CRUICKSHANK, D. W. J. (1961). *Computing Methods and the Phase Problem in X-ray Crystal Analysis*, édité par R. PEPINSKY, J. M. ROBERTSON & J. C. SPEAKMAN. Oxford: Pergamon Press.

KENNARD, O., KERR, K. A., WATSON, D. G., FAWCETT, J. K. & RIVA DI SANSEVERINO, L. (1970). *J. Chem. Soc. A*, pp. 1779–1783.

LEWIN, G., ROLLAND, Y. & POISSON, J. (1979). A paraître.

MAIN, P., LESSINGER, L., WOOLFSON, M. M., GERMAIN, G. & DECLERCQ, J. P. (1977). *MULTAN 77. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. de York, Angleterre, et Louvain-la-Neuve, Belgique.

MILLS, J. F. D. & NYBURG, S. C. (1960). *J. Chem. Soc.* pp. 1458–1461.

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8α-Hydroxyisopicrostegane

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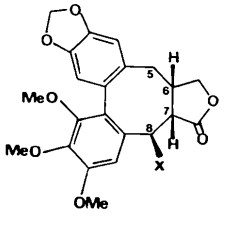
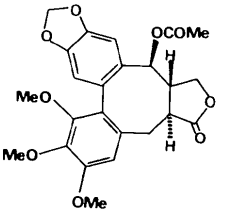
Abstract. $C_{22}H_{22}O_8$, monoclinic, $C2/c$, $a = 10{\cdot}331$ (6), $b = 16{\cdot}860$ (10), $c = 22{\cdot}460$ (10) Å, $\beta = 97{\cdot}60$ (10)°, $Z = 8$, $D_c = 1{\cdot}419$ Mg m^{-3}; final $R = 4{\cdot}1\%$. An internal hydrogen bond binds the hydroxyl group to the lactonic carbonyl.

Introduction. As part of a program pertaining to structure–activity relationships in the series of dibenzocyclooctadiene lignans, we have been prompted to elucidate the geometry of some antitubulin molecules by X-ray crystallography.

The present paper describes the analysis of 8α-hydroxyisopicrostegane (1). This compound, which we previously synthesized (Brown & Robin, 1978), is inactive towards tubulin, whereas its hydrogenolysis product, *i.e.* racemic isopicrostegane (2), shows strong antitubulin properties ($I_{50} \sim 10^{-6}$ *M*), comparable to those displayed by the natural lignan steganacin (3).



(1) X = OH
(2) X = H



(3)

Examination of Dreiding models of (1) and (2) revealed that the presence of the 8-hydroxyl group does not impair the general shape of the molecule despite the possibility of hydrogen bonding with the lactonic carbonyl in (1).

We decided to analyse (±)-8α-hydroxyisopicrostegane (1) rather than the pharmacologically active (2) because of the better crystalline properties of the former.

A single crystal (0·2 × 0·2 × 0·5 mm) was mounted on a Philips PW 1100 automatic four-circle diffractometer equipped with a graphite monochromator. Intensities were collected with Mo $K\alpha$ radiation. 3696 reflections were measured by the ω–2θ scan technique at a speed of 0·05° s^{-1} and with a scan width of 1·20°. Background measurements were made for 10 s on each side of the reflection. 2020 intensities were considered as observed [$I_o > 3\sigma(I_o)$].

The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). 20 out of 21 atoms appeared on the *E* map corresponding to the best figure of merit.

The H atoms which could be located theoretically were placed at C–H = 1·0 Å and C–C–H = 109 or 120°. The H atoms of the three methyl groups and that of the hydroxyl were found on a difference map and introduced in the refinement.

Full-matrix least-squares refinement with isotropic temperature factors for H atoms and anisotropic for C and O terminated when all shifts δ were such that $\delta/\sigma <$ 0·2. The final $R = 4{\cdot}1\%$.

