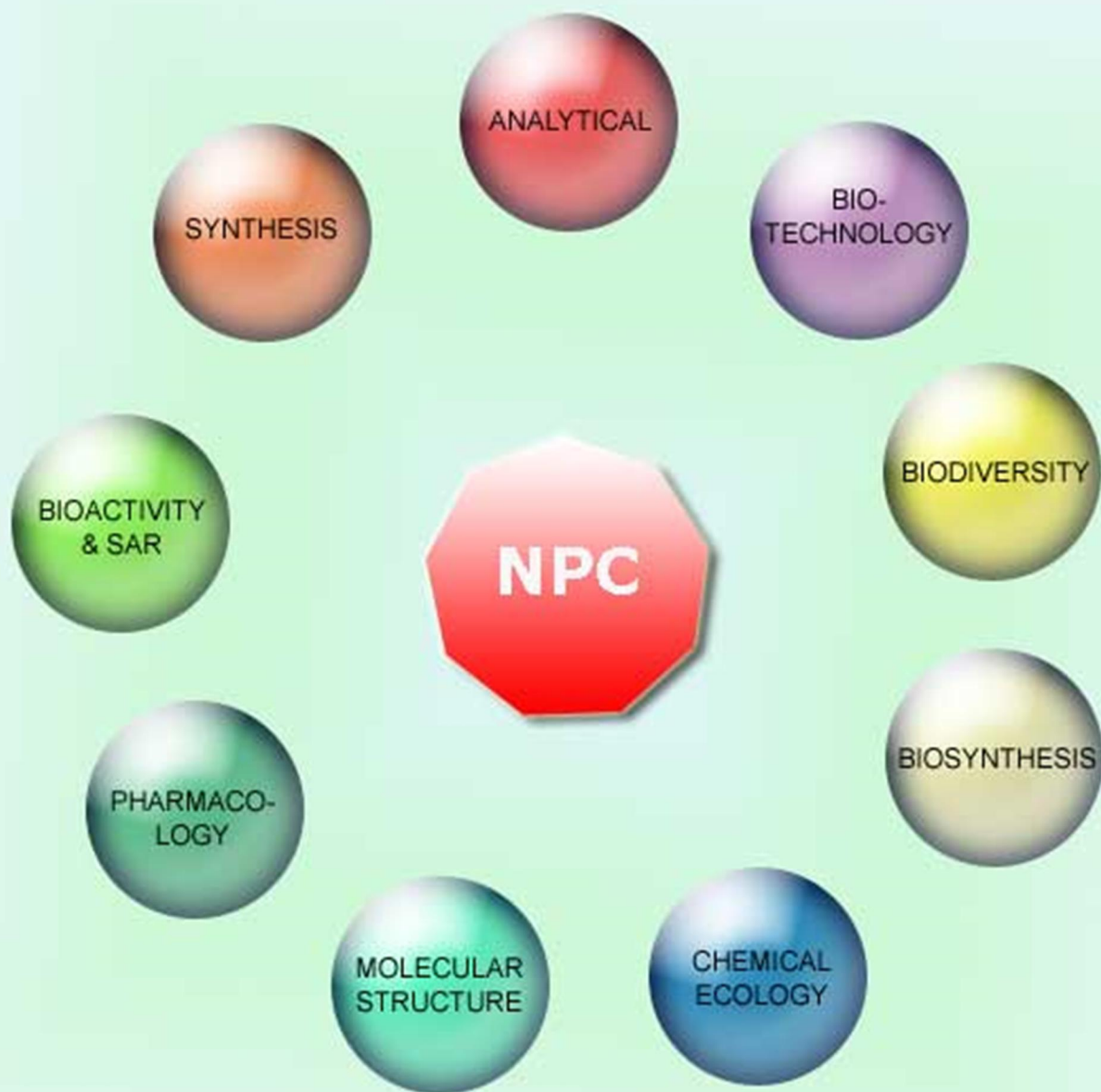


# NATURAL PRODUCT COMMUNICATIONS

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**This Issue is Dedicated to  
Professor Josep Coll Toledano  
On the Occasion of his 70th Birthday**

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**$^1\text{H}$  and  $^{13}\text{C}$  NMR Analysis of the *neo*-Clerodane Diterpenoid Scutecyprin**Plamen N. Penchev<sup>a,\*</sup>, Stefka R. Nachkova<sup>a</sup>, Tonka A. Vasileva<sup>b</sup> and Petko I. Bozov<sup>b</sup><sup>a</sup>Dept. of Analytical Chemistry, Plovdiv University, 24 Tzar Assen Str., 4000-Plovdiv, Bulgaria<sup>b</sup>Dept. of Biochemistry and Microbiology, Plovdiv University, 24 Tzar Assen Str., 4000-Plovdiv, Bulgaria

