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NEO-CLERODANE DITERPENOIDS FROM *SCUTELLARIA DRUMMONDII*

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Key Word Index—*Scutellaria drummondii*; Labiatae; neoclerodane diterpenes; 2α-hydroxyajugarin V; 2α-hydroxy-deacetylajugarin V; scutedrummonin.

Abstract—Three new neo-clerodane diterpenoids, 6α-acetoxy-4α,18-epoxy-2α-hydroxy-13-neocleroden-15,16-olide (2α-hydroxyajugarin V), 4α,18-epoxy-2α,6α-dihydroxy-13-neocleroden-15,16-olide (2α-hydroxy-deacetylajugarin V) and 2α,6α-dihydroxy-4(18),13-neoclerodadien-15,16-olide (scutedrummonin), have been isolated from the aerial parts of *Scutellaria drummondii*, in addition to the known flavone xanthomicrol. The structures of the new diterpenoids were established by chemical and spectroscopic means, including X-ray diffraction analysis for 2α-hydroxyajugarin V.

INTRODUCTION

Scutellaria L. is a large subcosmopolitan genus of the Labiatae with *ca* 360 currently recognized species [1]. Recently, plants belonging to this genus have attracted much attention owing to interesting biological activities found for some neoclerodane diterpenoids isolated from them, in particular their activities as insects antifeedants [2–4] and against plant pathogenic fungi [5]. In Mexico, *Scutellaria* is represented by *ca* 32 species, most of them growing in the mountains near the centre of the country [6]. As part of our ongoing search for diterpenoids from plants of the Labiatae, with potential antifeedant activity [7], we have started to study Mexican *Scutellaria* species. In this report we describe the structure of three new neoclerodane diterpenoids (**1–3**) isolated from *Scutellaria drummondii* Benth (subgenus, Scutellaria; section, Scutellaria) [8]. Compounds **1** and **2** are closely related to agujarin V (**6**), a neoclerodane diterpenoid isolated from *Ajuga remota* (Labiatae) [9]. Compound **3**, named scutedrummonin, could be considered as a biogenetic precursor of **1** and **2**. The structures of **1–3** were established from their spectroscopic data and by comparison with ajugarin V (**6**).

RESULTS AND DISCUSSION

Extraction of the aerial parts of *Scutellaria drummondii* afforded, after extensive chromatography, the flavone xanthomicrol [10] and three new neoclerodane diterpenoids to which we have assigned structures **1–3**.

Compound **1** was assigned the molecular formula $C_{22}H_{32}O_6$. Its IR spectrum show absorptions for hydroxyl (3608 cm^{-1}) and conjugated double bonds (1639 cm^{-1}). A weak absorption at 1782 cm^{-1} and a strong one at 1749 cm^{-1} can be attributed to the Fermi resonance [11] shown by the β-substituted butenolide function present in **1**. The UV spectrum [λ_{max} nm (log ε): 209 (4.8)] supports these assignments.

The ^1H and ^{13}C NMR spectra of **1** (Tables 1 and 2) showed signals for an acetate group (δ_H2.0, 3H, *s*; δ_C169.9 *s* and 21.9 *q*). A one-proton double doublet at δ4.65 can be assigned to the geminal proton of this acetate, which is located at C-6. The coupling constants of H-6 (J = 10.7 and 5.1 Hz) indicate an equatorial orientation for the acetate group. A three-protons doublet (J = 6 Hz) at δ0.84 and two three-protons singlets at δ0.83 and 1.29, can be assigned to the characteristics methyl groups of a neoclerodane structure. The ^1H NMR also showed typical signals of a β-substituted butenolide ring: a quintet at δ5.86 (J = 1.5, 1H) and a doublet at δ4.75, which can be assigned unambigously to the H-14 vinylic proton and to the CH_2-16 group, respectively, with the aid of 2D COSY experiments. Compound **1** possesses a 4α,18 oxirane group as indicated by the presence of a double doublets (J = 3.9 and 2.4 Hz, 1H, H-18 *pro-S*) and a doublet (J = 3.9 Hz, 1H, H-18 *pro-R*) at δ3.16 and 2.41, respectively, in the ^1H NMR spectrum, as in other neoclerodane diterpenoids isolated from *Ajuga* [12, 13], *Teucrium* [14, 15] and *Scutellaria* [2–4, 16–19]. Compound **1** contains, therefore, an identical B ring, 4α,18-oxirane ring and pendant chain, to those present in ajugarin V (**6**), a neoclerodane diterpenoid isolated from *Ajuga remota* [9]. Comparison of the ^1H NMR data of **1** and **6** supports these conclusions. The ^1H NMR spectrum of **1** shows, in addition, a triplet of triplets at δ3.72 (J

