une comparaison directe des deux molécules. L'enchaînement intermoléculaire s'effectue dans les deux cas, par des liaisons hydrogène décrites dans le Tableau 7: liaison N—H···O pour la PHM; formation de dimères entre atomes d'oxygène autour d'un centre de symétrie dans le cas de l'acide.

En conclusion, la conformation du groupement C_2H_5—CH=C(—C_3H_7)— observée dans deux composés, paraît donc particulièrement stable à l'état cristallin et a une grande probabilité d'exister en solution.

Nous remercions bien vivement Mme J. Lajzérowicz pour son aide et ses judicieux conseils et M A. Boucherle pour l'intérêt qu'il a porté à ce travail ainsi que M G. D'Assenza pour sa collaboration technique.

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The Structure and Absolute Configuration of Sinulariolide, a Cembranolide Diterpene

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Sinulariolide ($C_{20}H_{30}O_4$) is a cembranolide obtained from the soft coral *Sinularia flexibilis*. The crystals are orthorhombic, space group $P2_12_12_1$, with $a = 19{\cdot}8226\,(7)$, $b = 11{\cdot}3328\,(4)$, $c = 8{\cdot}9405\,(3)$ Å (25 °C), $Z = 4$, $D_m = 1{\cdot}15$, $D_x = 1{\cdot}105$ g cm^{-3}. The structure was refined to $R = 0{\cdot}05$ for 1948 independent diffractometer-measured X-ray reflexions. Twelve enantiomer-sensitive Bijvoet differences were measured with Cu $K\alpha$ and Cr $K\alpha$ radiation to determine the absolute configuration. A seven-membered conjugated lactone ring, an epoxide group and a *trans* double bond are attached to the 14-membered cembranolide ring. The ester group is twisted 68° from a planar configuration. As in ethylene oxide, substituents on the epoxide ring have larger C—C—C than C—C—O angles.

Introduction

This work is a part of a project on structural investigations of terpenoids isolated from soft corals (Tursch, Braekman, Daloze, Herin, Karlsson & Losman, 1975). The X-ray study was undertaken in order to verify an independent chemical investigation of the structure of sinulariolide (SIN) (Fig. 1). The three cembranolides SIN, lobophytolide (LOB) (Karlsson, 1977), also obtained from a soft coral, and eupalmerin acetate

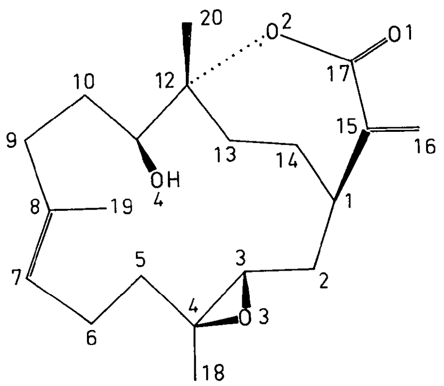

Fig. 1. Sinulariolide, absolute configuration.

(EPA) (Ealick, van der Helm & Weinheimer, 1975), obtained from a gorgonian, contain the same functional groups, but at different relative positions on the cembranolide skeleton.

Experimental

Crystals obtained from benzene were kindly supplied by Dr M. Herin (Brussels). The density was twice determined to be 1·15 g cm^{-3}, by flotation in CCl_4* and cyclohexane. A crystal was immersed in CCl_4 to obtain a spherical shape with diameter 0·35 mm. The space group and cell constants were determined on a Philips PW 1100 four-circle diffractometer with graphite-monochromatized Cr $K\alpha_1$ radiation. The constants were refined by a least-squares method from ten reflexions at 2θ *ca* 166°, and their equivalent reflexions.

Table 1. *Calculated* (X_c) *and observed* (X_o) *Bijvoet ratios* (×10^2) *for* Cu $K\alpha$ *and* Cr $K\alpha$ *radiations, with standard deviations based on counting statistics in parentheses*

N is the number of equivalent X_o's with correct sign, X_c(Cr)/X_c(Cu) = 2·3.