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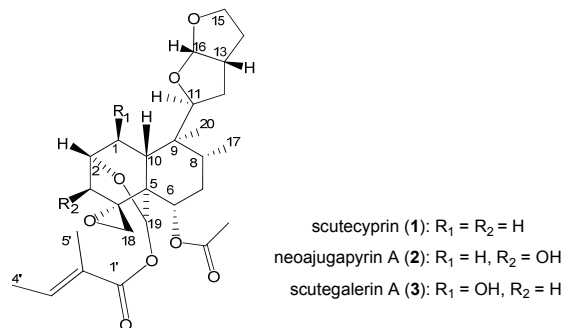
The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the *neo*-clerodane diterpenoid scutecyprin were completely assigned by using a combination of 2D NMR experiments, which included  $^1\text{H}$ - $^1\text{H}$  COSY, HSQC, HMBC and NOESY sequences.

**Keywords:** *Scutellaria altissima*, *Scutellaria cypria*, Labiatae, *neo*-Clerodane diterpenes, Scutecyprin.

Many *neo*-clerodane diterpenes with insect antifeedant activity have been isolated from the genus *Scutellaria* (family Labiatae) [1]. In a continuation of our search for such compounds [2, 3] we have studied *S. altissima* and *S. galericulata*. From the first of these species we isolated scutecyprin (**1**) and carried out a full assignment of its  $^1\text{H}$  NMR spectrum, which helped us elucidate the structures of two positional isomers, neoajugapyrin A (**2**) and scutegalerin A (**3**), recently isolated by us from the second species [4].

Scutecyprin has been previously isolated and identified by Bruno *et al.* from the aerial parts of *S. cypria* var. *elator* [5]. The authors assigned nearly all the carbon signals without 2D techniques, but eleven  $^1\text{H}$  NMR signals were not assigned: viz. those at  $1\alpha$ ,  $1\beta$ ,  $3\beta$ ,  $7\alpha$ ,  $7\beta$ ,  $8\beta$ ,  $10\beta$ ,  $12\alpha$ ,  $12\beta$ ,  $14\alpha$  and  $14\beta$ . We have revised the structure of ajugapyrin A (reported as  $1\beta$ -hydroxyscutecyprin [6]) to neoajugapyrin A (reported by us as  $3\beta$ -hydroxyscutecyprin [4]) and the correct assignment of the H- $1\alpha$ , H- $1\beta$  and H- $10\beta$  signals in both neoajugapyrin A and scutecyprin played an important role in our decision. Comparison of the carbon signals at C-4, C-18 (see Table 2 in [4]) and C-10 in both compounds and scupolin G [7] and 14,15-dihydrojodrellin T [8] also supported the newly proposed structure. Thus, considering the important biological properties of *neo*-clerodane type diterpenes [9], it seems appropriate to report the full spectral assignment of scutecyprin. Another important feature of this study is that scutecyprin is reported for the first time from *S. altissima*.

Scutecyprin has the molecular formula  $\text{C}_{27}\text{H}_{38}\text{O}_8$ . Its structure and the numbering of the atoms are given in Fig 1. The  $^1\text{H}$ -broadband-decoupled  $^{13}\text{C}$  NMR spectrum of **1** showed 27 signals and 21 resonances (5x CH<sub>3</sub>, 7x CH<sub>2</sub>, 9x CH) by DEPT. The carbon signals are indeed very close to those reported by Bruno *et al.* [5], the maximum deviation being 0.49 ppm for C-2'; the compound itself was identified by this comparison. The 2D NMR spectroscopic data (see Table 1) confirmed the assignment of  $^1\text{H}$  and  $^{13}\text{C}$  signals given earlier [5]. Moreover, their assignment was used as a starting point for spectral analysis. In the following paragraphs the most important arguments for assignment of the above mentioned eleven  $^1\text{H}$  signals are given. In the discussion, use is made of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data and  $^1\text{H}$ - $^1\text{H}$  COSY and  $^1\text{H}$ - $^{13}\text{C}$  HMBC correlations given in Table 1; 2D NOESY cross peaks and atom distances are presented in Table 2. The complete spectral data and enlarged



**Figure 1:** Structures of scutecyprin and *neo*-clerodanes used in the discussion.

detailed sections for multiplets and cross peaks, together with quantum chemistry results are included in 'Supplementary Data'.

