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Lobophytolide, a Cembranolide Diterpene

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Lobophytolide, $C_{20}H_{28}O_3$, $M_r = 316\cdot4$, orthorhombic, $P2_12_12_1$, with $a = 22\cdot27$ (1), $b = 13\cdot837$ (7), $c = 6\cdot000$ (1) Å, $Z = 4$, $D_m = 1\cdot14$, $D_x = 1\cdot135$ g cm^{-3}, m.p. 137°C. Lobophytolide was isolated from the soft coral *Lobophytum cristagalli*. The 14-membered carbon ring has two *trans* double bonds, one epoxide ring, and a quite flat five-membered lactone ring. The ester carbonyl is conjugated with an exocyclic methylene group. The absolute configuration was determined from ten enantiomer-sensitive Bijvoet differences.

Introduction

Chemical and spectroscopic investigations of lobophytolide (LOB) (Fig. 1) were performed by Tursch, Braekman, Daloze, Herin & Karlsson (1974). LOB crystallizes from a *n*-hexane–acetone mixture. The space group and refined cell constants were determined (and all data collection performed) with a Philips PW 1100 diffractometer. X-ray intensities from half the reciprocal sphere were collected (from a capillary-enclosed crystal) with graphite-monochromatized Cu $K\alpha$ radiation and the ω–2θ scan to a limit of $\theta < 50°$ set by the high temperature factor of the crystal. The data were reduced to 1138 independent intensities to which Lp factors were applied.

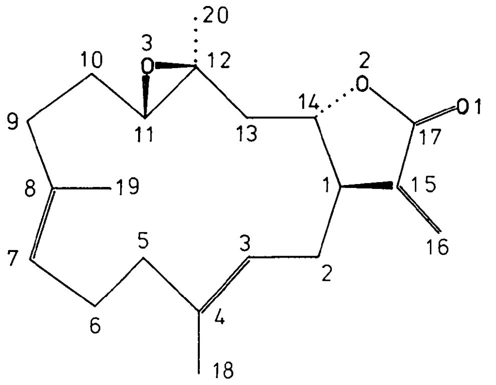

Fig. 1. The absolute configuration of lobophytolide.

Structure solution and refinement

Initial attempts to solve the structure by direct methods with 140 E values $> 1\cdot45$ were unsuccessful. A three-atom fragment later identified as C(1), C(2) and C(3), of which C(1) was the larger peak, was found in one of the E maps. However, it was not possible to expand the three-atom structure by the tangent-recycling method (Karle, 1968). The phase problem was, however, solved when the 34 *hk*0 phases were determined prior to the other 106 phases. In the following E map all non-hydrogen atoms appeared clearly.

The failure of the tangent formula to expand the three-atom structure is likely to be because of pseudocentrosymmetry; C(1), C(17), O(1) and O(2) have approximately the same Harker vectors, at the low resolution of the available data. The phases of the reflexions which were used for phase expansion [17,7,0

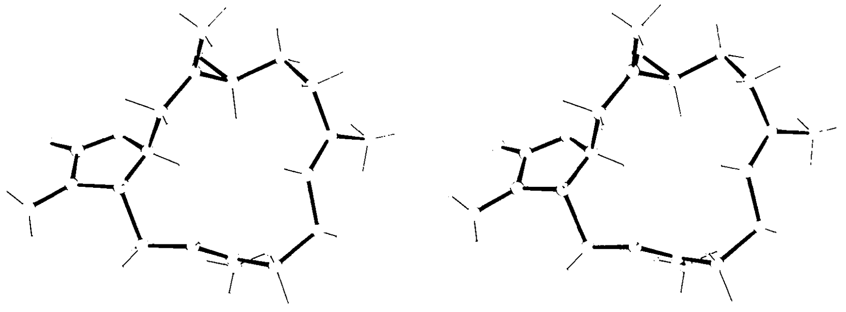

Fig. 2. A stereoscopic view of lobophytolide.

(90), 835 (292), 0,12,0 (180), 4,10,0 (0), 15,4,1 (12) and 193 (172°)] become close to 0 or 180° if the origin is shifted $\frac{1}{4}$,0,$\frac{1}{4}$. The starting phases were generated by the convergence procedure (Germain, Main & Woolfson, 1971) with $\Sigma_k|E_hE_kE_{-h-k}|^2$ as the criterion for the phase elimination. In order to break the centrosymmetry, reflexion 18,4,1 was given the phase of 0° and all phases were recycled to an average phase error of 24° by minimizing

$$P = \Sigma|E_hE_kE_{-h-k}|[1 - \cos(\varphi_h + \varphi_k + \varphi_{-h-k}]^2$$

by the procedure described by Hauptman & Weeks (1972). The common tangent formula which minimizes $S = \Sigma|E_hE_kE_{-h-k}|\{\sin[(\varphi_h + \varphi_k + \varphi_{-h-k})/2]\}^2$ is inadequate here since S has a minimum while P has a maximum for a centrosymmetric phase set (Lesk, 1976).