h k l	F_o	X_c (Cu $K\alpha$)	X_o (Cu $K\alpha$)	X_o (Cr $K\alpha$)	N (Cu $K\alpha$)	N (Cr $K\alpha$)
3 1 1	43·0	−0·8	−0·9 (2)	−1·6 (3)	3	4
8 1 1	11·1	−3·1	−4·8 (8)	−6·8 (10)	4	4
1 2 1	80·6	0·6	0·5 (3)	0·9 (2)	3	4
3 2 1	87·1	0·3	–	0·3 (2)	–	2
2 3 1	21·0	1·0	0·5 (3)	2·1 (5)	3	4
12 4 1	17·6	1·3	0·2 (6)	4·0 (7)	2	4
3 2 2	27·4	1·3	1·8 (3)	1·9 (6)	4	4
4 3 2	29·8	−0·7	−0·6 (3)	−1·8 (5)	3	4
7 3 2	26·7	0·5	0·5 (3)	–	2	–
3 4 2	16·9	1·7	–	4·5 (10)	–	4
2 1 3	23·8	0·9	0·6 (4)	2·7 (5)	4	4
6 4 3	14·4	−2·3	–	−7·0 (9)	–	4

1948 independent intensities were measured by the diffractometer for $\theta < 65°$ with Cu $K\alpha$ radiation and the ω–2θ scan technique.

The absolute configuration was determined from measurements of twelve enantiomer-sensitive Friedel pairs (with both Cu $K\alpha$ and Cr $K\alpha$ radiation) from the crystal used for data collection. The practical procedure is described by Karlsson (1977). Observed and calculated Bijvoet ratios, $2(I_h - I_{-h})/(I_h + I_{-h})$, are given in Table 1. The dispersion parameters were taken from Cromer & Liberman (1970).

Structure solution and refinement

The structure was solved by direct methods. The convergence procedure (Germain, Main & Woolfson, 1971) was used to generate initial phases and to guide the phase expansion. $\Sigma_k(E_hE_kE_{-h-k})^2$ was used as a criterion for the elimination of phases. One of the E maps yielded a three-atom fragment, later identified as C(2), C(3) and O(3). It was expanded into 19 atoms by the tangent-recycling procedure (Karle, 1968). It was later found that the structure could have been solved by the use of O(3) or O(4) as 'heavy atoms' in combination with the tangent recycling procedure. It was not possible to arrive at the correct solution by expansion of the initial reflexions given correct phases.

Table 2. *Positional parameters* (×10^4)

	x	*y*	*z*
C(1)	9024 (1)	707 (3)	6224 (3)
C(2)	8494 (2)	283 (3)	5096 (4)
C(3)	7809 (2)	468 (3)	5788 (4)
C(4)	7344 (2)	1424 (4)	5367 (4)
C(5)	6810 (2)	1834 (3)	6463 (4)
C(6)	6943 (2)	3024 (4)	7218 (5)
C(7)	7426 (2)	2974 (4)	8543 (6)
C(8)	7964 (2)	3630 (4)	8801 (5)
C(9)	8338 (2)	3547 (4)	10271 (5)
C(10)	9069 (2)	3087 (4)	10138 (6)
C(11)	9071 (2)	1787 (3)	9695 (4)
C(12)	9746 (2)	1342 (3)	9077 (4)
C(13)	9697 (2)	68 (3)	8548 (4)
C(14)	9115 (2)	−206 (3)	7493 (4)
C(15)	9693 (2)	995 (3)	5554 (4)
C(16)	9919 (2)	635 (4)	4224 (5)
C(17)	10158 (2)	1724 (3)	6491 (4)
C(18)	7511 (2)	2258 (4)	4120 (5)
C(19)	8236 (3)	4503 (4)	7635 (8)
C(20)	10331 (2)	1495 (5)	10170 (5)
O(1)	10699 (1)	2058 (3)	6098 (4)
O(2)	9910 (1)	2140 (2)	7814 (3)
O(3)	7227 (1)	210 (2)	4859 (3)
O(4)	8894 (1)	1083 (3)	10969 (3)

All 30 H atoms, as well as the five remaining heavier atoms, were found in difference Fourier maps. Full-matrix least-squares refinement of the atomic parameters with anisotropic C and O atoms and isotropic H atoms, *versus* all 1948 reflexions with unit

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* SIN is slightly soluble in CCl_4.

