

Stereochemistry of a Novel Sesquiterpene Lactone of Eudesmane Type. X-Ray Determination of the Structure of Isosilerolide

Urszula Rychlewska

Faculty of Chemistry, Department of Crystallography, A. Mickiewicz University, ul. Grunwaldzka 6, 60-780 Poznań, Poland

The crystal and molecular structure of isosilerolide has been determined by direct methods from intensity data collected on a diffractometer and has been refined by full-matrix least-squares to $R = 0.051$ over 1 407 reflections. Crystals are orthorhombic, space group $P2_12_12_1$, with $a = 9.665(1)$, $b = 12.182(1)$, $c = 17.835(2)$ Å, $Z = 4$. The ring junctions of the eudesmanolide nucleus are *trans* at C(5)–C(10) and *cis* at C(6)–C(7), respectively. The cyclohexene adopts a 10α -sofa conformation; the cyclohexane conformation is intermediate between a 5β , 8β -boat and 5β , 10α -twist. The γ -lactone is present in a flattened half-chair conformation. The compound investigated is the first representative of a new, so far undescribed, stereostructural group of native $5\beta\text{H}$, $6\alpha\text{H}$, $7\alpha\text{H}$, $10\alpha\text{CH}_3$ -eudesman-6,12-olides.

The isolation of isosilerolide from the roots of *Laserpitium siler* L. (Umbelliferae, Laserpitiese) followed by complex chemical and spectroscopic investigations led to the suggestion that this compound is actually a member of the new stereostructural group of natural eudesmanolides, $5\beta\text{H}$, $6\alpha\text{H}$, $7\alpha\text{H}$, $10\alpha\text{CH}_3$ -eudesman-6,12-olides. The present X-ray analysis study has unambiguously confirmed the earlier spectroscopic deductions. A preliminary report on the stereochemical results obtained has been published.¹ This paper reports details of the molecular conformation of isosilerolide as determined by an X-ray method.

Experimental

Crystal Data.— $\text{C}_{22}\text{H}_{30}\text{O}_6$, orthorhombic, $P2_12_12_1$, $a = 9.665(1)$, $b = 12.182(1)$, $c = 17.835(2)$ Å, $U = 2\,100.0(5)$ Å³, $D_m = 1.23$, $D_c = 1.24$ g cm⁻³, $Z = 4$.

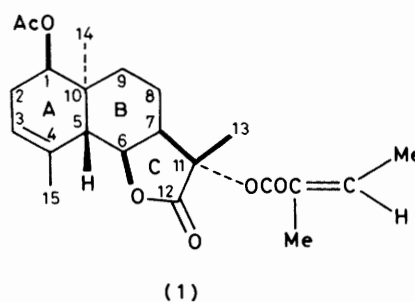
Crystallographic Measurements.—A crystal of dimensions $0.3 \times 0.3 \times 0.4$ mm grown from di-isopropyl ether was used to collect intensity data on a Syntex P2₁ diffractometer by θ - 2θ scanning technique using a variable scan speed and graphite-monochromated Cu- K_α radiation. Lattice parameters were refined by a least-squares procedure utilizing 15 reflections whose angles were measured by a centering routine associated with the diffractometer. The background and integrated intensity for each reflection were evaluated from a profile analysis according to the Lehmann and Larsen method² using the PRAN program.³ Those 1 416 reflections for which $I/\sigma(I) \geq 1.96$ were regarded as observed. Lorentz and polarization corrections were applied but no absorption corrections were made [$\mu(\text{Cu-}K_\alpha) = 0.74$ mm⁻¹]. Anomalous dispersion corrections were applied to the scattering factors of the oxygen and carbon atoms.

Structure Analysis.—MULTAN⁴ was used to calculate phases and the E map revealed the positions of 25 non-hydrogen atoms. Further calculations were performed with the SHELX program system.⁵ The difference Fourier map revealed the remaining non-hydrogen atom positions and refinement first with isotropic and later with anisotropic temperature factors gave $R = 0.099$. At this stage most of the H-atoms could be located from difference maps; however, for simplicity they were treated as follows. Methyl groups were set up and refined as rigid groups. All these H-atoms were assigned a common isotropic temperature factor which refined to $U = 0.155$ Å². The remaining H-atoms were placed in calculated positions and refined subject to the constraint that

the C–H vectors were constant in magnitude and direction but not position (*i.e.* a riding model). A common isotropic temperature factor for these H-atoms converged at $U = 0.0786$ Å². The quantity minimized in the least-squares calculations was $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma_F^2$ was determined from counting statistics. Nine reflections were omitted in the last cycle of refinement. The final R value was 0.051 for 1 407 reflections.

