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SESQUITERPENOIDS—27[1]

X-RAY CRYSTALLOGRAPHIC ANALYSIS OF ISTANBULIN-B, A 1-OXO-EREMOPHILENOLIDE

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Abstract The stereochemistry of istanbulin-B has been defined by X-ray crystal-structure analysis. Rings A and B are *trans* fused, with the Me groups at C(4) and C(5) *cis*. The α,β-unsaturated γ-lactone ring is essentially planar. Crystals of istanbulin-B are orthorhombic, space group $P2_12_12_1$, with $a = 6.729(2)$, $b = 13.447(3)$, $c = 14.721(3)$ Å, and $Z = 4$. The crystal structure was determined by direct phasing and the atomic parameters were subsequently adjusted by least-squares calculations that converged at R 3.8% over 1179 diffractometer $|F_o|$ values.

The eremophilenolides istanbulin-A and -B were isolated from the roots of *Smyrnium olusatrum* L. (Umbelliferae) and the constitution of the former was deduced as **1** by spectroscopic studies.[2] Only small amounts of istanbulin-B were obtained.

We undertook an X-ray analysis of istanbulin-B to confirm the proposed structure.[3] The crystal structure was determined by direct phasing procedures and the atomic parameters were adjusted by least-squares calculations. The molecular structure and the packing

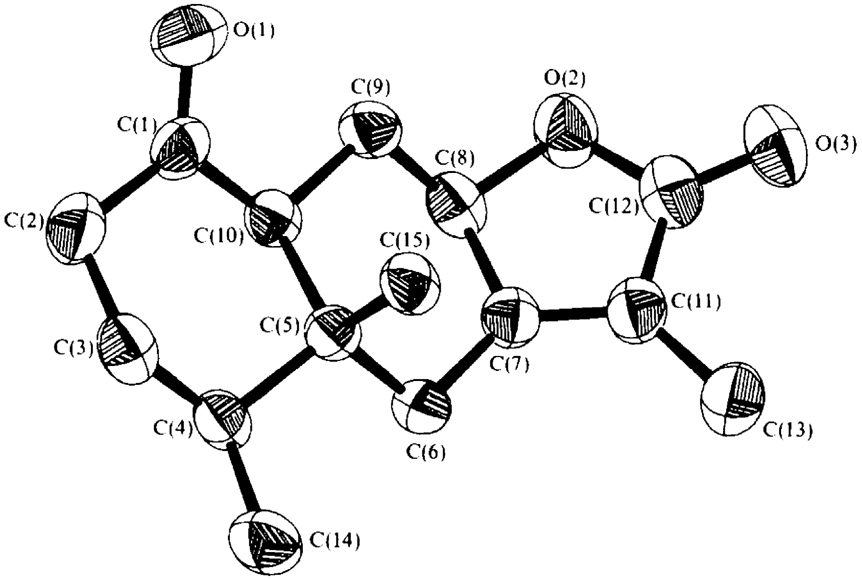


Fig. 1. Molecular structure of istanbulin-B.

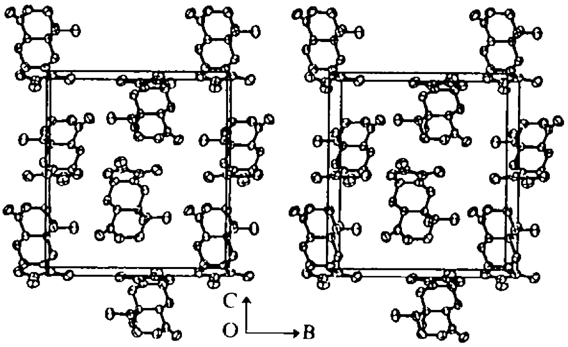


Fig. 2. Arrangement of molecules in the unit cell.

of the molecules in the unit cell are shown in Figs. 1 and 2. The atomic coordinates are listed in Table 1 and the bond lengths, interbond angles and torsion angles are in Tables 2–4.

Our results demonstrate that istanbulin-B has the constitution and relative stereochemistry (**2**).

