The Molecular Structures and Absolute Configurations of Two New Marine Cembranolides: Sinularin and Dihydrosinularin

BY M. BILAYET HOSSAIN AND DICK VAN DER HELM

Department of Chemistry, The University of Oklahoma, Norman, OK 73019, USA

AND J. A. MATSON AND A. J. WEINHEIMER

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Houston, Houston, TX 77004, USA

Abstract

The crystal and molecular structures of two marine diterpene cembranolides, sinularin, $C_{20}H_{30}O_4$, and dihydrosinularin, $C_{20}H_{32}O_4$, extracted from the soft coral *Sinularia flexibilis* have been determined by three-dimensional X-ray diffraction data. Sinularin crystallizes in the orthorhombic space group $P2_12_12_1$, $a = 5.751$ (1), $b = 10.591$ (1), $c = 30.160$ (2) Å; $Z = 4$, $D_x = 1.209$ Mg m^{-3}; dihydrosinularin crystallizes in the monoclinic space group $P2_1$, $a = 14.486$ (1), $b = 5.799$ (1), $c = 10.950$ (1) Å, $\beta = 93.10$ (1)°, $Z = 2$, $D_x = 1.216$ Mg m^{-3}. Intensity data were collected with Cu $K\alpha$ radiation at 138 K. The structures were solved by direct methods and refined by least-squares techniques. The final discrepancy factor is 0.036 for all 2221 reflections of sinularin and 0.043 for all 2087 reflections of dihydrosinularin. In each case, the absolute configuration of the molecule was determined by the Bijvoet method using anomalous dispersion of Cu radiation by oxygen atoms. The backbone molecular structure of the two compounds consists of a 14-membered cembrane ring fused to a 6-membered lactone ring and an epoxide function.

Introduction

The present structure investigation is a part of our general program to study structural details of biologically active marine terpenoids. Both sinularin (SLN) and dihydrosinularin (DSLN) (shown in Fig. 1) were extracted from soft coral *Sinularia flexibilis* collected from the Great Barrier Reef of Australia. Both compounds show significant antineoplastic activity. Isolation procedures, spectroscopic studies and the preliminary report on X-ray structures have already been reported (Weinheimer, Matson, Hossain & van der Helm, 1977).

Experimental

Both sinularin (SLN) and dihydrosinularin (DSLN) were crystallized from acetone/hexane by slow evaporation. SLN crystallizes as thin prismatic needles in the orthorhombic system, while the needle-shaped crystals of DSLN belong to monoclinic system. For

Table 1. *Crystal data for* SLN *and* DSLN

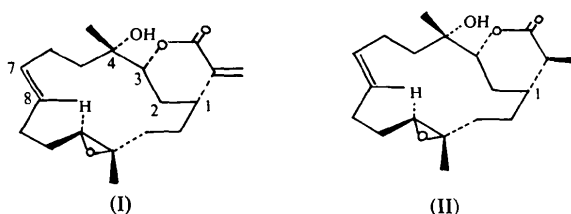| Compound	(I) Sinularin (SLN) $C_{20}H_{30}O_4$	(II) Dihydrosinularin (DSLN) $C_{20}H_{32}O_4$
FW	334.5	336.5
Crystal system	Orthorhombic	Monoclinic
Cell parameters (138 K)		
a	5.751 (1) Å	14.486 (1) Å
b	10.591 (1)	5.799 (1)
c	30.160 (2)	10.950 (1)
β	–	93.10 (1)°
V	1837.0 Å^3	918.5 Å^3
Z	4	2
D_x	1.209 Mg m^{-3}	1.216 Mg m^{-3}
Space group	$P2_12_12_1$	$P2_1$
Intensity data (138 K)	2221 independent reflections (137 unobserved)	2087 independent reflections (235 unobserved)
$2\theta_{max}$	150°	150°
Radiation	Cu $K\alpha(\lambda = 1.5418$ Å) for data	Cu $K\alpha(\lambda = 1.5418$ Å) for data

(I)   (II)

Fig. 1. (I) Sinularin (SLN), absolute configuration; (II) dihydrosinularin (DSLN), absolute configuration.

both the compounds the unit-cell dimensions and intensity data were obtained at 138 ± 2 K with a Nonius CAD-4 counter diffractometer controlled by a PDP8/E computer and fitted with low-temperature apparatus. The crystal data for the two compounds are given in Table 1.

