Sesquiterpenoids. Part XXII.[1] *X*-Ray Crystallographic Determination of the Stereochemistry and Conformation of Deacetylneotenulin †

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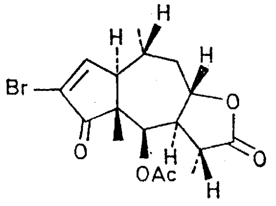
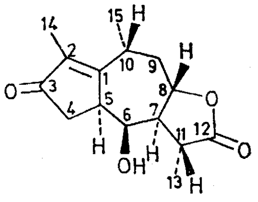
The stereochemistry of deacetylneotenulin (2) has been defined by *X*-ray crystal-structure analysis. The hydrogen atom at C(5) is shown to be α- and the hydroxy-group at C(6) β-oriented. The c.d. spectrum has a positive Cotton effect associated with the unsaturated ketone and the C:C·C:O chromophore has right-hand chirality (ω 175°). The cycloheptylidene ring adopts a twist-chair conformation. The crystals are monoclinic, space group $P2_1$, with $a = 7.475(2)$, $b = 7.905(1)$, $c = 12.022(2)$ Å, $\beta = 93° 26(1)'$, and $Z = 2$. *X*-Ray data were obtained by diffractometer, and the structure determined by direct phasing methods; least-squares adjustment of the atomic parameters converged to R 4.9% over 1 020 reflections.

THE chemistry of the pseudoguaianolide tenulin has been investigated by several groups,[2] and the stereochemistry of bromoisotenulin (1) determined by *X*-ray diffraction.[3]



(1)



(2)

One of the products formed on treatment of tenulin with sodium bicarbonate solution is deacetylneotenulin, for which Herz suggested structure (2; without stereochemistry) together with a rather remarkable series of rearrangements to account for its formation.[4] We have verified this structural assignment by *X*-ray methods and defined the relative stereochemistry as shown in (2). Our results also provide details of the conformation of the seven-membered carbocycle and a correlation of the c.d. spectrum of deacetylneotenulin with the stereochemistry of the cyclopentenone ring.

A direct-phasing approach was adopted for the elucidation of the crystal structure and subsequent least-squares adjustment of the atomic parameters converged at R 4.9% over 1 020 reflections. The resultant molecular structure is shown in Figure 1. Atomic coordinates are listed in Table 1, bond lengths, valency

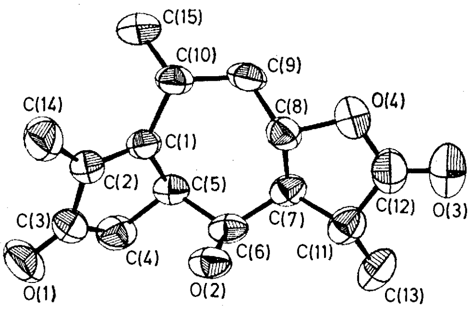


FIGURE 1 The atomic arrangement in the molecule of deacetylneotenulin (2)

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[1] Part XXI, D. N. J. White and G. A. Sim, *J.C.S. Perkin II*, 1975, 1826.

[2] E. P. Clark, *J. Amer. Chem. Soc.*, 1939, **61**, 1836; 1940, **62**, 597; D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 1956, 142; W. Herz, A. R. de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, 1963, **19**, 1359.

[3] D. Rogers and Mazhar-Ul-Haque, *Proc. Chem. Soc.*, 1963, 92; Mazhar-Ul-Haque, D. Rogers, and C. N. Caughlan, *J.C.S. Perkin II*, 1974, 223.

[4] W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Amer. Chem. Soc.*, 1962, **84**, 3857.

angles, torsion angles, displacements of the atoms from various planes, and intermolecular separations in Tables 2—6.

