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Clerodane diterpenoids from *Salvia blepharophylla*

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Abstract

Two clerodane diterpenoids, blepharolides A and B, have been isolated from *Salvia blepharophylla* Brandegee ex Epling. Their structures were determined using a combination of one- and two-dimensional NMR techniques. The relative stereochemistry for blepharolide A was determined by X-ray diffraction. To our knowledge this is the first crystal structure determination of a 5,6-unsaturated octahydro-1*H*-cyclopropa[*a*]naphthalene derivative. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Salvia blepharophylla*; Labiatae; Exudate; Clerodane diterpenoids; Blepharolides A and B

1. Introduction

In a previous study we isolated various flavonoids and ursolic acid from *Salvia blepharophylla* Brandegee ex Epling (Bisio, Romussi, Ciarallo & De Tommasi, 1997). In this paper we report the isolation and structure elucidation of two new diterpenoids, blepharolide A (**1**) and B (**2**), from the exudate of the aerial parts of this Mexican species.

2. Results and discussion

Repeated column chromatography of the exudate of aerial parts of *S. blepharophylla* yielded compounds **1** and **2**.

Blepharolide A (**1**) was assigned the molecular formula $C_{20}H_{20}O_6$ by microanalysis. IR absorption bands at 1758 and 1735; 3430 (br); 875, 1500, 3120 cm^{-1}; ^{13}C and ^{1}H NMR signals at δ_C 176.3 and 177.4; 109.4, 122.3, 140.1, 144.2 and δ_H 6.49, 7.50, 7.52 suggested the presence of two lactone rings, hydroxyl groups and one β-substituted furan ring. From the ^{1}H–^{1}H COSY, HMQC, HMBC spectral data the partial structures, I: >CH–CH(O-)[δ_H 2,59 (1H, d, J = 4.8 Hz), 5.71 (1H, d, J = 4.8 Hz); δ_C 38.2, 74.4]-furan ring; II: >CH–CH_2–CH=CH–CH <[δ_H 1.78 (1H, dd, J = 12.0, 5.0 Hz), 2.27 and 2.35 (both 1 H, m), 6.03 (1H, m), 5.60 (1H, nd, J = 9.6 Hz), 2.83 (1H, brs); δ_C 42.0, 25.2, 129.8, 120.4, 51.1]; III: -CH_2–CH(O-)–[δ_H 1.17 (1H, nt, J = 12.0 Hz) and 2.31 (1H, m), 4.91 (1H, dd, J = 10.0, 7.4 Hz); δ_C 40.7, 61.3] were established. The carbon signals at δ_C 38.2 and 74.4 of the partial structure I were assigned to the C-11 and C-12 of a probable clerodane skeleton. The quaternary carbon at δ_C 43.0 showed a long range correlation with the methine proton at δ_H 1.78. This fact suggested that the partial structure II could be put in the A ring of a clerodane diterpenoid with the C-5 and C-10 at δ_C 43.0 and 42.0, respectively. These results were also in agreement with the spectral data of *neo*-clerodane diterpenoids with identical A ring with a β-axial proton at C-4 (Rodríguez-Hahn, Esquivel & Cárdenas, 1994). From HBMC spectral data (Fig. 1), the oxygenated methyl-