The 6-membered rings are *trans*-fused. In eremophilenolide, on the other hand, the rings are *cis*-fused.[4] Ring A in **2** adopts a distorted chair conformation with endocyclic torsion angles 47.7-59.1, mean 54.2°; the Me substituent at C(4) is equatorial and that at C(5) axial. Ring B also adopts a distorted chair conformation but

Table 1. Fractional atomic coordinates, with standard deviations in parentheses

Atom	x	y	z
O(1)	0.1112(5)	0.2863(2)	0.3094(2)
O(2)	-0.2503(4)	0.3381(2)	0.0077(2)
O(3)	-0.5292(4)	0.4133(2)	-0.0367(2)
C(1)	0.2129(5)	0.3460(2)	0.2697(2)
C(2)	0.3984(6)	0.3893(2)	0.3109(3)
C(3)	0.4014(5)	0.5023(2)	0.3046(2)
C(4)	0.3485(5)	0.5407(2)	0.2100(2)
C(5)	0.1462(4)	0.4994(2)	0.1767(2)
C(6)	0.1049(5)	0.5353(2)	0.0788(2)
C(7)	-0.0651(4)	0.4799(2)	0.0392(2)
C(8)	-0.0570(5)	0.3693(2)	0.0411(2)
C(9)	-0.0195(5)	0.3312(2)	0.1358(2)
C(10)	0.1621(5)	0.3833(2)	0.1755(2)
C(11)	-0.2415(5)	0.5095(2)	0.0081(2)
C(12)	-0.3587(5)	0.4200(2)	-0.0109(2)
C(13)	-0.3200(6)	0.6111(3)	-0.0068(3)
C(14)	0.3631(6)	0.6542(2)	0.2087(3)
C(15)	-0.0251(5)	0.5321(2)	0.2381(2)
H(2a)	0.397(6)	0.366(3)	0.376(2)
H(2b)	0.506(6)	0.366(3)	0.272(3)
H(3a)	0.545(6)	0.529(3)	0.321(2)
H(3b)	0.315(5)	0.531(2)	0.353(2)
H(4)	0.450(6)	0.517(3)	0.170(2)
H(6a)	0.222(6)	0.523(2)	0.040(2)
H(6b)	0.075(5)	0.606(2)	0.077(2)
H(8)	0.043(6)	0.343(3)	-0.001(2)
H(9a)	-0.130(6)	0.348(2)	0.172(2)
H(9b)	-0.005(4)	0.262(2)	0.131(2)
H(10)	0.271(6)	0.367(2)	0.140(2)
H(13a)	-0.252(7)	0.662(3)	0.028(3)
H(13b)	-0.453(5)	0.621(4)	0.015(3)
H(13c)	-0.315(9)	0.631(4)	0.070(2)
H(14a)	0.346(8)	0.682(3)	0.146(2)
H(14b)	0.502(5)	0.674(3)	0.229(3)
H(14c)	0.278(9)	0.685(4)	0.255(3)
H(15a)	-0.009(6)	0.504(3)	0.302(2)
H(15b)	-0.151(5)	0.516(3)	0.208(2)
H(15c)	-0.031(8)	0.604(2)	0.244(3)

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

O(1)-C(1)	1.206(4)	C(2)-H(2a)	1.00(3)
O(2)-C(8)	1.452(4)	C(2)-H(2b)	0.97(4)
O(2)-C(12)	1.349(4)	C(3)-H(3a)	1.06(4)
O(3)-C(12)	1.212(4)	C(3)-H(3b)	1.00(3)
C(1)-C(2)	1.505(5)	C(4)-H(4)	0.96(4)
C(1)-C(10)	1.541(4)	C(6)-H(6a)	0.99(4)
C(2)-C(3)	1.522(4)	C(6)-H(6b)	0.97(3)
C(3)-C(4)	1.527(5)	C(8)-H(8)	0.98(4)
C(4)-C(5)	1.550(4)	C(9)-H(9a)	0.94(3)
C(4)-C(14)	1.530(4)	C(9)-H(9b)	0.94(3)
C(5)-C(6)	1.545(4)	C(10)-H(10)	0.93(4)
C(5)-C(10)	1.565(3)	C(13)-H(13a)	0.97(4)
C(5)-C(15)	1.529(4)	C(13)-H(13b)	0.96(4)
C(6)-C(7)	1.484(4)	C(13)-H(13c)	0.97(3)
C(7)-C(8)	1.489(4)	C(14)-H(14a)	1.00(3)
C(7)-C(11)	1.333(4)	C(14)-H(14b)	1.02(3)
C(8)-C(9)	1.507(4)	C(14)-H(14c)	0.98(5)
C(9)-C(10)	1.525(4)	C(15)-H(15a)	1.02(3)
C(11)-C(12)	1.466(4)	C(15)-H(15b)	0.98(3)
C(11)-C(13)	1.481(5)	C(15)-H(15c)	0.97(3)

