Sesquiterpenoids. Part 26.[1] *X*-Ray Crystallographic Analysis of Mikanokryptin, a Cytotoxic Guaianolide

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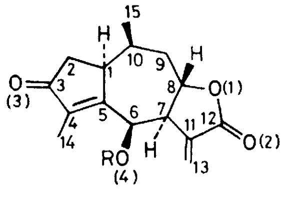
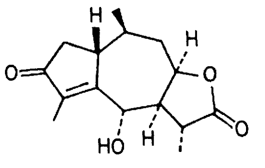
The stereochemistry of mikanokryptin, a cytotoxic guaianolide, has been defined by *X*-ray diffraction. In the α-methylene γ-lactone the C=C–C=O and C_α–C_β–C_γ–O torsion angles, 6 and 26°, are paired in sign. Whereas molecular mechanics calculations for a series of chair and twist chair conformers indicate that the most stable form of an isolated methylenecycloheptane is a twist chair in which an approximate C_2 axis of the ring passes through the carbon atom adjacent to that bearing the exocyclic methylene group, the methylenecycloheptane ring in the sesquiterpenoid has a conformation of the chair type and the difference is related to constraints imposed by the cyclopentenone and lactone ring fusions. Crystals of mikanokryptin are orthorhombic, space group $P2_12_12_1$, with a = 10.366, b = 9.479, c = 13.329 Å, and Z = 4. The crystal structure was elucidated by direct phasing methods and the atomic parameters were subsequently adjusted by least-squares calculations which converged at R 4.3% over 2 277 diffractometer $|F_0|$ values.

THE cytoxic guaianolide mikanokryptin (1) was isolated from a *Mikania* species [2] which was later identified with an aberrant form of *M. micrantha* H.B.K., and the compound has also been found in *Melampodium divaricatum* (Rich. in Pers.) DC.[3] The stereochemistry of the lactone ring junction was established as *trans* by spectroscopic studies and since the Cotton effect of the acetyl derivative (2) at 257 nm is positive the absolute stereochemistry at C(7) and C(8) is as shown.[4] The positive Cotton effect associated with the αβ-unsaturated ketone chromophore of (2) and its 11,13-dihydro-derivative suggested that C(1) in mikanokryptin has opposite configuration to C(1) in geigerin (3).[5]



(1) R = H
(2) R = Ac



(3)

Analysis of molecular models indicated that the observed n.m.r. coupling constants are accommodated most satisfactorily by a formula in which the orientation of the hydrogen atom at C(1) is α, that of the methyl group at C(10) is β, and the seven-membered ring adopts a chair-like conformation. Moreover, regardless of the orientation of 1-H and 10-Me, the small value of $J_{6,7}$ requires β-orientation of the hydroxy group on C(6), as in formula (1).