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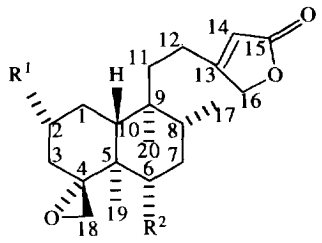
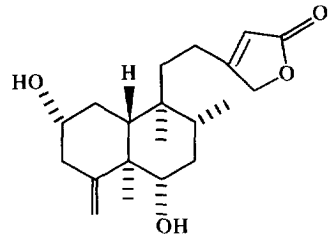


	R^1	R^2
1	OH	OAc
2	OH	OH
4	OAc	OAc
6	H	OAc



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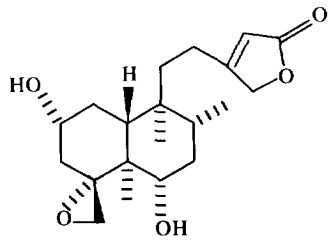

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Table 1. ^{1}H NMR spectral data for compounds **1–5** (200 MHz, $CDCl_3$, TMS)

H	1*	2	3	4	5
2	3.72 *tt* (10.2, 5.2)	3.72 *tt* (11, 5.0)	3.56 *tt* (11, 5.5)	4.70 *m*†	3.90 *tt* (11, 5.6)
6	4.65 *dd* (10.7, 5.1)	3.45 *m*	3.87 *dd* (10.3, 5.1)	4.65 *m*†	3.48 *dd* (10.6, 5.3)
14	5.86 *quin* (1.5)	5.85 *t* (1.6)	5.84 *quin* (1.6)	5.85 *quin* (1.8)	5.85 *quin* (1.7)
H_2-16	4.75 *d* (1.5)	4.75 *d* (1.6)	4.73 *d* (1.6)	4.76 *d* (1.8)	4.74 *d* (1.7)
H_3-17	0.84 *d* (6)	0.86 *d* (6)	0.87 *d* (6)	0.84 *d* (6)	0.81 *d* (6)
H-18 A	3.16 *dd* (3.9, 2.4)	3.41 *dd* (3.3, 2.9)	4.90 *br s*	3.17 *dd* (4, 2.4)	3.56 *d* (4.9)
H-18 B	2.41 *d* (3.9)	2.68 *d* (3.3)	4.78 *br s*	2.45 *d* (4.0)	2.48 *d* (4.9)
H_3-19	1.29 *s*	1.23 *s*	1.04 *s*	1.3 *s*	1.3 *s*
H_3-20	0.83 *s*	0.81 *s*	0.81 *s*	0.82 *s*	0.79 *s*
OAc	2.0 *s*			2.0 *s* 2.05 *s*	

*Run at 300 MHz, assignments confirmed by ^{1}H–^{1}H 2D COSY spectra.
†Overlapped signals.