TABLE 1

Fractional atomic co-ordinates, with standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	0.713 9(5)	0.748 3	0.565 4(3)
O(2)	0.609 0(4)	0.368 1(8)	0.378 2(2)
O(3)	0.673 8(7)	−0.054 6(10)	0.051 1(4)
O(4)	0.845 5(5)	0.163 7(8)	0.103 4(3)
C(1)	0.861 6(5)	0.616 1(9)	0.313 0(3)
C(2)	0.895 7(6)	0.657 8(9)	0.428 0(4)
C(3)	0.729 9(6)	0.713 7(9)	0.468 1(4)
C(4)	0.587 0(6)	0.724 1(10)	0.375 8(5)
C(5)	0.661 8(6)	0.624 9(9)	0.279 6(3)
C(6)	0.573 9(5)	0.447 4(9)	0.274 6(4)
C(7)	0.632 0(6)	0.337 9(9)	0.179 5(3)
C(8)	0.833 9(6)	0.308 8(9)	0.177 2(3)
C(9)	0.942 6(6)	0.455 6(10)	0.138 8(4)
C(10)	1.003 7(5)	0.569 7(9)	0.234 1(3)
C(11)	0.562 0(7)	0.158 6(10)	0.175 3(4)
C(12)	0.692 5(8)	0.073 4(11)	0.102 6(5)
C(13)	0.368 4(8)	0.129 6(10)	0.140 2(5)
C(14)	1.067 4(7)	0.650 6(12)	0.489 4(5)
C(15)	1.090 6(7)	0.731 1(11)	0.192 3(5)
H(4A)	0.579(5)	0.832(6)	0.363(3)
H(4B)	0.481(6)	0.687(7)	0.397(4)
H(5)	0.642(5)	0.675(5)	0.209(3)
H(6)	0.450(4)	0.463(4)	0.262(3)
H(7)	0.600(4)	0.394(5)	0.110(3)
H(8)	0.886(4)	0.274(5)	0.248(3)
H(9A)	0.862(5)	0.524(6)	0.086(3)
H(9B)	1.047(5)	0.425(5)	0.110(3)
H(10)	1.096(6)	0.520(7)	0.275(4)
H(11)	0.586(5)	0.120(6)	0.242(3)
H(13A)	0.289(6)	0.194(7)	0.198(4)
H(13B)	0.330(6)	0.182(7)	0.061(4)
H(13C)	0.337(6)	0.012(6)	0.129(4)
H(14A)	1.162(6)	0.580(6)	0.458(5)
H(14B)	1.106(6)	0.753(8)	0.510(4)
H(14C)	1.049(8)	0.619(9)	0.557(5)
H(15A)	1.197(6)	0.700(7)	0.157(4)
H(15B)	0.992(6)	0.793(7)	0.147(4)
H(15C)	1.140(8)	0.798(8)	0.256(5)
H(O2)	0.509(6)	0.321(7)	0.388(4)

TABLE 2

Intramolecular bonded distances (Å), with standard deviations in parentheses

O(1)–C(3)	1.214(7)	O(2)–H(O2)	0.85(5)
O(2)–C(6)	1.405(6)	C(4)–H(4A)	0.87(5)
O(3)–C(12)	1.190(11)	C(4)–H(4B)	0.89(5)
O(4)–C(8)	1.456(8)	C(5)–H(5)	0.94(4)
O(4)–C(12)	1.347(9)	C(6)–H(6)	0.94(3)
C(1)–C(2)	1.347(7)	C(7)–H(7)	0.96(3)
C(1)–C(5)	1.525(6)	C(8)–H(8)	0.95(3)
C(1)–C(10)	1.511(6)	C(9)–H(9A)	1.01(4)
C(2)–C(3)	1.463(7)	C(9)–H(9B)	0.91(4)
C(2)–C(14)	1.485(7)	C(10)–H(10)	0.92(5)
C(3)–C(4)	1.495(8)	C(11)–H(11)	0.87(4)
C(4)–C(5)	1.530(8)	C(13)–H(13A)	1.07(5)
C(5)–C(6)	1.549(10)	C(13)–H(13B)	1.06(5)
C(6)–C(7)	1.518(8)	C(13)–H(13C)	0.96(5)
C(7)–C(8)	1.528(7)	C(14)–H(14A)	0.99(5)
C(7)–C(11)	1.511(10)	C(14)–H(14B)	0.89(6)
C(8)–C(9)	1.504(9)	C(14)–H(14C)	0.87(6)
C(9)–C(10)	1.507(8)	C(15)–H(15A)	0.96(5)
C(10)–C(15)	1.530(10)	C(15)–H(15B)	1.02(5)
C(11)–C(12)	1.507(9)	C(15)–H(15C)	0.99(6)
C(11)–C(13)	1.501(8)		

Both deacetylneotenulin and bromoisotenulin are derived from tenulin, and the definition of the absolute

