



NEO-CLERODANE DITERPENOIDS FROM SCUTELLARIA ALPINA

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Key Word Index—*Scutellaria alpina*; Labiatae; *neo*-clerodane diterpenes; scutalpins G–M; absolute configuration; CD exciton chirality method.

Abstract—Seven new *neo*-clerodane derivatives, scutalpins G–M, have been isolated from the acetone extract of the aerial parts of *Scutellaria alpina*, in addition to the previously known diterpenes scutalpins B and D, and scutecolumnin C. The structures of the new compounds were established by spectroscopic means as (13S)-11 β ,19-diacetoxy-6 α -benzoyloxy-4 α ,18;8 β ,13-diepoxy-*neo*-clerodan-15,16-olide (scutalpin G), (11S)-11,19-diacetoxy-6 α -(2'S)-methylbutyryloxy-4 α ,18-epoxy-8 β -hydroxy-*neo*-clerod-13-en-15,16-olide (scutalpin H), (11S)-11,19-diacetoxy-6 α -benzoyloxy-4 α ,18-epoxy-8 β -hydroxy-*neo*-clerod-13-en-15,16-olide (scutalpin I), (11E)-19-acetoxy-6 α -benzoyloxy-4 α ,18-epoxy-8 β -hydroxy-*neo*-cleroda-11,13-dien-15,16-olide (scutalpin J), (11E)-19-acetoxy-6 α ,7 β -dibenzoyloxy-4 α ,18-epoxy-8 β -hydroxy-*neo*-cleroda-11,13-dien-15,16-olide (scutalpin K), 19-acetoxy-6 α ,7 β -dibenzoyloxy-4 α ,18-epoxy-8 β -hydroxy-*neo*-clerod-13-en-15,16-olide (scutalpin L) and (11S,13S,14S,16S)-6 α ,14,19-triacetoxy-4 α ,18;11,16;15,16-triepoxy-*neo*-clerodane (scutalpin M). In the case of the 6 α ,7 β -dibenzooate derivatives (scutalpins K and L) their *neo*-clerodane absolute configuration was established by the CD exciton chirality method.

INTRODUCTION

The *neo*-clerodane diterpenes isolated from *Scutellaria* species possess interesting biological activities [1–4], in particular as insect antifeedants and against plant pathogenic fungi. In a continuation of our search for new *neo*-clerodanes in *Scutellaria* plants [4–8], we have now investigated *S. alpina* collected in Italy. The acetone extract of the aerial parts of this plant provided the already known diterpenes scutalpins D and B (1 and 2, respectively) and scutecolumnin C (3), previously isolated from *S. alpina* subsp. *javalambreensis* growing in Spain [8] and *S. columnae* [5], together with seven new *neo*-clerodane derivatives, scutalpins G–M, whose structures (4–10, respectively) were established.

RESULTS AND DISCUSSION

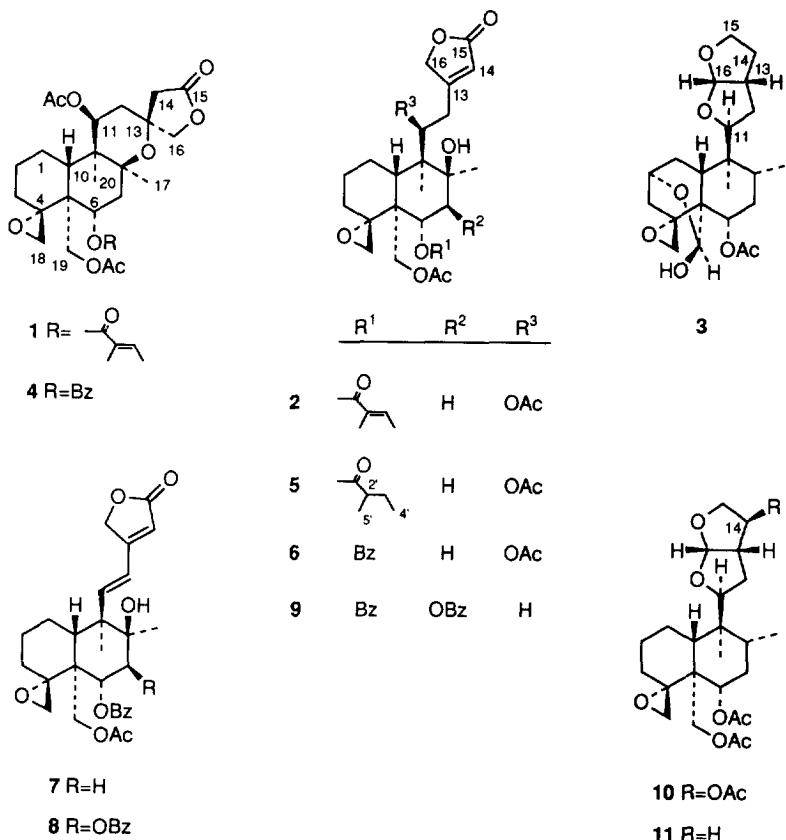
Scutalpin G (4) was assigned the molecular formula C₃₁H₃₈O₁₀. Its ¹H and ¹³C NMR spectra (Tables 1 and 2, respectively) were almost identical with those of scutalpin D (1) [8]. In fact, the observed differences were consistent with the existence in the former of a benzoate group [δ _H 7.97 *dd* (H-2' and H-6'), 7.50 *tt* (H-4'), 7.38 *td* (H-3' and H-5'), J_{2',3'} = 8.3 Hz, J_{2',4'} = 1.3 Hz, J_{3',4'} = 7.8 Hz; δ _C 165.4 *s* (PhCOO), 130.8 *s* (C-1'), 129.7 *d* (C-2' and C-6'),

128.1 *d* (C-3' and C-5') and 132.7 *d* (C-4')] instead of the tigloyloxy substituent present in the latter [8].