= 10.2 and 5.2 Hz), which can be assigned to the geminal proton of a secondary hydroxyl group (since it was shifted downfield upon acetylation), which must be located at C-2 with an equatorial orientation (Table 1). Acetylation of **1** (see Experimental) afforded the diacetate **4**. Compound **1** must therefore, be named, 2α-hydroxyajugarin V. The structure of **1** was confirmed by X-ray diffraction analysis of a single crystal. The molecular structure is illustrated in Fig. 1, which also shows the absolute stereochemistry (see Experimental). Both six-membered rings in the bicycle structure adopt slightly distorted chair conformations (Cramer and Pople [20] parameters: ring A; $q_2 = 0.051$, $q_3 = 0.578$, $Q_T = 0.580$ Å, $\theta = 5.02°$, $\phi_2 = 228°$ ring B; $q_2 = 0.054$, $q_3 = 0.55$, $Q_T = 0.553$ Å, $\theta = 5.58°$, $\phi_2 = 101°$). All the substituents, except the fully extended [torsion angle C-9, C-11, C-12, C-13 = −179.6(5)°] side chain are α oriented, including the O-atom in the epoxy moiety. The planar γ-lactone ring (maximum deviation from plane: O-6b 0.155 Å) is twisted by 16.6(5)° from the best mean-plane defined by the atoms of ring **B**, while the acetate group attached to C-6 lies nearly (angle between planes 99.9(5)°) perpendicular to the same plane. Figure 1 also

Table 2. ^{13}C NMR spectral data for compounds **1–3** ($CDCl_3$, TMS, 50 MHz)

C	1 (75 MHz)	2	3
1	30.5 *t*	30.6 *t*	30.8 *t*
2	68.8 *d*	68.8 *d*	71.7 *d*
3	41.2 *t*	40.6 *t*	42.7 *t*
4	64.4 *s*	67.2 *s*	152.7 *s*
5	40.7 *s*	40.8 *s*	45.1 *s*
6	73.2 *d*	74.1 *d*	73.9 *d*
7	32.8 *t*	33.9 *t*	35.2 *t*
8	34.6 *d*	34.6 *d*	34.6 *d*
9	38.5 *s*	38.8 *s*	38.9 *s*
10	43.2 *d*	42.5 *d*	44.7 *d*
11	34.8 *t*	34.9 *t*	34.9 *t*
12	21.9 *t*	22.1 *t*	22.0 *t*
13	170.5 *s*	170.0 *s*	170.2 *s*
14	115.4 *d*	115.4 *d*	115.2 *d*
15	173.8 *s*	173.8 *s*	173.8 *s*
16	73.0 *t*	73.0 *t*	73.1 *t*
17	15.3 *q*	15.5 *q*	15.2 *q*
18	51.9 *t*	52.9 *t*	106.8 *t*
19	14.4 *q*	13.8 *q*	15.6 *q*
20	17.6 *q*	17.9 *q*	17.6 *q*
21	169.9 *s*		
22	21.9 *q*		

Multiplicities were determined by the DEPT pulse sequence.

Assignments were confirmed by the ^1H–^{13}C HETCOR spectra.

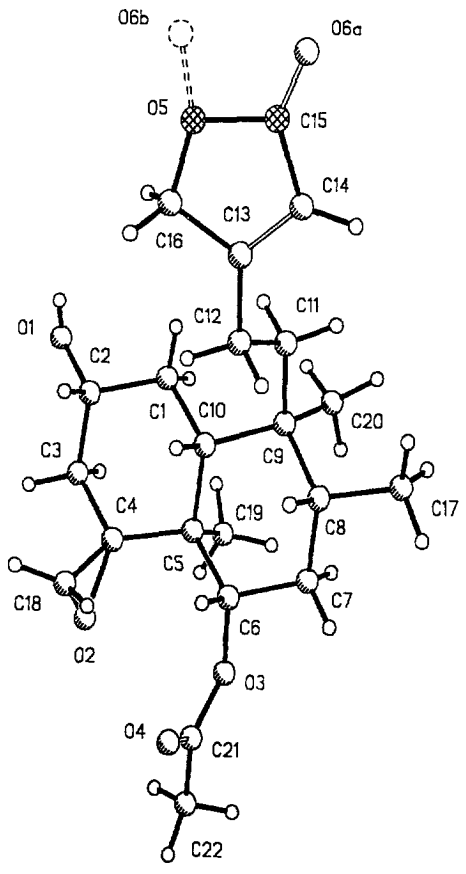

Fig. 1. Computer generated perspective drawing of **1**. Dotted circle represents the O atom of the minor component. Cross-hatched circles, atoms site-sharing (see text).

shows an orientational disorder involving the lactone ring. This moiety is disordered over two orientations, related by a *pseudo* C_2 axis parallel to the C-12/C-13 bond. In the crystal, the molecules are held together by hydrogen bonds, involving the hydroxyl group and the O atom of the lactone moiety of symmetry related molecules [*x*-0.5, 1.5-*y*, -*z*; O-1,H-1→O-6a: 2.20(6)Å, O-1, H-1→O-6b: 2.25 (10Å].

