*n*-hexane yielded **1** (210 mg). Not other diterpenoids were detected in the Me$_2$CO extract of this plant.

Scutebaicalin (**1**). Mp 129–131° (EtOAc–*n*-hexane), $[\alpha]_D^{23}$ −127.7° (CHCl$_3$; *c* 0.618). CD nm (Δε): 269 (0), 240 (−147.7), 231 (0), 226 (+76.8), 217 (0) (MeOH; *c* 0.0478); UV λ_{max}^{MeOH} nm (log ε): 220 sh (4.51), 227 (4.59), 273 (3.36), benzoate and α,β-unsaturated γ-lactone; IR ν_{max}^{KBr} cm^{-1}: 3520, 3480 (OH), 3080, 1640, 895 (exocyclic CH_2), 3040, 1735 vs, 1600, 1580, 1280, 710, 690 (OBz), 1780, 1750, 1630 (α,β-unsaturated γ-lactone), 2995, 2950, 2860, 1450, 1180, 1110, 1100, 1070, 1025, 970, 850; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EI-MS (70 eV, direct inlet) m/z (rel. int.):558 $[M]^+$ (0, 3), 540 $[M-H_2O]^+$ (0.3), 436 $[M\text{-}BzOH]^+$ (0.4), 418 $[M-H_2O-BzOH]^+$ (0.4), 331 (0.6), 271 (1.4), 217 (1.7), 203 (2.4), 175 (1.9), 122 (2.5), 105 $[Bz]^+$ (100), 98 (2), 77 (19), 67 (11). (Found: C, 72.81; H, 7.02. $C_{34}H_{38}O_7$ requires: C, 73.09; H, 6.86%.)

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