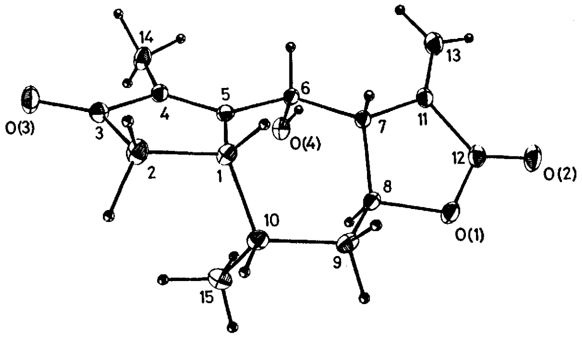


FIGURE 1 Molecular structure of mikanokryptin

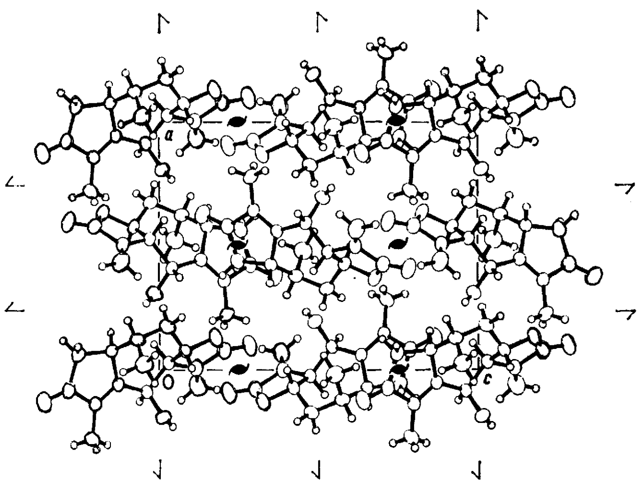


FIGURE 2 Arrangement of molecules in the unit cell

We undertook an *X*-ray analysis of mikanokryptin to supplement the spectroscopic investigation and secure the assignment of stereochemistry. The crystal structure was determined by direct phasing methods and the atomic parameters were adjusted by least-squares calculations. The derived molecular structure and the packing of the molecules in the unit cell are shown in Figures 1 and 2. The atomic co-ordinates are listed in Table 1 and the bond lengths, valency angles, torsion angles, and intermolecular separations are in Tables 2—5.

Our results confirm that mikanokryptin has the constitution and stereochemistry (1).

In the crystal, the seven-membered ring of mikanokryptin has a conformation that approximates more closely to a chair form than to a twist chair form. The conformations of cycloheptane have been discussed in various papers; pseudorotation can take place through a succession of twist chair (C_2) and chair (C_s) forms that differ in energy by *ca.* 1—2 kcal mol^{-1}, with the former at energy minima and the latter at energy maxima.[6]

For methylenecycloheptane four distinct twist chair and four distinct chair conformers have to be considered (*cf.* cycloheptanone);[7] one twist chair conformer has C_2 symmetry and one chair conformer has C_s symmetry. We have calculated steric energies and equilibrium geometries for these eight forms by means of the force field developed by White and Bovill,[8] with a full-matrix energy minimization procedure,[9] and the results obtained are summarized in Figure 3. The global energy minimum is the twist chair form of Figure 3(*b*). The twist chair conformers of Figures 3(*c*) and (*d*) correspond to energy minima whereas the twist chair conformer of Figure 3(*a*), which has C_2 symmetry, is actually at a shallow maximum in energy. The chair forms of Figures 3(*e*)—(*h*) all correspond to energy maxima. The methylenecycloheptane chair conformation found in mikanokryptin in the solid corresponds to that in Figure 3(*e*), in which the smallest torsion angle in the ring is adjacent to the exocyclic double bond, and since this is not the minimum energy form the question arises as to whether the adoption of this ring conformation can be accounted for by the constraints imposed by the cyclopentenone and lactone rings.