All the H atoms were found in a difference map. Least-squares refinement, with all atoms isotropic and all structure factors given equal weights, yielded R = 0·09.* The average coordinate shift in the last cycle was 0·09 e.s.d. The final difference map had no density exceeding 0·40 eÅ^{-3}. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968). Final parameters are given in Table 1.

Table 1. *Fractional coordinates and isotropic temperature factors*

Estimated standard deviations of final digits are given in parentheses.

	x (×10^4)	y (×10^4)	z (×10^3)	B(Å^2 ×10)
C(1)	6392 (3)	−528 (6)	786 (1)	39 (2)
C(2)	6988 (4)	−977 (6)	705 (2)	48 (2)
C(3)	6880 (4)	−1931 (6)	598 (2)	50 (2)
C(4)	7111 (3)	−2776 (6)	656 (1)	48 (2)
C(5)	6986 (4)	−3686 (6)	522 (2)	63 (2)
C(6)	6724 (5)	−4514 (7)	653 (2)	69 (3)
C(7)	6092 (4)	−4318 (7)	747 (2)	60 (2)
C(8)	5805 (4)	−4745 (6)	912 (2)	61 (2)
C(9)	5179 (4)	−4489 (7)	982 (2)	62 (2)
C(10)	5146 (4)	−3892 (7)	1196 (2)	58 (2)
C(11)	5435 (3)	−2904 (6)	1159 (2)	54 (2)
C(12)	5105 (3)	−2089 (6)	1058 (1)	49 (2)
C(13)	5427 (3)	−1340 (6)	921 (1)	41 (2)
C(14)	6083 (3)	−1171 (5)	968 (1)	40 (2)
C(15)	6490 (3)	413 (5)	911 (1)	40 (2)
C(16)	6633 (4)	1292 (7)	832 (2)	62 (2)
C(17)	6372 (3)	238 (6)	1151 (1)	45 (2)
C(18)	7531 (5)	−2895 (8)	860 (2)	71 (3)
C(19)	6123 (5)	−5563 (9)	1039 (2)	99 (4)
C(20)	4440 (4)	−2208 (8)	990 (2)	64 (2)
O(1)	6445 (2)	802 (4)	1301 (1)	57 (1)
O(2)	6153 (2)	−636 (4)	1181 (1)	51 (1)
O(3)	5220 (2)	−2115 (4)	1294 (1)	63 (2)
	x(×10^3)	y(×10^3)	z(×10^2)	B(Å^2)
H(C1)	608 (5)	−50 (8)	69 (2)	6 (3)
H(C2)*A*	720 (3)	−52 (5)	60 (1)	2 (2)
H(C2)*B*	726 (3)	−81 (5)	83 (1)	1 (2)
H(C3)	661 (3)	−205 (5)	48 (1)	1 (2)
H(C5)*A*	665 (4)	−347 (6)	39 (1)	5 (2)
H(C5)*B*	755 (4)	−390 (6)	47 (2)	5 (2)
H(C6)*A*	674 (5)	−493 (8)	56 (2)	12 (5)
H(C6)*B*	697 (3)	−466 (5)	80 (1)	3 (2)
H(C7)	593 (4)	−380 (6)	69 (2)	7 (3)
H(C9)*A*	498 (3)	−413 (4)	86 (1)	0 (1)
H(C9)*B*	500 (4)	−508 (6)	102 (2)	6 (2)
H(C10)*A*	474 (3)	−375 (5)	123 (1)	3 (2)
H(C10)*B*	540 (3)	−431 (6)	133 (2)	5 (2)
H(C11)	595 (3)	−296 (5)	116 (1)	5 (2)
H(C13)*A*	522 (3)	−65 (5)	92 (1)	1 (1)
H(C13)*B*	538 (3)	−140 (5)	76 (1)	0 (1)
H(C14)	630 (2)	−182 (4)	98 (1)	0 (1)
H(C16)*A*	659 (3)	177 (5)	95 (1)	7 (3)
H(C16)*B*	689 (3)	128 (5)	74 (1)	2 (2)
H(C18)*A*	732 (6)	−334 (10)	94 (2)	4 (2)
H(C18)*B*	776 (5)	−309 (8)	80 (2)	7 (3)
H(C18)*C*	786 (9)	−211 (14)	89 (4)	18 (4)
H(C19)*A*	587 (5)	−608 (8)	106 (2)	6 (3)
H(C19)*B*	609 (5)	−536 (8)	116 (2)	4 (3)
H(C19)*C*	658 (4)	−540 (7)	113 (2)	15 (6)
H(C20)*A*	424 (6)	−169 (10)	101 (3)	7 (4)
H(C20)*B*	441 (2)	−234 (3)	85 (1)	0 (1)
H(C20)*C*	423 (4)	−268 (7)	112 (2)	5 (2)