**H-1 $\alpha$  assignment.** The multiplet structure at  $\delta$  2.36 ppm (1H, apparent dtd) correlates in the HSQC experiment to the  $\delta$  28.45 methylene carbon signal; its counterpart in the HSQC (H- $1\beta$ , i.e. with the same  $\delta_{\text{C}}$  28.45) is one of the five proton resonances overlapped in the  $\delta_{\text{H}}$  region between 1.68–1.59 (H- $1\beta$ ). There is also a weak HMBC correlation  $\delta_{\text{H}}$  2.36– $\delta_{\text{C}}$  67.27 (C-2) and four  $^1\text{H}$ - $^1\text{H}$  COSY cross peaks at  $\delta_{\text{H}}$  2.36 with  $\delta_{\text{H}}$  1.68–1.59 (right part of the interval, H- $1\beta$ ),  $\delta_{\text{H}}$  4.18 (m, 1H, H-2 $\beta$ ),  $\delta_{\text{H}}$  2.04 (dd, 1H, H-10 $\beta$ ) and  $\delta_{\text{H}}$  2.55 (dt, 1H, H-3 $\alpha$ ). The last one is weak and points out a relatively large  $^4J$  constant between H-3 $\alpha$  and H-1 $\alpha$ , a consequence of a flat zig-zag (W) arrangement in the compound skeleton. That is why the resonance at  $\delta$  2.36 was assigned to H-1 $\alpha$ , and that around  $\delta$  1.60 to H- $1\beta$ . In the NOESY spectrum,  $\delta_{\text{H}}$  2.36 shows two cross peaks with  $\delta_{\text{H}}$  1.16 (H<sub>3</sub>-20 $\alpha$ ) and  $\delta_{\text{H}}$  4.08 (H-11 $\alpha$ ); this also supports its assignment to H-1 $\alpha$ , see Table 2.

**H-1 $\beta$  assignment.** As mentioned above, one out of five proton resonances heavily overlapped in the  $\delta$  1.68–1.59 interval is the HSQC counterpart of the H-1 $\alpha$  resonance (obviously H- $1\beta$ ). The other four are for H-7 $\alpha$  (ax), H-8 $\beta$ , H-12 $\alpha$  and H-14 $\alpha$  (see the discussion below). Despite this overlap in the  $^1\text{H}$  frequency axis, correlations in the  $^1\text{H}$ - $^1\text{H}$  COSY and HMBC spectra of H- $1\beta$  with H-1 $\alpha$  ( $\delta_{\text{H}}$  2.36) and H-10 $\beta$  ( $\delta_{\text{H}}$  2.04), and H- $1\beta$  with C-10 ( $\delta_{\text{C}}$  40.80) can be identified to support the  $\delta_{\text{H}}$  1.60 assignment to H- $1\beta$ .

**Table 1:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data and  $^1\text{H}$ - $^1\text{H}$  COSY and HMBC correlations for scutecyprin (**1**)<sup>a</sup>.