Table 3. *Hydrogen positional* (×10³) *and thermal parameters*

	x	*y*	*z*	*B* (Å²)
H(C1)	887	147	652	5
H(C2)*A*	853	86	402	6
H(C3)	857	−66	506	5
H(C2)*B*	780	19	683	4
H(C5)*A*	634	184	583	6
H(C5)*B*	671	117	741	8
H(C6)*A*	712	351	638	6
H(C6)*B*	643	310	768	7
H(C7)	727	244	939	10
H(C9)*A*	842	425	1083	10
H(C9)*B*	808	296	1094	5
H(C10)*A*	933	353	938	8
H(C10)*B*	926	315	1122	7
H(C11)	869	182	881	4
H(C13)*A*	1017	−19	812	4
H(C13)*B*	966	−52	954	7
H(C14)*A*	922	−108	696	5
H(C14)*B*	866	−13	807	3
H(C16)*A*	954	15	363	9
H(C16)*B*	34	79	378	11
H(C18)*A*	782	193	333	8
H(C18)*B*	715	271	371	6
H(C18)*C*	781	302	462	8
H(C19)*A*	833	501	824	13
H(C19)*B*	880	415	726	24
H(C19)*C*	787	460	704	30
H(C20)*A*	1030	240	1058	5
H(C20)*B*	1080	113	981	5
H(C20)*C*	1027	92	1120	9
H(O4)	858	51	65	6

Table 4. *Bond distances* (Å)

The average e.s.d. is 0·005 Å.

1–2	1·535	8–19	1·536
1–14	1·547	9–10	1·545
1–15	1·494	10–11	1·525
2–3	1·508	11–12	1·533
3–4	1·472	12–13	1·522
3–O(3)	1·451	12–20	1·527
4–5	1·515	12–O(2)	1·484
4–18	1·500	13–14	1·524
4–O(3)	1·468	15–16	1·334
5–6	1·531	15–17	1·495
6–7	1·525	17–O(1)	1·191
7–8	1·321	17–O(2)	1·366
8–9	1·513		

Table 5. *Bond angles* (°) *about the* C *and* O *atoms*

The average e.s.d. is 0·3°.

2–1–14	110·7	10–11–12	114·5
2–1–15	114·4	10–11–O(4)	109·3
14–1–15	109·6	12–11–O(4)	108·5
1–2–3	107·7	11–12–13	111·7
2–3–4	124·2	11–12–20	113·3
2–3–O(3)	117·0	11–12–O(2)	105·4
4–3–O(3)	60·3	13–12–20	110·8
3–4–5	119·9	13–12–O(2)	110·8
3–4–18	121·0	20–12–O(2)	104·5
3–4–O(3)	59·1	12–13–14	115·8
5–4–18	116·3	1–14–13	113·9
5–4–O(3)	112·2	1–15–16	126·1
18–4–O(3)	113·3	1–15–17	116·4
4–5–6	115·8	16–15–17	117·5
5–6–7	114·7	15–17–O(1)	124·5
6–7–8	128·5	15–17–O(2)	117·0
7–8–9	120·9	O(1)–17–O(2)	118·1
7–8–19	121·9	12–O(2)–17	121·9
9–8–19	117·3	3–O(3)–4	60·6
8–9–10	114·5		
9–10–11	110·5		

weights, lowered the conventional *R* value to 0·05.* The average shift to e.s.d. ratio was 0·13 in the last cycle; the final difference map had no peaks above 0·17 e Å^{-3}.

Final C and O parameters are given in Table 2, and H parameters in Table 3. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968). Interatomic distances and angles are given in Tables 4 and 5.

Discussion

A stereoscopic view of the least-squares plane of the 14-membered ring is shown in Fig. 2. The rings of SIN,* LOB and EPA exhibit the features of cyclotetradecane, the next completely strain-free molecule after cyclohexane in the cycloalkane series. It would be of interest to compare their conformations with those of simple derivatives (with little or no strain) of cyclotetradecane, $C_{14}H_{28}$. The conformation of cyclotetradecane (Fig. 3) is conveniently described as two $(CH_2)_5$ chains linked by two $-CH_2-CH_2-$ bridges. Cyclotetradecane and its derivatives might prove useful for deducing conformations of compounds containing a 14-membered ring. Evidence that replacement of the bridges by CO–O or CO–NH does not alter the basic conformation (Dale, 1963) is supported by a cyclic model for serratamolide (Karle, 1975). Replacement by a *trans* double bond involves a 180° rotation of the bridge to obtain (C=C)–C strain-free twist angles close to 120°. Some of the torsion angles of LOB resemble those derived from a model of symmetric *trans*-cyclotetradecadiene (Fig. 3). It should be noted that one of the double bonds in LOB forms the bridge with normal (C=C)–C torsion angles about 120°, while the corresponding angle about the other double bond, 160°, approaches the model value of 180°. The skeleton of SIN, with the C(7)–C(8) double

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32370 (4 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

* The atomic notations refer to SIN throughout this paper.