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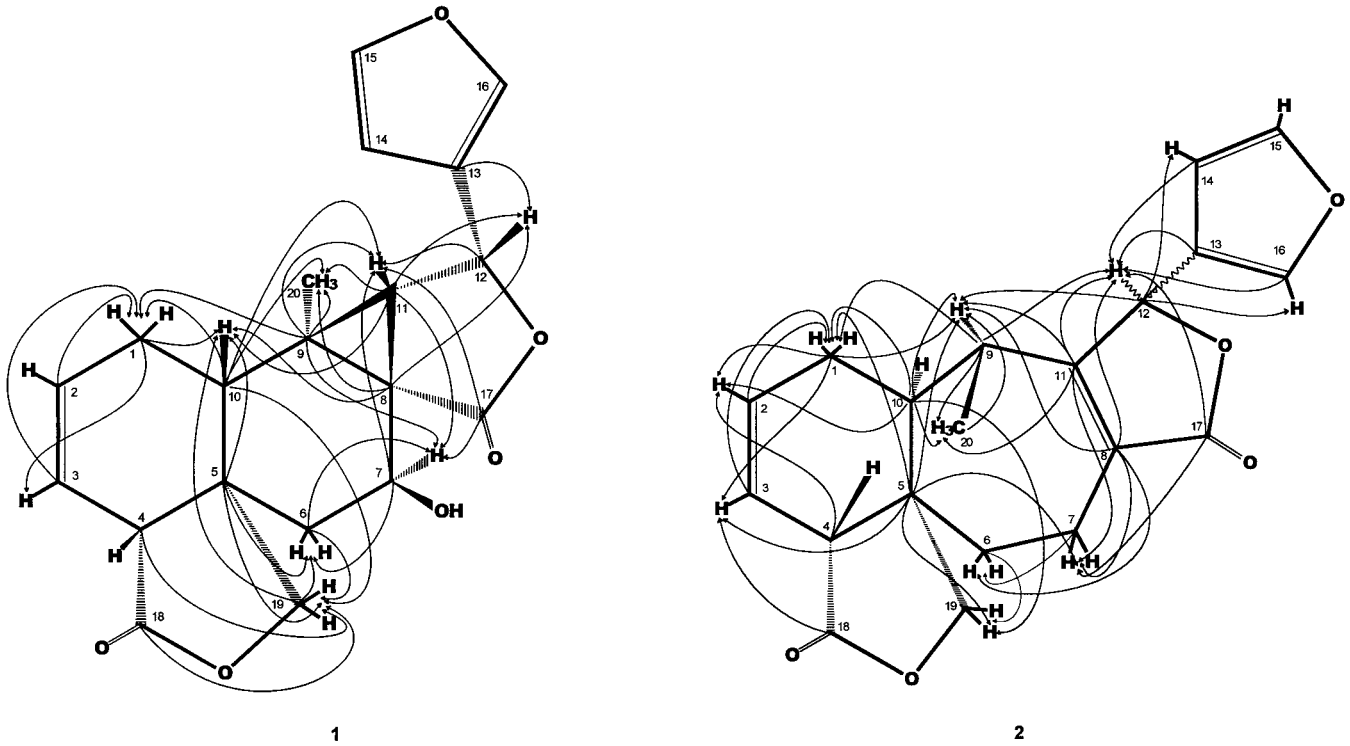


Fig. 1. Correlations observed in HMBC spectrum for compounds **1** and **2** (except those inside the furan ring).

ene at δ_C 68.9 and the carbonyl at δ_C 177.4 could be put in a 19,18-olide, the carbonyl at δ_C 176.3 in a 12,17-olide and the carbons at δ_C 14.7, 41.8, 40.7 and 61.3 could be assigned to the C-20, C-9, C-6 and C-7 respectively. The quaternary carbon at δ_C 30.4 was correlated, like the C-11, with the proton signals at δ_H 0.94 (20-CH_3), 1.78 (H-10), and 5.71 (H-12). These results suggested that this carbon could be the C-8 bonded to the C-11 in a three-membered ring. This structure could also explain the correlations of C-11 with H-7 and C-7 with H-11. The relative stereochemistry of blepharolide A could not be established by spectral analysis. In order to prove the structure proposed an X-ray diffraction analysis of a single crystal was undertaken. The corresponding results allow to determine unambiguously the complete (relative) stereochemistry of compound **1** (see Fig. 2). In particular, the C5–C10 junction is *trans*, the C19–C5–C10–H10 torsion angle being 171(1)°. The lactone ring defined by atoms O5, C8, C11, C12, C17 is only roughly planar (within 0.09 Å); the furane ring is planar within 0.008 Å. The B ring (C5, C6, C7, C8, C9, C10) is in a distorted half-chair conformation, with a displacement asymmetry parameter ΔC_2(C5–C6) = 0.031 (Duax, Weeks & Rohrer, 1976; Nardelli, 1983a).