The location of the acetyl and benzoyl substituents in scutalpin G (4) was established from the heteronuclear multiple bond connectivity (HMBC) spectrum, which showed cross peaks of correlation through three bonds between the carbonyl carbons of the two acetoxy groups (δ 170.1 *s* and 169.7 *s*) and the proton at δ 5.36 (H-1 α) and the protons of the C-19 methylene group (δ 4.66 and 4.75), whereas the carbonyl carbon of the benzoate (δ 165.4) was connected with the H-6 β proton (δ 5.33). NOE experiments confirmed that scutalpin G (4) and scutalpin D (1) [8] possessed the same stereochemistry, because irradiation at δ 0.97 (Me-20 protons) caused a positive NOE enhancement of the signals of the H-1 α (δ 1.63), H-7 α (δ 1.95), H-11 α (δ 5.36), Me-17 (δ 1.27) and C-19 methylene (δ 4.66 and 4.75) protons, whereas a positive NOE enhancement of the signals of the H-7 α , H-7 β (δ 1.86), H-11 α , Me-20 and C-16 methylene protons (δ 4.21 and 4.39) was observed when the Me-17 protons (δ 1.27) were irradiated. In particular, the NOE between the Me-17 and C-16 methylene protons, but not between Me-17 and those of the C-14 methylene group (at δ 2.57 and 3.00), firmly supported [7–9] the relative stereochemistry of the spiran centre at C-13 in this new diterpenoid.

From all the above data, it was evident that scutalpin G had the structure depicted in 4, except for its absolute configuration.

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Scutalpin B (2) [8] and the new diterpenoids scutalpins H ($\text{C}_{29}\text{H}_{42}\text{O}_{10}$) and I ($\text{C}_{31}\text{H}_{38}\text{O}_{10}$) (5 and 6, respectively), gave ^1H and ^{13}C NMR spectra (ref [8] and Tables 1 and 2) which indicated that all these compounds possessed the same (11*S*)-11,19-diacetoxo-4*α*,18-epoxy-8*β*-hydroxy-*neo*-clerod-13-en-15,16-olide structural framework and that they differed from each other only in the ester group attached to the C-6*α* position. The 6*α*-tigloyloxy group of 2 [8] was substituted by a 2'-methylbutyryloxy group in scutalpin H [5: $\delta_{\text{H}} 0.88$ *t*, 3*H* ($\text{Me-4}'$), 1.08 *d*, 3*H* ($\text{Me-5}'$), 1.39 *septet*, 1*H* (H_A-3'), 1.70 *m*, 1*H* (H_B-3'), 2.23 *m*, 1*H* ($\text{H}-2'$), $J_{2',3'} = 7.0$ Hz, $J_{2',5'} = 7.0$ Hz, $J_{3',4'} = 7.5$ Hz; $\delta_{\text{C}} 175.7$ *s* ($\text{C-1}'$), 41.4 *d* ($\text{C-2}'$), 26.2 *t* ($\text{C-3}'$), 11.6 *q* ($\text{Me-4}'$) and 16.3 *q* ($\text{Me-5}'$)] and by a benzoate in scutalpin I [6: $\delta_{\text{H}} 7.98$ *dd* ($\text{H-2}'$ and $\text{H-6}'$), 7.52 *tt* ($\text{H-4}'$), 7.39 *td* ($\text{H-3}'$ and $\text{H-5}'$), $J_{2',3'} = 8.4$ Hz, $J_{2',4'} = 1.3$ Hz, $J_{3',4'} = 7.7$ Hz; $\delta_{\text{C}} 166.0$ *s* (PhCOO), 130.6 *s* ($\text{C-1}'$), 129.7 *d* ($\text{C-2}'$ and $\text{C-6}'$), 128.2 *d* ($\text{C-3}'$ and $\text{C-5}'$) and 132.9 *d* ($\text{C-4}'$)]. This conclusion was rigorously corroborated by the HMBC spectra of 5 and 6, in which connectivities through three bonds between the carbonyl carbons of the 2'-methylbutyrate (5: δ 175.7) and the benzoate (6: δ 166.0) and the H-6*β* proton (at δ 5.15 and 5.41 in 5 and 6, respectively) were observed.

The absolute stereochemistry of the C-2' asymmetric centre of the 2'-methylbutyric ester group of scutalpin H (5) was not ascertained. However, on biogenetic grounds, it is reasonable to assume that it possesses a 2'S absolute configuration as in scutalpin A, a *neo*-clerodane diterpen-

oid recently isolated by us from *Scutellaria alpina* collected in Bulgaria, whose absolute stereochemistry was established by X-ray diffraction analysis [7].

The ^1H and ^{13}C NMR spectra of scutalpin J (7, $\text{C}_{29}\text{H}_{34}\text{O}_8$) revealed that this new diterpenoid had the same substituted decalin moiety as that in 6 (Tables 1 and 2). In addition, it possessed an (11*E*)-11,13-dien-15,16-olide side-chain at C-9, in which the C-11 to C-16 carbons are involved [λ_{max} 259 nm ($\log \epsilon$ 4.44), $\delta_{\text{H}} 6.29$ *d* (H-11), 6.39 *br d* (H-12), 5.91 *br s* (H-14), 4.99 *br s* (2H-16), $J_{11,12} = 16.8$ Hz; $\delta_{\text{C}} 146.8$ *d* (C-11), 122.0 *d* (C-12), 161.9 *s* (C-13), 114.9 *d* (C-14), 174.0 *s* (C-15) and 70.6 *t* (C-16)]. This structural part has previously been found in some *neo*-clerodane diterpenes isolated from other *Scutellaria* species [10-13]. Consequently, scutalpin J has structure 7.