Results and Discussion

Lists of structure factors, anisotropic thermal parameters for non-hydrogen atoms, and positional parameters for hydrogen atoms have been deposited as Supplementary Publication No. SUP 23712 (10 pp.).* Atomic parameters for non-hydrogen atoms are given in Table 1. Tables 2–4 list the bond lengths, valency angles, and torsion angles. The molecule is depicted in Figure 1 and the packing diagram is shown in Figure 2.



X-Ray analysis establishes the structure and relative configuration of isosilerolide as shown in (1). Moreover, on the basis on c.d. studies¹ it can be stated that (1) also represents the absolute configuration. All drawings are presented with respect to the right-hand set of crystal axes and show the absolute configuration. The most interesting result of this structure analysis is the confirmation that the isosilerolide molecule possesses an unprecedented stereochemistry among eudesmanolides. The present structure differs from all previously known eudesmanolides in that it exhibits the enantio-

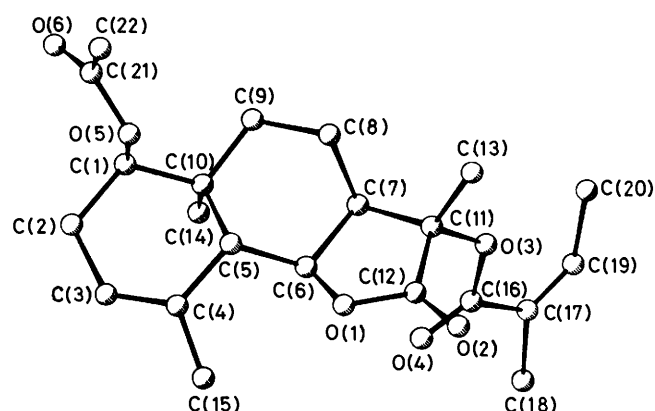
* For details of the Supplementary Publications Scheme see Instructions to Authors, *J. Chem. Soc., Perkin Trans. 2*, 1983, Issue 1.

Table 1. Fractional co-ordinates for non-hydrogen atoms ($\times 10^4$)

	x	y	z
C(1)	5 884(6)	5 361(5)	5 572(3)
C(2)	5 203(7)	4 440(6)	6 007(3)
C(3)	4 280(7)	3 735(6)	5 531(3)
C(4)	3 929(6)	3 934(4)	4 816(3)
C(5)	4 536(5)	4 920(4)	4 401(3)
C(6)	3 552(5)	5 397(4)	3 813(3)
C(7)	4 010(5)	6 533(4)	3 494(3)
C(8)	5 534(5)	6 751(5)	3 683(3)
C(9)	5 751(6)	6 759(5)	4 535(3)
C(10)	4 963(6)	5 840(5)	4 948(3)
C(11)	3 720(5)	6 432(4)	2 638(3)
C(12)	3 347(5)	5 236(4)	2 521(3)
C(13)	4 863(7)	6 746(6)	2 111(4)
C(14)	3 679(7)	6 332(6)	5 348(4)
C(15)	2 942(6)	3 171(5)	4 413(3)
C(16)	1 276(6)	6 938(5)	2 697(4)
C(17)	188(7)	7 775(6)	2 455(3)
C(18)	-1 289(6)	7 415(5)	2 621(4)
C(19)	482(9)	8 697(6)	2 156(4)
C(20)	1 863(7)	9 220(5)	1 952(5)
C(21)	8 341(7)	5 201(6)	5 531(4)
C(22)	9 553(6)	4 767(7)	5 102(4)
O(1)	3 504(4)	4 659(3)	3 168(2)
O(2)	3 065(4)	4 797(3)	1 942(2)
O(3)	2 550(4)	7 147(3)	2 415(2)
O(4)	1 024(4)	6 179(4)	3 084(3)
O(5)	7 135(4)	4 943(4)	5 213(2)
O(6)	8 418(5)	5 694(5)	6 117(3)

Table 2. Bond lengths (\AA)