For both compounds cell parameters were obtained by a least-squares fit to the $+2\theta$ and -2θ values of a number of reflections (44 reflections for SLN and 38 reflections for DSLN) measured at 138 ± 2 K using Cu $K\alpha_1$ ($\lambda = 1.5405$ Å) radiation. For each compound, intensities of all reflections with $2\theta \leq 150°$ were measured using Cu $K\bar\alpha$ radiation ($\lambda = 1.5418$ Å) and the θ–2θ scan technique. The angular scan width was variable and was taken to be $(0.80 + 0.08 \tan \theta)$ for SLN, and $(1.20 + 0.12 \tan \theta)°$ for DSLN. A receiving aperture with a variable width of $(2.8 + 0.86 \tan \theta)$ for SLN and $(3.5 + 0.86 \tan \theta)$ mm for DSLN and a constant height of 6 mm was located at a distance of 173 mm from the crystal. The maximum scan time for a reflection was 90 s for SLN and 60 s for DSLN. For every reflection $\frac{2}{3}$ of the scan time was spent scanning the peak and $\frac{1}{6}$ was spent scanning each of the two backgrounds. During the intensity measurements, the intensity of a standard reflection was monitored after every 25 reflections for each compound. A total of 2221 intensity data, comprising all unique reflections with $2\theta \leq 150°$, were measured for SLN. Out of these, 137 reflections had an intensity less than $2\sigma(I)$. For DSLN, out of 2087 independent reflections, 235 had an intensity less than $2\sigma(I)$. All intensity data were corrected for Lorentz and polarization factors, but no absorption correction was applied.

Structure determination and refinement

The structures of both SLN and DSLN were determined by direct methods with the help of the program *MULTAN* (Germain, Main & Woolfson, 1971). For SLN, the phases of 200 reflections having a normalized structure factor (E) greater than 1.58 were used to evaluate the E map. All non-hydrogen atoms obtained from the E map were refined by least-squares methods in stages with isotropic and anisotropic thermal parameters. A difference Fourier map was calculated when $R = 0.088$. All the hydrogen atoms were located from the difference map and the hydrogen parameters were refined isotropically. The refinement was terminated when all parameter shifts were less than 0.4 of their corresponding standard deviations. The final R ($R = \sum ||kF_o| - |F_c||/\sum |kF_o|$) for all 2221 reflections was 0.036.

For DSLN, 250 reflections with $E > 1.50$ were used in *MULTAN* to obtain the preliminary structure. The structure was refined first isotropically and later with anisotropic thermal parameters. All the hydrogen

atoms were located from a difference Fourier map and hydrogen parameters were refined. The final R for all 2087 reflections is 0.043.

All least-squares refinements were carried out by a block-diagonal least-squares program (Ahmed, 1966) in which the quantity minimized was $\sum w_F(|kF_o| - |F_c|)^2$. The atomic scattering factors for the C and O atoms were taken from *International Tables for X-ray Crystallography* (1974, p. 73), while the atomic scattering factors for the hydrogen atoms were those given by Stewart, Davidson & Simpson (1965). The weights in the least-squares calculations were obtained from intensity statistics as given by van der Helm, Ealick & Burks (1975). An analysis of the function $w_F(|F_o| - |F_c|)^2$ vs $|F_o|$ and $\sin^2 \theta$, in each case, showed no significant variation of the average values of

Table 2. *Comparison of observed and calculated Bijvoet differences*

The two parameters which are used for the purpose are defined as below:

$$DEL = [F^2(+) - F^2(-)]/\tfrac{1}{2}[F^2(+) + F^2(-)] \times 100$$
$$SF = [F^2(+) - F^2(-)]/\sigma(F^2)$$
where $F^2(+) = F^2(hkl)$, $F^2(-) = F^2(\bar h \bar k \bar l)$.

			DEL		SF	
h	k	l	obs	calc	obs	calc
(I) Sinularin						
2	4	1	7.30	7.44	0.64	1.11
2	6	7	5.60	10.43	0.54	1.43
1	1	12	2.90	5.19	0.64	1.12
4	3	6	4.08	5.63	0.72	1.06
2	2	16	−4.05	−6.21	−0.84	−1.06
1	3	16	3.76	4.28	1.38	0.97
6	3	10	1.29	4.98	0.20	0.90
4	5	14	7.75	4.97	1.22	0.88
1	5	11	3.80	4.07	1.53	0.88
3	1	18	3.36	4.86	0.56	0.88
4	3	24	0.99	3.92	0.34	0.87
1	3	10	3.60	4.89	0.58	0.88
2	10	6	3.53	4.35	0.78	0.85
4	6	13	0.96	4.23	0.23	0.84
3	2	20	−3.46	−5.18	−0.40	−0.84
(II) Dihydrosinularin						
6	1	0	−4.57	−4.61	−1.45	−0.62
6̄	1	2	1.84	2.89	1.07	0.40
0	1	8	2.23	3.34	0.76	0.47
2̄	1	4	−1.66	−2.57	−1.48	−0.41
8̄	1	9	6.33	4.57	0.91	0.43
2̄	2	8	−1.33	−3.23	−0.40	−0.43
3	2	0	1.36	4.94	0.25	0.48
4̄	2	11	3.85	3.41	1.32	0.44
5	1	4	1.52	2.78	0.90	0.43
1	1	6	1.75	3.05	0.93	0.45
1	2	2	−4.95	−6.51	−0.80	−0.58
6	1	3	−0.38	−3.41	−0.24	−0.53
7	2	3	−1.46	−3.47	−0.64	−0.49
6̄	1	1	1.76	3.45	1.28	0.51
1̄	2	7	0.68	−3.66	0.21	−0.47