The 7*β*-benzoyloxy derivative of scutalpin J was also present in the acetone extract of *S. alpina*. The ^1H and ^{13}C NMR spectra of this compound (8, scutalpin K, $\text{C}_{36}\text{H}_{38}\text{O}_{10}$) showed signals for two benzoate groups and for an AB system corresponding to the C-6*β* and C-7*α* axial protons ($\delta_{\text{H-6\beta}} 5.77$ *d*, $\delta_{\text{H-7\alpha}} 5.85$ *d*, $J_{6\beta,7\alpha} = 10.0$ Hz) [7] instead of the ABX pattern of scutalpin J (7: $\delta_{\text{H-6\beta}} 5.53$ *dd*, $\delta_{\text{H-7\alpha}} 2.07$ *dd*, $\delta_{\text{H-7\beta}} 1.82$ *dd*, $J_{6\beta,7\alpha} = 11.7$ Hz, $J_{6\beta,7\beta} = 4.9$ Hz, $J_{7\alpha,7\beta} = 14.6$ Hz), whereas the remaining signals were almost identical in both compounds (Tables 1 and 2). Apart from the above data, the existence of an ester group at the C-7*β* position in scutalpin K (8) was supported by the ^{13}C NMR spectrum of this compound when compared with that of scutalpin J (7): downfield

Table 1. ^1H NMR spectral data of 4-9 (CDCl_3)^{*}

H	4	5	6	7	8	9	J (Hz)	4	5	6	7	8	9
1 α	1.63 <i>dddd</i>	~1.70 \dagger	1.76 <i>dddd</i>	~1.60 \ddagger	~1.61 <i>dddd</i>	1.73 <i>dddd</i>	1 $\alpha,1\beta$	12.4	†	12.8	†	12.7	13.2
1 β	2.31 <i>dddd</i>	~1.90 \ddagger	~1.92 \dagger	~1.38 \ddagger	~1.43 \ddagger	~1.54 \dagger	1 $\alpha,2\alpha$	3.9	†	3.7	†	3.7	3.2
2 α	1.96 <i>m</i>	~1.95 \dagger	~1.95 \dagger	~1.91 \dagger	1.91 <i>m</i>	~1.99 \dagger	1 $\alpha,2\beta$	13.7	†	12.9	†	12.8	13.2
2 β	1.47 <i>ddddd</i>	~1.50 \dagger	1.56 <i>dddd</i>	~1.48 \dagger	~1.50 \dagger	~1.52 \dagger	1 $\beta,2\alpha$	2.0	†	†	†	†	†
3 α	2.02 <i>m</i>	~2.10 \dagger	2.09 <i>dddd</i>	~2.10 \dagger	~2.04 \dagger	~2.02 \dagger	1 $\beta,2\beta$	4.3	†	3.9	†	†	†
3 β	1.04 <i>ddd</i>	~1.08 \dagger	1.10 <i>ddd</i>	~1.06 \dagger	~1.05 \dagger	~1.06 \dagger	2 $\alpha,2\beta$	13.2	†	12.9	†	12.8	†
6 β	5.33 <i>br dd</i>	5.15 <i>br dd</i>	5.41 <i>br dd</i>	5.53 <i>br dd</i>	5.77 <i>br d</i>	5.66 <i>br d</i>	2 $\alpha,3\alpha$	3.9	†	3.0	†	†	†
7 α	1.95 <i>dd</i>	~2.04 \dagger	2.20 <i>dd</i>	2.07 <i>dd</i>	5.85 <i>d</i>	5.78 <i>d</i>	2 $\alpha,3\beta$	3.1	†	3.1	†	†	†
7 β	1.86 <i>dd</i>	1.49 <i>dd</i>	1.70 <i>dd</i>	1.82 <i>dd</i>	—	—	2 $\beta,3\alpha$	13.1	†	13.4	†	†	†
10 β	2.39 <i>dd</i>	~2.22 \dagger	2.31 <i>dd</i>	2.31 <i>dd</i>	2.43 <i>dd</i>	2.39 <i>dd</i>	2 $\beta,3\beta$	4.3	†	3.9	†	†	†
11A (α in 4)	5.36 <i>dd</i>	5.53 <i>br d</i>	5.58 <i>dd</i>	6.29 <i>d</i>	6.38 <i>d</i>	1.62 <i>ddd</i>	3 $\alpha,3\beta$	13.4	†	13.4	†	†	†
11B	—	—	—	—	—	1.95 <i>ddd</i>	6 $\beta,7\alpha$	11.5	11.7	11.7	11.7	10.0	10.1
12A (β in 4)	1.88 <i>t</i>	2.53 <i>dd</i>	2.58 <i>dd</i>	6.39 <i>br d</i>	6.44 <i>br d</i>	2.27 <i>ddd</i>	6 $\beta,7\beta$	6.4	4.4	4.4	4.9	—	—
12B (α in 4)	2.04 <i>dd</i>	3.53 <i>br d</i>	3.56 <i>br d</i>	—	—	3.11 <i>ddd</i>	7 $\alpha,7\beta$	13.9	14.5	14.4	14.6	—	—
14A	2.57 <i>d</i>	5.84 <i>br s</i>	5.86 <i>br s</i>	5.91 <i>br s</i>	5.95 <i>br s</i>	5.83 <i>br s</i>	10 $\beta,1\alpha$	12.6	†	12.6	12.4	12.6	12.6
14B	3.00 <i>d</i>	—	—	—	—	10 $\beta,1\beta$	3.1	†	2.6	2.7	2.6	2.6	2.6
16A	4.21 <i>d</i>	4.65 <i>br d</i>	4.67 <i>dd</i>	4.99 <i>br s</i>	5.00 <i>br s</i>	4.74 <i>br s</i>	11 $\alpha,11\beta$	—	—	—	—	—	12.2
16B	4.39 <i>d</i>	4.85 <i>br d</i>	4.87 <i>dd</i>	(2H)	(2H)	(2H)	11 $\alpha,12\alpha$	13.2	10.5	10.7	16.8	16.7	12.2
Me-17	1.27 <i>s</i>	1.30 <i>s</i>	1.34 <i>s</i>	1.09 <i>s</i>	1.07 <i>s</i>	1.21 <i>s</i>	11 $\alpha,12\beta$	4.2	<1.0	1.5	—	—	4.2
18A \ddagger	2.25 <i>d</i>	2.24 <i>d</i>	2.27 <i>d</i>	2.27 <i>d</i>	2.34 <i>d</i>	2.32 <i>d</i>	11B,12A	—	—	—	—	—	4.2
18B \ddagger	3.10 <i>dd</i>	3.02 <i>dd</i>	3.12 <i>dd</i>	3.15 <i>dd</i>	3.38 <i>dd</i>	3.36 <i>dd</i>	11B,12B	—	—	—	—	—	12.2
19A	4.66 <i>br d</i>	4.49 <i>br d</i>	4.71 <i>br d</i>	4.64 <i>br d</i>	4.76 <i>d</i>	4.75 <i>d</i>	12A,12B	13.1	15.2	15.3	—	—	14.9
19B	4.75 <i>d</i>	4.71 <i>d</i>	4.75 <i>d</i>	4.79 <i>d</i>	4.81 <i>br d</i>	4.81 <i>br d</i>	14A,14B	17.3	—	—	—	—	—
Me-20	0.97 <i>s</i>	0.76 <i>s</i>	0.82 <i>s</i>	1.07 <i>s</i>	1.27 <i>s</i>	1.06 <i>s</i>	14A,16A	0	<1.0	1.8	<1.0	<1.0	<1.0
OAc	2.08 <i>s</i>	2.09 <i>s</i>	2.06 <i>s</i>	2.04 <i>s</i>	2.04 <i>s</i>	2.01 <i>s</i>	14A,16B	0	<1.0	1.9	<1.0	<1.0	<1.0
2.03 <i>s</i>	2.00 <i>s</i>	2.02 <i>s</i>	—	—	—	—	16A,16B	9.0	17.1	17.3	0	0	0
OBz \parallel	—	—	—	—	—	—	18A,18B	3.9	4.0	3.9	3.9	3.9	3.9
2 \cdot 6'	7.97 <i>dd</i>	7.98 <i>dd</i>	7.97 <i>dd</i>	7.87 <i>dd</i>	7.86 <i>dd</i>	18B,3 α	2.2	2.2	2.2	2.2	2.2	2.2	2.2
3 \cdot 5'	7.38 <i>td</i>	—	—	7.75 <i>dd</i>	7.75 <i>dd</i>	19A,19B	12.2	12.2	12.3	12.2	12.2	12.2	12.2
4'	7.50 <i>tt</i>	—	—	7.33 <i>td</i>	7.33 <i>td</i>	19A,6 β	<0.3	<0.3	<0.3	<0.3	0	0	0
	7.52 <i>tt</i>	7.52 <i>tt</i>	7.52 <i>tt</i>	7.47 <i>tt</i>	7.47 <i>tt</i>	19B,6 β	0	0	0	0	<0.3	<0.3	<0.3
	—	—	—	7.38 <i>tt</i>	7.38 <i>tt</i>	—	—	—	—	—	—	—	—

