Chemical Studies of Marine Invertebrates. Part 46.[1] Confirmation of the Molecular Structure of Sigmosceptrellin-B by *X*-Ray Diffraction Analysis

Carla Piccinni-Leopardi
Laboratoire de Chimie Organique E.P. (C.P. 165), Université Libre de Bruxelles, Av. F. D. Roosevelt 50, 1050 Brussels, Belgium
Gabriel Germain and Maurice Van Meerssche
Laboratoire de Chimie Physique et de Cristallographie, Université Catholique de Louvain, Place L. Pasteur 1, 1348 Louvain-la-Neuve, Belgium
Martine Albericci, Jean-Claude Braekman, Désiré Daloze,* and Bernard Tursch
Collectif de Bio-écologie, Faculté des Sciences, Université Libre de Bruxelles, Av. F. D. Roosevelt 50, 1050 Brussels, Belgium

---

The structure of sigmosceptrellin-B (3), a norsesterterpene peroxide isolated from the sponge *Sigmosceptrella laevis*, had previously been proposed on the basis of chemical correlations. This structure has now been independently confirmed by an *X*-ray diffraction analysis on the crystalline derivative (1*S*,4a*R*,5*S*,6*R*,8a*R*)-1-hydroxymethyl-5-{2-[(3*R*,6*S*)-3-(1*R*)-(2-hydroxy-1-methylethyl)-6-methyl-1,2-dioxan-6-yl]ethyl}-5,6,8a-trimethylbicyclo[4.4.0]decan-1-ol (6). This paper discusses the conformational parameters of the 1,2-dioxan ring of (6).

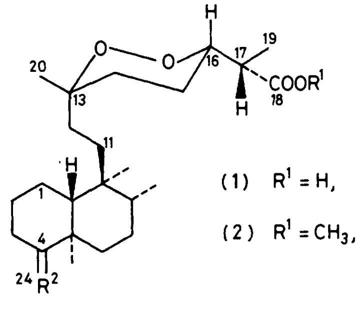
In previous papers [1,2] we reported the isolation of three novel norsesterterpene peroxides, sigmosceptrellin-A (1), -B (3), and -C (7), from the ichthyotoxic fraction of the sponge *Sigmosceptrella laevis*.† The structure and relative configuration of sigmosceptrellin-A were determined by *X*-ray diffraction analysis on its crystalline derivative (2),[2] while those of the two other compounds were deduced by chemical intercorrelations.[1]

The absolute configurations of (1), (3), and (7) followed [1] from c.d. measurements performed on the ketone (4) obtained by oxidative cleavage of the 4(24)-methylene function of (3). In particular, it was established that the absolute configurations at C(16) and C(17) were 16*S* and 17*S* for (1), 16*R* and 17*S* for (3), and 16*S* and 17*R* for (7).

Moreover, the comparison of the ^{1}H n.m.r. spectra of the sigmosceptrellin-A, -B, and -C methyl esters led us to assume [1] that the 1,2-dioxan ring in sigmosceptrellin-A and -C has a chair conformation with the C(20) methyl group equatorial and the hydrogen atom at C(16) axial. In sigmosceptrellin-B, however, the configuration at C(16) is inverted and the conformation with C(20) and H[at C(16)] both axial is preferred. This observation is in agreement with straightforward arguments based on conformational analysis of six-membered rings: a CH_3 group and a CH_2–CH_2 chain have almost the same steric requirements while a 1-carboxyethyl substituent obviously prefers an equatorial orientation (for comparison, $\Delta G°_{25}$ for isopropylcyclohexane [3] is -2.15 kcal mol^{-1}).

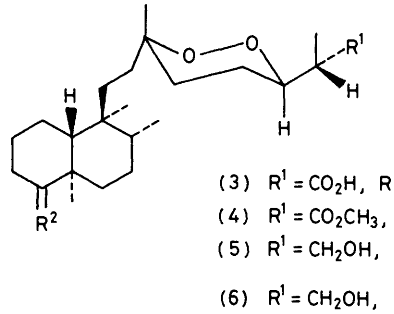
When this work was completed, we were informed that another group [4] had reached different conclusions on the stereochemistry at C(16) and C(17), and on the conformation of the 1,2-dioxane ring of (3).

By way of conclusive proof of our structure proposal, we decided to perform an *X*-ray diffraction study on a crystalline derivative of sigmosceptrellin-B. To this end, the primary alcohol (5) obtained by selective $LiAlH_4$ reduction of sigmosceptrellin-B methyl ester [1] was treated with OsO_4 to give the triol (6).