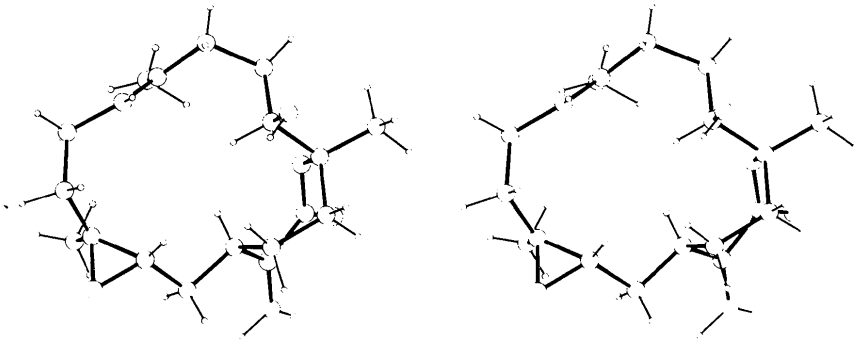

Fig. 2. A stereoscopic view of sinulariolide.

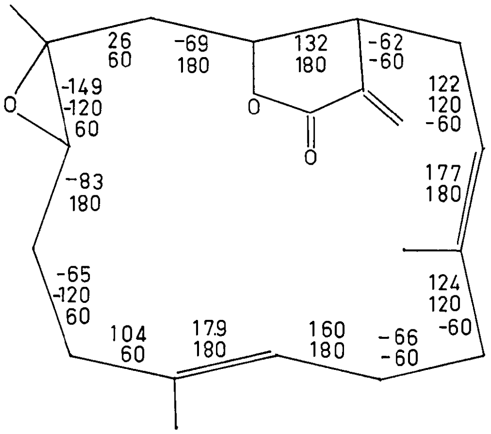

Fig. 3. Torsion angles (°) for lobophytolide (upper values), the models of cyclotetradecadiene (lower or middle values), and cyclotetradecane (lower values if different from cyclotetradecadiene).

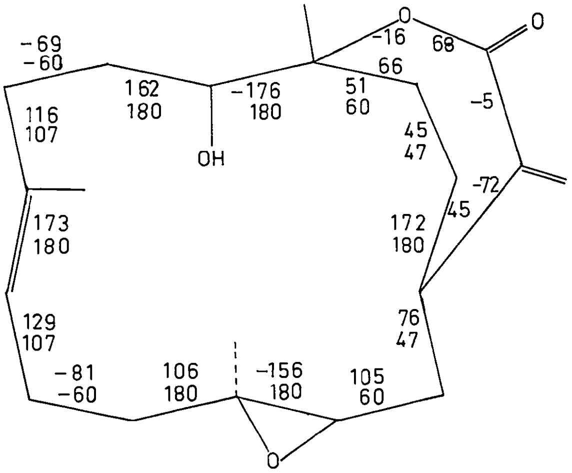

Fig. 4. Torsion angles (°) of sinulariolide (upper values) and the model of cyclotetradecene.

bond and the C(1)—C(14) bond as bridge links, closely resembles a slightly strained model (Fig. 4) of *trans*-cyclotetradecene. The model is constructed so that the C=C and C—C bridge bonds lie in parallel planes, but with different directions.

The conformation of cyclotetradecene also has features in common with EPA, in which the epoxide C—C bond forms one of the bridges.

Chemical reactions

SIN reacts with *N*-iodosuccinimide to add iodine in high yield (Tursch, Braekman, Daloze, Herin, Karlsson & Losman, 1975). In the first step the double bond reacts to form an iodonium ion intermediate. The second step involves an attack at C(8) by O(4) to form a C(7)—I bond and a five-membered cyclic ether closed by the C(8)—O(4) link. The I atom was indicated by NMR to be close to H(1) and H(2). The course of the reaction is consistent with an attack by the reagent from the exterior of a molecule having the conformation found in the crystal.