* At 500 MHz, except for 7 (300 MHz). Chemical shifts are relative to residual CHCl_3 (δ 7.25). All these assignments were in agreement with the HMQC (Heteronuclear Multiple Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Connectivity) spectra.

\ddagger Overlapped signal. The chemical shift of these protons was measured on the HMQC spectra.

\ddagger *Exo* hydrogen with respect to ring B.

\ddagger *Endo* hydrogen with respect to ring B.

\parallel *J* values for the benzoates of 4 and 6-9: 2'(6),3'(5)=8.3 Hz; 2'(6)',4'=1.3 Hz; 4',3'(5)=7.7 Hz.

\parallel 2'-Methylbutyryloxy substituent: δ ~2.23 (H-2), 1.39 *septet* (H-3'), ~1.70 (H-3') \ddagger , 0.88 *t* (Me-4'), 1.08 *d* (Me-5'), $J_{2',3'}=7.0$ Hz, $J_{2',\text{Me-5'}}=7.5$ Hz.

Table 2. ^{13}C NMR spectral data of **4–10** (125.7 MHz, CDCl_3)*

C	4	5	6	7	8	9	10
1	21.8 <i>t</i> †	23.0 <i>t</i>	23.1 <i>t</i>	22.7 <i>t</i>	22.5 <i>t</i>	21.6 <i>t</i>	22.2 <i>t</i>
2	25.1 <i>t</i>	24.8 <i>t</i>	24.8 <i>t</i>	24.9 <i>t</i>	24.7 <i>t</i>	24.8 <i>t</i>	25.0 <i>t</i>
3	32.4 <i>t</i>	32.8 <i>t</i>	32.8 <i>t</i>	32.7 <i>t</i>	32.2 <i>t</i>	32.3 <i>t</i>	32.7 <i>t</i>
4	64.8 <i>s</i>	64.6 <i>s</i>	64.6 <i>s</i>	64.7 <i>s</i>	65.1 <i>s</i>	65.1 <i>s</i>	65.0 <i>s</i>
5	45.5 <i>s</i>	45.3 <i>s</i>	45.5 <i>s</i>	44.9 <i>s</i>	45.9 <i>s</i>	45.8 <i>s</i>	45.6 <i>s</i>
6	68.7 <i>d</i>	68.5 <i>d</i>	69.7 <i>d</i>	69.9 <i>d</i>	70.7 <i>d</i>	70.9 <i>d</i>	71.9 <i>d</i>
7	38.5 <i>t</i>	40.5 <i>t</i>	40.6 <i>t</i>	38.7 <i>t</i>	74.9 <i>d</i>	75.3 <i>d</i>	33.4 <i>t</i>
8	81.8 <i>s</i>	76.5 <i>s</i>	76.6 <i>s</i>	75.3 <i>s</i>	77.3 <i>s</i>	79.1 <i>s</i>	35.7 <i>d</i>
9	42.3 <i>s</i>	46.5 <i>s</i>	46.5 <i>s</i>	47.3 <i>s</i>	48.0 <i>s</i>	42.7 <i>s</i>	40.7 <i>s</i>
10	42.9 <i>d</i>	43.5 <i>d</i>	43.6 <i>d</i>	45.8 <i>d</i>	45.2 <i>d</i>	42.9 <i>d</i>	48.1 <i>d</i>
11	72.5 <i>d</i>	74.1 <i>d</i>	74.1 <i>d</i>	146.8 <i>d</i>	145.7 <i>d</i>	35.0 <i>t</i>	85.4 <i>d</i>
12	34.9 <i>t</i>	33.1 <i>t</i>	33.1 <i>t</i>	122.0 <i>d</i>	122.3 <i>d</i>	25.1 <i>t</i>	29.3 <i>t</i>
13	77.8 <i>s</i>	167.7 <i>s</i>	167.6 <i>s</i>	161.9 <i>s</i>	161.6 <i>s</i>	171.2 <i>s</i>	49.2 <i>d</i>
14	43.8 <i>t</i>	116.7 <i>d</i>	116.8 <i>d</i>	114.9 <i>d</i>	115.5 <i>d</i>	114.7 <i>d</i>	80.0 <i>d</i>
15	171.3 <i>s</i>	173.8 <i>s</i>	173.8 <i>s</i>	174.0 <i>s</i>	173.7 <i>s</i>	173.9 <i>s</i>	73.3 <i>t</i>
16	77.1 <i>t</i>	73.1 <i>t</i>	73.1 <i>t</i>	70.6 <i>t</i>	70.6 <i>t</i>	73.1 <i>t</i>	107.4 <i>d</i>
17	24.2 <i>q</i>	26.8 <i>q</i>	27.0 <i>q</i>	26.5 <i>q</i>	22.4 <i>q</i>	21.7 <i>q</i>	16.6 <i>q</i>
18	48.4 <i>t</i>	48.4 <i>t</i>	48.5 <i>t</i>	48.6 <i>t</i>	49.7 <i>t</i>	49.6 <i>t</i>	48.5 <i>t</i>
19	61.9 <i>t</i>	61.5 <i>t</i>	61.8 <i>t</i>	61.8 <i>t</i>	62.3 <i>t</i>	62.5 <i>t</i>	61.7 <i>t</i>
20	16.2 <i>q</i>	15.9 <i>q</i>	16.0 <i>q</i>	15.1 <i>q</i>	14.6 <i>q</i>	20.8 <i>q</i>	13.9 <i>q</i>
OAc	170.1 <i>s</i>	171.0 <i>s</i>	171.3 <i>s</i>	171.4 <i>s</i>	170.9 <i>s</i>	171.0 <i>s</i>	170.9 <i>s</i>
	169.7 <i>s</i>	170.6 <i>s</i>	170.7 <i>s</i>	21.2 <i>q</i>	21.0 <i>q</i>	21.0 <i>q</i>	170.6 <i>s</i>