Selected bond lengths and bond angles between heavier atoms are reported in Table 3. For the whole molecule, the corresponding standard deviations are in the ranges 0.002–0.004 Å and 0.1–0.2°, respectively. In keeping with the stiffness of the structure if deprived of the hydroxyl and methyl hydrogens and the furane group, thermal vibration amplitudes lie within bounds, the U(eq) values ranging between 0.032(1) and 0.067(1) $Å^2$ for heavier atoms, and between 0.037(6) and 0.066(9) $Å^2$ for the hydrogen atoms. In the crystal the molecules of **1** are connected by O3–H···O4 hydrogen bonds [O3···O4 2.821(3) Å, H···O4 1.96(4) Å, O3–H···O4 176(3)°; O4 in $-1/2+x$, $-1/2-y$, $2-z$]. With the exception of a rather short C(methyl)···hydrogen intermolecular distance (C20···H3, 2.86 Å) there are no further contacts noticeably shorter than the sum of the van der Waals radii involved. All geometry calculations were done using PARST (Nardelli, 1983b). Atomic coordinates, thermal parameters, bond distances and bond angles have been deposited at the Cambridge Crystallographic Data Centre[1].

Blepharolide B (**2**) was assigned the molecular formula $C_{20}H_{20}O_5$ by microanalysis. IR absorption bands at 1750 (br); 875, 1508, 3140 cm^{-1}; ^{13}C and ^1H NMR signals at δ_C 172.7 and 174.9; 107.8, 119.7, 141.2, 144.1 and δ_H 6.23, 7.45, 7.57 suggested the presence of two γ-lactone rings and one β-substituted furan ring.

[1] CCDC, 12 Union Rd., Cambridge, CB2 1EZ, UK. Tables of anisotropic thermal parameters and calculated structure factors are available from an author (A.M.) on request.

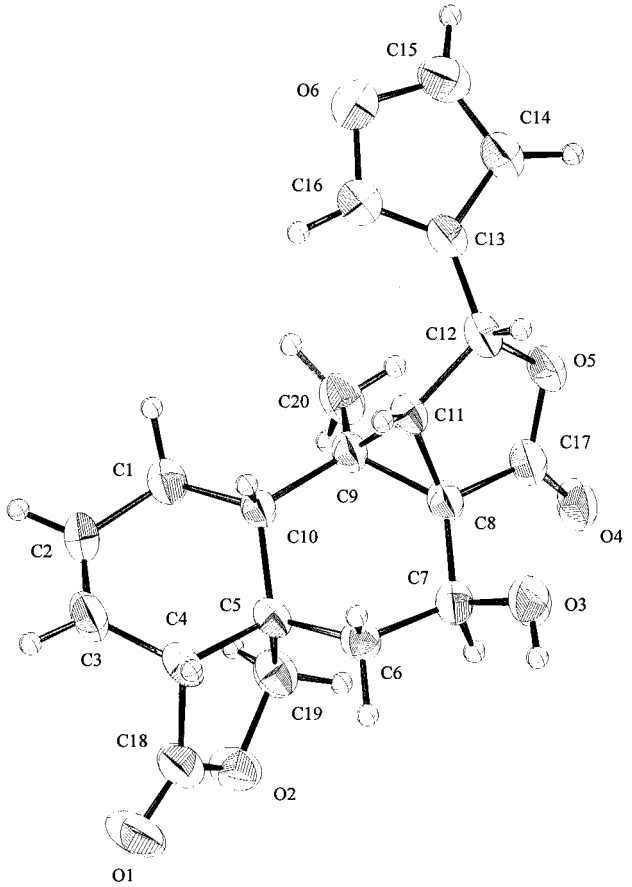


Fig. 2. ORTEP (Johnson, 1976) drawing of the structure of compound **1**, with numbering of atoms. Thermal ellipsoids are drawn at the 50% probability level; hydrogen atoms, treated as isotropic, are on an arbitrary scale. Atom H1B is hidden by atom C1.