$w_F(\Delta F)^2$ for various ranges of $|F_o|$ and $\sin^2 \theta$, indicating the validity of the weighting scheme used during the refinements.

Determination of absolute configuration

The absolute configurations of both the molecules were determined by the Bijvoet method using anomalous dispersion of the Cu radiation by oxygen atoms. The general procedure for selecting the proper Friedel pairs and subsequent measurements has been described by Ealick, van der Helm & Weinheimer (1975). After refining both compounds with non-anomalous scattering factors, $F^2(hkl)$ and $F^2(\bar{h}\bar{k}\bar{l})$ were calculated for each reflection using the anomalous scattering of the oxygen atoms. The f' and f'' for oxygen atoms were taken from *International Tables for X-ray Crystallography* (1974, p. 149). A set of 15 reflections with a high sensitivity factor [SF $= \{F^2(+) - F^2(-)\}/\sigma(I)]$ was chosen for each structure. In SLN, for every reflection of the set, intensities of hkl, $hk\bar{l}$, $h\bar{k}l$ and $hk\bar{l}$ were measured, each of them 15 times at 138 K, and the results were averaged for hkl and $h\bar{k}\bar{l}$ on one hand, and $h\bar{k}l$ and $hk\bar{l}$ on the other. In DSLN, for each Friedel pair, intensities of hkl, $\bar{h}kl$, $h\bar{k}l$ and $hk\bar{l}$ were measured, 15 times each at 138 K, and intensities were averaged for hkl and $\bar{h}kl$ on one hand and $h\bar{k}l$ and $hk\bar{l}$ on the other. The observed and calculated values of all the relevant parameters are summarized in Table 2. The

parameters 'DEL' and 'SF' are defined in Table 2. The calculated values of these parameters are obtained on the basis of absolute configurations shown in this report. Calculated and observed values of the DEL and SF of all 15 pairs in SLN are in agreement, indicating that the absolute configuration of molecule (I) as shown in Fig. 1 (I) is the correct one. For DSLN, out of 15 pairs there is only one disagreement with the absolute configuration shown in Fig. 1 (II).

Table 4. *Hydrogen positional parameters* ($\times 10^3$) *and isotropic temperature factors for* SLN

	x	y	z	B (Å^2)
H(1)	927 (4)	436 (2)	344 (1)	2·0 (4)
H(2)$_1$	574 (4)	497 (2)	375 (1)	1·7 (4)
H(2)$_2$	447 (4)	491 (2)	328 (1)	2·0 (4)
H(3)	798 (3)	680 (2)	348 (1)	1·2 (3)
H(5)$_1$	387 (4)	639 (2)	414 (1)	2·2 (4)
H(5)$_2$	320 (3)	786 (2)	417 (1)	1·7 (4)
H(6)$_1$	601 (5)	770 (2)	466 (1)	3·9 (5)
H(6)$_2$	759 (4)	835 (2)	425 (1)	3·6 (5)
H(7)	942 (4)	641 (2)	411 (1)	2·1 (4)
H(9)$_1$	1161 (5)	464 (2)	483 (1)	3·7 (5)
H(9)$_2$	1110 (4)	460 (2)	431 (1)	2·2 (4)
H(10)$_1$	893 (5)	300 (2)	496 (1)	3·2 (5)
H(10)$_2$	1080 (5)	254 (2)	461 (1)	3·5 (5)
H(11)	627 (4)	350 (2)	432 (1)	2·0 (4)
H(13)$_1$	482 (4)	275 (2)	366 (1)	2·0 (4)
H(13)$_2$	562 (4)	144 (2)	343 (1)	1·9 (4)
H(14)$_1$	590 (4)	300 (2)	290 (1)	2·6 (5)
H(14)$_2$	862 (4)	251 (2)	301 (1)	2·2 (4)
H(17)$_1$	1154 (5)	381 (2)	267 (1)	3·2 (5)
H(17)$_2$	1105 (4)	494 (2)	230 (1)	2·9 (5)
H(18)$_1$	501 (4)	893 (2)	312 (1)	3·3 (5)
H(18)$_2$	401 (5)	936 (2)	362 (1)	3·9 (5)
H(18)$_3$	679 (5)	904 (2)	354 (1)	3·7 (5)
H(19)$_1$	601 (4)	471 (2)	505 (1)	2·9 (5)
H(19)$_2$	811 (5)	522 (2)	534 (1)	3·6 (5)
H(19)$_3$	632 (5)	620 (2)	514 (1)	3·9 (5)
H(20)$_1$	1106 (5)	128 (2)	409 (1)	4·2 (6)
H(20)$_2$	1098 (4)	195 (2)	359 (1)	3·3 (5)
H(20)$_3$	976 (5)	61 (2)	366 (1)	5·0 (7)
H(O$_3$)	248 (6)	724 (2)	310 (1)	6·0 (7)