(1) R^1 = H, R^2 = CH$_2$

(2) R^1 = CH$_3$, R^2 = OH, CH$_2$OCOC$_6$H$_4$Br-*p*

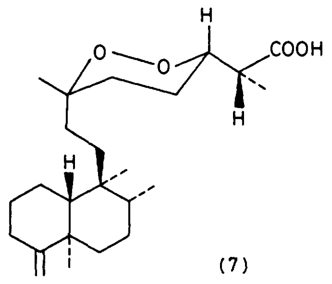


(3) R^1 = CO$_2$H, R^2 = CH$_2$

(4) R^1 = CO$_2$CH$_3$, R^2 = O

(5) R^1 = CH$_2$OH, R^2 = CH$_2$

(6) R^1 = CH$_2$OH, R^2 = OH, CH$_2$OH



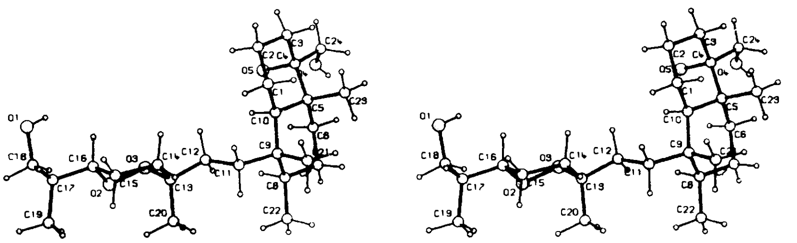
(7)

Experimental

Synthesis.—Mono-ol (5) (22 mg, 0.058 mmol) obtained by selective $LiAlH_4$ reduction of the ester function was treated

---

† For the sake of convenience, the numbering we use for these compounds and their derivatives is that defined in our previous papers [1,2] and not the IUPAC numbering.



Stereoscopic drawing of the triol (6)

with OsO_4 (50 mg, 0.196 mmol) in dry pyridine. The solution was stirred overnight at room temperature. The mixture was treated with $NaHSO_3$ for 1 h. This was followed by extraction, first with CH_2Cl_2, and then with $CHCl_3$–EtOH (3 : 2). Chromatography on SiO_2 (hexane–acetone 8 : 2) yielded (6) (19 mg, 0.046 mmol), homogeneous in t.l.c. in at least three different solvent mixtures (Found: *m*/*z*, 412. Calc. for $C_{24}H_{44}O_5$: M^+, 412), δ 0.67 (3 H, s), 0.68 (3 H, d, *J* 5 Hz), 0.88 (3 H, s), 0.92 (3 H, d, *J* 7 Hz), 1.28 (3 H, s), 3.50 (2 H, AB), 3.60 (2 H, AB), and 4.10 (1 H, m), υ_{OH} (KBr) 3 400 cm^{-1}. The triol (6) crystallized from hexane–acetone in small rods, m.p. 148—150°.

Crystal Data.—$C_{24}H_{44}O_5$ (6), $M = 412.6$. Orthorhombic, $a = 6.272(1)$, $b = 14.094(3)$, $c = 26.818(5)$ Å, $U = 2370.6(8)$ Å^3, $D_c = 1.16$ g cm^{-3}, $Z = 4$, $F(000) = 912$, Cu-K_α radiation ($\lambda = 1.5418$ Å), space group $P2_12_12_1$.

Structure Determination.—15 reflections measured on a Syntex P2$_1$ automated diffractometer and refined using a least-squares method produced the unit cell dimensions and the orientation matrix for the data collection. Intensities were measured by the ω-scan technique. Reflections were collected for 2θ values <114° using graphite monochromated Cu-K_α radiation. The criterion which qualified a reflection for observation was $I > 2.5\sigma(I)$. Of the 1 879 independent reflections collected, 1 632 fulfilled this condition. The intensity of one standard reflection was essentially constant over the duration of the experiment.

Data were corrected for Lorentz and polarization effects, but not for absorption.

All our calculations were carried out on the IBM 370/158 computer in the Computing Centre, Louvain-la-Neuve. The structure of (6) was solved by direct methods using the MULTAN 80 program[5] and was refined by least-squares procedure using the SHELX 76 program.[6]

Some of the hydrogen atoms, including the hydrogen at O(5) (see Figure), were not apparent in the difference-Fourier map. With the exception of H [at O(1)] and H [at O(4)] (which were further refined at the positions found in the difference-Fourier map), all the hydrogens were then located at their ideal positions and refined with one overall isotropic temperature factor (5.65 Å^2). The final *R* factor was 0.047 (observed reflections only).