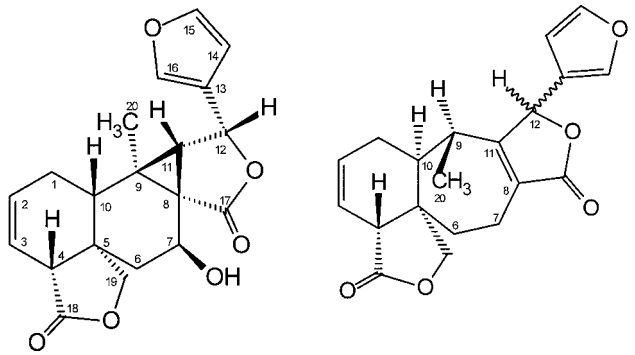
The ^{1}H, ^{13}C NMR and HMQC spectral data also showed the presence of one disubstituted double bond [δ_H, 6.00 (1H, m), 5.64 (1H + 1H, m: the HMQC spectrum showed that this signal was also correlated to an oxygenated carbon methine a δ_C 76.7), δ_C 129.3, 121.2], one tetrasubstituted double bond [δ_C 167.2, 128.8] and one methylene attached to an oxygen function [δ_H 4.18 (1H, m), 4.38 (1H, nd, J = 9.0 Hz); δ_C 72.0].

From the ^{1}H–^{1}H COSY, TOCSY, HMQC, HMBC spectral data the partial structures, I: -CH(O-)[(δ_H 5.64, δ_C 76.7]-furan ring; II: CH_3–CH–CH–CH_2–CH=CH–CH< δ_H 0.78 (3H, d, J = 7.2 Hz), 2.38 (1H, nq, J = 7.2 Hz), 2.31 (1H, m), 2.00 and 2.25 (both 1H, m), 6.00 (1H, m), 5.64 (2H, m), 2.94 (1H, brs); δ_C 15.0, 37.0, 39.2, 28.1, 129.3, 121.2, 51.3]; III: -CH_2–CH_2- [δ_H 1.85 and 2.02 (both 1H, m), 2.47 and 2.63 (both 1H, m); δ_C 36.0, 18.6] were established. The signal at δ_C 76.7 was assigned to a C-12 attached to the furan ring of a clerodane diterpenoid. Long range correlations between the quaternary carbon at δ_C 45.2 and the methine and methylene protons at δ_H 2.38, 5.64 and 2.00 suggested that the structure II could be put partially in the ring A of a clerodane diterpenoid with the C-5 and C-10 at δ_C 45.2 and 39.2, respectively. The other carbon signals of the partial structure II were thus assigned to the C-1 (28.1) C-2 (129.3), C-3 (121.2), C-4 (51.3), C-9 (37.0), C-20 (15.0). The C-12 signal and the olefinic carbon signals at δ_C 167.2 and 128.8 showed long range correlations with the H-9 and the carbon at δ_C 167.2 also with the 20 methyl protons. These facts suggested that the C-9 was also bonded to the olefinic carbon at δ_C 167.2 and that this last carbon to the C-12. The signals at δ_C 167.2 and 128.8 were thus assigned to the C-11 and C-8 of a probable seven-membered ring B of a salvigenane diterpenoid, because compounds with this rearranged clerodane skeleton were found previously only in *Salvia* species (Esquivel, Domínguez, Hernández-Ortega, Toscano & Rodríguez-Hahn, 1994). From HMBC spectral data these olefinic carbons resulted bonded to the partial structure III and the carbonyl signal at δ_C 172.7 could be assigned to the 17-CO of a 12,17-olide bonded to the carbon at δ_C 128.8 attached to the methylene carbon at δ_C 18.6 (thus C-7). The carbons C-5 and C-10 showed a long range correlation with the methylene proton at δ_H 4.38 and the carbonyl signal at δ_C 174.9 with the olefinic proton signal at δ_H 5.64, thus methylene and carbonyl could be put in a 19,18-olide ring. Since the carbon signals at δ_C 45.2 (C-5) and 36.0 (partial structure III) were correlated with the methylene proton signals at δ_H 2.63 (partial structure III) and 4.38 (19-H), respectively, the carbon signal at δ_C 36.0 was assigned to the C-6.