	21.2 <i>q</i>	21.1 <i>q</i>	21.2 <i>q</i>	—	—	—	170.1 <i>s</i>
	21.2 <i>q</i>	20.7 <i>q</i>	20.8 <i>q</i>	—	—	—	21.2 <i>q</i>
	—	—	—	—	—	—	21.2 <i>q</i>
	—	—	—	—	—	—	21.0 <i>q</i>
OCOPh	165.4 <i>s</i>	‡	166.0 <i>s</i>	165.9 <i>s</i>	165.9 <i>s</i>	165.7 <i>s</i>	165.7 <i>s</i>
1'	130.8 <i>s</i>		130.6 <i>s</i>	130.6 <i>s</i>	130.1 <i>s</i>	128.9 <i>s</i>	131.0 <i>s</i>
2',6'	129.7 <i>d</i>		129.7 <i>d</i>	129.7 <i>d</i>	129.7 <i>d</i>	129.7 <i>d</i>	129.4 <i>d</i>
3',5'	128.1 <i>d</i>		128.2 <i>d</i>	128.2 <i>d</i>	128.4 <i>d</i>	128.0 <i>d</i>	128.4 <i>d</i>
4'	132.7 <i>d</i>		132.9 <i>d</i>	132.8 <i>d</i>	133.3 <i>d</i>	132.6 <i>d</i>	132.5 <i>d</i>

*Chemical shifts are relative to the solvent signal (CDCl_3 , δ 75.0). All these assignments were confirmed by the HMQC and HMBC spectra.

†Multiplicities were established from the HMQC spectra.

‡2-Methylbutyryloxy substituent: δ 175.7 *s* (C-1'), 41.4 *d* (C-2'), 26.2 *t* (C-3'), 11.6 *q* (C-4') and 16.3 *q* (C-5').

shift of the C-6, C-7 and C-8 carbons ($\Delta\delta +0.8$, +36.2 and +2.0 ppm, respectively) and upfield resonance of the C-17 carbon ($\Delta\delta -4.1$ ppm, γ -gauche effect, see Table 2). Finally, the HMBC spectrum of scutalpin K (**8**) showed correlations between the carbonyl carbon of the benzoates (δ 165.9 and 165.7) and the H-6 β (δ 5.77) and H-7 α (δ 5.85) protons and between the carbonyl carbon of the acetate (δ 170.9) and the C-19 methylene protons (δ 4.76 and 4.81), thus establishing the positions of the acetate (C-19) and the two benzoate (C-6 and C-7) groups.

Scutalpin L (**9**, $\text{C}_{36}\text{H}_{40}\text{O}_{10}$) is the 11,12-dihydro derivative of scutalpin K (**8**). The ^1H and ^{13}C NMR spectra of this diterpenoid were in complete agreement with structure **9**, because they showed almost identical patterns to those of scutalpin K (**8**) for the substituted decalin moiety (Tables 1 and 2), whereas the existence of two vicinal methylene groups at the C-11 and C-12 positions was revealed by four one-proton signals at δ 1.62 *ddd* and 1.95 *ddd* ($\text{H}_{\text{A}}\text{-11}$ and $\text{H}_{\text{B}}\text{-11}$ protons, respectively) and at δ 2.27 *ddd* and 3.11 *ddd* ($\text{H}_{\text{A}}\text{-12}$ and $\text{H}_{\text{B}}\text{-12}$, respectively) instead of the AB system of the 11,12-olefinic protons of scutalpin

8 (see above and Table 1). The ^{13}C NMR spectrum of **9** (Table 2) was also in agreement with the proposed structure ($\delta_{\text{C-11}}$ 35.0 *t* and $\delta_{\text{C-12}}$ 25.1 *t*) and the identical chemical shift of the C-6, C-7 and C-19 carbons in **8** and **9** (Table 2) indicated the same locations of the two benzoates and the acetate in both compounds. The same chemical shifts for the C-19 methylene protons in **8** (δ 4.76 and 4.81) and **9** (δ 4.75 and 4.81), as well as the similarity in the H-6 β and H-7 α proton resonances (**8**: δ 5.77 and 5.85; **9**: δ 5.66 and 5.78, respectively), further supported this point.