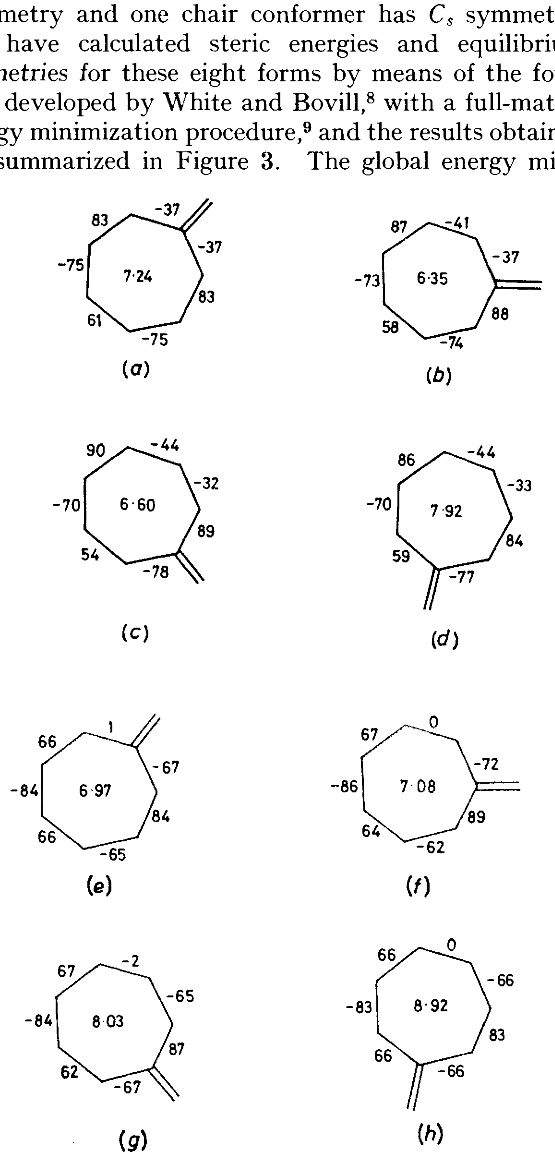


FIGURE 3 Calculated torsion angles (°) for twist chair (*a*)—(*d*) and chair (*e*)—(*h*) conformations of methylenecycloheptane. Steric energies (kcal mol^{-1}) are inset

The torsion angle C(2)–C(1)–C(5)–C(4) in the cyclopentenone ring in (1) must be *ca.* 0° (experimentally, −4°) and the torsion angle C(10)–C(1)–C(5)–C(6) in the seven-membered ring, adjacent to the exocyclic methylene group, must therefore be *ca.* ±60°. This restricts the choice of possible chair and twist chair conformers for mikanokryptin to those shown in Figures 3(*d*), (*e*), (*g*), and (*h*). With regard to the C(7),C(8)-*trans*-fused α-methylene γ-lactone, the torsion angle C(11)–C(7)–C(8)–O(1) is 26° and we have previously established that the angle is 25° in bromogaillardin and 32° in deacetyldihydrogaillardin *p*-bromobenzoate;[10] it follows that the ring torsion angle C(6)–C(7)–C(8)–C(9) must be *ca.* −90°. A restriction that the angle C(6)–C(7)–C(8)–C(9) should be *ca.* ±90° eliminates the conformations of Figures 3(*d*), (*g*), and (*h*) from consideration and leaves Figure 3(*e*) to define the region of conformational space accessible to the methylenecycloheptane ring in mikanokryption. We hope that Figures 3(*a*)—(*h*) may prove to be of utility in the analysis and prediction of guaianolide conformations.

The torion angles C_α–C_β–C_γ–O and C=C–C=O of the α-methylene γ-lactone, 26 and 6°, have the same sign. We have noted that this correlation applies widely in sesquiterpenoids and have discussed its significance in earlier papers.[11]

TABLE 1

Fractional atomic co-ordinates, with standard deviations in parentheses

Atom	*x*	*y*	*z*
C(1)	−0.076 7(2)	0.582 5(2)	0.650 0(1)
C(2)	−0.062 0(2)	0.647 7(3)	0.755 2(1)
C(3)	0.076 8(2)	0.626 4(2)	0.784 7(1)
C(4)	0.141 3(2)	0.547 9(2)	0.704 1(1)
C(5)	0.056 6(2)	0.520 4(2)	0.630 4(1)
C(6)	0.089 4(2)	0.432 1(2)	0.539 6(1)
C(7)	−0.026 9(2)	0.406 3(2)	0.471 5(1)
C(8)	−0.074 6(2)	0.539 8(2)	0.419 1(1)
C(9)	−0.174 6(2)	0.623 6(2)	0.474 6(2)
C(10)	−0.123 4(2)	0.692 1(2)	0.571 4(1)
C(11)	−0.003 5(2)	0.307 6(2)	0.385 4(1)
C(12)	−0.077 5(2)	0.362 6(2)	0.298 8(1)
C(13)	0.065 7(3)	0.192 1(3)	0.381 2(2)
C(14)	0.279 4(2)	0.505 4(3)	0.711 6(2)
C(15)	−0.021 7(2)	0.804 3(2)	0.549 5(2)
O(1)	−0.130 3(2)	0.488 4(2)	0.324 3(1)
O(2)	−0.094 9(2)	0.311 3(2)	0.217 7(1)
O(3)	0.125 9(2)	0.664 4(2)	0.863 3(1)
O(4)	0.192 2(1)	0.499 5(2)	0.487 2(1)
H(1)	−0.142 9(24)	0.506 3(27)	0.650 9(18)
H(2a)	−0.117 2(24)	0.602 2(26)	0.802 2(18)
H(2b)	−0.087 5(29)	0.753 0(31)	0.758 3(22)
H(6)	0.122 5(21)	0.344 0(24)	0.563 4(17)
H(7)	−0.096 3(22)	0.364 4(24)	0.515 6(17)
H(8)	−0.003 7(20)	0.598 2(23)	0.401 0(16)
H(9a)	−0.246 1(24)	0.570 1(26)	0.489 9(18)
H(9b)	−0.205 4(25)	0.698 4(29)	0.429 7(19)
H(10)	−0.197 6(24)	0.736 2(25)	0.604 0(18)
H(13a)	0.081 7(27)	0.139 0(29)	0.319 9(20)
H(13b)	0.120 6(30)	0.156 9(34)	0.438 7(24)
H(14a)	0.305 1(28)	0.436 0(31)	0.663 2(21)
H(14b)	0.328 6(50)	0.575 1(48)	0.704 7(35)
H(14c)	0.303 9(32)	0.450 3(35)	0.772 6(23)
H(15a)	0.008 9(24)	0.847 0(30)	0.615 9(21)
H(15b)	−0.054 3(32)	0.878 6(33)	0.511 5(23)
H(15c)	0.053 1(28)	0.764 7(31)	0.511 0(21)
H[O(4)]	0.227 0(29)	0.443 2(30)	0.454 0(22)