Table 3. *Positional parameters* ($\times 10^4$ *for* x, $\times 10^5$ *for* y, z) *of non-hydrogen atoms for* SLN

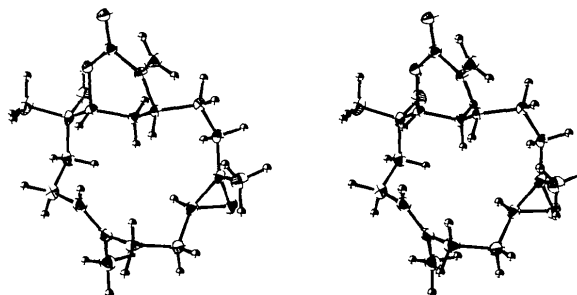|	x	y	z
C(1)	7921 (3)	43662 (14)	32219 (5)
C(2)	5931 (3)	51448 (15)	34200 (5)
C(3)	6390 (3)	65424 (14)	33567 (5)
C(4)	4597 (3)	74362 (15)	35676 (5)
C(5)	4422 (3)	72673 (15)	40726 (6)
C(6)	6636 (4)	75104 (16)	43519 (6)
C(7)	8353 (3)	64378 (16)	43552 (6)
C(8)	8571 (3)	55262 (16)	46601 (5)
C(9)	10402 (3)	45096 (18)	46076 (6)
C(10)	9483 (3)	31530 (17)	46493 (6)
C(11)	7570 (3)	28699 (15)	43226 (5)
C(12)	7828 (3)	20907 (15)	39188 (5)
C(13)	6165 (3)	22946 (14)	35367 (5)
C(14)	7177 (3)	29883 (14)	31339 (5)
C(15)	8781 (3)	49599 (14)	27915 (5)
C(16)	7542 (3)	60789 (15)	26019 (5)
C(17)	10615 (4)	45371 (18)	25664 (6)
C(18)	5141 (4)	88076 (16)	34502 (7)
C(19)	7111 (4)	54251 (18)	50737 (6)
C(20)	10083 (3)	14371 (18)	38067 (6)
O(1)	6282 (2)	68096 (11)	28794 (4)
O(2)	6676 (2)	15912 (11)	43134 (4)
O(3)	2312 (2)	71160 (13)	34054 (4)
O(4)	7614 (3)	63737 (12)	22141 (4)

Fig. 2. Stereoview of the single molecule of SLN. Thermal ellipsoids correspond to 50% probability. All hydrogens were given arbitrary but equal temperature factors for clarity of the drawing.

Table 5. *Positional parameters* ($\times 10^5$ *for* x, z; $\times 10^4$ *for* y) *of non-hydrogen atoms for* DSLN

	x	y	z
C(1)	12921 (15)	8369 (5)	68814 (20)
C(2)	18998 (14)	6781 (5)	76969 (19)
C(3)	18470 (14)	7433 (5)	90349 (19)
C(4)	24585 (15)	6017 (5)	99448 (20)
C(5)	34844 (15)	6054 (5)	96624 (20)
C(6)	39884 (17)	8390 (6)	97582 (22)
C(7)	38190 (17)	9968 (5)	86820 (23)
C(8)	43261 (17)	10175 (5)	77104 (23)
C(9)	40674 (20)	11901 (6)	67146 (25)
C(10)	40455 (20)	10922 (6)	54085 (24)
C(11)	34548 (18)	8806 (6)	52454 (21)
C(12)	25474 (17)	8670 (6)	45746 (20)
C(13)	19029 (18)	6715 (5)	48772 (21)
C(14)	10675 (17)	7358 (5)	56025 (21)
C(15)	3730 (16)	8987 (5)	74813 (22)
C(16)	1874 (15)	7664 (5)	86402 (21)
C(17)	3112 (19)	11570 (5)	77657 (27)
C(18)	23270 (17)	6829 (6)	112473 (21)
C(19)	51850 (17)	8763 (7)	75177 (24)
C(20)	20973 (20)	10725 (6)	39462 (24)
O(1)	9010 (10)	7033 (4)	93935 (14)
O(2)	33736 (13)	7831 (4)	40290 (15)
O(3)	22033 (11)	3622 (4)	98273 (15)
O(4)	−5870 (11)	7202 (4)	89196 (16)