Results and Discussion

A stereoscopic drawing of the sigmosceptrellin-B derivative (6) is given in the Figure. It shows the absolute configuration of the triol. Only its relative configuration can be deduced from our *X*-ray data, but, as we have already said, its absolute configuration was previously obtained from c.d. measurements.[1] The *X*-ray results fully confirm the structure which we suggested for sigmosceptrellin-B.[1]

The final atomic parameters for the non-hydrogen atoms

Table 1. Final fractional co-ordinates (× 10^4) for the non-hydrogen atoms of (6). Estimated standard deviations are in parentheses

	x	*y*	*z*
C(1)	−480(7)	4 218(3)	6 849(2)
C(2)	−202(8)	4 232(3)	7 416(2)
C(3)	442(8)	3 246(3)	7 624(2)
C(4)	2 314(7)	2 816(3)	7 354(2)
C(5)	1 908(7)	2 768(3)	6 771(2)
C(6)	3 906(7)	2 373(3)	6 508(2)
C(7)	3 826(7)	2 483(3)	5 947(2)
C(8)	3 587(7)	3 523(3)	5 797(2)
C(9)	1 534(7)	3 975(3)	6 013(2)
C(10)	1 503(6)	3 810(3)	6 592(1)
C(11)	1 584(7)	5 062(3)	5 908(2)
C(12)	3 336(8)	5 653(3)	6 138(2)
C(13)	3 534(8)	6 657(3)	5 923(1)
C(14)	1 457(8)	7 213(3)	6 006(2)
C(15)	1 802(9)	8 288(3)	5 939(2)
C(16)	3 781(8)	8 608(3)	6 222(2)
C(17)	4 426(9)	9 635(3)	6 131(2)
C(18)	6 190(8)	9 948(3)	6 492(2)
C(19)	5 157(15)	9 822(4)	5 593(2)
C(20)	4 290(11)	6 659(4)	5 385(2)
C(21)	−467(8)	3 597(4)	5 744(2)
C(22)	3 886(9)	3 633(4)	5 231(2)
C(23)	16(8)	2 088(3)	6 677(2)
C(24)	2 905(9)	1 860(3)	7 605(2)
O(1)	5 377(6)	10 035(2)	6 988(1)
O(2)	5 585(5)	8 042(2)	6 070(1)
O(3)	5 165(5)	7 067(2)	6 230(1)
O(4)	5 106(7)	1 656(2)	7 559(1)
O(5)	4 162(5)	3 419(2)	7 449(1)

Table 2. Bond lengths (Å) with estimated standard deviations in parentheses

C(1)–C(2)	1.530(6)	C(9)–C(21)	1.543(6)
C(1)–C(10)	1.534(6)	C(11)–C(12)	1.511(6)
C(2)–C(3)	1.551(6)	C(12)–C(13)	1.533(5)
C(3)–C(4)	1.506(6)	C(13)–C(14)	1.537(7)
C(4)–C(5)	1.585(6)	C(13)–C(20)	1.518(6)
C(4)–C(24)	1.551(6)	C(13)–O(3)	1.435(5)
C(4)–O(5)	1.460(5)	C(14)–C(15)	1.541(6)
C(5)–C(6)	1.542(5)	C(15)–C(16)	1.523(7)
C(5)–C(10)	1.565(5)	C(16)–C(17)	1.522(6)
C(5)–C(23)	1.547(6)	C(16)–O(2)	1.443(6)
C(6)–C(7)	1.513(6)	C(17)–C(18)	1.535(7)
C(7)–C(8)	1.527(6)	C(17)–C(19)	1.536(7)
C(8)–C(9)	1.549(6)	C(18)–O(1)	1.431(6)
C(8)–C(22)	1.536(6)	C(24)–O(4)	1.415(7)
C(9)–C(10)	1.569(5)	O(2)–O(3)	1.464(4)
C(9)–C(11)	1.558(5)		

