O1—C1—C6	119.0 (4)	O2—C7—C8	107.1 (4)
O1—C1—C2	121.3 (4)	N—C8—C7	107.9 (4)
C2—C1—C6	119.8 (4)	C7—C8—C9	113.4 (4)
C1—C2—C3	119.4 (4)	N—C8—C9	110.3 (4)
C2—C3—C4	121.2 (4)		
C10—N—C8—C7	−169.5 (4)	C5—C4—C7—C8	−76.3 (5)
C10—N—C8—C9	66.1 (5)	O2—C7—C8—N	−71.0 (4)
C3—C4—C7—O2	−16.2 (6)	C4—C7—C8—N	164.5 (3)
C5—C4—C7—O2	163.3 (4)	C4—C7—C8—C9	−73.1 (5)
C3—C4—C7—C8	104.2 (5)	O2—C7—C8—C9	51.4 (5)

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N—H1(N)···O4	1.08	1.95	2.818 (4)	135.4 (2)
N—H2(N)···O4^{i}	1.08	1.65	2.727 (5)	172.1 (2)
O6—H(O6)···O3^{ii}	0.87	1.74	2.594 (5)	168.5 (3)
O2—H(O2)···O5^{iii}	0.97	1.84	2.773 (5)	162.1 (2)
O1—H*···O3^{iv}	-	-	2.583 (5)	-
O1—H*···O5^{v}	-	-	2.599 (4)	-

Symmetry codes: (i) $1-x, 1-y, 1-z$; (ii) $-x, 1-y, -z$; (iii) $1-x, 1-y, -z$; (iv) $1+x, y-1, z$; (v) $1+x, y-1, 1+z$.

* This H atom could not be located.

Refinement was by full-matrix least-squares methods. Of 18 H atoms, only four were located on the difference Fourier map, 12 were calculated and the other two could not be located. The high *R* values may be due to the poor quality of the crystal. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELX*76 (Sheldrick, 1976). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used for geometrical calculations and to prepare material for publication: *PARST* (Nardelli, 1983). All calculations were performed on a Super 32 computer (VECC, Calcutta).

The authors thank Dr Bishnu Prasad Mukhopadhyay for preparing the complex and the crystals and Ms Sudipta Datta for participation in the early stages of the work.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: LI1075). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Brand, E. D. & Westfall, T. C. (1970). *Medicinal Chemistry, Part II, Adrenergic Hormones and Drugs*, edited by A. Burger, pp. 1190–1234. New York: Wiley Interscience.

Carlström, D., Bergin, R. & Falkenberg, G. (1973). *Q. Rev. Biophys.* **6**, 257–310.

Cassel, D. & Selinger, Z. (1978). *Proc. Natl Acad. Sci. USA*, **75**, 4155–4159.

Dattagupta, J. K., Meyer, E. F. & Mukhopadhyay, B. P. (1982). *Acta Cryst.* B**38**, 2830–2834.

Dattagupta, J. K., Pattanayek, R. R. & Saha, N. N. (1981). *Acta Cryst.* B**37**, 1439–1441.

Giesecke, J. (1973). *Acta Cryst.* B**29**, 1785–1791.

Hahn, T. (1957). *Z. Kristallogr.* **109**, 438–466.

Hearn, R. A., Freeman, G. R. & Bugg, C. E. (1973). *J. Am. Chem. Soc.* **95**, 7150–7154.

Hebert, H. (1978). *Acta Cryst.* B**34**, 611–615.

Hebert, H. (1979). *Studies on the Molecular Structure of α- and β-Adrenergic Agents*. Thesis, Karolinska Institute, Stockholm.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Klein, R. L., Lagercrantz, H. & Zimmermann, H. (1982). *Neurotransmitter Vesicles*, pp. 142–146, 310–311. London: Academic Press.

Lad, P. M., Nielson, T. B., Preston, M. S. & Rodbell, M. (1980). *J. Biol. Chem.* **255**, 988–995.

McLean, R. A. (1960). *Medicinal Chemistry*, 2nd ed., edited by A. Burger, p. 599. New York: Interscience.

Mukhopadhyay, B. P., Dattagupta, J. K. & Simonetta, M. (1989). *Z. Kristallogr.* **187**, 221–229.

Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.

Pai, V. S. & Maynert, E. W. (1972). *Mol. Pharmacol.* **8**, 82–87.

Post, M. L. & Kennard, O. (1974). *Nature (London)*, **252**, 493–495.

Rodbell, M. (1980). *Nature (London)*, **284**, 17–22.