The molecules in the crystal are linked by a hydrogen bond between the 6-hydroxy function of one molecule and the 3-carbonyl group of another; the O(4) · · · O(3) and H[O(4)] · · · O(3) distances are 2.95 and 2.2 Å and the O(4)–H[O(4)] · · · O(3) angle is 162°.

EXPERIMENTAL

Crystal Data.—$\mathrm{C_{15}H_{18}O_4}$, $M = 262.31$. Orthorhombic, $a = 10.366$, $b = 9.479$, $c = 13.329$ Å (all ±0.1%), $U = 1\,301$ Å^3, $Z = 4$, $D_c = 1.330$ g cm^{-3}, $F(000) = 560$. Space group $P2_12_12_1$ (D_2^4). Mo-K_α radiation, $\lambda = 0.710\,7$ Å; μ(Mo-K_α) = 1.04 cm^{-1}.

Crystallographic Measurements.—Final values of the cell dimensions were determined from angular measurements on a four-circle diffractometer. For the intensity measurements, reflections were measured in the range θ(Mo-K_α) ≤ 32°, with θ–ω scans of 40 steps of 0.02° s^{-1} and background counts of 20 s at each end of the scan range; 2 277 intensities with $I > 2\sigma(I)$ were obtained.

TABLE 2

Bond lengths (Å), with estimated standard deviations in parentheses

C(1)–C(2)	1.528(2)	C(12)–O(2)	1.193(2)
C(1)–C(5)	1.524(2)	C(1)–H(1)	1.00(2)
C(1)–C(10)	1.550(2)	C(2)–H(2a)	0.95(2)
C(2)–C(3)	1.506(2)	C(2)–H(2b)	1.04(3)
C(3)–C(4)	1.461(2)	C(6)–H(6)	0.96(2)
C(3)–O(3)	1.213(2)	C(7)–H(7)	1.01(2)
C(4)–C(5)	1.338(2)	C(8)–H(8)	0.95(2)
C(4)–C(14)	1.491(2)	C(9)–H(9a)	0.92(2)
C(5)–C(6)	1.504(1)	C(9)–H(9b)	0.98(2)
C(6)–C(7)	1.523(2)	C(10)–H(10)	0.98(2)
C(6)–O(4)	1.423(2)	C(13)–H(13a)	0.97(2)
C(7)–C(8)	1.526(2)	C(13)–H(13b)	1.01(3)
C(7)–C(11)	1.495(2)	C(14)–H(14a)	0.96(3)
C(8)–C(9)	1.499(2)	C(14)–H(14b)	0.84(4)
C(8)–O(1)	1.466(1)	C(14)–H(14c)	1.00(2)
C(9)–C(10)	1.528(2)	C(15)–H(15a)	1.02(2)
C(10)–C(15)	1.526(3)	C(15)–H(15b)	0.93(3)
C(11)–C(12)	1.475(2)	C(15)–H(15c)	1.00(3)
C(11)–C(13)	1.312(3)	O(4)–H[O(4)]	0.78(3)
C(12)–O(1)	1.353(2)		