Atom	$\delta$ ( $^{13}\text{C}$ ) ppm	DEPT <sup>b</sup>	$\delta$ ( $^1\text{H}$ ) ppm	Multiplicity ( $J$ , Hz)	$^1\text{H}$ - $^1\text{H}$ COSY	HMBC
1	28.45	CH <sub>2</sub>	2.36 ( $\alpha$ ) 1.60 <sup>c</sup> ( $\beta$ )	m m	1 $\beta$ , 2 $\beta$ , 10 $\beta$ , 3 $\alpha$ <sup>c</sup> 1 $\alpha$ , 10 $\beta$	2 <sup>c</sup> - <sup>f</sup>
2	67.27	CH	4.18 ( $\beta$ , eq)	m	1 $\alpha$ , 3 $\alpha$ <sup>b</sup> , 3 $\beta$ <sup>c</sup>	4 <sup>c</sup> , 19 <sup>c</sup>
3	36.90	CH <sub>2</sub>	2.55 ( $\alpha$ ) 1.79 ( $\beta$ )	dt (13.8, 2.3) dd (-, 2.7) <sup>d</sup>	2 $\beta$ <sup>b</sup> , 3 $\beta$ , 1 $\alpha$ <sup>c</sup> 2 $\beta$ <sup>c</sup> , 3 $\alpha$	1 <sup>c</sup> , 2 <sup>c</sup> 4 <sup>b</sup> , 5 <sup>c</sup> , 6 <sup>c</sup> , 18 <sup>c</sup>
4	60.66	C				
5	41.46 <sup>f</sup>	C				
6	68.35	CH	4.62 ( $\beta$ )	dd (11.6, 4.5)	7 $\alpha$ , 7 $\beta$	4 <sup>b</sup> , 5 <sup>b</sup> , 7 <sup>b</sup> , 19, CH <sub>3</sub> CO, - <sup>f</sup>
7	33.16 <sup>h</sup>	CH <sub>2</sub>	1.65 <sup>c</sup> ( $\alpha$ , ax) 1.38 ( $\beta$ , eq)	m ddd (12.6, 4.4, 2.7)	6 $\beta$ , 7 $\beta$ , 6 $\beta$ , 7 $\alpha$ , 8 $\beta$	5 <sup>b</sup> or 9 <sup>b</sup> , 6 <sup>c</sup> , 8 <sup>c</sup> - <sup>f</sup>
8	35.16	CH	1.64 <sup>c</sup> ( $\beta$ )	m	7 $\beta$ , 17	- <sup>f</sup>
9	41.85 <sup>f</sup>	C				
10	40.80	CH	2.04 ( $\beta$ )	dd (11.4, 4.3)	1 $\alpha$ , 1 $\beta$	1, 2 <sup>c</sup> , 4, 9, 11 <sup>c</sup> , 19 <sup>c</sup> , 20
11	86.02	CH	4.08 ( $\alpha$ )	dd (10.9, 5.8)	12 $\alpha$ , 12 $\beta$	8 <sup>b</sup> , 10, 20 <sup>b</sup>
12	33.53 <sup>h</sup>	CH <sub>2</sub>	1.65 <sup>c</sup> ( $\alpha$ ) 1.97 ( $\beta$ )	m m	11 $\alpha$ , 12 $\beta$ 11 $\alpha$ , 12 $\alpha$ , 13 $\beta$ <sup>c</sup>	- <sup>f</sup> none
13	41.85	CH	2.85 ( $\beta$ )	m	12 $\beta$ <sup>c</sup> , 14 $\beta$ <sup>c</sup> , 16 $\beta$ <sup>c</sup>	none
14	32.64	CH <sub>2</sub>	1.68 <sup>c</sup> ( $\alpha$ ) 2.15 ( $\beta$ )	m m	14 $\beta$ , 15 14 $\alpha$ , 13 $\beta$ <sup>c</sup> , 15	- <sup>f</sup> 12 <sup>b</sup> , 13 <sup>b</sup> , 15 <sup>b</sup>
15	68.31	CH <sub>2</sub>	3.88	m, 2H	14 $\alpha$ , 14 $\beta$	13 <sup>b</sup> , 16 <sup>b</sup>
16	108.28	CH	5.64 ( $\beta$ )	d (5.1)	13 $\beta$ <sup>c</sup>	11, 13, 15, 12 <sup>b</sup> or 14 <sup>b</sup>
17	16.71	CH <sub>3</sub>	0.90	d (6.5)	8 $\beta$	6 <sup>c</sup> , 7, 8, 9
18	50.20	CH <sub>2</sub>	2.44 (A) 3.00 (B)	d (4.4) d (4.4)	18B 18A	3 <sup>c</sup> , 4 <sup>c</sup> 4 <sup>c</sup>
19	91.46	CH	6.81	s		4, 6, 1 <sup>c</sup>
20	14.06	CH <sub>3</sub>	1.16	s		8, 5 or 9 or 10, 11
1'(C=O)	166.39	C				
2'	128.89	C				
3'	138.46	CH	7.10	qq (7.1, 1.4)	4', 5' <sup>c</sup>	1 <sup>h</sup> , 4', 5', 5 <sup>b</sup>
4'	14.57	CH <sub>3</sub>	1.81	dq (7.1, 1.2)	3', 5' <sup>c</sup>	1 <sup>c</sup> , 2', 3'
5'	11.94	CH <sub>3</sub>	1.89	qui = dq (1.2)	3' <sup>c</sup> , 4' <sup>c</sup>	1', 2', 3'
CH <sub>3</sub> CO	170.07	C				
CH <sub>3</sub> CO	21.03	CH <sub>3</sub>	1.80	s		CH <sub>3</sub> CO,

<sup>a</sup> CDCl<sub>3</sub>,  $^1\text{H}$  600.13 MHz,  $\delta_{\text{ref}}$  7.26;  $^{13}\text{C}$  150.9 MHz,  $\delta_{\text{ref}}$  77.0 ppm; All these assignments were in agreement with COSY, HSQC, HMBC and NOESY spectra; <sup>b</sup> These correlations are weak. <sup>c</sup> These correlations are extremely weak; <sup>d</sup>  $^1\text{H}$  signal of H-3 $\beta$  is overlapped and only  $^3J = 2.7$  Hz could be determined; <sup>e</sup> data from HSQC <sup>f</sup> could not be determined because of the overlapped signals. <sup>g-h</sup> signals with the same letters may be interchangeable.