Sheldrick, G. M. (1976). *SHELX*76. *Program for Crystal Structure Determination*. Univ. of Cambridge, England.

Sheldrick, G. M. (1985). *SHELXS*86. *Program for the Solution of Crystal Structures*. Univ. of Göttingen, Germany.

Triggle, D. J. (1970). *Medicinal Chemistry, Part II, Adrenergic Hormones and Drugs*, edited by A. Burger, pp. 1206, 1235. New York: Wiley Interscience.

Weiner, N. & Jardetzky, O. (1964). *Arch. Exp. Pathol. Pharmakol.* **248**, 308–318.

Acta Cryst. (1994). C**50**, 1135–1138

N-(*N*-Benzyloxycarbonyl-L-1,2,3,4-tetrahydroisoquinol-3-ylcarbonyl)-L-phenylalanine Methyl Ester, Z-L-Tic-L-Phe-OMe

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(*Received* 27 *May* 1993; *accepted* 25 *October* 1993)

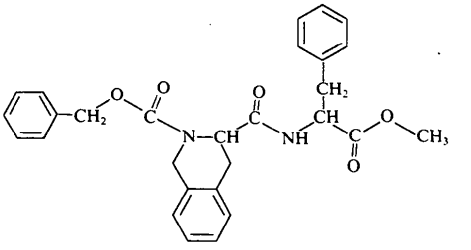
Abstract

The title compound, $C_{28}H_{28}N_2O_5$, is a terminally blocked dipeptide, conformationally constrained by the presence of a 1,2,3,4-tetrahydroisoquinoline residue (Tic). The conformation of the peptide linkage is *trans* [$\omega_1 = -177.0\ (3)°$] and the main chain conformation is determined by the parameters $\varphi_1 = -86.7\ (4)$, $\psi_1 = 171.5\ (3)$, $\varphi_2 = -77.2\ (4)$, $\psi_\tau = 160.1\ (3)°$. The side chain of Tic is in a g^+ conformation [$\chi_1^1 = 56.0\ (4)°$], whereas the phenylalanine side chain is in a g^- conformation [$\chi_2^1 = -68.8\ (5)°$]. In

the crystal the molecules are held together by an intermolecular hydrogen bond and van der Waals forces between hydrophobic phenyl groups.

Comment

The biological activity of small peptides is markedly related to their molecular conformation at the receptor site. For this reason an increasing number of structural studies are being devoted to peptides (Toniolo, 1990) which are conformationally restrained. Often this limited flexibility is achieved by a short-range cyclization of a modified residue. In this regard, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (hereafter referred to as Tic) is of particular interest. It is a derivative of phenylalanine in which the *ortho* C atom C9*B* of the phenyl ring is linked to the N atom through a methylene group, forming a six-membered cycle (see Fig. 1). The insertion of this amino acid in a polypeptide chain induces relevant conformational constraints at the backbone level, as well as decreasing the conformational freedom of the Phe side chain. Recent studies have demonstrated that Tic substitution in place of a specific residue in opioid peptides affects their biological properties (Kazmierski & Hruby, 1988; Schiller *et al.*, 1991). In particular, the affinity and/or selectivity toward different receptor types, as well as the agonist–antagonist properties, are markedly influenced (Schiller *et al.*, 1992). We have undertaken structural studies of some peptides containing this residue in different environments, in order to relate the conformational preferences to the biological properties. The structure of *N*-(*N*-benzyloxycarbonyl-L-1,2,3,4-tetrahydroisoquinol-3-ylcarbonyl)-L-phenylalanine methyl ester, Z-L-Tic-L-Phe-OMe, represents our first contribution. While this work was in progress, a paper describing the preferred conformations of the Tic residue in solution and the solid state was published (Valle *et al.*, 1992).



Z-L-Tic-L-Phe-OMe

A view of the molecule together with the numbering scheme is shown in Fig. 1. The intramolecular geometrical parameters (Table 2) agree, on average, with the generally accepted values for peptides (Ashida, Tsunogae, Tanaka & Yamane, 1987). In particular, they are very close to the values recently derived from a statistical survey of the X-ray structures of small compounds (Engh & Huber, 1991). The differences in bond lengths are smaller than the standard deviations of the observations, with a few exceptions for the distances C2*C*—O*C*, C6*B*—C7*B*, C8*B*—C9*B* and NC—C2*B*. Slightly larger differences, up to 3σ, occur for only two bond angles, C3*C*—C4*C*—C9*C* and C4*C*—C3*C*—C1*C*.