Structure Analysis.—The crystal structure was elucidated by direct phasing procedures, using the program MULTAN.

TABLE 3

Valency angles (°), with estimated standard deviations in parentheses

C(5)–C(1)–C(2)	102.8(1)	C(6)–C(7)–C(11)	115.1(1)
C(10)–C(1)–C(2)	112.0(1)	C(8)–C(7)–C(11)	102.9(1)
C(10)–C(1)–C(5)	115.3(1)	C(7)–C(8)–C(9)	116.1(1)
C(1)–C(2)–C(3)	106.1(1)	C(7)–C(8)–O(1)	104.0(1)
C(2)–C(3)–C(4)	108.3(1)	C(9)–C(8)–O(1)	109.0(1)
C(2)–C(3)–O(3)	125.8(1)	C(8)–C(9)–C(10)	113.3(1)
C(4)–C(3)–O(3)	125.9(1)	C(9)–C(10)–C(1)	112.9(1)
C(3)–C(4)–C(5)	109.4(1)	C(9)–C(10)–C(15)	112.2(1)
C(3)–C(4)–C(14)	121.9(1)	C(1)–C(10)–C(15)	112.2(1)
C(5)–C(4)–C(14)	128.7(1)	C(7)–C(11)–C(12)	106.7(1)
C(1)–C(5)–C(4)	113.2(1)	C(7)–C(11)–C(13)	130.1(1)
C(1)–C(5)–C(6)	123.8(1)	C(12)–C(11)–C(13)	123.2(1)
C(4)–C(5)–C(6)	123.0(1)	C(11)–C(12)–O(1)	109.2(1)
C(5)–C(6)–C(7)	112.6(1)	C(11)–C(12)–O(2)	129.3(2)
C(5)–C(6)–O(4)	108.0(1)	O(1)–C(12)–O(2)	121.5(1)
C(7)–C(6)–O(4)	112.1(1)	C(8)–O(1)–C(12)	110.3(1)
C(6)–C(7)–C(8)	113.1(1)		

An initial structure-factor calculation based on all the carbon and oxygen atoms gave R 35.5% and subsequent least-squares adjustment of the positional and anisotropic thermal parameters of these atoms gave $R = 12.1\%$. A difference electron-density distribution disclosed the hydrogen atom positions and further least-squares refinement incorporating isotropic thermal parameters for the hydrogen atoms converged at R 4.3%. The weighting scheme adopted was $w = (A + B|F_o| + C|F_o|^2)^{-1}$, where A—C were chosen so as to minimize the deviation from constant $w\Delta^2$ over the range of $|F_o|$, the final weights being defined by A 0.176, B −0.016 7, and C 0.001 8. Observed and calculated structure amplitudes and the thermal parameters of the atoms are listed in Supplementary Publication No. SUP 22357 (18 pp.).*