C(1)-C(2)	1.515(9)	C(10)-C(14)	1.552(9)
C(1)-C(10)	1.540(8)	C(11)-C(12)	1.515(7)
C(1)-O(5)	1.460(7)	C(11)-C(13)	1.500(9)
C(2)-C(3)	1.501(9)	C(11)-O(3)	1.482(6)
C(3)-C(4)	1.342(8)	C(12)-O(1)	1.360(6)
C(4)-C(5)	1.528(7)	C(12)-O(2)	1.194(6)
C(4)-C(15)	1.513(8)	C(16)-O(3)	1.354(7)
C(5)-C(6)	1.530(7)	C(16)-O(4)	1.179(8)
C(5)-C(10)	1.542(8)	C(16)-C(17)	1.527(9)
C(6)-C(7)	1.560(7)	C(17)-C(18)	1.522(9)
C(6)-O(1)	1.461(6)	C(17)-C(19)	1.275(10)
C(7)-C(8)	1.534(7)	C(19)-C(20)	1.523(11)
C(7)-C(11)	1.557(8)	C(21)-O(5)	1.334(8)
C(8)-C(9)	1.534(8)	C(21)-O(6)	1.208(9)
C(9)-C(10)	1.541(8)	C(21)-C(22)	1.496(10)

**Figure 1.** View of the β -face of isosilerolide and atom-numbering scheme

meric stereochemistry at the C(5)-C(10) ring junction. The eudesmane skeleton typically contains a C(10) β -methyl group, whereas in isosilerolide the C(10) methyl group is α . Another characteristic feature of the isosilerolide molecule is the *cis*-junction of the γ -lactone ring while the *trans*-configuration for C(6)-lactonized compounds is normally encountered.

The change of configuration at C(5), C(10), and C(6) considerably alters the shape of the molecule. The conformations of the three fused rings are given by the torsion angles (Table 4). They are also described in another way with some additional comments in Table 5. As might be seen from this

Table, in the cyclohexene ring the mirror symmetry about the plane through C(3) and C(10) is dominant indicating a sofa conformation with the C(10) carbon atom being out of the ring plane and directed toward the α -face of the molecule.

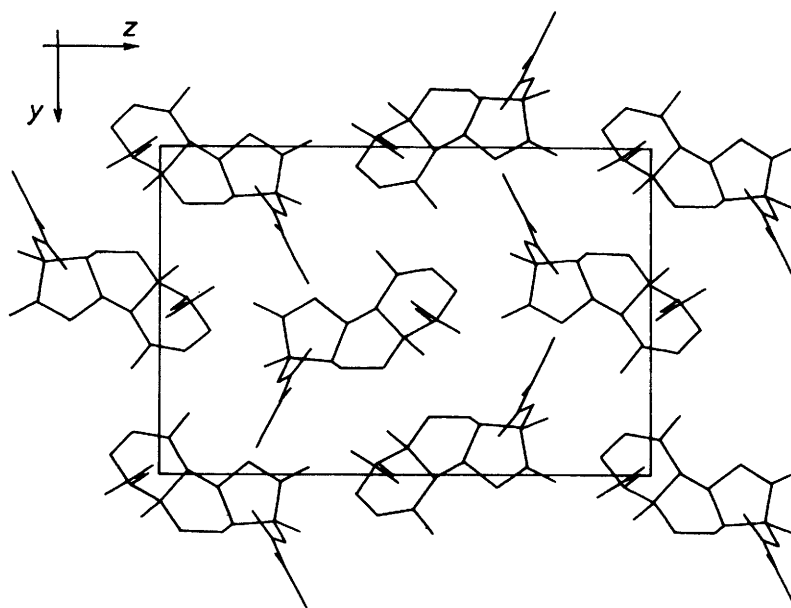
**Figure 2.** Crystal structure of isosilerolide viewed in projection along the x -axis

Table 3. Valency angles (°)