TABLE 3

Valency angles (°), with standard deviations in parentheses

C(5)–C(1)–C(2)	111.6(4)	C(11)–C(7)–C(6)	116.5(4)
C(10)–C(1)–C(2)	124.3(3)	C(11)–C(7)–C(8)	101.5(6)
C(10)–C(1)–C(5)	124.1(3)	C(7)–C(8)–O(4)	102.9(4)
C(3)–C(2)–C(1)	109.4(4)	C(9)–C(8)–O(4)	111.6(3)
C(14)–C(2)–C(1)	129.2(4)	C(9)–C(8)–C(7)	116.2(5)
C(14)–C(2)–C(3)	121.4(4)	C(10)–C(9)–C(8)	111.9(3)
C(2)–C(3)–O(1)	125.2(4)	C(9)–C(10)–C(1)	115.4(3)
C(4)–C(3)–O(1)	126.5(4)	C(15)–C(10)–C(1)	109.3(6)
C(4)–C(3)–C(2)	108.2(4)	C(15)–C(10)–C(9)	111.4(4)
C(5)–C(4)–C(3)	104.8(4)	C(12)–C(11)–C(7)	101.7(4)
C(4)–C(5)–C(1)	102.8(4)	C(13)–C(11)–C(7)	118.6(4)
C(6)–C(5)–C(1)	112.1(5)	C(13)–C(11)–C(12)	114.6(4)
C(6)–C(5)–C(4)	108.7(4)	O(4)–C(12)–O(3)	121.8(5)
C(5)–C(6)–O(2)	108.2(5)	C(11)–C(12)–O(3)	128.4(5)
C(7)–C(6)–O(2)	111.5(4)	C(11)–C(12)–O(4)	109.8(4)
C(7)–C(6)–C(5)	113.9(3)	C(12)–O(4)–C(8)	109.9(4)
C(8)–C(7)–C(6)	115.3(3)		

TABLE 4

Torsion angles (°)

C(12)–O(4)–C(8)–C(7)	−24
C(12)–O(4)–C(8)–C(9)	−150
C(8)–O(4)–C(12)–O(3)	−177
C(8)–O(4)–C(12)–C(11)	2
C(5)–C(1)–C(2)–C(3)	−5
C(5)–C(1)–C(2)–C(14)	174
C(10)–C(1)–C(2)–C(3)	174
C(10)–C(1)–C(2)–C(14)	−7
C(2)–C(1)–C(5)–C(4)	15
C(2)–C(1)–C(5)–C(6)	−102
C(10)–C(1)–C(5)–C(4)	−164
C(10)–C(1)–C(5)–C(6)	79
C(2)–C(1)–C(10)–C(9)	153
C(2)–C(1)–C(10)–C(15)	−80
C(5)–C(1)–C(10)–C(9)	−28
C(5)–C(1)–C(10)–C(15)	99
C(1)–C(2)–C(3)–O(1)	175
C(1)–C(2)–C(3)–C(4)	−7
C(14)–C(2)–C(3)–O(1)	−5
C(14)–C(2)–C(3)–C(4)	174
O(1)–C(3)–C(4)–C(5)	−166
C(2)–C(3)–C(4)–C(5)	16
C(3)–C(4)–C(5)–C(1)	−18
C(3)–C(4)–C(5)–C(6)	101
C(1)–C(5)–C(6)–O(2)	55
C(1)–C(5)–C(6)–C(7)	−69
C(4)–C(5)–C(6)–O(2)	−57
C(4)–C(5)–C(6)–C(7)	178
O(2)–C(6)–C(7)–C(8)	−66
O(2)–C(6)–C(7)–C(11)	53
C(5)–C(6)–C(7)–C(8)	57
C(5)–C(6)–C(7)–C(11)	175
C(6)–C(7)–C(8)–O(4)	163
C(6)–C(7)–C(8)–C(9)	−75
C(11)–C(7)–C(8)–O(4)	36
C(11)–C(7)–C(8)–C(9)	158
C(6)–C(7)–C(11)–C(12)	−160
C(6)–C(7)–C(11)–C(13)	73
C(8)–C(7)–C(11)–C(12)	−34
C(8)–C(7)–C(11)–C(13)	−161
O(4)–C(8)–C(9)–C(10)	−153
C(7)–C(8)–C(9)–C(10)	89
C(8)–C(9)–C(10)–C(1)	−46
C(8)–C(9)–C(10)–C(15)	−172
C(7)–C(11)–C(12)–O(3)	−160
C(7)–C(11)–C(12)–O(4)	21
C(13)–C(11)–C(12)–O(3)	−30
C(13)–C(11)–C(12)–O(4)	151

The sign convention of the torsion angles is such that the sign is negative if an anticlockwise rotation is required of atom (1) to eclipse atom (4), whilst looking down the (2)–(3) bond. Mean σ 0.7°.

configuration of the latter[3] requires that (2) correctly represents the absolute stereochemistry of deacetylneotenulin. The iso- and neo-tenulin derivatives have opposite stereochemistries at C(5).