The absolute stereochemistry of scutalpines K and L (**8** and **9**, respectively) was established by using the CD exciton chirality method [14]. The 6 α ,7 β -dibenzoyloxy binary system of these compounds showed a negative first and a positive second Cotton effect (**8**: $\Delta\epsilon_{236} -30.7$, $\Delta\epsilon_{222} +2.4$; **9**: $\Delta\epsilon_{238} -21.5$, $\Delta\epsilon_{224} +10.6$), thus establishing a negative chirality and, consequently, a *neo*-clerodane absolute configuration [15] for these diterpenoids.

The last diterpenoid isolated from *Scutellaria alpina*, scutalpin M (**10**, $\text{C}_{26}\text{H}_{38}\text{O}_9$), was devoid of hydroxyl

absorptions in its IR spectrum and its ^1H NMR spectrum (Table 3) was very similar to those of dihydroclerodin (**11**) [16] and other *neo*-clerodane diterpenoids having a hexahydrofuro-furan moiety previously isolated from *Scutellaria* [2, 4–6] and *Ajuga* [17, 18] plants. Scutalpin M (**10**) possessed three acetate groups [δ_{H} 2.08 s, 2.06 s, 1.93 s; δ_{C} 170.9 s, 170.6 s, 170.1 s, 21.2 *q* (double signal) and 21.0 *q*] and a *neo*-clerodane hydrocarbon skeleton (Me-17 at δ 0.84 *d*, J = 6.3 Hz; Me-20 at δ 0.93 s) having a 4 α ,18-oxirane group (δ 2.19 *d* and 2.97 *dd*, J_{gem} = 4.0 Hz), two acetoxyl groups at C-6 α and C-19 positions ($\delta_{\text{H-6}\beta}$ 4.66 *dd*, $J_{6\beta,7\alpha}$ = 11.8 Hz, $J_{6\beta,7\beta}$ = 4.3 Hz; C-19 protons at δ 4.37 *d* and 4.86 *d*, J_{gem} = 12.2 Hz) and a hexahydrofuro-furan moiety (see Tables 1 and 3, resonances for the C-11 to C-16 fragment). The attachment of the third acetoxyl group to the *neo*-clerodane nucleus was revealed by the signal of one proton on a carbon atom bearing an oxygen atom (δ 5.03 *br d*, J = 3.9 Hz). This acetate must be placed at the C-14 position on the basis of the following facts. (i) The mass spectrum of scutalpin M (**10**) showed prominent peaks at m/z 171 (12%) and 111 (base peak) corresponding to an acetoxylhexahydrofuro-furan side chain ($[\text{C}_8\text{H}_{11}\text{O}_4]^+$) and a tetrahydrofuro-furan ion ($[\text{C}_6\text{H}_7\text{O}_2]^+$) formed from the former by loss of acetic acid. Since the base peak in the mass spectra of hexahydrofuro-furan-*neo*-clerodanes appears at m/z 113, as in scutecolumnin C (**3**) [5], it was evident that scutalpin M (**10**) possessed an acetoxyl group at the C-12, C-14 or C-15 position, taking into account that it is attached to a secondary carbon (see above). (ii) Position C-12 must be excluded because the C-11 methine proton appeared as a doublet (J_1 = 11.2 Hz, J_2 = 6.3 Hz; $\delta_{\text{H-11}}$ 4.05, Table 3), coupled with the two protons of the C-12 methylene group [2, 4–6]. (iii) The ^{13}C NMR spectrum of scutalpin M (**10**, Table 2) showed only one acetalic carbon (δ 107.4 *d*) which must be assigned to the C-16 carbon [2, 4–6]. Consequently, position C-15 for the attachment of the

acetoxyl group must be discarded. (iv) A comparison of the ^{13}C NMR spectra of scutecolumnin C (**3**) [5] and scutalpin M (**10**, Table 2) showed that the latter compound had an oxygenated function at C-14 ($\delta_{\text{C-14}}$ 80.0 *d*), because it contained paramagnetically shifted signals for the C-13 and C-15 β -carbons [$\Delta\delta$ (**10**–**3**) +7.4 and +5.0 ppm, respectively] and upfield resonances for the C-12 and C-16 γ -carbons ($\Delta\delta$ –3.6 and –0.9 ppm, respectively) with respect to 3.

The *exo*-configuration of the C-14 acetoxyl group of scutalpin M (**10**) was in agreement with the following. The geminal proton (δ 5.03) of the 14-acetoxyl group appeared as a broad doublet in the ^1H NMR spectrum, with a $J_{14,15\text{B}}$ value of 3.9 Hz, thus suggesting that it has a *cis* spatial relationship with only one of the three vicinal protons, namely with $\text{H}_{\text{B-15}}$ (δ 4.02 *dd*, J_{gem} = 10.9 Hz, J_{vic} = 3.9 Hz). The sum of the two remaining *trans* coupling values (with $\text{H-13}\beta$ and $\text{H}_{\text{A-15}}$) was not larger than 0.8 Hz, as deduced from the $W_{1/2}$ value of the signal of the H-14 proton. These data resemble the spectroscopic behaviour of some tetrahydrofuran derivatives [19], in which the J_{cis} coupling is larger than the J_{trans} value. Conclusive proof on the *exo*-configuration of the 14-acetoxyl group of **10** was achieved by NOE experiments. Irradiation at δ 2.85 (H-13 β proton) caused positive NOE enhancement in the signals of the H-12 β , H-14 and H-16 β protons (4%, 3% and 10% NOE enhancement, respectively), whereas on irradiating at δ 5.79 (H-16 β proton) positive NOE enhancement was observed for the H-12 β (2%) and H-13 β (7.5%) protons, but not in the signal corresponding to the C-14 proton (δ 5.03). All the above results pointed towards an *exo*-configuration (β in formula **10**) for the 14-acetoxyl substituent of scutalpin M and also allowed the unequivocal assignment of both protons at the C-12 methylene group (Table 3).