O(5)-C(1)-C(2)	109.0(4)	C(14)-C(10)-C(9)	109.5(5)
O(5)-C(1)-C(10)	107.1(4)	O(3)-C(11)-C(7)	110.7(4)
C(10)-C(1)-C(2)	113.6(4)	O(3)-C(11)-C(12)	110.3(4)
C(1)-C(2)-C(3)	113.1(5)	C(12)-C(11)-C(7)	104.7(4)
C(2)-C(3)-C(4)	125.8(5)	O(3)-C(11)-C(13)	104.1(4)
C(3)-C(4)-C(5)	120.4(5)	C(7)-C(11)-C(13)	117.5(4)
C(3)-C(4)-C(15)	120.0(5)	C(12)-C(11)-C(13)	109.5(4)
C(5)-C(4)-C(15)	119.7(4)	O(1)-C(12)-O(2)	121.9(4)
C(4)-C(5)-C(6)	113.1(4)	O(1)-C(12)-C(11)	110.7(4)
C(4)-C(5)-C(10)	111.6(4)	O(2)-C(12)-C(11)	127.1(4)
C(6)-C(5)-C(10)	108.9(4)	O(3)-C(16)-O(4)	123.5(5)
C(5)-C(6)-O(1)	109.0(4)	O(3)-C(16)-C(17)	113.3(5)
O(1)-C(6)-C(7)	105.5(4)	O(4)-C(16)-C(17)	123.1(5)
C(5)-C(6)-C(7)	114.2(4)	C(16)-C(17)-C(18)	113.5(5)
C(6)-C(7)-C(8)	110.2(4)	C(16)-C(17)-C(19)	123.6(6)
C(6)-C(7)-C(11)	103.7(4)	C(18)-C(17)-C(19)	123.0(6)
C(8)-C(7)-C(11)	113.7(4)	C(17)-C(19)-C(20)	131.6(6)
C(7)-C(8)-C(9)	110.5(4)	O(5)-C(21)-O(6)	122.6(5)
C(8)-C(9)-C(10)	113.7(4)	O(5)-C(21)-C(22)	112.6(5)
C(1)-C(10)-C(5)	109.7(4)	O(6)-C(21)-C(22)	124.8(6)
C(1)-C(10)-C(9)	109.6(4)	C(6)-O(1)-C(12)	110.7(4)
C(9)-C(10)-C(5)	111.0(4)	C(11)-O(3)-C(16)	118.9(4)
C(14)-C(10)-C(1)	106.0(5)	C(1)-O(5)-C(21)	117.1(4)
C(14)-C(10)-C(5)	111.0(4)		

Table 4. Torsion angles (°)

C(12)-O(1)-C(6)-C(5)	-145.9(4)
C(12)-O(1)-C(6)-C(7)	-22.8(4)
C(6)-O(1)-C(12)-O(2)	-168.0(5)
C(6)-O(1)-C(12)-C(11)	17.8(5)
C(16)-O(3)-C(11)-C(7)	-64.2(5)
C(16)-O(3)-C(11)-C(12)	51.3(5)
C(16)-O(3)-C(11)-C(13)	168.7(5)
C(11)-O(3)-C(16)-O(4)	-4.0(7)
C(11)-O(3)-C(16)-C(17)	176.8(5)
C(21)-O(5)-C(1)-C(2)	-102.9(6)
C(21)-O(5)-C(1)-C(10)	133.8(6)
C(1)-O(5)-C(21)-O(6)	4.9(8)
C(1)-O(5)-C(21)-C(22)	-177.8(6)
O(5)-C(1)-C(2)-C(3)	-84.5(6)
O(5)-C(1)-C(10)-C(5)	63.0(5)
O(5)-C(1)-C(10)-C(9)	-59.0(5)
O(5)-C(1)-C(10)-C(14)	-177.1(5)
C(10)-C(1)-C(2)-C(3)	34.8(6)
C(2)-C(1)-C(10)-C(5)	-57.4(5)
C(2)-C(1)-C(10)-C(9)	-179.4(5)
C(2)-C(1)-C(10)-C(14)	62.5(6)
C(1)-C(2)-C(3)-C(4)	-7.5(7)
C(2)-C(3)-C(4)-C(5)	3.2(7)
C(2)-C(3)-C(4)-C(15)	-177.7(7)
C(3)-C(4)-C(5)-C(6)	-148.8(6)
C(3)-C(4)-C(5)-C(10)	-25.7(5)
C(15)-C(4)-C(5)-C(6)	32.0(5)
C(15)-C(4)-C(5)-C(10)	155.2(5)
C(4)-C(5)-C(6)-O(1)	-73.8(4)
C(4)-C(5)-C(6)-C(7)	168.4(5)
C(4)-C(5)-C(10)-C(1)	51.1(5)
C(4)-C(5)-C(10)-C(9)	172.3(5)
C(4)-C(5)-C(10)-C(14)	-65.7(5)
C(10)-C(5)-C(6)-O(1)	161.5(4)
C(10)-C(5)-C(6)-C(7)	43.8(5)
C(6)-C(5)-C(10)-C(1)	176.6(5)
C(6)-C(5)-C(10)-C(9)	-62.2(5)
C(6)-C(5)-C(10)-C(14)	59.8(5)
O(1)-C(6)-C(7)-C(8)	-103.9(4)
O(1)-C(6)-C(7)-C(11)	18.1(4)
C(5)-C(6)-C(7)-C(8)	15.8(5)
C(5)-C(6)-C(7)-C(11)	137.8(5)
C(6)-C(7)-C(8)-C(9)	-60.1(5)

Table 4 (continued)