The c.d. spectrum of deacetylneotenulin exhibits a positive Cotton effect for the $n \rightarrow \pi^*$ transition of the αβ-unsaturated ketone, whereas isotenulin has a negative Cotton effect.[5] The sign of the Cotton effect of a non-planar enone chromophore has been attributed to the C:C·C:O chirality,[6] and ω(C:C·C:O) is 175° for deacetylneotenulin, and −168°, −174° for the two molecules in the asymmetric unit of bromoisotenulin. Pseudoguaianolide cyclopentenones, such as (1), with α-hydrogen and β-methyl substituents, respectively, at C(1) and C(5), quite generally have negative Cotton effects for the $n \rightarrow \pi^*$ transition of the enone[7] and Herz has suggested that these *trans*-fused cyclopentenone rings have essentially identical conformations;[8] in accord with this plenolin *p*-iodobenzoate and bromohelenalin have C:C·C:O torsion angles of −169 and −175°, respectively.[9]

TABLE 5

Displacements (Å) of atoms from various planes

Plane (1): C(1), C(6), C(7), C(10)
[C(6) 0.01, C(7) −0.01, C(1) −0.01, C(10) 0.01, C(5) 0.75, C(8) −0.61, C(9) 0.24]

Plane (2): C(1)—(3)
[C(4) 0.17, C(5) −0.13]

Plane (3): O(4), C(8), C(11), C(12)
[O(4) 0.01, C(8) −0.01 C(11) 0.01, C(12) −0.01, C(7) 0.58

TABLE 6

Intermolecular contacts (<3.85 Å)

$O(3) \cdots C(5^{I})$	3.74	$O(3) \cdots C(7^{III})$	3.59
$O(1) \cdots O(2^{II})$	2.72	$O(3) \cdots C(13^{III})$	3.40
$O(1) \cdots C(6^{II})$	3.36	$O(2) \cdots C(3^{IV})$	3.45
$O(1) \cdots C(13^{II})$	3.75	$O(2) \cdots C(4^{IV})$	3.57

Superscripts refer to the following transformations of atomic co-ordinates:

I	$x, -1 + y, z$	III	$1 - x, -\frac{1}{2} + y, -z$
II	$1 - x, \frac{1}{2} + y, 1 - z$	IV	$1 - x, -\frac{1}{2} + y, 1 - z$

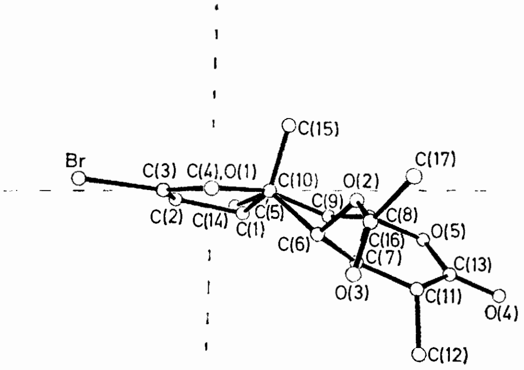

FIGURE 2 The bromoisotenulin molecule (1) viewed along the O=C bond of the enone

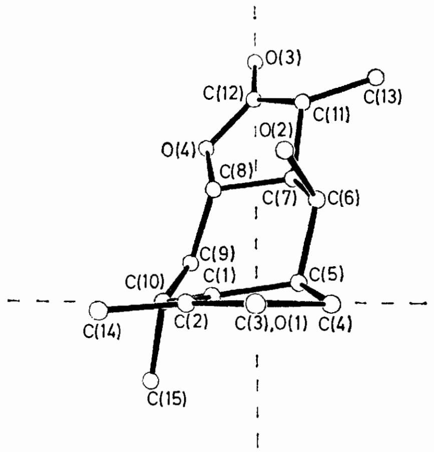

FIGURE 3 The molecule of (2) viewed along the O=C bond of the enone

An alternative view of the origin of the Cotton effect would attribute it to perturbation of an essentially planar enone function, and when compound (1) is viewed along the O · · · C vector of the enone (Figure 2) the C(15)-methyl substituent at C(5) is seen to be in a negative rear octant. A similar view of compound (2) is less easily interpreted (Figure 3).

The seven-membered rings in both deacetylneotenulin and bromoisotenulin approximate more closely to twist-chair (C_2) than to chair (C_s) forms, the approximate C_2 axis of the ring passing through C(10) in the former and

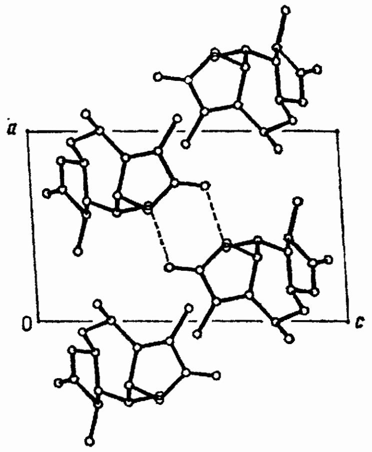

FIGURE 4 The arrangement of molecules in the crystal structure of (2)

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[5] C. Djerassi, J. Osiecki, and W. Herz, *J. Org. Chem.*, 1957, **22**, 1361.