The methyl proton signal at δ_H 0.78 (CH_3-20) was correlated in the ROESY spectrum with the proton signal at δ_H 2.94 (H-4). This last proton could be assigned by its chemical shift (Rodríguez-Hahn et al., 1994) to β axial with a deshielding effect ($\Delta\delta = +0.11$ ppm) deriving from the neighbouring CH_3-20. This methyl group was thus assigned to β axial with an A/B *cis* fusion. This structure with a dihedral angle between H-9 and H-10 of about 90° could furthermore explain the very low coupling constant between these two protons (H-9/H-10 TOCSY sequence interruption and H-9 signal as near quartet). The relative configuration of C-12 could not be determined. From these facts the structure of blepharolide-B was determined as shown (**2**).

The diterpenoids constituents of *Salvia* species are closely related to the subgenus and sections to which they belong (Rodríguez-Hahn, Esquivel & Cárdenas, 1992). Diterpenoids with a salvigenane skeleton were isolated until now only from *Salvia fulgens* Cav. and *Salvia leucantha* Cav. (both subgenus Calosphace sections Fulgentes and Albolanatae, respectively) (Esquivel et al., 1994). *Salvia blepharophylla* is a species classified in the subgenus Calosphace, section

Brandegeia (Epling, 1939). Blepharolide-B constitutes the third salvigenane diterpenoid isolated from a natural source. Blepharolide-A shows a new rearranged clerodane structure with a C_3–C_6–C_6 ring system. An other clerodane diterpenoid, salvipuberulin, with a different rearranged C_3–C_6–C_6 ring system was found in *Salvia puberula* Fern. (Esquivel et al., 1994; Rodríguez-Hahn et al., 1988; Rodríguez-Hahn et al., 1992). From this last American species, furthermore, an isomeric correlated diterpenoid, isosalvipuberulin was isolated, in which the benzonorcaradiene structure of salvipuberulin was transformed into the isomeric benzocycloheptatriene structure. In *Salvia blepharophylla* compounds **1** and **2** show a similar correlation and thus we propose for the new skeleton of **1** the name isosalvigenane. The presence of these clerodane diterpenoids in *Salvia blepharophylla* is in agreement with Rodríguez-Hahn et al. (1994), who underlined that such diterpenoids are typical of *Salvia* species of the American Continent which belong to subgenera Leonia and Calosphace. Furthermore it is interesting to draw attention to the isolation of salvigenane and isosalvigenane diterpenoids from this species, because this fact could suggest a botanical chemotaxonomic relation between sections Fulgentes, Albolanatae and Brandegeia of subgenus Calosphace.



1 2

3. Experimental

3.1. General

The ^1H and ^{13}C NMR spectra were performed with a Bruker DRX 600 spectrometer. The IR spectra were performed with a Perkin-Elmer 1310 infrared spectrophotometer. The UV spectra were obtained with a Hewlett-Packard diode array spectrophotometer 8452A. The optical rotation was recorded on a Perkin-Elmer 241 MC polarimeter. TLC: silica gel 60 F_{254}; $CHCl_3$–MeOH (10:0.5).