Table 3. Interbond angles, with estimated standard deviations in parentheses

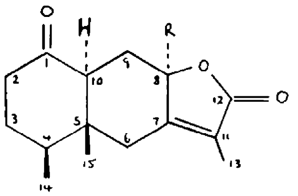
C(2)-C(1)-O(1)	122.2(3)	C(6)-C(7)-C(11)	132.2(3)
C(10)-C(1)-O(1)	122.4(3)	C(8)-C(7)-C(11)	109.7(3)
C(10)-C(1)-C(2)	115.4(3)	C(7)-C(8)-C(9)	111.3(2)
C(1)-C(2)-C(3)	111.9(3)	C(7)-C(8)-O(2)	104.4(2)
C(2)-C(3)-C(4)	112.9(3)	C(9)-C(8)-O(2)	111.4(2)
C(3)-C(4)-C(5)	111.8(2)	C(8)-C(9)-C(10)	109.4(2)
C(3)-C(4)-C(14)	109.5(3)	C(1)-C(10)-C(5)	109.6(2)
C(5)-C(4)-C(14)	114.2(3)	C(1)-C(10)-C(9)	112.3(2)
C(4)-C(5)-C(6)	109.9(2)	C(5)-C(10)-C(9)	114.1(2)
C(4)-C(5)-C(10)	107.5(2)	C(7)-C(11)-C(12)	107.4(3)
C(4)-C(5)-C(15)	111.8(2)	C(7)-C(11)-C(13)	130.1(3)
C(6)-C(5)-C(10)	108.3(2)	C(12)-C(11)-C(13)	122.5(3)
C(6)-C(5)-C(15)	109.0(2)	C(11)-C(12)-O(2)	109.9(3)
C(10)-C(5)-C(15)	110.2(2)	C(11)-C(12)-O(3)	129.1(3)
C(5)-C(6)-C(7)	110.4(2)	O(2)-C(12)-O(3)	121.0(3)
C(6)-C(7)-C(8)	117.8(2)	C(8)-O(2)-C(12)	108.5(2)

Table 4. Torsion angles

C(10)-C(1)-C(2)-C(3)	49.6(4)	C(15)-C(5)-C(10)-C(9)	62.2(3)
O(1)-C(1)-C(2)-C(3)	-129.8(3)	C(5)-C(6)-C(7)-C(8)	-53.1(3)
C(2)-C(1)-C(10)-C(9)	176.2(3)	C(5)-C(6)-C(7)-C(11)	119.3(3)
C(2)-C(1)-C(10)-C(5)	-55.9(3)	C(6)-C(7)-C(8)-C(9)	53.4(3)
O(1)-C(1)-C(10)-C(5)	123.6(3)	C(6)-C(7)-C(8)-O(2)	173.8(2)
O(1)-C(1)-C(10)-C(9)	-4.3(4)	C(11)-C(7)-C(8)-O(2)	-0.2(3)
C(1)-C(2)-C(3)-C(4)	-47.7(4)	C(11)-C(7)-C(8)-C(9)	-120.6(3)
C(2)-C(3)-C(4)-C(5)	54.6(3)	C(6)-C(7)-C(11)-C(12)	-172.2(3)
C(2)-C(3)-C(4)-C(14)	-177.8(3)	C(6)-C(7)-C(11)-C(13)	7.6(3)
C(3)-C(4)-C(5)-C(6)	-176.7(2)	C(8)-C(7)-C(11)-C(12)	0.7(3)
C(3)-C(4)-C(5)-C(10)	-59.1(3)	C(8)-C(7)-C(11)-C(13)	-179.5(3)
C(3)-C(4)-C(5)-C(15)	62.0(3)	C(7)-C(8)-C(9)-C(10)	-51.8(3)
C(14)-C(4)-C(5)-C(6)	58.2(3)	O(2)-C(8)-C(9)-C(10)	-167.9(2)
C(14)-C(4)-C(5)-C(10)	175.9(3)	C(8)-C(9)-C(10)-C(1)	-178.0(2)
C(14)-C(4)-C(5)-C(15)	-63.1(3)	C(8)-C(9)-C(10)-C(5)	56.4(3)
C(4)-C(5)-C(6)-C(7)	168.1(2)	C(7)-C(11)-C(12)-O(2)	-0.9(3)
C(10)-C(5)-C(6)-C(7)	50.9(3)	C(7)-C(11)-C(12)-O(3)	176.9(3)
C(15)-C(5)-C(6)-C(7)	-69.0(3)	C(13)-C(11)-C(12)-O(2)	179.3(3)
C(4)-C(5)-C(10)-C(1)	58.4(3)	C(13)-C(11)-C(12)-O(3)	-2.9(5)
C(4)-C(5)-C(10)-C(9)	-174.7(2)	C(12)-O(2)-C(8)-C(7)	-0.4(3)
C(6)-C(5)-C(10)-C(1)	177.2(2)	C(12)-O(2)-C(8)-C(9)	119.9(3)
C(6)-C(5)-C(10)-C(9)	-55.9(3)	C(8)-O(2)-C(12)-O(3)	-177.2(3)
C(15)-C(5)-C(10)-C(1)	-63.7(3)	C(8)-O(2)-C(12)-C(11)	0.8(3)