The conformational freedom of the peptide is restricted by the presence of Tic, whose backbone and side-chain torsional angles are greatly constrained. Due to the ring closure, the φ angle is limited to values around $-90°$ (for L-Tic) and the side chain can adopt only two possible conformations, g^+ and g^-. Specifically, the results reported by Valle *et al.* (1992) provide evidence that D-Tic can be embodied into helical or bended structures [for D-Tic, $\varphi = 63.5\ (8)$, $\psi = 33.4\ (8)°$ and $\varphi = 94.8\ (6)$, $\psi = -21.8\ (8)°$ in the sequences -$(Aib)_2$-D-Tic-$(Aib)_2$- and -L-Pro-D-Tic-, respectively]. Finally, NMR studies (Kazmiersky & Hruby, 1988) have shown that if L-Tic is located either at the N-terminal end or in the interior of the peptide chain, the g^- or g^+ side-chain conformation would be preferred, respectively. This finding compares well with the conformations observed for the Tic side chain of the above two peptides (Valle *et al.*, 1992).

The most relevant torsional angles for the title compound are shown in Table 2. The main chain

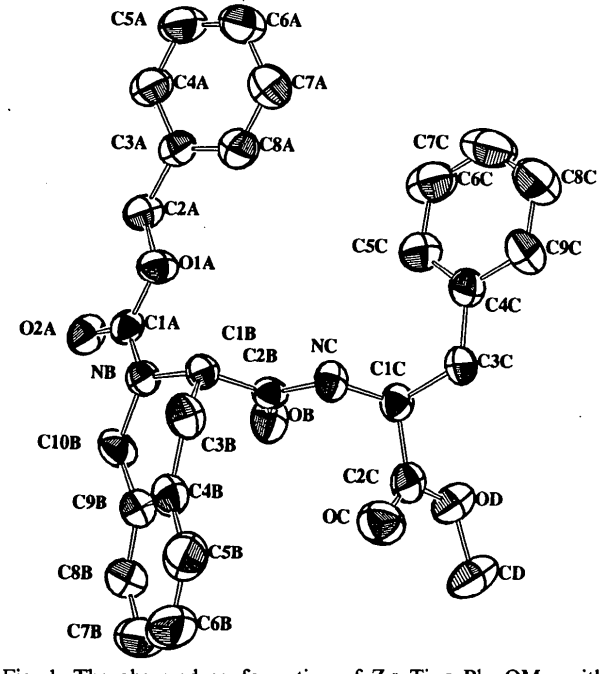


Fig. 1. The observed conformation of Z-L-Tic-L-Phe-OMe, with the numbering scheme, drawn using *ORTEP* (Johnson, 1976). H-atoms are omitted; displacement ellipsoids are drawn at the 50% probability level.

conformation is not completely extended. The peptide bond is *trans*, whereas the urethane bond is *cis*, so that the Z group (benzyloxycarbonyl) is folded back on the peptide, allowing the Z and Phe aromatic rings to face each other slightly, with an angle between the two planes of 164.4 (2)°. As expected, the φ angle of the Tic residue is close to $-90°$ and its side chain adopts a g^+ conformation. The expected conformation for Phe (Table 1) is observed, with the side chain in the g^- conformation, which is most frequently found for this residue (Ashida *et al.*, 1987). The phenyl rings of the phenylalanine and Z groups are strictly planar, with no atom deviating more than 0.06 Å from the respective least-squares plane. A small deviation from planarity is shown by the phenyl ring of the Tic residue. In this case, larger deviations (from the least-squares plane) are observed for atoms which are common to both cycles of Tic, *i.e.* C4*B* and C9*B* (0.10 and 0.14 Å, respectively).

According to the Cremer & Pople (1975) treatment, the Tic non-aromatic six-membered ring can be described by a puckering amplitude of 0.486 (4) Å, a phase angle $\phi = 193.1$ (6)° and a polar position $\theta = 118.7$ (5)°, calculated for the C1*B*, C3*B*, C4*B*, C9*B*, C10*B*, N*B* sequence. These values are close to those of a regular half-boat conformation ($\phi = 180$, $\theta = 125.3°$), with the atom C1*B* out of the plane.