Table 6. *Hydrogen positional parameters* ($\times 10^3$) *and isotropic temperature factors for* DSLN

	x	y	z	B (Å^2)
H(1)	164 (2)	983 (3)	680 (3)	2·6 (6)
H(2)$_1$	167 (2)	514 (6)	759 (3)	2·8 (7)
H(2)$_2$	254 (2)	704 (7)	742 (2)	2·3 (6)
H(3)	197 (2)	895 (6)	916 (2)	1·9 (5)
H(5)$_1$	376 (2)	492 (5)	1027 (2)	1·3 (5)
H(5)$_2$	358 (2)	552 (6)	886 (2)	2·1 (6)
H(6)$_1$	387 (2)	917 (6)	1057 (2)	2·5 (6)
H(6)$_2$	464 (2)	814 (7)	987 (3)	4·1 (8)
H(7)	331 (2)	1108 (7)	868 (3)	3·2 (7)
H(9)$_1$	350 (2)	1256 (8)	689 (3)	4·4 (8)
H(9)$_2$	451 (2)	1328 (8)	673 (3)	5·3 (9)
H(10)$_1$	469 (2)	1049 (6)	522 (3)	3·0 (7)
H(10)$_2$	384 (2)	1206 (7)	482 (3)	2·9 (7)
H(11)	357 (2)	769 (6)	589 (2)	2·3 (6)
H(13)$_1$	225 (2)	560 (6)	527 (3)	2·6 (6)
H(13)$_2$	168 (2)	609 (6)	408 (3)	2·8 (7)
H(14)$_1$	65 (2)	607 (7)	571 (3)	3·7 (7)
H(14)$_2$	65 (2)	855 (6)	513 (2)	2·5 (6)
H(15)	−20 (2)	845 (6)	692 (2)	2·1 (6)
H(17)$_1$	84 (2)	1204 (9)	834 (3)	5·1 (9)
H(17)$_2$	−27 (2)	1223 (7)	811 (3)	4·2 (8)
H(17)$_3$	32 (2)	1236 (7)	696 (3)	3·5 (7)
H(18)$_1$	276 (2)	630 (6)	1181 (3)	2·4 (7)
H(18)$_2$	168 (2)	656 (6)	1149 (3)	2·4 (6)
H(18)$_3$	244 (2)	850 (8)	1133 (3)	3·6 (7)
H(19)$_1$	507 (2)	767 (7)	688 (3)	3·9 (8)
H(19)$_2$	540 (2)	792 (8)	827 (3)	4·8 (9)
H(19)$_3$	573 (2)	974 (8)	730 (3)	4·6 (9)
H(20)$_1$	164 (2)	1024 (7)	322 (3)	3·4 (7)
H(20)$_2$	168 (2)	1152 (6)	447 (3)	3·0 (7)
H(20)$_3$	253 (2)	1170 (7)	365 (3)	3·5 (7)
H(O$_3$)	174 (2)	337 (8)	1019 (3)	4·2 (8)

Description and discussion of the structures

The final atomic parameters for SLN are listed in Tables 3 and 4 respectively. The corresponding parameters for DSLN are given in Tables 5 and 6.*

The stereoview of an *ORTEP* (Johnson, 1965) drawing of SLN is shown in Fig. 2 and the corresponding drawing of DSLN is shown in Fig. 3. The bond distances and angles of the two molecules for non-hydrogen atoms, calculated on the basis of final parameters, are shown in Figs. 4, 5, 6 and 7. Figs. 4 and 5 also show the atom-numbering schemes in the two molecules.

The overall backbone geometry of the two molecules consists of a 14-membered cembrane ring fused to a δ-lactone at C(1) and C(3) and an epoxide function at C(11) and C(12). The only double bond in the ring is C(7)—C(8), and its geometry with respect to the ring system is *trans* [torsion angle C(6)—C(7)—C(8)—C(9), 180° in SLN and −179° in DSLN]. The epoxide is also *trans*-fused with the ring system [torsion angle C(10)—C(11)—C(12)—C(13), −156° in SLN and −158° in DSLN].