Table 3. Bond angles (°) with estimated standard deviations in parentheses

C(2)-C(1)-C(10)	111.1(4)
C(1)-C(2)-C(3)	112.0(4)
C(2)-C(3)-C(4)	113.0(4)
C(3)-C(4)-C(5)	111.5(4)
C(3)-C(4)-C(24)	109.1(4)
C(5)-C(4)-C(24)	115.5(3)
C(3)-C(4)-O(5)	107.5(3)
C(5)-C(4)-O(5)	108.9(3)
C(24)-C(4)-O(5)	103.9(3)
C(4)-C(5)-C(6)	109.7(3)
C(4)-C(5)-C(10)	106.8(3)
C(6)-C(5)-C(10)	109.3(3)
C(4)-C(5)-C(23)	108.1(3)
C(6)-C(5)-C(23)	108.9(3)
C(10)-C(5)-C(23)	114.0(3)
C(5)-C(6)-C(7)	113.0(4)
C(6)-C(7)-C(8)	111.4(3)
C(7)-C(8)-C(9)	112.2(4)
C(7)-C(8)-C(22)	110.2(4)
C(9)-C(8)-C(22)	115.5(4)
C(8)-C(9)-C(10)	108.7(3)
C(8)-C(9)-C(11)	108.6(3)
C(10)-C(9)-C(11)	109.0(3)
C(8)-C(9)-C(21)	111.0(3)
C(10)-C(9)-C(21)	113.6(4)
C(11)-C(9)-C(21)	105.7(3)
C(1)-C(10)-C(5)	110.2(3)
C(1)-C(10)-C(9)	113.5(3)
C(5)-C(10)-C(9)	116.2(3)
C(9)-C(11)-C(12)	118.9(3)
C(11)-C(12)-C(13)	114.5(4)
C(12)-C(13)-C(14)	110.3(4)
C(12)-C(13)-C(20)	112.6(4)
C(14)-C(13)-C(20)	113.7(4)
C(12)-C(13)-O(3)	102.3(3)
C(14)-C(13)-O(3)	108.4(3)
C(20)-C(13)-O(3)	108.8(4)
C(13)-C(14)-C(15)	111.4(4)
C(14)-C(15)-C(16)	110.4(4)
C(15)-C(16)-C(17)	114.7(4)
C(15)-C(16)-O(2)	109.5(3)
C(17)-C(16)-O(2)	105.8(4)
C(16)-C(17)-C(18)	111.3(4)
C(16)-C(17)-(C19)	113.2(4)
C(18)-C(17)-C(19)	109.1(5)
C(17)-C(18)-O(1)	110.7(4)
C(4)-C(24)-O(4)	111.8(4)
C(16)-O(2)-O(3)	107.2(3)
C(13)-O(3)-O(2)	109.7(3)

Table 4. Torsion angles (°) (estimated standard deviations are $\leqslant 1°$)

C(10)-C(1)-C(2)-C(3)	−53
C(2)-C(1)-C(10)-C(5)	60
C(2)-C(1)-C(10)-C(9)	−168
C(1)-C(2)-C(3)-C(4)	51
C(2)-C(3)-C(4)-C(5)	−54
C(2)-C(3)-C(4)-C(24)	177
C(2)-C(3)-C(4)-O(5)	65
C(3)-C(4)-C(5)-C(6)	177
C(3)-C(4)-C(5)-C(10)	59
C(3)-C(4)-C(5)-C(23)	−64
C(24)-C(4)-C(5)-C(6)	−58
C(24)-C(4)-C(5)-C(10)	−176
C(24)-C(4)-C(5)-C(23)	61
O(5)-C(4)-C(5)-C(6)	59
O(5)-C(4)-C(5)-C(10)	−60
O(5)-C(4)-C(5)-C(23)	177
C(3)-C(4)-C(24)-O(4)	−150
C(5)-C(4)-C(24)-O(4)	83
O(5)-C(4)-C(24)-O(4)	−36
C(4)-C(5)-C(6)-C(7)	−169
C(10)-C(5)-C(6)-C(7)	−52
C(23)-C(5)-C(6)-C(7)	73
C(4)-C(5)-C(10)-C(1)	−62
C(4)-C(5)-C(10)-C(9)	168
C(6)-C(5)-C(10)-C(1)	180
C(6)-C(5)-C(10)-C(9)	49
C(23)-C(5)-C(10)-C(1)	58
C(23)-C(5)-C(10)-C(9)	−73
C(5)-C(6)-C(7)-C(8)	59
C(6)-C(7)-C(8)-C(9)	−59
C(6)-C(7)-C(8)-C(22)	171
C(7)-C(8)-C(9)-C(10)	53
C(7)-C(8)-C(9)-C(11)	172
C(7)-C(8)-C(9)-C(21)	−72
C(22)-C(8)-C(9)-C(10)	−179
C(22)-C(8)-C(9)-C(11)	−61
C(22)-C(8)-C(9)-C(21)	55
C(8)-C(9)-C(10)-C(1)	180
C(8)-C(9)-C(10)-C(5)	−50
C(11)-C(9)-C(10)-C(1)	62
C(11)-C(9)-C(10)-C(5)	−168
C(21)-C(9)-C(10)-C(1)	−55
C(21)-C(9)-C(10)-C(5)	74
C(8)-C(9)-C(11)-C(12)	−63
C(10)-C(9)-C(11)-C(12)	55
C(21)-C(9)-C(11)-C(12)	178
C(9)-C(11)-C(12)-C(13)	167
C(11)-C(12)-C(13)-C(14)	60
C(11)-C(12)-C(13)-C(20)	−68
C(11)-C(12)-C(13)-O(3)	176
C(12)-C(13)-C(14)-C(15)	163
C(20)-C(13)-C(14)-C(15)	−69
O(3)-C(13)-C(14)-C(15)	52
C(12)-C(13)-O(3)-O(2)	180
C(14)-C(13)-O(3)-O(2)	−64
C(20)-C(13)-O(3)-O(2)	60
C(13)-C(14)-C(15)-C(16)	−47
C(14)-C(15)-C(16)-C(17)	173
C(14)-C(15)-C(16)-O(2)	54
C(15)-C(16)-C(17)-C(18)	171
C(15)-C(16)-C(17)-C(19)	−66
O(2)-C(16)-C(17)-C(18)	−69
O(2)-C(16)-C(17)-C(19)	55
C(15)-C(16)-O(2)-O(3)	−65
C(17)-C(16)-O(2)-O(3)	171
C(16)-C(17)-C(18)-O(1)	—70
C(19)-C(17)-C(18)-O(1)	164
C(16)-O(2)-O(3)-C(13)	72