Table 1
NMR spectral data for compound **1** (CD_3OD, ^{13}C NMR at 150 MHz, ^1H NMR at 600 MHz)

C	^{13}C	DEPT	^1H (*J* in Hz)
1	25.2	CH_2	2.27, 2.35 both m
2	129.8	CH	6.03 m
3	120.4	CH	5.60 nd (9.6)
4	51.1	CH	2.83 brs
5	43.0	C	–
6	40.7	CH_2	1.17 nt (12.0), 2.31 m
7	61.3	CH	4.91 dd (10.0, 7.4)
8	30.4	C	–
9	41.8	C	–
10	42.0	CH	1.78 dd (12.0, 5.0)
11	38.2	CH	2.59 d (4.8)
12	74.4	CH	5.71 d (4.8)
13	122.3	C	–
14	109.4	CH	6.49 ns
15	144.2	CH	7.50 ns
16	140.1	CH	7.52 ns
17	176.3	C	–
18	177.4	C	–
19	68.9	CH_2	4.22 m[a]
20	14.7	CH_3	0.94 s

[a] In $CDC1_3$: 4.13 and 4.19, both d (11.0).

3.2. Plant material

Aerial parts of *S. blepharophylla* were collected in December 1996–January 1997 from the collection of *Salvia* species established and available in the Hanbury Botanical Gardens of La Mortola, Ventimiglia (Italy).

3.3. Isolation

Fresh aerial parts (2 kg) were immersed in CH_2Cl_2 for 20 sec. After filtration the extraction solvent was removed under reduced pressure. The exudate (8 g) was chromatographed on Sephadex LH-20 columns, guided by analytical TLC, using $CHCl_3$–MeOH (1:1) as eluent to give in order of elution fractions with **2** and fractions with mixture of **2** and **1**. These last fractions were chromatographed on silica gel columns with mixtures of *n*-hexane–$CHCl_3$ of increasing polarity. Compound **2** was eluted with *n*-hexane–$CHCl_3$ (75:25) and compound **1** with $CHCl_3$. Yields: 200 and 520 mg of crude **1** and **2** respectively, which were recrystallised from $CHCl_3$–MeOH.

3.3.1. Blepharolide A (*1*)

Colourless crystals, mp. 252–4°. $[\alpha]_D^{20}$ −13.7 ($CHCl_3$, *c* 0.204). UV λ_{max}^{MeOH} nm: 206. IR ν_{max}^{KBr} cm^{-1}: 3430, 3120, 1758 and 1735 (>CO), 1500, 875. ^1H and ^{13}C NMR: Table 1. Found: C, 67.72; H, 5.66. $C_{20}H_{20}O_6$ requires: C, 67.41; H, 5.66%.

Table 2
NMR spectral data for compound **2** ($CDCl_3$, ^{13}C NMR at 150 MHz, ^1H NMR at 600 MHz)

C	^{13}C	DEPT	^1H (J in Hz)
1	28.1	CH_2	2.00 m, 2.25 m
2	129.3	CH	6.00 m
3	121.2	CH	5.64 m
4	51.3	CH	2.94 brs
5	45.2	C	–
6	36.0	CH_2	1.85 m, 2.02 m
7	18.6	CH_2	2.47 m, 2.63 m
8	128.8	C	–
9	37.0	CH	2.38 nq (7.2)
10	39.2	CH	2.31 m
11	167.2	C	–
12	76.7	CH	5.64 m
13	119.7	C	–
14	107.8	CH	6.23 ns
15	144.1	CH	7.45 ns
16	141.2	CH	7.57 ns
17	172.7	C	–
18	174.9	C	–
19	72.0	CH_2	4.18 m, 4.38 nd (9.0)
20	15.0	CH_3	0.78 d (7.2)

3.3.2. X-ray analysis of diterpene *1*

Transparent, colourless single crystals were grown from $CHCl_3$–CH_3OH. After preliminary Laue photographs, X-ray data were recorded on a Enraf-Nonius CAD4 diffractometer with graphite monochromated MoKα ($\lambda = 0.7107$ Å) radiation. Cell constants were determined by least-squares refinement of diffractometer angles for 25 automatically centred reflections. During the data collection the centring of six reflections was repeated periodically to test the crystal orientation, and two reflections were monitored every 60 min to check the crystal stability. No crystal decay was observed.