From a biogenetic point of view, and to the best of our knowledge, it is of interest to note that scutalpin M (**10**) is

Table 3. ^1H NMR spectral data of **10** (300 MHz, CDCl_3)*

H	10	H	10	H	10	H	10
1 α	~1.56 \ddagger	7A	~1.44 \ddagger	13 β	2.85 <i>m</i>	18B \S	2.97 <i>dd</i>
1B	~2.00 \ddagger	7B	~1.66 \ddagger	14 α	5.03 <i>br d</i>	19A	4.37 <i>br d</i>
2A	~1.38 \ddagger	8 β	~1.47 \ddagger	15 α	4.02 <i>dd</i>	19B	4.86 <i>d</i>
2B	~1.88 \ddagger	10 β	~1.64 \ddagger	15 β	3.93 <i>br d</i>	Me-20	0.93 <i>s</i>
3 α	~2.10 \ddagger	11 α	4.05 <i>dd</i>	16 β	5.79 <i>d</i>	OAc	2.08 <i>s</i>
3 β	1.10 <i>ddd</i>	12 α	~1.76 \ddagger	Me-17	0.84 <i>d</i>		2.06 <i>s</i>
6 β	4.66 <i>br dd</i>	12 β	~1.98 \ddagger	18A \ddagger	2.19 <i>d</i>		1.93 <i>s</i>

J values (Hz): 2 α ,3 β = 4.9; 2 β ,3 β = 4.0; 3 α ,3 β = 13.2; 6 β ,7 α = 11.8; 6 β ,7 β = 4.3; 8 β ,17 = 6.3; 11 α ,12 α = 11.2; 11 α ,12 β = 6.3; 13 β ,14 α + 14 α ,15 β < 0.8; 13 β ,16 β = 5.1; 14 α ,15 α = 3.9; 15 α ,15 β = 10.9; 18A,18B = 4.0; 18B,3 α = 2.3; 19A,19B = 12.2; 19A,6 β < 0.3.

*Chemical shifts are relative to residual CHCl_3 (δ 7.25). All these assignments were confirmed by double resonance experiments and were in agreement with the HMQC spectrum.

\ddagger Overlapped signal. The chemical shift of these protons was measured on the HMQC spectrum. The configuration of the C-1, C-2, C-7 and C-19 protons was not assigned.

\ddagger Exo hydrogen with respect to ring B.

\S Endo hydrogen with respect to ring B.

the first 14-oxidized hexahydrofuro-furan-neo-clerodane derivative isolated from natural sources [20–22].

The absolute stereochemistry of scutalpins G–J and M (4–7 and 10, respectively) was not ascertained. However, they presumably belong to the neo-clerodane series [15], like scutalpins K (8) and L (9) (see above) and other *neo*-clerodanes isolated from *Scutellaria* species whose absolute configuration has been established from X-ray diffraction analyses [4, 7].

EXPERIMENTAL

Mps: uncorr. Plant materials were collected in July 1992 at Valle d'Aosta, Italy, and voucher specimens are deposited in the Herbarium of the 'Dipartimento di Biologia', University of Milan, Italy.

Extraction and isolation of the diterpenoids. Dried and finely powdered aerial parts of *Scutellaria alpina* L. (600 g) were extracted with Me_2CO (3×3 l) at room temp. for 1 week. After filtration, the solvent was evapd to dryness under red. pres. and low temp. (25°) yielding a residue (30 g), which was subjected to CC (silica gel, Merck No. 7734, deactivated with 15% H_2O , w/w, 700 g) eluting with a hexane–EtOAc gradient. The frs eluted with hexane–EtOAc (1:1) which contained different mixts of the diterpenoids were subjected to radial chromatography (silica gel disc, CH_2Cl_2 –MeOH, 49:1 as eluent) to give the following compounds in order of increasing chromatographic polarity: scutalpin K (8, 16 mg), scutalpin L (9, 18 mg), scutalpin D (1, 22 mg), scutalpin B (2, 17 mg), scutalpin G (4, 8 mg), scutalpin M (10, 7 mg), scutecolumnin C (3, 8 mg), scutalpin I (6, 10 mg), scutalpin H (5, 40 mg) and scutalpin J (7, 15 mg).

The previously known compounds, scutalpins B (2) and D (1) [8] and scutecolumnin C (3) [5], were identified by their mp, $[\alpha]_D$, ^1H NMR and mass spectra and by comparison (mmp, TLC) with authentic samples.

Scutalpin G (4). Mp 226–228° (from EtOAc–*n*-hexane); $[\alpha]_D^{18} - 2.9^\circ$ (CHCl_3 ; c 0.104). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3090, 1720, 1600, 1585, 1280, 710 (OBz), 3060 (oxirane), 1795 (spiro γ -lactone), 1740, 1730, 1240 (OAc), 2930, 2880, 1450, 1375, 1120, 1030, 995, 850, 800; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 570 [M] $^+$ (0.02), 540 (1.4), 511 (0.03), 510 (0.02), 497 (1), 465 (2), 375 (3), 227 (2), 213 (2), 203 (2.5), 201 (5), 185 (6), 171 (5), 105 (100), 91 (5), 77 (20), 55 (3), 43 (30). (Found: C, 65.12; H, 6.84. $\text{C}_{31}\text{H}_{38}\text{O}_{10}$ requires: C, 65.25; H, 6.71%).

Scutalpin H (5). Mp 191–192° (EtOAc–*n*-hexane); $[\alpha]_D^{18} - 8.8^\circ$ (CHCl_3 ; c 0.716). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3440 (OH), 3100, 1775, 1740, 1640 (α,β -unsaturated γ -lactone), 3040 (oxirane), 1740 *br*, 1710, 1250 (OAc and 2-methylbutyrate), 2950, 2870, 1465, 1395, 1380, 1365, 1190, 1090, 1020, 975, 885, 840, 810; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 550 [M] $^+$ (0.02), 520 (0.4), 490 (0.1), 477 (0.4), 465 (2), 393 (4), 375 (2), 357 (2), 328 (3), 297 (4), 231 (6), 201 (7), 189 (10), 176 (13), 171 (14), 127 (11), 121 (13), 105 (12), 95 (10), 93 (10), 91 (16), 85 (32), 57 (84), 55 (12), 43 (100), 41 (16). (Found: C, 63.59; H, 7.72. $\text{C}_{29}\text{H}_{42}\text{O}_{10}$ requires: C, 63.25; H, 7.69%).