C(6)-C(7)-C(11)-O(3)	110.6(5)
C(6)-C(7)-C(11)-C(12)	-8.3(4)
C(6)-C(7)-C(11)-C(13)	-130.0(5)
C(11)-C(7)-C(8)-C(9)	-176.0(5)
C(8)-C(7)-C(11)-O(3)	-129.8(5)
C(8)-C(7)-C(11)-C(12)	111.4(5)
C(8)-C(7)-C(11)-C(13)	-10.3(5)
C(7)-C(8)-C(9)-C(10)	42.2(5)
C(8)-C(9)-C(10)-C(1)	139.7(5)
C(8)-C(9)-C(10)-C(5)	18.5(5)
C(8)-C(9)-C(10)-C(14)	-104.4(5)
O(3)-C(11)-C(12)-O(1)	-124.3(5)
O(3)-C(11)-C(12)-O(2)	61.9(6)
C(7)-C(11)-C(12)-O(1)	-5.1(4)
C(7)-C(11)-C(12)-O(2)	-179.0(5)
C(13)-C(11)-C(12)-O(1)	121.7(5)
C(13)-C(11)-C(12)-O(2)	-52.1(6)
O(3)-C(16)-C(17)-C(18)	167.2(5)
O(3)-C(16)-C(17)-C(19)	-14.1(7)
O(4)-C(16)-C(17)-C(18)	-12.0(7)
O(4)-C(16)-C(17)-C(19)	166.7(8)
C(16)-C(17)-C(19)-C(20)	0.7(9)
C(18)-C(17)-C(19)-C(20)	179.2(8)

Table 5. Ring conformations (°)

Ring	A	B	C
Description	cyclohexene Sofa	cyclohexane Twist-boat	lactone Flattened half-chair
Asymmetry	$\Delta C_s^3 = 6.9$	$\Delta C_s^5 = 24.7$	$\Delta C_2^{6,01} = 2.3$
parameters ⁶	$\Delta C_2^{3,4} = 17.3$ $\Delta C_2^{1,2} = 48.9$	$\Delta C_s^{6,7} = 18.2$ $\Delta C_2^{5,10} = 25.9$ $\Delta C_2^6 = 21.2$	$\Delta C_s^6 = 7.5$ $\Delta C_s^{01} = 9.8$
Average torsion angle magnitude	30.0	40.4	14.4

In the cyclohexane ring the presence of a two-fold axis perpendicular to the ring at its centre indicates a flexible form. The approximate symmetry of this ring can best be described by two mutually perpendicular mirror planes and two mutually perpendicular two-fold axes, consistent with the presence of the conformation intermediate between 5 β , 8 β -boat and 5 β , 10 α -twist. The observed conformation of the cyclohexane is different from those of other eudesmanolides which usually take a chair form. However, in isosilerolide, the axial orientation of the C(10) methyl would require C(7)-C(11) to be axial and C(6)-O(1) equatorial if ring B had a chair form. Such a conformation would lead to C(13) having severe interactions with axial H-atoms at C(5) and C(9). These interactions destabilize the chair form of ring B and favour the twist-boat conformation.*

The γ -lactone is present in a flattened half-chair conformation. The two-fold axis runs through C(11) and the midpoint of the C(6)-O(1) bond. Several sesquiterpene γ -lactones have been reported to adopt a half-chair conformation. However, in all examples previously reported, atoms at the ring fusion, *i.e.* C(7) and C(6), or C(7) and C(8), were out of the ring plane while in the isosilerolide molecule it is O(1), which together with C(6), is displaced above and below the plane, respectively.

In the crystal the molecules are packed together mainly by van der Waals forces. No unusual intermolecular contacts are

* The author wishes to acknowledge the referee for drawing her attention to this fact.

observed, the shortest being between O(4) in the reference molecule and C(19) in the molecule at $-x, y - 1/2, 1/2 - z$ (3.382 Å).

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References

- 1 M. Holub, M. Budesinsky, Z. Smitalova, D. Saman, and U. Rychlewska, *Tetrahedron Lett.*, 1982, **23**, 4853.
- 2 M. S. Lehmann and F. K. Larsen, *Acta Crystallogr.*, 1974, **A30**, 580.
- 3 M. Jaskolski, PhD Dissertation, A. Mickiewicz University, Poznań, 1979.
- 4 G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, 1971, **A27**, 368.
- 5 G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determinations, University of Cambridge, 1976.
- 6 W. L. Duax and D. A. Norton, 'Atlas of Steroid Structure,' Plenum, New York, 1975, vol. 1.

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