**Table 2:** The NOESY correlations and distances between non-geminal protons in scutecyprin<sup>a</sup>.

NOESY	Distance, Å	NOESY	Distance, Å
1 $\alpha$ - 2 $\beta$	2.43	7 $\beta$ - 17 (CH <sub>3</sub> )	3.01 <sup>b</sup>
1 $\beta$ - 2 $\beta$	2.58	8 $\beta$ - 10 $\beta$	2.35
1 $\alpha$ - 11 $\alpha$	2.10	8 $\beta$ - 17 (CH <sub>3</sub> )	2.66 <sup>b</sup>
1 $\alpha$ - 20 (CH <sub>3</sub> )	3.02 <sup>b</sup>	10 $\beta$ - 11 $\alpha$	1.92 <sup>c</sup>
1 $\beta$ - 11 $\alpha$	2.10	10 $\beta$ - 12 $\beta$	1.82 <sup>c</sup>
2 $\beta$ - 3 $\alpha$	2.55	11 $\alpha$ - 15	3.85
2 $\beta$ - 3 $\beta$	2.48	11 $\alpha$ - 12 $\alpha$	2.39
3 $\beta$ - 18A	2.44	11 $\alpha$ - 17 (CH <sub>3</sub> )	1.24 <sup>c</sup>
6 $\beta$ - 7 $\beta$	2.41	11 $\alpha$ - 20 (CH <sub>3</sub> )	1.24 <sup>c</sup>
6 $\beta$ - 8 $\beta$	2.58	12 $\beta$ - 13 $\beta$	2.37
6 $\beta$ - 10 $\beta$	2.69	13 $\beta$ - 16 $\beta$	2.42
6 $\beta$ - 18B	2.12	13 $\beta$ - 14 $\beta$	2.39
7 $\alpha$ - 19 $\alpha$	2.42	14 $\beta$ - 15 $\beta$	2.44
7 $\alpha$ - 20 (CH <sub>3</sub> )	3.07 <sup>b</sup>	14 $\alpha$ - 15 $\alpha$	2.43
7 $\beta$ - 8 $\beta$	2.50		

<sup>a</sup> Distances as calculated by quantum chemistry; <sup>b</sup> average distance; <sup>c</sup> minimum distance (see the text).

**H-3 $\beta$  assignment.** The assignment of  $\delta_{\text{H}}$  1.79 (1H, dd,  $J = ?$ , 2.8) to H-3 $\beta$  (ax) is straightforward, despite the overlap of its low-field part with the acetoxy singlet at  $\delta$  1.80. Correlations are observed in the COSY spectrum of  $\delta_{\text{H}}$  1.79 with  $\delta_{\text{H}}$  2.55 (H-3 $\alpha$ ) and  $\delta_{\text{H}}$  4.18 (H-2 $\beta$ ). In the HSQC, the proton resonances of H-3 $\alpha$  and H-3 $\beta$  ( $\delta_{\text{H}}$  2.55 and  $\delta_{\text{H}}$  1.79) have cross peaks with  $\delta_{\text{C}}$  36.90 (C-3). The HMBC correlations for H-3 $\beta$  (ax) in Table 1 confirm additionally its assignment. It is interesting to note the two NOESY correlations H-18A-H-3 $\beta$  and H-18B-H-6 $\beta$  (see Table 2), which specify the C-18 protons assignment; they confirmed the previous reports – a NOE experiment had established the H-18B-H-6 $\beta$  relationship in ajugarins for A ring chair structures [10], and jodrellin B as C-2, C-19 oxygen bridged (boat A ring) [11].