Compound **2** ($C_{20}H_{30}O_5$) is the deacetyl derivative of **1**, as shown by comparison of their ^1H and ^{13}C NMR spectra (Tables 1 and 2). Acetylation of **2**, in the presence of DMAP, yielded a compound identical in all respects to the diacetate **4** obtained from **1**. This product, must therefore, be named 2α-hydroxy-deacetylajugarin V, and has the structure and absolute stereochemistry depicted in **2**.

The last diterpenoid isolated from *S. drummondii*, scutedrummonin (**3**), has the molecular formula $C_{20}H_{30}O_4$ (mass spectrum) and its IR spectrum showed bands for hydroxyl (3456 cm^{-1}), conjugated double bonds (1633 cm^{-1}) and β-substituted butenolide (1777, 1740 cm^{-1}) groups. The ^1H and ^{13}C NMR spectra of this compound are similar to those of **2**, and reveal that it is devoid of the 4α, 18 oxirane group. In the ^1H NMR spectra of **3**, two one-proton broad singlets were seen at δ4.90 (H-18A) and 4.78 (H-18B). This fact, together with the presence of two sp^2 carbon atoms in the ^{13}C NMR spectrum of **3** [at δ152.7 (*s*, C-4) and 106.76 (*t*, C-18) (Table 2)], indicate the presence of an exocyclic double bond in **3**. Treatment of **3** with MCPBA afforded a *ca* 2:1 mixture of 4,18 epoxide derivatives. The less abundant component of the mixture was identical in all respects to **2**. The structure of the more abundant product is as shown in **5**. The 4β,18 oxirane group was responsible for two doublets at δ3.56 (J = 4.9 Hz) and 2.48 in the ^1H NMR spectrum of **5**. The exocyclic double bond present in **3**, can be considered as the biogenetic precursor of the 4α,18 oxirane group present in **1** and **2**. Structure **3** also shows the most probable absolute stereochemistry of scutedrummonin, since this compound is chemically correlated with **1** and **2**.

From a chemotaxonomic point of view, it is of interest to note that **1–3** lack an oxygenated substituent at C-19 and hence the 19,2α-hemiketalic function, commonly found in European *Scutellaria* spp. [2–4, 16–19], although the C-2 position is oxygenated in **1–3**. The diterpenoids of *Scutellaria drummondii* share these features with some neoclerodane diterpenoids isolated from the Chinese species *Scutellaria rivularis* [21, 22]. To the best of our knowledge this is the first report of neoclerodane diterpenoids from an American *Scutellaria* spp.

EXPERIMENTAL

Mps: uncorr.; EI-MS: 70 eV, direct inlet; UV MeOH; ^{1}H and ^{13}C NMR: 200 and 50 MHz respectively, unless noted otherwise, $CDCl_3$, TMS as int. standard. Plant material was collected in the state of Hidalgo (México) in August 1992 and a Voucher specimen (MEXU 563427) is deposited at the herbarium of the Instituto de Biología UNAM.