Scutalpin I (6). Amorphous solid, mp 90–105°; $[\alpha]_D^{16} + 14.4^\circ$ (CHCl_3 ; c 0.118). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3470 (OH), 3100, 1780, 1740, 1640 (α,β -unsaturated γ -lactone), 3060, 1720, 1600, 1585, 710 (OBz), 1740 *br*, 1240 (OAc), 2930, 2860, 1450, 1375, 1120, 1085, 1020, 960, 890, 840, 800; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 570 [M] $^+$ (0.1), 510 (0.4), 446 (3), 257 (5), 236 (6), 167 (6), 149 (16), 129 (11), 123 (15), 111 (34), 105 (100), 97 (64), 95 (36), 83 (79), 69 (83), 57 (28), 55 (72), 43 (83), 41 (39). (Found: C, 64.81; H, 6.96. $\text{C}_{31}\text{H}_{38}\text{O}_{10}$ requires: C, 65.25; H, 6.71%).

Scutalpin J (7). Mp 274–276° (EtOAc–*n*-hexane); $[\alpha]_D^{18} + 57.5^\circ$ (CHCl_3 ; c 0.193). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 233 (4.24), 259 (4.44), benzoate and $\alpha,\beta,\gamma',\delta'$ -diunsaturated γ -lactone, respectively; IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3470 (OH), 3060, 1800, 1750, 1645 ($\alpha,\beta,\gamma',\delta'$ -diunsaturated γ -lactone), 1730, 1600, 1590, 720 (OBz), 1730, 1260 (OAc), 2950, 2930, 2870, 1450, 1380, 1375, 1335, 1120, 1090, 1025, 975, 940, 900, 835, 800; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 510 [M] $^+$ (0.1), 437 (0.4), 388 (0.5), 357 (4), 328 (3), 297 (4), 176 (15), 105 (100), 91 (11), 77 (33), 67 (4), 55 (4), 43 (43). (Found: C, 68.41; H, 6.98. $\text{C}_{29}\text{H}_{34}\text{O}_8$ requires: C, 68.22; H, 6.71%).

Scutalpin K (8). Amorphous solid, mp 130–135°; $[\alpha]_D^{16} - 27.3^\circ$ (CHCl_3 ; c 0.165). CD nm ($\Delta\epsilon$): 246 (0), 236 (–30.7), 225 (0), 222 (+2.4), 218 (0), 197 (–48.5) (MeOH; c 0.0118); UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log ϵ): 233 (4.41), 257 (4.43), benzoate and $\alpha,\beta,\gamma',\delta'$ -diunsaturated γ -lactone; IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3480 (OH), 3100, 1780, 1750, 1645 ($\alpha,\beta,\gamma',\delta'$ -diunsaturated γ -lactone), 3060, 1725, 1600, 1585, 710 (OBz), 1740, 1250 (OAc), 2940, 2870, 1450, 1375, 1280, 1120, 1070, 1025, 860, 800; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 630 [M] $^+$ (0.5), 559 (0.3), 557 (0.2), 525 (0.2), 477 (1), 448 (2), 417 (2), 326 (4), 283 (8), 176 (15), 121 (5), 105 (100), 77 (2), 43 (2). (Found: C, 68.22; H, 6.27. $\text{C}_{36}\text{H}_{38}\text{O}_{10}$ requires: C, 68.56; H, 6.07%).

Scutalpin L (9). Amorphous solid, mp 100–115°; $[\alpha]_D^{16} - 38.9^\circ$ (CHCl_3 ; c 0.172). CD nm ($\Delta\epsilon$): 258 (0), 238 (–21.5), 231 (0), 224 (+10.6), 215 (0), 196 (–48) (MeOH; c 0.0074); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3480 (OH), 3100, 1780, 1750, 1640 (α,β -unsaturated γ -lactone), 3060, 1725, 1600, 1585, 1285, 710 (OBz), 1740, 1250 (OAc), 2950, 2860, 1450, 1375, 1120, 1070, 1030, 850, 800; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 632 [M] $^+$ (0.1), 602 (4), 559 (6), 541 (2), 527 (4), 437 (2), 315 (4), 122 (2), 121 (1), 105 (100), 98 (1), 91 (1), 77 (5), 43 (0.5). (Found: C, 68.71; H, 6.26. $\text{C}_{36}\text{H}_{40}\text{O}_{10}$ requires: C, 68.34; H, 6.37%).

Scutalpin M (10). Amorphous solid, mp 60–70°; $[\alpha]_D^{18} - 21.9^\circ$ (CHCl_3 ; c 0.114). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1740 *br*, 1250 *br* (OAc), 2930, 2880, 1450, 1370, 1080, 1020, 970, 915, 860; ^1H NMR: Table 3; ^{13}C NMR: Table 2; EIMS (70 eV, direct inlet) m/z (rel. int.): 494 [M] $^+$ (0.01), 464 (0.03), 451 (0.2), 434 (0.03), 374 (0.1), 361 (0.4), 323 (0.3), 307 (2), 233 (1), 203 (4), 173 (11), 171 (12), 149 (14), 121 (5), 111 (100), 97 (4), 91 (4), 69 (8), 55 (7), 43 (22). (Found: C, 62.87; H, 7.61. $\text{C}_{26}\text{H}_{38}\text{O}_9$ requires: C, 63.14; H, 7.75%).

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*Note added in proof. Compounds 7 and 8 have recently been published as constituents of *Scutellaria alpina* by Miyachi, Y., Kizu, H., Yamaguchi, Y. and Tomimori, T. (1994) *Yakugaku Zasshi* **114**, 264.

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