A comparison of the molecular dimensions of the two compounds shows that the hydrogenation has very little effect on the cembrane ring, while as expected, lactone dimensions are changed significantly. In DSLN, the bond lengths C(1)—C(15) and C(15)—C(16) and the angles C(3)—O(1)—C(16), C(2)—C(1)—C(15) and C(1)—C(15)—C(16) are all larger than those in SLN by seven to ten times their corresponding standard deviations. The average tetrahedral angle within the cembrane ring is 114·0° in molecule (I) and 114·5° in molecule (II). These values are considerably larger than the normal tetrahedral angle. However, they
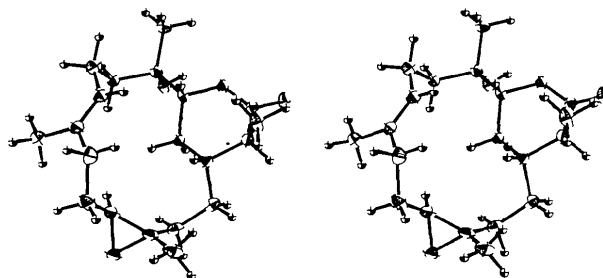
Fig. 3. Stereoview of the single molecule of DSLN. Thermal ellipsoids correspond to 50% probability. All hydrogens were given arbitrary but equal temperature factors for clarity of the drawing.
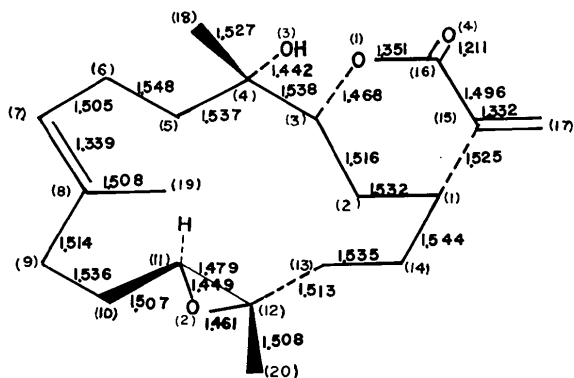
Fig. 4. Chemical structure, numbering convention, and bond distances (Å) for SLN. Estimated standard deviations range between 0·002 and 0·003 Å.
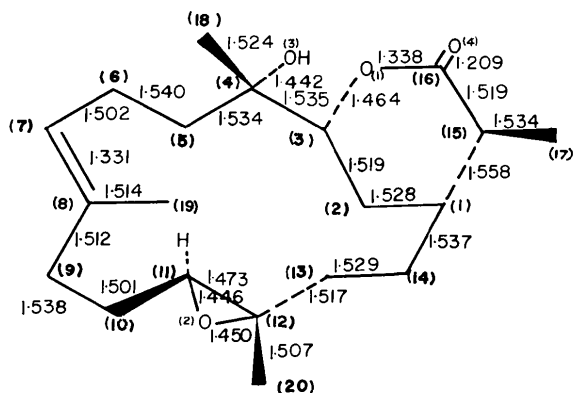

Fig. 5. Chemical structure, numbering convention, and bond distances (Å) for DSLN. Estimated standard deviations range between 0·003 and 0·005 Å.
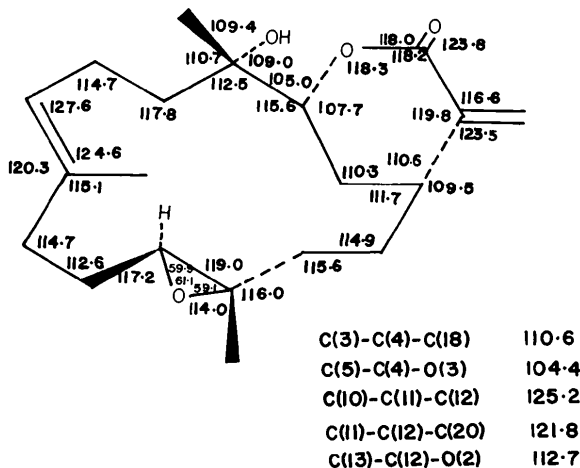
are in good agreement with those normally observed in other marine cembranolides. This can be seen in part of Table 7, where average endocyclic tetrahedral angles for some of the known cembranolides are tabulated.

The epoxide dimensions observed in the present structures are also given in Table 7 along with those found in other known structures. As can be seen the epoxide function is quite similar in all the molecules, and deviates very slightly from an equilateral triangle.