Isolation procedure. Dried and powdered aerial parts of *S. drummondii* (40 g) were extracted (×3) with Me_2CO (2 l) for 5 days at room temp. The solvent of the combined extracts was removed *in vacuo* to yield 2.86 g of a gummy residue which was partitioned between MeOH–H_2O (4:1) and C_6H_6–petrol (1:1). The less polar phase was concentrated *in vacuo* to yield 1.85 g of residue. The aq. methanolic fraction was concd *in vacuo*, H_2O added and the mixture extracted with EtOAc. The organic extract was dried and the solvent removed to yield 0.508 g of a gum, which was subjected to vacuum chromatography over silica gel. Mixtures of petrol–EtOAc of increasing polarity were used as eluents. From the fractions eluted with petrol–EtOAc (1:4) 13 mg of **1** was isolated. Elution with petrol–EtOAc (2:3) yielded 18 mg of **3** and elution with EtOAc gave 10 mg of **2**. Some fractions eluted with petrol–EtOAc (2:3) were combined (32 mg) and subjected to flash chromatography to yield an additional crop (3 mg) of **3**. Vacuum chromatography of the less polar phase of the original extract, in the same conditions as above, yield 15 mg of **1** in the fractions eluted with petrol–EtOAc (1:3). Some fractions eluted with EtOAc were combined (453 mg) and subjected to successive purification by flash chromatography to yield 10 mg **2** and 5 mg xanthomicrol, which were identified by their ^{1}H NMR, IR and mass spectra as compared with the published data [10].

2α-Hydroxyajugarin V. Crystalline solid, mp 238–240°; $[\alpha]_D$ −7.65° (MeOH; *c* 0.17); UV λ_{max} nm (log ε): 209 (4.28); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3608, 1782, 1749, 1721, 1639; ^{1}H NMR (300 MHz): Table 1; ^{13}C NMR (75 MHz): Table 2; MS *m/z* (rel. int.): 362 (0.9), 350 (1.5), 349 (4), 336 (1), 335 (3), 333 (1), 332 (5), 331 (20), 317 (2), 221 (5), 207 (5), 189 (10), 191 (10), 147 (15), 111 (20), 109 (18), 97 (15), 95 (23), 91 (23.7), 81 (20), 79 (20), 43 (100). $C_{22}H_{32}O_6$ requires $[M^+]$ at *m/z* 392.

2α-Hydroxydeacetylajugarin V. Crystalline solid, mp 149–151°; $[\alpha]_D$ −13.33° (MeOH; *c* 0.3); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3446, 1778, 1743, 1635, 837; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; MS *m/z* (rel. int.): 335 (30), 332 (15), 317 (20), 221 (20), 189 (10), 171 (20), 121 (20), 119 (20), 111 (40), 107 (50), 91 (74), 81 (30), 79 (60), 55 (75), 43 (100), 41 (96). $C_{20}H_{30}O_5$ requires $[M]^+$ at *m/z* 350.

Scutedrummonin (**3**). Oily compound; $[\alpha]_D$ +18.4° (MeOH; *c* 0.375); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3456, 3287, 3214, 1777, 1740, 1633, 1010, 896; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; MS *m/z* (rel. int.): 334 (0.8), 333 (1), 332 (0.7), 301 (10), 298 (15), 283 (10), 205 (20), 187 (30), 173 (15), 121 (30), 119 (30), 111 (70), 107 (60), 91 (50), 69 (70), 55 (82), 43 (85), 41 (100). $C_{20}H_{30}O_4$ requires $[M]^+$ at *m/z* 334.

Acetylation of **1**. Compound **1** (20 mg) in pyridine (0.2 ml) was treated with Ac_2O (0.2 ml) for 8 hr at room temp. After usual work-up and flash chromatography, 10 mg **4** was obtained as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782, 1747, 1728, 1639, 1035, 891, 854; ^{1}H NMR: Table 1; MS *m/z* (rel. int.): 404 (1), 375 (0.1), 362 (0.2), 333 (0.1), 331 (0.5), 121 (4), 119 (3), 98 (10), 95 (8), 91 (10), 81 (10), 79 (10), 43 (100). $C_{24}H_{34}O_7$ requires $[M]^+$ at *m/z* 434.

Acetylation of **2**. Compound **2** (10 mg) in pyridine (0.2 ml) was treated with Ac_2O (0.2 ml) and DMAP (1 mg) for 10 hr at room temp. After usual work-up and flash chromatography, 7 mg of **4** were obtained.

Treatment of **3** with MCPBA. Compound **3** (10 mg) in CH_2Cl_2 (5 ml) was treated with *m*-chloroperbenzoic acid (10 mg) for 5 hr at room temp. After usual work-up and flash chromatography a 2:1 mixture of **5** and **2** was obtained. Compound **5**: oily product, ^{1}H NMR: Table 1.

