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11-EPISCUTECYPRIN A *NEO*-CLERODANE DITERPENOID FROM *SCUTELLARIA COLUMNAE*

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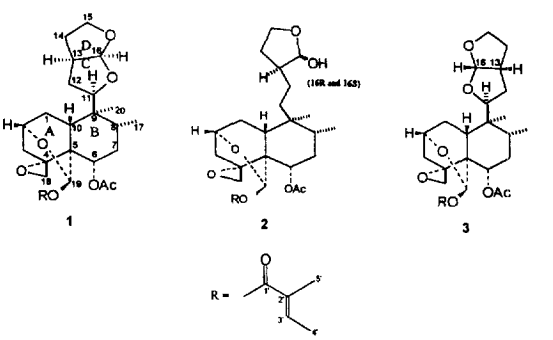
Key Word Index—*Scutellaria columnae*; Labiatae *neo*-clerodane diterpenoids; 11*R*-scutecyprin and scutegalin D.

Abstract—A new *neo*-clerodane, 11-episcutecyprin has been isolated from the aerial parts of *Scutellaria columnae* var. *columnae*, in addition to the known diterpene scutegalin D. The structure of the new compound was established by spectroscopic means as (11*R*, 13*R*, 16*S*, 19*R*)-6α-acetoxy-4α, 18; 11, 16,: 15,16-triepoxy *neo*-cleroda-(19-*O*-tigloyl)-19,2α-hemiacetal. The biogenesis of this compound is briefly discussed. © 1997 Elsevier Science Ltd

INTRODUCTION

In continuation of our studies on the diterpenes from *Scutellaria* species [1–6] we have now investigated *S. columnae* var. *columnae*. We wish to report here the isolation and structure determination of a new *neo*-clerodane diterpene 11- episcutecyprin (**1**), which to the best of our knowledge is the first *neo*-clerodane diterpene with a hexahydrofurofuran moiety possessing the 11*R*-configuration isolated from plants.



RESULTS AND DISCUSSION

11-Episcutecyprin (**1**) had the molecular formula $C_{27}H_{38}O_8$ as determined by combustion and ^{13}C NMR analysis. Its ^1H and ^{13}C NMR spectra (Tables 1 and 2, respectively) were almost identical with these of scutecyprin (**3**), a *neo*-clerodane diterpene recently isolated from *Scutellaria cypria* var. *elatior* [7]. In fact, the difference between the ^1H NMR spectra of **1** and **3** were in the chemical shifts corresponding to the H-11α(Δδ −0.44 ppm), H-16α(Δδ −0.10 ppm), CH_3-17(Δδ +0.12 ppm) and the signals of the C-15 protons only. The signals of H_2-15 were split [H_A-15(δ 3.78 *ddd*) and H_B-15 (δ 3.96 *ddd*)], while the H_2-15 in **3** resonated at δ 3.88 as a multiplet, as observed in all the hexahydrofurofuran *neo*-clerodane diterpenoids isolated from *Labiatae* [7–12].

Moreover, a comparison between the ^{13}C NMR spectra of **1** and **3** (Table 2) showed a significant difference in the C-7(Δδ −1.8), C-11(Δδ −2.4), C-15(Δδ −2.2) and C-20(Δδ −1.8) chemical shifts. A similar behaviour in the ^1H and ^{13}C NMR spectra was previously pointed out for some pairs of C-12 epimers of the furo-*neo*-clerodane derivatives belonging to the H-10β series [13–15]. These data, in principle, could be attributed to an opposite stereochemistry at the hexahydrofurofuran moiety C-11*R*(H-11α); C-13*R*(H-13α) and C-16*S*(H-16α) in compound **1** in comparison with the hexahydrofurofuran moiety of **3** in which the protons at C-13 and C-16 were β-orientated [7].

Important information about the stereochemistry of the hexahydrofurofuran moiety was obtained from the NOE experiments at the C-11, C-13 and C-16 protons. Irradiation at δ 3.64 (H-11α) produced a strong NOE enhancement of the H-1α, H-12B, Me-20 and medium enhancement of the Me-17, H-16α and H-13α. Moreover, irradiation at δ 2.80(H-13α) caused a positive NOE enhancement of the H-16α, H_B-12, H_B-14 and H-11α. Positive NOE enhancements were observed also upon irradiation of the H-16α proton at δ 5.54 (for H-11α and H-13α). All these experi-

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Table 1. ^{1}H NMR spectral data of compounds **1*** and **3**†