**H-7 $\beta$  and H-7 $\alpha$  assignments.** The two cross peaks in the HSQC spectrum of  $\delta_{\text{C}}$  33.16 (C-7) with  $\delta_{\text{H}}$  1.65 (overlapped) and  $\delta_{\text{H}}$  1.38 (1H, ddd,  $J=12.6, 4.4, 2.7$  Hz) identifies them as H<sub>2</sub>-7 methylene

protons. In the 2D NOESY spectrum there are two cross peaks of  $\delta_{\text{H}}$  1.38 with  $\delta_{\text{H}}$  4.62 (H-6 $\beta$ ) and  $\delta_{\text{H}}$  0.90 (H<sub>3</sub>-17, weak correlation), which hints at  $\delta_{\text{H}}$  1.38 being the signal for H-7 $\beta$ . The NOESY cross peak  $\delta_{\text{H}}$  1.65 -  $\delta_{\text{H}}$  6.81, i.e. H-7 $\alpha$  - H-19, supports the assignment of  $\delta_{\text{H}}$  1.38 to H-7 $\beta$  and that around  $\delta_{\text{H}}$  1.65 to H-7 $\alpha$ .

**H-8 $\beta$  assignment.** As can be seen from the HSQC spectrum, just one methine proton signal lays in the  $\delta_{\text{H}}$  1.68–1.59 region (cross peak  $\delta_{\text{H}}$  1.64– $\delta_{\text{C}}$  35.16, C-8). One of the proton signals in this zone gives a COSY correlation with  $\delta_{\text{H}}$  0.90 (1H, d,  $J=6.6$  Hz, H<sub>3</sub>-17); this could only be H-8 $\beta$  and none of H-1 $\beta$ , H-7 $\alpha$  (ax), H-12 $\alpha$ , and H-14 $\alpha$ . These reasons are enough to assign  $\delta_{\text{H}}$  1.64 to H-8 $\beta$  (ax). The other COSY cross peaks with  $\delta_{\text{H}}$  around 1.64 have on the second axis  $\delta_{\text{H}}$  4.62 (H-6 $\beta$ ), 4.08 (H-11 $\alpha$ ), 3.88 (H<sub>2</sub>-15), 2.36 (H-1 $\alpha$ ), 2.15 (H-14 $\beta$ ), 2.04 (H-10 $\beta$ ), 1.97 (H-12 $\beta$ ), and 1.38 (H-7 $\beta$ ); they are attributed to couplings between H-7 $\alpha$ -H-6 $\beta$ , H-12 $\alpha$ -H-11 $\alpha$ , 14 $\alpha$ -H<sub>2</sub>-15, H-1 $\beta$ -H-1 $\alpha$ , H-14 $\alpha$ -H-14 $\beta$ , H-1 $\beta$ -H-10 $\beta$ , H-12 $\alpha$ -H-12 $\beta$  and H-7 $\alpha$ -H-7 $\beta$ .

**H-10 $\beta$  assignment.** There are two COSY cross peaks from  $\delta_{\text{H}}$  2.04 (dd,  $J = 11.4, 4.3$  Hz, 1H), namely with  $\delta_{\text{H}}$  1.60 and  $\delta_{\text{H}}$  2.36, pointing it out obviously as H-10 $\beta$ . The second correlation is weaker [12] than the first one, which is consistent with dihedral angles H-1 $\beta$ -C-1-C-10-H-10 $\beta$  and H-1 $\alpha$ -C-1-C-10-H-10 $\beta$  (calculated by quantum chemistry 4.5° and 123°, respectively). The HMBC correlations for H-10 $\beta$  to C-1, C-4, C-9 and C-20, as well as H-11-C-10 and H<sub>3</sub>-20-C-10, confirm this assignment.

**H-12 $\alpha$  and H-12 $\beta$  assignments.** Bruno *et al.* could not obtain an unambiguous assignment for C-7, C-12 and C-14 (reported as  $\delta_{\text{C}}$  32.6, 33.1 and 33.5, with a statement “assignments may be reversed”) [5]. In our  $^1\text{H}$ -broadband-decoupled  $^{13}\text{C}$  NMR spectrum these shifts were  $\delta_{\text{C}}$  32.64, 33.16 and 33.53, i.e. nearly the same as