[6] G. Snatzke, *Tetrahedron*, 1965, **21**, 421.

[7] W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, 1970, **26**, 2397.

[8] W. Herz, M. V. Lakshmikantham, and R. N. Mirrington, *Tetrahedron*, 1966, **22**, 1709.

[9] A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1975, 487.

C(6) in the latter. Cycloheptane rings in several perhydroazulene sesquiterpenoids that have been subjected to *X*-ray study are close to twist-chair forms,[10] though conformational calculations indicate that the chair and boat pseudorotational families of cycloheptane differ little in energy.[11]

The cyclopentenone ring has a rather flat half-chair conformation with endocyclic torsion angles of −5, −7, 16, −18, and 15°. The γ-lactone ring has an envelope conformation in which C(7) is the out-of-plane atom.

The crystal structure is shown in Figure 4. There is an intermolecular hydrogen bond involving the hydroxy-group and the oxygen atom of the cyclopentenone; $O(1) \cdots O(2^{II})$ is 2.717(7) Å and the associated $O–H \cdots O$ angle is 168(3)°. This hydrogen bond is repeated in a spiral around the *b* axis (Figure 4).

EXPERIMENTAL

Crystal Data.—$C_{15}O_4H_{20}$, *M* 264.2. Monoclinic, *a* 7.475(2), *b* 7.905(1), *c* 12.022(2) Å, β 93° 26(1)′, *U* 709.1 Å^3, D_c 1.24 g cm^{-3}, *Z* 2, *F*(000) 284. Space group $P2_1(C_2^2)$. Mo-K_α radiation, λ 0.7107 Å; μ(Mo-K_α) 0.96 cm^{-1}.

Crystallographic Measurements.—Preliminary cell dimensions, obtained from rotation and Weissenberg photographs, were adjusted by a least-squares procedure to comply with the θ, χ, and ϕ setting angles of 12 reflections measured on a Hilger and Watts Y 290 automatic diffractometer with Zr-filtered Mo-K_α radiation. For intensity measurements the octants hkl and $hk\bar{l}$ were scanned out to $\theta \leqslant 28°$ by means of 2θ—ω scans, which consisted of 40 steps of 0.02° s^{-1}. Background counts were taken at each end of the scan range for 15 s. In all, 1 831 independent reflections were surveyed, of which 1 020, having $I > 3\sigma(I)$, were considered observed. No absorption correction was applied.

Structure Analysis.—The crystal structure was elucidated by direct-phasing methods using the ' *X*-Ray ' series of programmes.[12] $|E|$ Values were calculated based on an overall temperature factor *B* 4.67 Å^2, and Σ_2 relationships were generated for 201 reflections with $|E| \geqslant 1.59$. The initial set of phases consisted of three to define the origin and one the enantiomorph, together with three phases to which values of $\pm\pi/2$ were given (see Supplementary Publication). This procedure gave eight possible starting sets of seven phases for input to the ' Tangen ' programme, which then generated phase sets characterized by values of R_K 0.21—0.28. An *E* map derived from the phases with the lowest value of R_K yielded positions for all 19 non-hydrogen atoms.

The initial structure-factor calculation gave *R* 31.2% and three cycles of full-matrix least-squares refinement with isotropic thermal parameters lowered *R* to 13.5%. Subsequent anisotropic refinement converged at *R* 9.1%, at which stage a difference electron-density distribution revealed the sites of all the hydrogen atoms. Hydrogen atoms were then included in the calculations with isotropic temperature parameters and convergence was reached at *R* 4.9%, *R′* 5.2%. The weighting scheme used in the final cycles of least-squares calculations was of the form $w = XY$, where *X* and *Y*, defined by $X = (\sin\theta)/0.28$ and $Y = 10.7/|F_o|$, were chosen so as to minimise the deviation from constant $\langle w\Delta^2 \rangle$ over the range of sin θ and $|F_o|$, respectively. Observed and calculated structure amplitudes, thermal parameters, and the initial set of phases are included in Supplementary Publication No. SUP 21688 (19 pp., 1 microfiche).*

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* See Notice to Authors No. 7, in *J.C.S. Perkin II*, 1975, Index issue.

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