Both the molecules show striking structural and stereochemical similarity to crassin acetate (Hossain & van der Helm, 1969), another cembranolide extracted from Caribbean gorgonians. Each of these three molecules possesses the infrequently encountered δ-lactone, each has an all cis-substitution pattern at C(1), C(3) and C(4) and each possesses similar backbone geometry about C(7), C(8) and C(11), C(12). The conformational similarity between the three molecules can be seen from Fig. 8, where the torsion angles for the cembrane ring in the three molecules are given. However, as the torsion angles indicate, the configuration of crassin acetate is fundamentally enantiomeric to that of SLN and DSLN. The only major differences in torsion angles ($\simeq 22°$) are those of C(11)—C(12) and C(12)—C(13). The epoxide is fused on C(11)—C(12) in the present structures while it is a double bond in crassin acetate. The cembrane ring in both molecules is folded in such a way as to give rather short contacts between atoms H(3) and H(7) on one end and H(1) and H(9) on the other. These distances in SLN are 2·12 and 2·85 Å, while in DSLN, they are 2·39 and 3·12 Å. Such folding is absent in either lobophytolide or sinulariolide.

The deviations of individual atoms from the least-squares planes through the 14 atoms of the cembrane ring are shown in Fig. 9. The least-squares plane in each case is indicated by a dashed horizontal line and
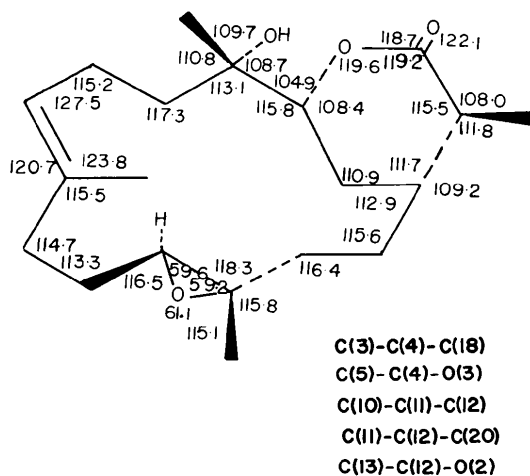

C(3)-C(4)-C(18)	110·6
C(5)-C(4)-O(3)	104·4
C(10)-C(11)-C(12)	125·2
C(11)-C(12)-C(20)	121·8
C(13)-C(12)-O(2)	112·7

Fig. 6. Bond angles (°) for SLN. Estimated standard deviations range between 0·10 and 0·16°.

C(3)-C(4)-C(18)	110·2
C(5)-C(4)-O(3)	104·0
C(10)-C(11)-C(12)	126·2
C(11)-C(12)-C(20)	122·6
C(13)-C(12)-O(2)	111·7

Fig. 7. Bond angles (°) for DSLN. Estimated standard deviations range between 0·17 and 0·24°.

Table 7. *Average tetrahedral angle in cembrane rings and epoxide dimensions in some of the known cembranolides*

Compound	Average tetrahedral angle (°) in cembrane ring	Epoxide dimensions, lengths (Å), angles (°)			
		C–C	C–O	C–O–C	O–C–O
Crassin acetate (Hossain & van der Helm, 1969)	112·9				
Jeunicin (van der Helm, Enwall, Weinheimer, Karns & Ciereszko, 1976)	114·8				
EPA (Ealick, van der Helm & Weinheimer, 1975)	114·6	1·469	1·450	60·8	59·6
Asperdiol A (Weinheimer, Matson, van der Helm & Poling, 1977)	112·9	1·474	1·469	60·3	59·7
Lobophytolide (Karlsson, 1977a)	113·3	1·480	1·440	61·8	59·1
Sinulariolide (Karlsson, 1977b)	113·0	1·472	1·460	60·6	59·7
SLN	114·0	1·479	1·455	61·1	59·4
DSLN	114·5	1·473	1·448	61·1	59·5
Average	113·8	1·475	1·453	61·0	59·5
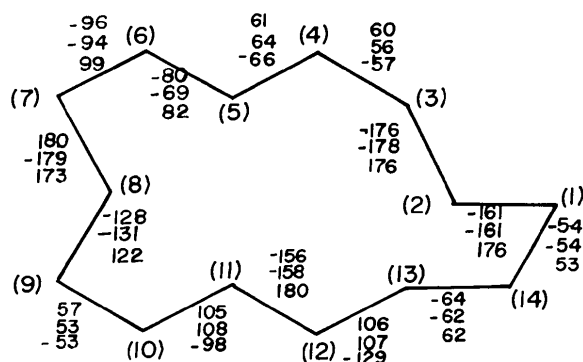
Fig. 8. Torsion angles (°) in the cembrane ring for SLN (upper value), DSLN (middle value) and crassin acetate (lower value).

atoms are indicated by their numbers. The figure once again shows the striking similarity between SLN, DSLN and crassin acetate.