The packing is determined by an intermolecular hydrogen bond and weak van der Waals interactions between all the phenyl rings (Fig. 2). The hydrogen bond is oriented approximately parallel to the *a* axis and joins the atom N*C* of Tic to the carbonyl atom O2*A* of the Z group [symmetry operation $1+x, y, z$; O2*A*···N*C* = 2.842 (5), O2*A*···H12 = 1.947 (3) Å, N*C*—H12···O2*A* = 172.1 (3)°]. The aromatic rings of the Z, Tic and Phe groups of three adjacent symmetry-related molecules [symmetry operations (i) x, y, z, (ii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$ and (iii) $\frac{1}{2}-x, -y, z-\frac{1}{2}$, respectively] are close to each other. The closest intermolecular distances between non-H atoms are C7*A*···C9*C* [3.725 (9) Å] and C6*A*···C6*B* [3.552 (9) Å]. However, the relative orientation of the aromatic least-squares planes does not allow stacking interactions.

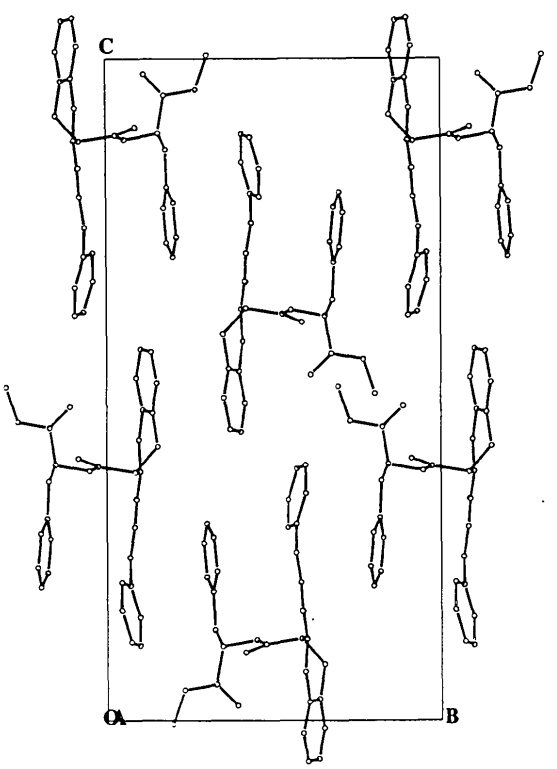


Fig. 2. Packing diagram projected on the *bc* plane. For clarity, the intermolecular hydrogen bond, along the *a* axis, is not shown.

Experimental

Crystal data

$C_{28}H_{28}N_2O_5$
$M_r = 472.55$
Orthorhombic
$P2_12_12_1$
$a = 6.866$ (1) Å
$b = 13.492$ (1) Å
$c = 26.334$ (2) Å
$V = 2439.3$ (6) Å^3
$Z = 4$
$D_x = 1.29$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 20$–$32°$
$\mu = 0.68$ mm^{-1}
$T = 293$ K
Prism
0.50 × 0.10 × 0.10 mm
Colourless
Crystal source: slow evaporation from methanol

Data collection

Enraf–Nonius CAD-4F diffractometer
ω–2θ scans
Absorption correction: none
2691 measured reflections
2691 independent reflections
2197 observed reflections [$I \geq 2.5\sigma(I)$]
$\theta_{max} = 70°$
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 32$
2 standard reflections
frequency: 90 min
intensity variation: 3%