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Table 1. *Atomic coordinates* ($\times 10^4$) *for the heavy atoms*

E.s.d.'s are in parentheses.

	x	y	z	B_{eq} (Å^2)
O(1)	7786 (2)	5093 (1)	7620 (1)	4·4
O(2)	6537 (2)	4121 (1)	7084 (1)	4·3
O(3)	1388 (2)	6974 (1)	5196 (1)	3·9
O(4)	1532 (2)	8029 (1)	5801 (1)	4·0
O(5)	2769 (2)	7645 (1)	7023 (1)	3·2
O(6)	5304 (2)	9685 (1)	5980 (1)	3·5
O(7)	7494 (2)	8953 (1)	5783 (1)	3·5
O(8)	7864 (2)	7340 (1)	6068 (1)	3·8
C(1)	6860 (3)	6212 (2)	6992 (1)	2·6
C(2)	6958 (3)	5432 (2)	7150 (1)	2·8
C(3)	6220 (3)	4857 (2)	6828 (1)	3·0
C(4)	5356 (3)	5026 (2)	6329 (1)	2·9
C(5)	4202 (3)	6039 (2)	5627 (1)	2·7
C(6)	2815 (3)	6057 (2)	5791 (1)	2·9
C(7)	2472 (3)	6761 (2)	6178 (1)	2·6
C(8)	3475 (3)	7169 (2)	6652 (1)	2·5
C(9)	4411 (3)	8451 (2)	6316 (1)	2·5
C(10)	5384 (3)	8883 (2)	6104 (1)	2·5
C(11)	6530 (3)	8512 (2)	5994 (1)	2·6
C(12)	6707 (3)	7717 (2)	6134 (1)	2·5
C(13)	1784 (3)	6149 (2)	5232 (2)	3·6
C(14)	1773 (3)	7340 (2)	5726 (1)	3·3
C(15)	4551 (3)	7644 (2)	6418 (1)	2·3
C(16)	5724 (3)	7267 (2)	6339 (1)	2·4
C(17)	5947 (3)	6410 (2)	6487 (1)	2·3
C(18)	5211 (3)	5826 (2)	6156 (1)	2·4
C(19)	7337 (4)	4294 (2)	7646 (2)	4·9
C(20)	4349 (3)	10124 (2)	6237 (2)	4·3
C(21)	7628 (5)	8810 (3)	5179 (2)	7·6
C(22)	8973 (3)	7600 (2)	6485 (2)	5·3

Table 2. *Atomic coordinates* ($\times 10^3$) *and isotropic temperature factors for the* H *atoms*

	x	y	z	B (Å^2)
H(1)	742	661	723	2·6
H(4)	486	459	610	2·9
H(5*A*)	424	564	530	2·7
H(5*B*)	442	658	548	2·7
H(6)	264	555	600	2·9
H(7)	178	655	641	2·6
H(8)	391	673	691	2·5
H(9)	359	873	640	2·5
H(13*A*)	215	601	486	3·6
H(13*B*)	100	581	527	3·6
H(19*A*)	681	423	799	4·9
H(19*B*)	810	393	771	4·9
H(20*A*)	344 (2)	1000 (1)	605 (1)	4·0
H(20*B*)	451 (2)	1067 (1)	614 (1)	4·0
H(20*C*)	444 (2)	1000 (1)	666 (1)	4·0
H(21*A*)	815 (3)	920 (2)	504 (1)	6·8
H(21*B*)	703 (3)	849 (2)	494 (1)	6·8
H(21*C*)	815 (3)	830 (2)	513 (1)	6·8
H(22*A*)	61 (2)	809 (1)	863 (1)	4·6
H(22*B*)	38 (3)	717 (1)	847 (1)	4·6
H(22*C*)	127 (3)	766 (1)	809 (1)	4·6
H(O5)	219 (2)	802 (1)	673 (1)	3·2

Scattering factors for C and O atoms were taken from *International Tables for X-ray Crystallography* (1974), that for H from Stewart, Davidson & Simpson (1965). Atomic coordinates are listed in Tables 1 and 2, bond lengths and angles in Tables 3 and 4.*

Table 3. *Bond lengths* (Å)

O(1)–C(2)	1·391 (4)	C(3)–C(4)	1·368 (5)
O(1)–C(19)	1·429 (4)	C(4)–C(18)	1·407 (4)
O(2)–C(3)	1·388 (4)	C(5)–C(6)	1·525 (4)
O(2)–C(19)	1·443 (4)	C(5)–C(18)	1·517 (4)
O(3)–C(13)	1·450 (4)	C(6)–C(7)	1·541 (4)
O(3)–C(14)	1·352 (4)	C(6)–C(13)	1·543 (5)
O(4)–C(14)	1·205 (4)	C(7)–C(8)	1·545 (4)
O(5)–C(8)	1·427 (3)	C(7)–C(14)	1·520 (4)
O(6)–C(10)	1·380 (3)	C(8)–C(15)	1·520 (4)
O(6)–C(20)	1·416 (4)	C(9)–C(10)	1·376 (4)
O(7)–C(11)	1·375 (4)	C(9)–C(15)	1·385 (4)
O(7)–C(21)	1·402 (5)	C(10)–C(11)	1·390 (4)
O(8)–C(12)	1·380 (4)	C(11)–C(12)	1·382 (4)
O(8)–C(22)	1·448 (4)	C(12)–C(16)	1·394 (4)
C(1)–C(2)	1·363 (4)	C(15)–C(16)	1·400 (4)
C(1)–C(17)	1·415 (4)	C(16)–C(17)	1·493 (4)
C(2)–C(3)	1·377 (4)	C(17)–C(18)	1·397 (4)
		O(5)–H(O5)	1·05 (4)