the above mentioned. In an enlarged section of the HSQC spectrum, the two cross peaks with  $\delta_{\text{C}}$  32.64 (the lowest  $\delta_{\text{C}}$ ) are well separated in the  $\delta_{\text{C}}$  axis from the other four cross peaks (overlapped in this axis); here, use is made of the fact that there are five proton resonances in the 1.68–1.59 ppm region, i.e. there are two overlapped cross peaks at  $\delta_{\text{H}}$  1.65 /  $\delta_{\text{C}}$  33.24. The assignment of  $\delta_{\text{C}}$  32.64 to C-14 and, respectively,  $\delta_{\text{H}}$  2.15 to H-14 $\beta$  and  $\delta_{\text{H}}$  1.70 to H-14 $\alpha$ , is thoroughly discussed in the next paragraph. Thus, considering that H-7 $\alpha$  and H-7 $\beta$  have  $\delta_{\text{H}}$  1.67 (overlapped) and  $\delta_{\text{H}}$  1.38, the HSQC cross peaks with  $\delta_{\text{H}}$  1.97 and  $\delta_{\text{H}}$  around  $\delta$  1.65 are discussed here. Some of the COSY cross peaks with  $\delta_{\text{H}}$  around 1.64 (all are listed above in the “H-8 $\beta$  assignment” paragraph) and the fact that  $\delta_{\text{H}}$  1.97 shows strong correlation in the COSY spectrum with  $\delta_{\text{H}}$  1.64 (H-12 $\alpha$ ), 2.85 (H-13 $\beta$ ) and 4.08 (H-11 $\alpha$ ) confirm that the C-12 methylene protons have signals at  $\delta_{\text{H}}$  1.97 and around  $\delta_{\text{H}}$  1.65. Furthermore, in the NOESY spectrum, there is a cross peak  $\delta_{\text{H}}$  1.97 /  $\delta_{\text{H}}$  2.85 (H-12 $\beta$  / H-13 $\beta$ ), but no cross peak  $\delta_{\text{H}}$  1.97 /  $\delta_{\text{H}}$  4.08 ppm (H-12 $\beta$  / H-11 $\alpha$ ), so that  $\delta_{\text{H}}$  1.97 is assigned to H-12 $\beta$ . Obviously  $\delta_{\text{H}}$  1.67 is assigned to the H-12 $\alpha$  proton. Moreover, there is a NOESY cross peak  $\delta_{\text{H}}$  1.67 /  $\delta_{\text{H}}$  4.08 (H-11 $\alpha$ ) and an extremely weak cross peak  $\delta_{\text{H}}$  1.65 /  $\delta_{\text{H}}$  2.85 (H-12 $\alpha$  / H-13 $\beta$ ). Here it is interesting to note a NOESY correlation between H-12 $\beta$  and H-10 $\beta$ . The molecular geometry calculated by quantum chemistry represents the most stable conformer of scutecyprin and does not account for possible rotation around the C-10 – C-11 bond. In solution, such rotation is possible, and that is why the distance between H-12 $\beta$  and H-10 $\beta$  varies with time. A minimum distance of 1.82 Å between H-12 $\beta$  and H-10 $\beta$  is found when the dihedral angle C-10 – C-9 – C-11 – C12 is changed in the 0–360° range, thus justifying this NOESY correlation (see Table 2).

**H-14 $\alpha$  and H-14 $\beta$  assignments.** As mentioned above, the carbon signal of C-14 is close to those of C-7 and C-12, but in the HSQC spectrum the cross peaks of the methylene protons at C-14 are distinguishable from those of the C-7 and C-12 methylene groups. The COSY and HMBC correlations of  $\delta_{\text{H}}$  1.68 listed in Table 1 prove that it is for one of the C-14 protons; the same refers to  $\delta_{\text{H}}$  2.15. Additionally,  $\delta_{\text{H}}$  2.15 is NOESY-coupled with  $\delta_{\text{H}}$  1.68 (H-14 $\alpha$ ), 2.85 (H-13 $\beta$ ) and 3.88 (H-15). On the other side,  $\delta_{\text{H}}$  1.68 has NOESY cross peaks with  $\delta_{\text{H}}$  2.15 (H-14 $\beta$ ) and 3.88 (H-15), but a NOESY correlation  $\delta_{\text{H}}$  1.68/ $\delta_{\text{H}}$  2.85 (H-14 $\alpha$ /H-13 $\beta$ ) is extremely weak as expected from the stereochemistry of the hexahydro furofuran moiety. That is why  $\delta_{\text{H}}$  2.15 is assigned to H-14 $\beta$ , and  $\delta_{\text{H}}$  1.68 to H-14 $\alpha$ .

The H-12 $\alpha$  and H-14 $\alpha$  assignment is supported by the molecular geometry calculated by quantum chemistry. The most favored conformation of the two five-member rings in the hexahydrofurofuran moiety is of the envelope type. This leads to the two dihedral angles, H-13 $\beta$ –C-13–C-12–H-12 $\alpha$  and H-13 $\beta$ –C-13–C-14–H-14 $\alpha$  being nearly 90°. According to the Karplus Equation [12] the corresponding vicinal coupling constants have to be very small, as it is in our case: there is no COSY correlation of  $\delta_{\text{H}}$  2.85 (H-13 $\beta$ ) with a proton signal in the 1.68–1.59 ppm range (where the H-12 $\alpha$  and H-14 $\alpha$  overlap with H-1 $\beta$ , H-7 $\alpha$  and H-8 $\beta$ ).