3.3.3. Crystal data

Compound **1**, $C_{20}H_{20}O_6$, $M = 356.4$. Orthorhombic, $a = 8.187(2)$, $b = 12.262(2)$, $c = 16.854(3)$ Å, $V = 1692.0(6)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $D_c = 1.399$ g cm^{-3}. Crystal dimensions $0.32 \times 0.44 \times 0.46$ mm, $\mu = 0.10$ mm^{-1}; ω/θ scan mode, scan width 1.35°, scan speed 1.0–16.5 min^{-1}; 2789 unique reflections measured ($2.5 \leq \theta \leq 30°$).

3.3.4. Structure solution and refinement

The structure was solved by direct methods (NRCVAX; Gabe, Le Page, Charland, Lee & White, 1989). In the *E*-map the identity of the furane peaks was assessed during the refinement, by monitoring of bond distances and isotropic thermal factors. All the hydrogen atoms were obtained from difference Fourier syntheses. Final refinement on F^2 by full-matrix least squares (SHELXL97; Sheldrick, 1997), with all heavier atoms refined as anisotropic and all hydrogens as isotropic. Convergence was reached with a maximum shift-to-ESD ratio less than 0.01. No correlation matrix elements larger than 0.50 were found. Final reliability factors are $R_1 = 0.043$ on 2244 $F_0 \geq 4\sigma(F_0)$, $wR_2 = 0.111$ (on F^2) for all 2789 data and 315 parameters, with a goodness of fit $S = 1.019$. The final difference Fourier map was essentially flat, the electron density ranging between 0.26 and −0.22 e Å^{-3}.

Table 3
Selected bond lengths (Å) and angles (°) for **1**

C(4)–C(18)	1.516(3)	C(18)–C(4)–C(5)	103.2(2)
C(4)–C(5)	1.541(3)	C(19)–C(5)–C(4)	100.9(2)
C(5)–C(19)	1.535(3)	O(3)–C(7)–C(8)	106.4(2)
C(5)–C(10)	1.538(3)	O(3)–C(7)–C(6)	111.9(2)
C(7)–O(3)	1.423(3)	C(17)–C(8)–C(11)	104.2(2)
C(8)–C(17)	1.495(3)	C(11)–C(8)–C(9)	59.1(1)
C(8)–C(11)	1.510(3)	C(11)–C(9)–C(8)	59.5(1)
C(8)–C(9)	1.538(3)	C(9)–C(11)–C(8)	61.4(1)
C(9)–C(11)	1.503(3)	C(12)–C(11)–C(8)	106.5(2)
C(9)–C(10)	1.554(2)	O(5)–C(12)–C(11)	105.3(2)
C(11)–C(12)	1.510(3)	O(5)–C(17)–C(8)	111.8(2)
C(12)–O(5)	1.477(3)	O(2)–C(18)–C(4)	110.4(2)
C(17)–O(5)	1.341(3)	O(2)–C(19)–C(5)	105.5(2)
C(18)–O(1)	1.201(3)	C(18)–O(2)–C(19)	110.3(2)
C(18)–O(2)	1.337(3)	C(17)–O(5)–C(12)	110.7(1)
C(19)–O(2)	1.457(3)		

3.3.5. Blepharolide B (*2*)

Colourless crystals, mp 260–2°. $[\alpha]_D^{20}$ −98.1 ($CHCl_3$, *c* 0.212). UV λ_{max}^{MeOH} nm: 212. IR ν_{max}^{KBr} cm^{-1}: 3140, 1750 (>CO), 1508, 875. ^1H and ^{13}C NMR: Table 2. Found: C, 71.03; H, 5.93. $C_{20}H_{20}O_5$ requires: C, 70.57; H, 5.92%.

Acknowledgements

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