Refinement

Refinement on F
$R = 0.053$
$wR = 0.061$
$S = 0.91$
2197 reflections
316 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o) + (0.02F_o)^2 + 1]$
$(\Delta/\sigma)_{max} < 0.01$
$\Delta\rho_{max} = 0.18$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$B_{eq} = (1/3)\sum_i\sum_j B_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
O1A	−0.1356 (4)	0.0811 (2)	0.2927 (1)	4.22 (6)
O2A	−0.4194 (4)	0.0842 (2)	0.3359 (1)	4.47 (6)
OC	0.4129 (5)	−0.1118 (3)	0.4769 (1)	5.73 (8)
OB	0.0022 (4)	−0.0863 (2)	0.3972 (1)	4.75 (7)
OD	0.3861 (5)	−0.2701 (2)	0.4535 (1)	4.82 (7)
NB	−0.1308 (5)	0.0980 (3)	0.3771 (1)	3.57 (7)
NC	0.3132 (5)	−0.0534 (2)	0.3785 (1)	3.59 (7)
C2A	−0.2437 (7)	0.0662 (3)	0.2466 (2)	4.30 (9)
C10B	−0.2332 (6)	0.0937 (4)	0.4260 (2)	4.23 (9)
C3A	−0.1068 (7)	0.0683 (3)	0.2028 (2)	3.95 (9)
C1A	−0.2382 (6)	0.0866 (3)	0.3352 (2)	3.37 (7)
C6A	0.1432 (9)	0.0702 (4)	0.1185 (2)	6.3 (1)
CD	0.4072 (8)	−0.3052 (4)	0.5053 (2)	6.2 (1)
C4B	0.0900 (7)	0.1350 (3)	0.4672 (2)	4.15 (9)
C7A	0.2112 (8)	0.0424 (4)	0.1655 (2)	6.0 (1)
C7B	−0.079 (1)	0.0991 (4)	0.5623 (2)	6.6 (1)
C8A	0.0931 (8)	0.0421 (4)	0.2078 (2)	5.2 (1)
C2B	0.1255 (6)	−0.0265 (3)	0.3851 (1)	3.18 (7)
C3B	0.1731 (7)	0.1510 (3)	0.4153 (2)	4.29 (9)
C1B	0.0812 (5)	0.0832 (3)	0.3763 (1)	3.31 (7)
C3C	0.5711 (6)	−0.1772 (3)	0.3637 (2)	3.95 (9)
C1C	0.3739 (6)	−0.1543 (3)	0.3882 (2)	3.60 (8)
C5A	−0.0515 (9)	0.0958 (4)	0.1133 (2)	6.1 (1)
C2C	0.3928 (6)	−0.1733 (3)	0.4448 (2)	3.89 (8)
C4A	−0.1711 (8)	0.0955 (4)	0.1556 (2)	5.2 (1)
C4C	0.5768 (7)	−0.1814 (3)	0.3064 (2)	4.15 (9)
C7C	0.608 (1)	−0.1997 (4)	0.2017 (2)	7.7 (2)
C8B	−0.1819 (8)	0.0861 (4)	0.5190 (2)	5.1 (1)
C9B	−0.1061 (7)	0.1048 (3)	0.4714 (2)	3.95 (8)
C5B	0.1965 (9)	0.1487 (4)	0.5113 (2)	5.7 (1)
C6B	0.116 (1)	0.1313 (4)	0.5584 (2)	6.8 (1)
C8C	0.773 (1)	−0.2098 (5)	0.2315 (2)	7.6 (2)
C9C	0.7563 (8)	−0.2003 (4)	0.2839 (2)	6.0 (1)
C6C	0.429 (1)	−0.1801 (4)	0.2231 (2)	6.4 (1)
C5C	0.4137 (8)	−0.1706 (4)	0.2758 (2)	5.1 (1)

Table 2. *Geometric and conformational parameters* (Å, °)