TABLE 4

Torsion angles (°) *

C(5)–C(1)–C(2)–C(3)	3	C(5)–C(6)–C(7)–C(8)	68
C(10)–C(1)–C(2)–C(3)	−121	C(5)–C(6)–C(7)–C(11)	−174
C(2)–C(1)–C(5)–C(4)	−4	O(4)–C(6)–C(7)–C(8)	−54
C(2)–C(1)–C(5)–C(6)	174	O(4)–C(6)–C(7)–C(11)	64
C(10)–C(1)–C(5)–C(4)	119	C(6)–C(7)–C(8)–C(9)	−90
C(10)–C(1)–C(5)–C(6)	−64	C(6)–C(7)–C(8)–O(1)	150
C(2)–C(1)–C(10)–C(9)	−164	C(11)–C(7)–C(8)–C(9)	145
C(2)–C(1)–C(10)–C(15)	68	C(11)–C(7)–C(8)–O(1)	26
C(5)–C(1)–C(10)–C(9)	79	C(6)–C(7)–C(11)–C(12)	−143
C(5)–C(1)–C(10)–C(15)	−49	C(6)–C(7)–C(11)–C(13)	38
C(1)–C(2)–C(3)–C(4)	−2	C(8)–C(7)–C(11)–C(12)	−19
C(1)–C(2)–C(3)–O(3)	180	C(8)–C(7)–C(11)–C(13)	161
C(2)–C(3)–C(4)–C(5)	0	C(7)–C(8)–C(9)–C(10)	67
C(2)–C(3)–C(4)–C(14)	−178	O(1)–C(8)–C(9)–C(10)	−176
O(3)–C(3)–C(4)–C(5)	178	C(7)–C(8)–O(1)–C(12)	−24
O(3)–C(3)–C(4)–C(14)	0	C(9)–C(8)–O(1)–C(12)	−148
C(3)–C(4)–C(5)–C(1)	2	C(8)–C(9)–C(10)–C(1)	−62
C(14)–C(4)–C(5)–C(1)	−180	C(8)–C(9)–C(10)–C(15)	66
C(3)–C(4)–C(5)–C(6)	−176	C(7)–C(11)–C(12)–O(1)	6
C(14)–C(4)–C(5)–C(6)	2	C(7)–C(11)–C(12)–O(2)	−173
C(1)–C(5)–C(6)–C(7)	−3	C(13)–C(11)–C(12)–O(1)	−175
C(1)–C(5)–C(6)–O(4)	122	C(13)–C(11)–C(12)–O(2)	6
C(4)–C(5)–C(6)–C(7)	175	C(11)–C(12)–O(1)–C(8)	12
C(4)–C(5)–C(6)–O(4)	−61	O(2)–C(12)–O(1)–C(8)	−169

* The mean standard deviation of the torsion angles is 0.2°. An angle is positive when a clockwise rotation is required of atom (1) to eclipse atom (4) whilst looking down the (2)–(3) bond.

TABLE 5

Intermolecular separations (<4 Å)

O(3) · · · O(4)$^{\mathrm{I}}$	2.95	C(14) · · · C(11)$^{\mathrm{I}}$	3.73
O(2) · · · C(14)$^{\mathrm{II}}$	3.41	C(12) · · · C(14)$^{\mathrm{II}}$	3.79
O(3) · · · C(13)$^{\mathrm{I}}$	3.48	C(3) · · · O(4)$^{\mathrm{I}}$	3.80
C(14) · · · C(12)$^{\mathrm{I}}$	3.53	C(9) · · · O(4)$^{\mathrm{III}}$	3.86
C(15) · · · O(4)$^{\mathrm{III}}$	3.53	O(3) · · · C(6)$^{\mathrm{I}}$	3.88
C(10) · · · O(4)$^{\mathrm{III}}$	3.58	O(3) · · · C(11)$^{\mathrm{I}}$	3.93
C(9) · · · C(15)$^{\mathrm{III}}$	3.68	C(14) · · · O(1)$^{\mathrm{I}}$	3.94
C(14) · · · O(4)$^{\mathrm{I}}$	3.69	C(11) · · · C(14)$^{\mathrm{II}}$	3.94
C(14) · · · O(2)$^{\mathrm{I}}$	3.70	C(14) · · · C(13)$^{\mathrm{I}}$	3.99
C(13) · · · C(14)$^{\mathrm{II}}$	3.72		

Roman numeral superscripts refer to the following transformations of the atomic co-ordinates:

I $1.5 - x, 1 - y, 0.5 + z$
II $0.5 + x, 0.5 - y, 1 - z$
III $0.5 + x, 1.5 - y, 1 - z$

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* For details of Supplementary Publications see Notice to Authors, *J.C.S. Perkin I*, 1977, Index issue.

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