In the SLN structure, there is no short intermolecular contact, and the packing is entirely due to weak van der Waals interactions. In DSLN, the hydroxyl group forms a hydrogen bond with the carbonyl oxygen of the lactone ring belonging to a neighbouring molecule $(-1 - x, -\frac{1}{2} + y, 1 - z)$. The corresponding hydrogen-bond parameters are: O(3)–H···O(4)' = 2·90, O(3)–H = 0·82, H···O(4)' = 2·09 Å, O(3)–H–O(4)' = 171·0°.
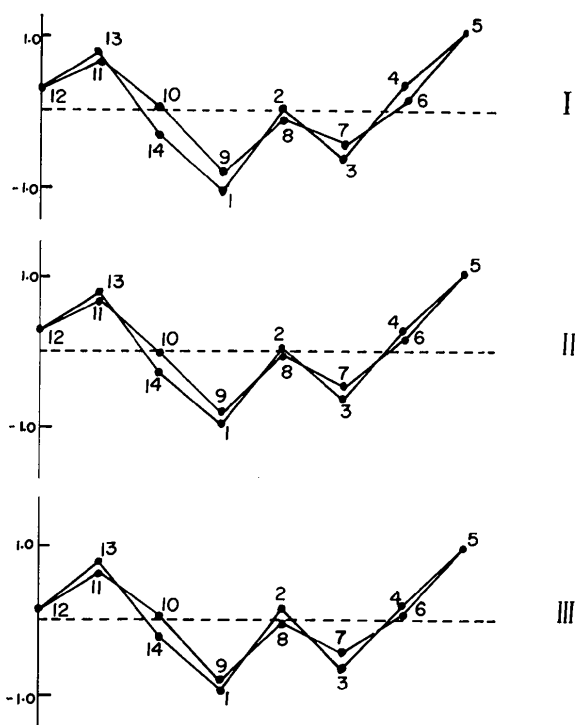
Fig. 9. Deviations (Å) of atoms from the least-squares planes through 14 atoms of the cembrane ring in SLN (I), DSLN (II) and crassin acetate (II).

Note added in proof: Following the acceptance of this paper and after our initial note (Weinheimer, Matson, Hossain & van der Helm, 1977), the structure determination and relative stereochemistry of sinularin (SLN) was published by Kazlauskas, Murphy, Wells, Schönholzer & Coll. (1978), using the name of flexibilide. Although the formal drawings in their publication show the correct absolute configuration for SLN and DSLN, the *ORTEP* drawing and torsion angles are for

the enantiomer of the correct absolute configuration as determined in the present paper and described in our previous note.

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Structure et Stéréochimie d'Alcaloïdes Indoliques.
IV.* Structure de l'Andranginine

PAR CLAUDE RICHE ET CLAUDINE PASCARD-BILLY

Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette, France

Abstract

The crystal structure of andranginine, $C_{21}H_{22}N_2O_2$, M_r = 334, a novel indole alkaloid extracted from *Craspidospermum verticillatum Boj. var. petiolare*, has been determined from three-dimensional X-ray diffraction data. Unit-cell dimensions are a = 8·418 (4), b = 7·786 (4), c = 26·009 (9) Å, β = 100·13 (8)°. The space group is $P2/c$ and Z = 4, D_c = 1·322 Mg m^{-3}, V = 1678 Å^3. The refinement converged at R = 0·051 with 2145 observed intensities. The methoxycarbonyl group at C(16) and the nitrogen lone pair at N(4) are *trans* with respect to the H atom at C(21). In the crystal two molecules form a dimer through the hydrogen bond N(1)–H···O=C of 2·90 Å.

dans la Fig. 1 a été attribuée à l'andranginine (Kan-Fan, Massiot, Ahond, Das, Husson, Potier, Scott & Wei, 1974) et la stéréochimie H(21) α et méthoxy-carbonyl en C(16) α a été proposée par analogie avec des travaux précédents (Scott & Wei, 1972). La synthèse biomimétique de ce composé avait, en effet, été réalisée indépendamment par ces auteurs.

La détermination de la structure cristalline de l'andranginine a été entreprise pour établir la stéréochimie en C(16) et C(21).

L'andranginine cristallise sous la forme d'un racémique. L'importance de l'absence d'activité optique pour ce composé naturel a déjà été soulignée (Kan-Fan, Massiot *et al.*, 1974). Elle suggère en effet l'intervention d'une étape non-enzymatique lors de la biosynthèse.
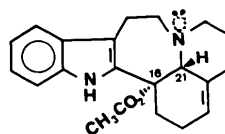
Introduction

L'andranginine, $C_{21}H_{22}N_2O_2$ (M_r = 334, F = 513 K, $[\alpha]_D^{25}$ = 0°), est un des alcaloïdes isolés des feuilles de *Craspidospermum verticillatum Boj. var. petiolare* (Kan-Fan, Das, Husson & Potier, 1974). La formule

Fig. 1. Stéréochimie de l'andranginine.

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* Partie III: Damak & Riche (1977).