O1A—C2A	1.437 (5)	C4B—C9B	1.411 (7)
OC—C2C	1.193 (6)	C7B—C8B	1.353 (8)
OD—C2C	1.327 (6)	C3B—C1B	1.514 (6)
NB—C1B	1.470 (5)	C1C—C2C	1.519 (6)
C2A—C3A	1.487 (7)	C4C—C5C	1.388 (8)
C3A—C4A	1.370 (7)	C8B—C9B	1.380 (8)
C4B—C3B	1.497 (7)	C6C—C5C	1.397 (7)
C7A—C8A	1.377 (8)	O2A—C1A	1.244 (5)
C2B—C1B	1.529 (6)	OD—CD	1.451 (6)
C3C—C4C	1.509 (6)	NB—C1A	1.336 (6)
C4C—C9C	1.391 (8)	NC—C1C	1.446 (6)
C7C—C6C	1.38 (1)	C3A—C8A	1.423 (8)
C8C—C9C	1.390 (8)	C6A—C5A	1.39 (1)
O1A—C1A	1.326 (5)	C4B—C5B	1.385 (7)
OB—C2B	1.212 (5)	C7B—C6B	1.42 (1)
NB—C10B	1.467 (5)	C3C—C1C	1.531 (6)
NC—C2B	1.350 (5)	C5A—C4A	1.382 (8)
C10B—C9B	1.488 (7)	C7C—C8C	1.38 (1)
C6A—C7A	1.377 (9)	C5B—C6B	1.377 (9)
C2A—O1A—C1A	116.6 (3)	CD—OD—C2C	118.6 (4)
C10B—NB—C1A	117.1 (4)	C10B—NB—C1B	118.9 (4)
C1A—NB—C1B	121.2 (4)	C2B—NC—C1C	120.3 (4)
O1A—C2A—C3A	109.0 (4)	NB—C10B—C9B	114.8 (4)
C2A—C3A—C8A	122.2 (5)	C2A—C3A—C4A	120.3 (5)
C8A—C3A—C4A	117.5 (5)	O1A—C1A—O2A	122.7 (4)
O1A—C1A—NB	114.3 (4)	O2A—C1A—NB	122.9 (4)
C7A—C6A—C5A	118.8 (6)	C3B—C4B—C9B	118.5 (4)
C3B—C4B—C5B	123.0 (5)	C9B—C4B—C5B	118.4 (5)
OB—C2B—NC	121.5 (4)	OB—C2B—C1B	123.1 (4)
NC—C2B—C1B	115.4 (4)	C4B—C3B—C1B	111.9 (4)
NB—C1B—C2B	109.1 (4)	NB—C1B—C3B	108.6 (4)
C2B—C1B—C3B	113.6 (4)	C1C—C3C—C4C	116.8 (4)
NC—C1C—C3C	111.7 (4)	NC—C1C—C2C	110.9 (4)
C3C—C1C—C2C	107.7 (4)	C6A—C5A—C4A	119.6 (5)
OC—C2C—OD	124.5 (5)	OC—C2C—C1C	126.0 (5)
OD—C2C—C1C	109.4 (4)	C3A—C4A—C5A	122.6 (6)
C3C—C4C—C9C	117.1 (5)	C3C—C4C—C5C	123.8 (5)
C9C—C4C—C5C	119.1 (5)	C8C—C7C—C6C	121.0 (6)
C7B—C8B—C9B	123.1 (6)	C10B—C9B—C4B	121.7 (4)
C3A—C8A—C7A	119.5 (5)	C6A—C7A—C8A	121.9 (6)
C10B—C9B—C8B	119.4 (5)	C4B—C9B—C8B	119.0 (5)
C4B—C5B—C6B	121.5 (6)	C7B—C6B—C5B	119.8 (6)
C7C—C8C—C9C	119.3 (7)	C4C—C9C—C8C	120.7 (7)
C7C—C6C—C5C	119.5 (7)	C4C—C5C—C6C	120.3 (6)
C6B—C7B—C8B	118.2 (6)		
ω_0	C1B—NB—C1A—O1A	−12.8 (5)	
φ_1	C1A—NB—C1B—C2B	−86.7 (4)	
ψ_1	NC—C2B—C1B—NB	171.5 (3)	
χ_1^1	C4B—C3B—C1B—NB	56.0 (4)	
ω_1	C1C—NC—C2B—C1B	177.0 (3)	
φ_2	C2B—NC—C1C—C2C	−77.2 (4)	
ψ_2	NC—C1C—C2C—OD	160.1 (3)	
χ_1^2	C4C—C3C—C1C—NC	−68.8 (5)	

A linear decay correction was applied to the data (maximum correction on F_o = 1.015). The structure was solved using *MULTAN*11/82 (Main *et al.*, 1982). All calculations were performed using Enraf–Nonius *SDP* software (B. A. Frenz & Associates, Inc., 1985) on a MicroVAX 3100 computer.

We are grateful to Professor L. Mazzarella for helpful discussions.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71790 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: NA1057]

References

Ashida, T., Tsunogae, Y., Tanaka, I. & Yamane, T. (1987). *Acta Cryst.* B**43**, 212–218.

B. A. Frenz & Associates, Inc. (1985). *Enraf–Nonius SDP-Plus Structure Determination Package*. Version 3.0. Enraf–Nonius, Delft, The Netherlands.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Engh, R. A. & Huber, R. (1991). *Acta Cryst.* A**47**, 392–400.

Johnson, C. K. (19876). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Kazmierski, W. M. & Hruby, V. J. (1988). *Tetrahedron*, **44**, 697–710.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1982). *MULTAN*11/82. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

Schiller, P. W., Nguyen, T. M. D., Weltrowska, G., Wilkes, B. C., Mardsen, B. J., Lemieux, C. & Chung, N. N. (1992). *Proc. Natl Acad. Sci. USA*, **89**, 11871–11875.

Schiller, P. W., Weltrowska, G., Nguyen, T. M. D., Lemieux, C., Chung, N. N. & Wilkes, B. C. (1991). *J. Med. Chem.* **34**, 125–132.

Toniolo, C. (1990). *Int. J. Pept. Protein Res.* **35**, 287–300.

Valle, G., Kazmierski, W. M., Crisma, M., Bonora, G. M., Toniolo, C. & Hruby, V. J. (1992). *Int. J. Pept. Protein Res.* **40**, 222–232.