H	1	3	Δppm	J(Hz)	1	3
1α	≈2.08‡	—	—	2β,3α	2.0	~2.0
1β	≈1.58‡	—	—	3α,3β	14.3	14.3
2β§	4.21 *m*	4.18 *m*	+0.03	3α,1α	2.0	~2.0
3α(eq)	2.56 *br d*	2.55 *br d*	+0.01	6β,7α	12.1	11.3
3β	≈1.76‡	—	—	6β,7β	5.1	4.6
6β	4.64 *dd*	4.62 *dd*	+0.02	10β,1α	11.0	—
7α	≈1.68‡	—	—	10β,1β	5.7	—
7β	≈1.46‡	—	—	11α,12A	11.7	10.9
8β	≈1.88‡	—	—	11α,12B	4.7	5.8
10β	≈1.94 *dd*	—	—	13α,16α	5.5	—
11α	3.64 *dd*	4.08 *dd*	−0.44	13β,16β	—	5.1
12A	≈1.65‡	—	—	15A,15B	8.0	—
12B**	≈1.92‡	—	—	15A,14B	4.8	—
13α¶	2.80 *m*	2.85 *m*	−0.05			
14A	≈1.44‡	—	—	15A,14A	8.2	—
14B**	≈1.84‡	—	—	15B,14A	8.2	—
15A	3.78 *ddd*	3.88 *m*	−0.10	15B,14B	<1	—
15B	3.96 *td*	3.88 *m*	+0.8	17,8β	6.6	7.0
16α	5.54 *d*	5.64 *d*	−0.10	18A,18B	4.4	4.3
Me-17	1.02 *d*	0.90 *d*	+0.12	3′,4′	7.1	7.1
18A	2.42 *d*	2.43 *d*	−0.01	3′,5′	1.3	1.3
18B	3.00 *d*	3.00 *d*	0.0	—	—	—
19α	6.82 *s*	6.82 *s*	0.0	—	—	—
Me-20	1.11 *s*	1.16 *s*	−0.05	—	—	—
OAc	1.89 *s*	1.80 *s*	—	—	—	—
3′	7.08 *qq*	7.08 *qq*	—	—	—	—
Me-4′	1.80 *br d*	1.81 *br d*	—	—	—	—
Me-5′	1.79 *br s*	1.89 *br s*	—	—	—	—

* At 250 MHz in $CDCl_3$ solution. Chemical shifts are in ppm (δ) referenced to the signal of residual $CHCl_3$ (δ 7.25). Spectral parameters were obtained by first order approximation. All these assignments were in agreement with the HMQC and ^{1}H-^{13}C COSY spectra.

† taken from ref [7].

‡ overlapped signal

§ $W_{1/2}$ = 20 Hz.

¶ $W_{1/2}$ = 10 Hz.

** were also distinguished by NOE experiments.

ments showed that the protons at C-11, C-13 and C-16 are on the same side of a ring-C/D *cis*-junction hexahydrofurofuran moiety ($J_{13\alpha,16\alpha}$ = 5.5 Hz) and were α- orientated. Furthermore, irradiation at δ 1.11 (Me-20) produced a positive NOE enhancement of the signals at δ 2.08(H-1α), 1.68(H-7α), 3.64(H-11α), 5.54(H-16α) and 6.82(H-19α). This showed unambiguously that the hydrogens at C-11, C-13, C-16 and C-20 are α-orientated. On the other hand irradiation at δ 1.02(Me-17) caused a positive NOE enhancement of the H-7α, H-11α, H_A-15 and H-16α, which also confirmed the 11*R*-configuration of **1**. The relative stereochemistry of the remaining asymmetric centres of **1** was firmly established also by NOE experiments. An irradiation at δ 4.64 (H-6β) caused a positive NOE enhancement in the signals of H-7β, H-8β, H-10β and H_B-18 and a negative NOE effect on the H_A-18 [1, 2] thereby establishing that these protons are β-orientated. Moreover, on irradiating the H-19α(δ 6.28) NOE effects were produced in the signals of the H-7α and Me-20 thus establishing a *cis*-1,3-diaxial relationship between these groups. Consequently, a *trans*-junction of the A and B rings of the diterpenoid is indicated [2]. From all the above data it was evident that 11-episcutecyprin possessed the structure depicted in **1** and it can be assigned as (11*R*, 13*R*, 16*S*, 19*R*)-6α-acetoxy-4α, 18; 11, 16; 15, 16-triepoxy-*neo*-cleroda-(19-*O*-tigloyl)-19,2α-hemiacetal. The absolute configuration of **1** was not ascertained. However, on biogenetic grounds it may be supposed that **1** belongs to the *neo*-clerodane series.