are listed in Table 1. Supplementary Publication No. SUP 23395 (14 pp.) * contains tables showing the positions of the hydrogen atoms, the observed and calculated structure factors, and the thermal parameters of the atoms. Interatomic distances are listed in Table 2. Tables 3 and 4 show the bond and torsion angle values, respectively.

Although cyclic peroxides are well known compounds from the synthetic point of view, little is known about their conformation.[7] To our knowledge, the present work and that carried out on sigmosceptrellin-A [2] are the first *X*-ray studies concerning 1,2-dioxan derivatives. It therefore seems interesting to point out some features of this six-membered heterocycle as it appears in sigmosceptrellin-B.

The conformation of the ring can certainly be described as a chair, since the successive dihedral angles are of opposite signs. Nevertheless, the chair conformation is strongly distorted in relation to that of cyclohexane. This distortion clearly appears at the level of the dihedral angle values. All the dihedral angles involving oxygen atoms are wider in relation to the normal value [8] of 55° for cyclohexane (the maximum value is observed for the dihedral angle about the O-O bond which is 72°). The widening of the dihedral angle about the O-O bond is a direct consequence of the shape of the potential energy curve associated with the rotation about this bond. This curve is well known for hydrogen peroxide [7] and clearly shows that the minimum energy corresponds to a dihedral angle of *ca.* 115° compared to the value of 60° for ethane (or 55° for the flattened chair of cyclohexane). It is not of course possible to have a six-membered ring with a dihedral angle of 120°, and the observed 72° value corresponds to the best free-energy compromise. Keeping H_2O_2 as crude model compound, the torsional energy about the O-O bond could be estimated at *ca.* 3 kcal mol^{-1} in 1,2-dioxan.

The heterocyclic ring has an approximate two-fold axis

---

* For details of Supplementary Publications see Notice to Authors No. 7, in *J. Chem. Soc., Perkin Trans. 2,* 1981, Index issue.

passing through the middle points of the O(2)–O(3) and C(14)–C(15) bonds. The torsion angle values increase as one proceeds from the C(14)–C(15) bond to the O(2)–O(3) bond. This observation can probably be explained by the fact that the bonds are longer in the part of the ring which contains carbon atoms than in the part which contains oxygen atoms.

Allowing for error, no significant difference can be observed between the 1,2-dioxan structural parameters of (6) and (7).[2]

References

1 Part 45, M. Albericci, J. C. Braekman, D. Daloze, and B. Tursch, *Tetrahedron*, 1982, **38**, 1881.

2 M. Albericci, M. Collart-Lempereur, J. C. Braekman, D. Daloze, B. Tursch, J. P. Declercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 1979, 2687.

3 J. A. Hirsch, in 'Topics in Stereochemistry,' eds. N. L. Allinger and E. L. Eliel, Interscience, New York, 1967, vol. I, p. 199.

4 S. Sokoloff, S. Halevy, V. Usieli, A. Colorni, and S. Sarel, *Experientia*, 1982, **38**, 337.

5 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, 'MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data,' Universities of York and Louvain-la-Neuve, 1980.

6 G. M. Sheldrick, 'SHELX 76. Program for Crystal Structure Determination,' University of Cambridge, 1976.

7 F. G. Riddell, 'The Conformational Analysis of Heterocyclic Compounds,' Academic Press, London, 1980.

8 E. M. Engler, J. D. Andose, and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1973, **95**, 8005.

Received 22nd February 1982; *Paper* 2/321