Table 4. *Bond angles* (°)

C(2)–O(1)–C(19)	104·4 (2)	O(6)–C(10)–C(11)	115·8 (3)
C(3)–O(2)–C(19)	104·9 (2)	C(9)–C(10)–C(11)	120·1 (3)
C(13)–O(3)–C(14)	109·9 (2)	O(7)–C(11)–C(10)	119·3 (3)
C(10)–O(6)–C(20)	117·1 (2)	O(7)–C(11)–C(12)	121·5 (3)
C(11)–O(7)–C(21)	114·1 (3)	C(10)–C(11)–C(12)	119·0 (3)
C(12)–O(8)–C(22)	114·4 (2)	O(8)–C(12)–C(11)	120·8 (3)
C(2)–C(1)–C(17)	117·1 (3)	O(8)–C(12)–C(16)	117·6 (3)
O(1)–C(2)–C(1)	127·7 (3)	C(11)–C(12)–C(16)	121·6 (3)
O(1)–C(2)–C(3)	110·6 (3)	O(3)–C(13)–C(6)	107·5 (2)
C(1)–C(2)–C(3)	121·7 (3)	O(3)–C(14)–O(4)	121·4 (3)
O(2)–C(3)–C(2)	109·2 (3)	O(3)–C(14)–C(7)	110·7 (3)
O(2)–C(3)–C(4)	128·1 (3)	O(4)–C(14)–C(7)	127·8 (3)
C(2)–C(3)–C(4)	122·6 (3)	C(8)–C(15)–C(9)	120·7 (3)
C(3)–C(4)–C(18)	117·4 (3)	C(8)–C(15)–C(16)	119·3 (3)
C(6)–C(5)–C(18)	112·8 (2)	C(9)–C(15)–C(16)	119·9 (3)
C(5)–C(6)–C(7)	116·4 (2)	C(12)–C(16)–C(15)	118·3 (3)
C(5)–C(6)–C(13)	112·1 (3)	C(12)–C(16)–C(17)	120·2 (3)
C(7)–C(6)–C(13)	101·3 (2)	C(15)–C(16)–C(17)	121·4 (3)
C(6)–C(7)–C(8)	123·2 (2)	C(1)–C(17)–C(16)	118·3 (3)
C(6)–C(7)–C(14)	104·0 (2)	C(1)–C(17)–C(18)	121·2 (3)
C(8)–C(7)–C(14)	113·0 (2)	C(16)–C(17)–C(18)	120·4 (3)
O(5)–C(8)–C(7)	107·8 (2)	C(4)–C(18)–C(5)	118·7 (3)
O(5)–C(8)–C(15)	111·1 (2)	C(4)–C(18)–C(17)	119·9 (3)
C(7)–C(8)–C(15)	116·8 (2)	C(5)–C(18)–C(17)	121·3 (3)
C(10)–C(9)–C(15)	120·8 (3)	O(1)–C(19)–O(2)	107·9 (3)
O(6)–C(10)–C(9)	124·1 (3)	C(8)–O(5)–H(O5)	105 (1)

Discussion. A perspective view of the molecule is presented in Fig. 1; as both enantiomers exist in the racemic crystal, the arbitrary configuration was chosen according to the scheme presented in the *Introduction.*

* Lists of structure factors, anisotropic thermal parameters and mean planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34720 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

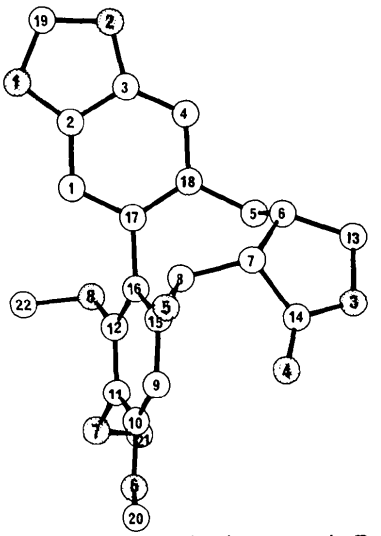
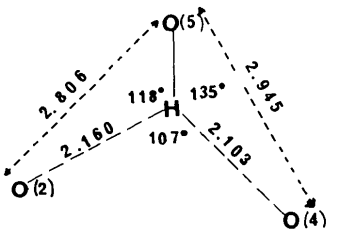


Fig. 1. Molecular structure of isopicrosteganol. Dotted circles are O atoms.