Table 2. *Comparison of calculated* (X_c) *with observed* (X_o) *Bijvoet ratios* (×10^2)

Standard deviations based on counting statistics are in parentheses. Measurements from the small crystal are indicated by asterisks.

$h\,k\,l$	X_c	X_o
10 1 1	−1·1	−1·1 (2)
10 1 1	−1·1	−1·0 (5)*
11 1 1	1·6	1·0 (2)
3 4 1	−1·7	−1·0 (4)
2 5 1	−2·0	−1·8 (7)
4 5 1	−0·7	0·3 (4)*
1 6 1	−0·9	−0·6 (2)
1 6 1	−0·9	−0·8 (5)*
1 3 2	−5·8	−7·3 (13)
3 2 3	2·0	3·7 (8)

Table 3. *Bond distances* (Å)

The average e.s.d. is 0·01 Å.

1–2	1·54	10–11	1·53
1–14	1·57	11–12	1·48
1–15	1·52	11–O(3)	1·44
2–3	1·49	12–13	1·51
3–4	1·32	12–20	1·54
4–5	1·52	12–O(3)	1·44
4–18	1·55	13–14	1·51
5–6	1·51	14–O(2)	1·49
6–7	1·54	15–16	1·34
7–8	1·32	15–17	1·48
8–9	1·50	17–O(1)	1·21
8–19	1·54	17–O(2)	1·32
9–10	1·53		

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32371 (3pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond angles* (°)

The average e.s.d. is 0·7°.

2–1–14	111·7	11–12–13	120·8
2–1–15	112·1	11–12–20	120·3
14–1–15	102·1	11–12–O(3)	59·1
1–2–3	110·8	13–12–20	112·8
2–3–4	127·5	13–12–O(3)	117·9
3–4–5	121·6	20–12–O(3)	115·2
3–4–18	122·2	12–13–14	117·9
5–4–18	116·2	1–14–13	112·6
4–5–6	115·2	1–14–O(2)	105·6
5–6–7	114·3	13–14–O(2)	109·9
6–7–8	129·7	1–15–16	129·8
7–8–9	123·7	1–15–17	108·2
7–8–19	118·5	16–15–17	122·0
9–8–19	117·8	15–17–O(1)	126·8
8–9–10	114·0	15–17–O(2)	110·6
9–10–11	109·8	O(1)–17–O(2)	122·6
10–11–12	122·2	14–O(2)–17	112·1
10–11–O(3)	117·2	11–O(3)–12	61·8
12–11–O(3)	59·1		

Absolute configuration

Ten enantiomer-sensitive Bijvoet differences were measured (Table 2), by the diffractometer with Cu $K\alpha$ radiation under conditions described by Karlsson (1976), from two crystals enclosed in capillaries. The dispersion parameters were taken from Cromer & Liberman (1970). The signs of all the Bijvoet ratios, $2(I_h - I_{-h})/(I_h + I_{-h})$, measured for all equivalent reflexions from the larger crystal proved correct.

Discussion

It can be seen from a stereoscopic view of LOB (Fig. 2) that the conformation of the 14-membered ring is similar to that expected for a strain-free model of *trans,trans*-1,8-tetradecadiene, except for the part from C(10) to C(14), which is influenced by the epoxide and lactone rings. Bond distances and bond angles are given in Tables 3 and 4, torsion angles in Fig. 3. Comparisons with other cembranolides are included in the discussion of sinulariolide (Karlsson, 1977).

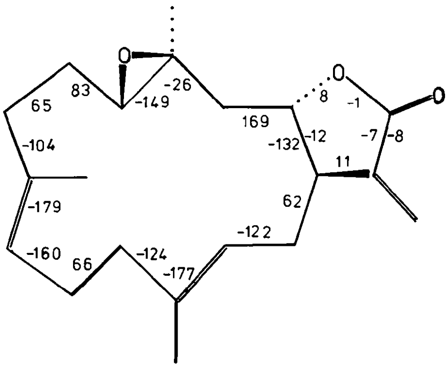

Fig. 3. Torsion angles (°) in lobophytolide.

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