In the bromination of EPA with Br_2 the *trans* double bond and the neighbouring epoxide ring are simultaneously involved to form an intramolecular C—O bridge (Ealick *et al.*, 1975).

The seven-membered lactone ring

The ring might be considered to be rather strained by the 68° twist of the ester bond from a planar configuration. The barrier to rotation is estimated from IR spectroscopy (Miyazawa & Pitzer, 1959) and from *ab initio* calculations performed for the twist angles 0, 90 and 180° (Schwartz, Hayes & Rothenberg, 1970) to be 10–13 kcal mol^{-1}. The carbonyl group is bent 7° out of the C(15)–C(17)–O(2) plane in the same direction as the twist about the CO—O bond. A similar observation has been made for cyclolactams (Dunitz & Winkler, 1975). The lactone ring of SIN has the twisted-boat conformation (Hendrickson, 1967) (Fig. 4). A twisted-chair conformation is unfavourable, for steric reasons, for the formation of a 14-membered ring. A twisted conformation with a planar ester group is impossible since the C(20) methyl group comes too close to C(15).

Table 6. *Angles (°) of the epoxide in SIN, LOB and EPA with corresponding values for ethylene oxide*

α is the angle between the bisecting plane of the epoxide C—C—O angle and the H—C—H or C′—C—C″ plane. C″ is the mirror atom of C′ relative to the C—C—O plane.

	SIN	LOB	EPA	C_2H_4O
α, C(18)	13·0	8·4	11·8	7·6
C(5)	13·5	7·7	8·5	
C(2)	10·4	4·5	10·3	
C(2)—C(3)—C(4)—C(5)	−156	−149	152·5	153·88
C(3)—C(4)—C(5)—C(6)	106	26	41	
C(1)—C(2)—C(3)—C(4)	105	−83	−81	
C(5)—C(4)—C(18)	116·3	113·0	113·1	116·25

In fact, the lactone ring is stable; it is unaffected by treatment with a 6% aqueous solution of hydroiodic acid at 50 °C for 3 h (Tursch *et al.*, 1975).

The epoxide group

In all three cembranolides the epoxide ring has the same substitution pattern, and the conformation of the C(18) methyl group is such that one H is *trans* to C(5). A comparison of the ring geometries is given in Table 6. In LOB and EPA, C(1) and C(6) are *trans* to H(3) and C(18) respectively, with the C—C—C(2)—C(3) and C—C—C(4)—C(5) torsion angles close to the strain-free values of −85, 35 or 155°. The values are based on the ethylene oxide C_2H_4O geometry (Cunningham, Boyd, Myers, Gwinn & Le Van, 1951).

The methyl C(19) group in SIN, LOB and EPA is close to an eclipsed position for the double bond, and all the C=C—C—C torsion angles are about 120°, except one of 160° in LOB as mentioned above. The C(6)—C(7)—C(8) angles are in the range 126–129° while C(7)—C(8)—C(9) and C(7)—C(8)—C(19) are about 120°.

The absolute configurations

It is notable that SIN and LOB each have a double bond between C(7) and C(8), while EPA and the other cembranolides found in gorgonians (Ealick *et al.*, 1975), as well as cembrene* itself (Drew, Templeton & Zalkin, 1969), have the double bond between C(8) and C(9). The numbering of the atoms in all the 14-membered rings is based here on the stereochemistry at C(1) (Fig. 1).

The structure contains one hydrogen bond, from O(4) to O(3′) at $(\frac{1}{2}-x, -y, \frac{1}{2}+z)$, with an O—O′ distance of 2·86 Å and a H—O—C—O′ torsion angle of −12°. Short intramolecular contacts are given in Table 7.

Table 7. *Intramolecular contacts less than 2·45 Å between hydrogen atoms separated by at least three atoms*

H(C1)—H(C11)	2·1	H(C9)*A*—H(C19)*C*	2·0
H(C2)*A*—H(C16)*A*	2·2	H(C10)*A*—H(C19)*B*	2·3
H(C2)*A*—H(C18)*A*	2·0	H(C10)*B*—H(C20)*A*	2·3
H(C3)—H(C14)*B*	2·1	H(C11)—H(C14)*B*	2·3
H(C6)*A*—H(C18)*C*	2·2		

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* *Note added in proof:–* Drew *et al.* gave the wrong configuration in a diagram (Prasad & Dev, 1976).

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