X-ray structural determination of 2α-hydroxyajugarin V. Crystal data: $C_{22}H_{32}O_6$, M_r = 392.5, orthorhombic, *a* = 10.164(2), *b* = 11.842(2), *c* = 17.524(4) Å, V = 2099.2 Å^3, *Z* = 4, D_{calc} = 1.242 g cm^{-3}, μ (CuK_α) radiation, (λ = 1.54178 Å) = 0.73 mm^{-1}. Space group $P2_12_12_1$ (D_2^4) uniquely from the systematic absences: *h*00 when *h* = 2n + 1, 0*k*0 when *k* = 2*n* + 1, 1, 001 when *l* = 2n + 1. Sample dimensions: 0.34 × 0.24 × 0.20 mm.

Crystallographic measurements. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles of 25 reflections ($10 < 2\theta < 25°$) widely separated in reciprocal space. Intensity data (h:0→10, k:0→12, 1:0→18) up to $2\theta = 105°$ were recorded on a Nicolet P3F diffractometer (CuK_α radiation, Ni-filter, ω-2θ scans) with variable scan speed (min. 4.0, max. 30° min^{-1}) and scan width 2.0 + K_α-separation. From a total of 1397 independent measurements, those 1226 reflections with $F > 4.0\sigma(F)$ were retained for the structure analysis and the usual Lorentz and polarization corrections were applied.

Structure analysis. The crystal structure was solved by direct methods (SIR92) [23]. The E-map shows all non-hydrogen atoms of the structure, but also an orientational disorder involving the lactone ring; this moiety is disordered over two orientations related by a pseudo-C_2 axis parallel to the C-12/C-13 bond. From an occupancy refinement the O–6a atom was given three-quarters and the O-6b was given one-quarter of the full scattering power of an oxygen atom. Because of this pseudo-C_2 symmetry atoms labelled O-5 (0.75O/0.25C), C-15 (0.25O/0.75C) were used instead of the normal factors. Hydrogen atoms were all located in a difference Fourier synthesis evaluated following several cycles of full-matrix least squares [24] adjustment of non-hydrogen atom positional and anisotropic thermal parameters. With the inclusion of the hydrogen atoms in a ride-on fashion (except that bonded to O-1) with a fixed isotropic U value (0.06 Å^2) in subsequent least-squares iterations, the refinement converged at $R = 0.049$ ($R_w = 0.059$).

The absolute configuration determination was done by the analysis of the Bijvoet differences of 22 Friedel pairs

Table 3. Observed and calculated rB_{ij}(× 100)

h	k	l	Obs.	Calc.	h	k	l	Obs.	Calc.
3	1	4	−13.6	−6.76	3	7	2	−5.90	−3.21
2	3	4	10.03	3.23	6	3	5	1.91	−4.16
2	4	6	−9.89	−5.81	2	2	12	6.62	6.21
2	3	8	7.33	3.17	6	5	4	−8.47	−5.93
3	6	4	17.83	10.06	4	4	10	−6.85	−2.85
4	8	3	2.48	3.26	7	2	7	10.53	22.40
3	8	7	7.78	5.90	7	5	5	0.37	3.40
1	1	15	−0.70	−3.13	8	3	5	9.36	8.33
1	8	11	−3.03	−7.23	6	8	5	−8.96	−6.70
6	5	11	−4.67	−2.20	6	4	12	15.25	4.11
9	4	6	−3.71	−3.43	3	1	17	45.16	24.01

$rB_{ij} = (2(I_{(+)} - I_{(-)})/(I_{(+)} + I_{(-)})$.

carefully selected and intensity data collected at high precision (scan speed 0.25° min^{-1}) conditions (Table 3).

Non-hydrogen atom positional parameters, bond lengths and angles, anisotropic thermal parameters, hydrogen atom parameters and a list of observed and calculated structure amplitudes have been deposited at the Cambridge Crystallographic Data Centre. Neutral atom scattering factors used in the structure–factor calculations were taken from the literature [25].

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