From a biogenetic point of view, it is interesting to note that compound **1** is the first *neo*-clerodane diterpenoid with a furofuran moiety isolated from plants so far possessing the 11*R*-configuration, and its biogenesis may be rationalized by the mechanistic pathway depicted in Scheme 1. A suitable *neo*-clerodane precursor such as scutegalin D (**2**) (16*R*-isomer) [16], after oxidation at C-11 (intermediate **4**) and dehydration between the hydroxyl groups at C-11*R* and

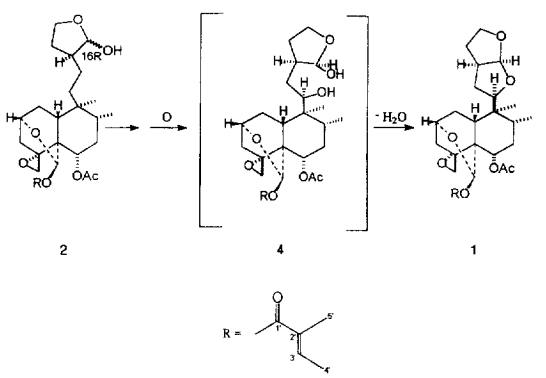
Table 2. ^{13}C NMR spectral data of compounds **1*** and **3**†

C	**1**	**3**	ΔδC	C	**1**	**3**	ΔδC
1	28.3 *t*	28.4 *t*	−0.1	15	66.1 *t*	68.3 *t*	−2.2
2	67.0 *d*	67.2 *d*	−0.2	16	107.7 *d*	108.2 *d*	−0.5
3	36.7 *t*	36.9 *t*	−0.2	17	17.3 *d*	16.7 *q*	+0.6
4	60.4 *s*	60.6 *s*	−0.2	18	50.1 *t*	50.2 *t*	−0.1
5	41.5 *s*‡	41.4 *s*	+0.1	19	91.2 *d*	91.4 *d*	−0.2
6	68.2 *d*	68.3 *d*	−0.1	20	12.2 *q*	14.0 *q*	−1.8
7	31.3 *t*	32.6 *t*	−1.3	OAc	169.9 *s*	170.0 *s*	—
8	34.6 *d*	35.1 *d*	−0.5		11.8 *q*	21.0 *q*	—
9	41.6 *s*‡	41.6 *s*	0.0	1′	166.2 *s*	166.3 *s*	—
10	41.7 *d*	40.8 *d*	+0.9	2′	128.4 *s*	128.4 *s*	—
11	83.6 *d*	86.0 *d*	−2.4	3′	138.4 *d*	138.4 *d*	—
12	32.3 *t*	33.1 *t*	−0.8	4′	20.9 *q*	14.5 *q*	—
13	42.4 *d*	41.8 *d*	+0.6	5′	14.5 *q*	11.9 *q*	—
14	33.6 *t*	33.5 *t*	+0.1				

* At 62.9 MHz in $CDCl_3$ solution, TMS as int. standard. Multiplicities were determined by DEPT pulse sequences.

† Taken from ref. 7.

‡ These assignments may be interchanged.



Scheme 1. Possible route for the biosynthesis of compound **1**.

C-16*R* leads to the formation of the 11-episcutecyprin (**1**), or from **2** via enzymatic dehydroxylation on C-16 and then cyclization with the hydroxyl group at C-11*R*.

EXPERIMENTAL

General. Mps: uncorr. Plant materials were collected in July 1995 near Kardjali (Bulgaria) and voucher specimens (no 17506) are deposited in the Herbarium of the Department of the Botanica at the Higher Institute of Agriculture at Plovdiv, Bulgaria.

Extraction and isolation of the diterpenoids. Dried and powdered aerial parts of *S. columnae subsp. columnae* (820 g) were extracted with Me_2CO (3 × 4 l) at room temp. for 7 days. The combined extracts were evapd. *in vacuo* to near-dryness (16 g). MeOH (500 ml) was added and then extracted with petrol (5 × 150 ml). The MeOH phase was concd, yielding a residue (5 g) to which H_2O was added and the mixt. extracted with $CHCl_3$. The organic extract was dried and the solvent removed to yield 3.5 g of a gum, which was subject to CC on silica gel (Merck No. 3374, deactivated with 15% H_2O (v/w), 160 g). Elution with petrol–EtOAc (9:1) gave crude 11-episcutecyprin (**1**, 60 mg) and further elution with petrol–EtOAc (8:2) gave scutegalin D (**2**) (48 mg). 11*R*-scutecyprin was recrystallized from petrol–EtOAc to yield pure **1** (54 mg).

Mp. 204–205°, $[\alpha]_D^{20}$ +31° ($CHCl_3$, *c*, 0.250). IR ν_{max}^{KBr} cm^{-1}: 3041, 2966, 2934, 2877, 1736, 1708, 1647, 1463, 1451, 1373, 1297, 1264, 1242, 1227, 1072, 1056, 1020, 966, 940, 917, 882, 642; ^1H NMR (Table 1) ^{13}C NMR (Table 2); EIMS (70 eV, direct inlet) *m/z* (rel. int.) $[M]^+$ absent, 392(1), 391(5), 218(4), 172(5), 171(3), 159(4), 157(4), 145(4), 134(3), 133(4), 131(3), 121(3), 114(4), 113(67), 111(3), 105(6), 91(10), 83(57), 69(75), 67(15), 57(11), 55(90), 43(100). Anal. Calcd for $C_{27}H_{38}O_8$: C 66.10; H 7.81 Found: C 65.81; H 7.54%.

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