The  $^{13}\text{C}$  NMR spectrum of scutecyprin was searched in a database of nearly 39,000 fully-assigned  $^{13}\text{C}$  NMR spectra. The search method, the so called interpretive library search [13], retrieves substructures common to both the unknown and reference compounds and estimates the probability of substructure-presence by comprehensive statistics. Two of the retrieved substructures with high estimated prediction accuracy contain a hexahydrofurofuran

moiety, thus confirming, at least, the  $^{13}\text{C}$  assignment of its carbons. The predicted chemical shifts by quantum chemistry calculations given in the "Supplementary Data" section support most of the assignments discussed above; only for H-1 $\alpha$  and H-1 $\beta$  were the order of the predicted shift values reversed from that of the experimental ones. The  $^{13}\text{C}$  shift predictions have a standard error of 7.2 ppm with a maximum deviation of 13.9 ppm (for carbon 3') and those for the  $^1\text{H}$  shift have a standard error of 0.44 ppm with a maximum deviation of 1.3 ppm (for H-3 $\alpha$ ).

## Experimental

**General:**  $^1\text{H}$ ,  $^{13}\text{C}$  and 2D NMR spectra of **1** were recorded on a Bruker Avance II+ 600MHz NMR spectrometer operating at 600.130 MHz ( $^1\text{H}$ ) and 150.903 MHz ( $^{13}\text{C}$ ), using TMS as internal standard and  $\text{CDCl}_3$  as solvent. The temperature was kept at 293.0 K for all NMR experiments. Chemical shifts ( $\delta$ ) are expressed in ppm and coupling constants ( $J$ ) in Hertz. 1D and 2D NMR spectra were recorded using the standard Bruker pulse. For  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and 2D NMR spectral data of **1** see Table 1. The IR spectrum of **1** was registered in a KBr pellet on a VERTEX 70 FT-IR spectrometer (Bruker Optics) from 4000  $\text{cm}^{-1}$  to 400  $\text{cm}^{-1}$  at a resolution of 2  $\text{cm}^{-1}$  with 25 scans.

**Plant material:** Aerial parts of *Scutellaria altissima* L. were collected when in flower in June 2012 around Balkanec village, near Troian, Bulgaria. The plant was identified by Prof. R. D. Mladenov (Dept. Botany, Plovdiv University) and voucher specimens (n. 17494) were deposited in the Herbarium of the Higher Institute of Agriculture at Plovdiv, Bulgaria.

**Extraction and isolation:** Dried and finely powdered stems of *Scutellaria altissima* (200 g) were extracted with  $\text{Me}_2\text{CO}$  (2 x 2 L) at room temperature for 1 week. After filtration, the solvent was evaporated to dryness under reduced pressure yielding a gum (3.5 g). This residue was chromatographed (CC silica gel, deactivated with 10 %  $\text{H}_2\text{O}$ , w/w, 40 g; light petroleum, light petroleum/EtOAc solvent gradient from 10:0 to 6:4 as eluent). Fractions eluted with light petroleum/EtOAc (8:2) were enriched with scutecyprin (**1**). After removal of the solvent, crude **1** was obtained (25 mg). Acetone re-crystallization yielded 18 mg purified **1**.

## Scutecyprin (1)

Colorless prisms from acetone.

MP: 145–148°C (lit. [5] amorphous solid, MP: 65–70°C).

IR (KBr): 3050, 2961, 2930, 1731, 1710, 1650, 1454, 1373, 1263, 1246, 1083, 1022, 969, 939, 920, 880, 870, 733  $\text{cm}^{-1}$ .

$^1\text{H}$  and  $^{13}\text{C}$  NMR: Table 1.

**Computational details:** To verify the proposed assignments, quantum chemistry calculations were performed by using Gaussian 98, Revision A.7 [14]. For the geometry optimization the B3LYP density functional with a 6-31G(d) basis set was used, and for the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra prediction the B3LYP / 6-311+G(2d,p) calculations were carried out at the optimized geometry. The interatomic distances in the optimized structure are presented in Table 2, together with NOESY correlations.

**Supplementary data:** Tables of complete spectral data and the  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and 2D NMR spectra (with enlarged detailed sections for multiplets and cross peaks) are included in a "Supplementary Data" section.

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