An absolute configuration of episteganol ('natural' series) was proposed by Kupchan, Britton, Ziegler, Gilmore, Restivo & Bryan (1973) on the basis of the anomalous scattering of the O atoms. Although the results are not convincing, we shall keep the term 'iso' for the 'unnatural' biphenyl torsion.

The principal features are the *cis*-fused lactone ring, and the *S* configuration of C(8). The OH group fixed on this atom is hydrogen bonded to the carbonyl of the lactone. This hydrogen, H(O5), has an intermediate position between O(4) of the same molecule and O(2) of another molecule in the unit cell:



O(5), O(4), H(O5) are of the same molecule situated at x,y,z, O(2) is of the molecule situated at $x-\frac{1}{2},\frac{1}{2}+y,z$.

The plane defined by the three O atoms contains H(O5), which is equidistant from O(4) and O(2).

Mean planes. Aromatic ring *B* is planar ($\delta < 3\sigma$). Trimethoxybenzene ring *A* is more twisted and bent along C(11)–C(15); the angle between the C(15)–C(9)–C(10)–C(11) and C(11)–C(12)–C(16)–C(15) planes is 3·8°.

Rings *D* (dioxolane) and *E* (lactone) are pure envelopes; ring *D*: $\Delta = 36°$, $\varphi_m = 18°$, C(19) *exo* (Altona, Geise & Romers, 1968); ring *E*: $\Delta = 36°$, $\varphi_m = 25°$, C(6) *exo*.

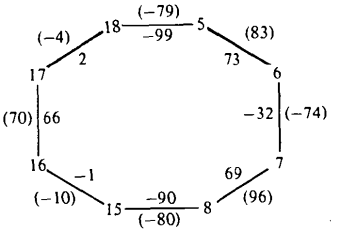


Fig. 2. Cyclooctadiene: torsion angles (°). Values for iso(epi)-steganol (Hull, Hughes, Kennard & Raphael, 1978) are in parentheses ($\sigma \simeq 0{\cdot}5°$).

Cyclooctadiene ring C. Fig. 2 shows the torsion angles along the bonds (Klyne & Prelog, 1960).

There is practically no distortion around the aromatic bonds: C(15)–C(16) 1° and C(17)–C(18) 2°. The torsion is much more important along C(18)–C(5). The hydrogen bond between O(5) and O(4) induces a flattening of the torsion angle along C(6)–C(7).

The shape of the cyclooctadiene ring is twist–boat–chair (TBC) as in iso(epi)steganol. It has a nearly perfect binary axis passing through C(16)–C(17) and the middle of C(6)–C(7). This axis is also a binary axis for nearly the complete molecule itself, rings *A* and *B* being symmetrical, and O(1) and O(2) being related to O(7) and O(6) respectively. In isosteganol, the diad axis also passes through the endocyclic O atom of the lactone, C(13) and C(14) being symmetrically related.

The results of the present studies fully confirm the structure we already assigned to (±)-isopicrostegane (2) (Brown & Robin, 1978) on the basis of IR and NMR data as well as chemical evidence.

The knowledge of the precise conformation of (±)-isopicrostegane (2) was made necessary by the fact that this compound is the only antitubulin dibenzocyclooctadiene known so far which is not of natural origin.

References

ALTONA, C., GEISE, H. J. & ROMERS, C. (1968). *Tetrahedron*, **24**, 13–32.

BROWN, E. & ROBIN, J. P. (1978). *Tetrahedron Lett.* pp. 3613–3616.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

HULL, S. E., HUGHES, L. R., KENNARD, O. & RAPHAEL, R. A. (1978). *Acta Cryst.* B**34**, 1154–1157.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 72–78. Birmingham: Kynoch Press.

KLYNE, W. & PRELOG, V. (1960). *Experientia*, **16**, 521–523.

KUPCHAN, S. M., BRITTON, R. W., ZIEGLER, M. F., GILMORE, C. J., RESTIVO, R. J. & BRYAN, R. F. (1973). *J. Am. Chem. Soc.* **95**, 1335–1336.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.