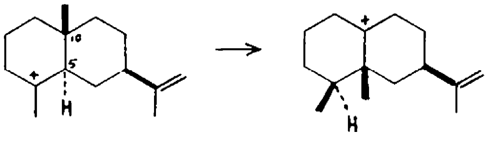
the range of torsion angles is smaller, 50.9–56.4, mean 53.7°. The γ-lactone ring is essentially planar, the torsion angles being 0.2–0.9, mean 0.6°.

Sesquiterpenoids of the eremophilane type are of particular interest since they represent exception to the isoprene rule. The biosynthesis of such compounds is believed to involve a Me shift from C(10) to C(5) in a precursor of the eudesmane type.[5] Calculation of the potential energies of the postulated precursor cation (**3**) and the eremophilane cation (**4**) by means of the hydrocarbon force field developed by White and Bovill[6] with a full-matrix minimization procedure, yielded values of 11.1 kcal for **3** and 10.8 kcal for **4**. The very small difference in energy is consistent with the occurrence of natural products some of which are related to **3** and others to **4**.



1 R = OH

2 R = H



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EXPERIMENTAL

Crystal data. $C_{15}H_{20}O_3$, $M = 248.3$. Orthorhombic, $a = 6.729(2)$, $b = 13.447(3)$, $c = 14.721(3)$ Å, $U = 1332$ Å^3, $D_c = 1.24$ g cm^{-3}, $Z = 4$, $F(000) = 536$. Space group $P2_12_12_1(D_2^4)$. Mo – K_α radiation, $\lambda = 0.7107$ Å, μ(Mo-K_α) = 0.92 cm^{-1}.

Crystallographic measurements. Final values of the cell dimensions were determined from angular measurements on an Enraf-Nonius CAD-4 automatic diffractometer. For the intensity measurements, reflections in the range θ(Mo-K_α) ≤ 27° were subjected to a scan of 0.6° and background counts were taken at each end of the scan. Two standard intensities were monitored during the data collection and showed no significant changes. The measurements produced 1179 intensities with $I > 2.5\sigma(I)$.

Structure analysis. The crystal structure was elucidated by direct phasing, using the program MULTAN.[7] All the C and O atoms were identified in the E-map, and an initial structure-factor calculation with these atoms gave R 28.9%. Subsequent least-squares adjustment of the positional and isotropic thermal parameters reduced R to 11.3%. The adoption of anisotropic thermal parameters resulted in the lowering of R to

8.5 %, at which stage a difference electron-density distribution disclosed the hydrogen sites. The H atoms were included in further least-squares calculations with isotropic thermal parameters and convergence was reached at R 3.8 %. The weighting scheme adopted in the final calculations was

$$w = (\sigma^2(F_o) + 0.0028F_0^2)^{-1}.$$

Observed and calculated structure amplitudes and the thermal parameters of the atoms are listed in Supplementary Publication No. SUP.

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