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Synthesis and absolute configuration of (+) α-hydroxymethyltyrosine by X-ray analysis of its N-benzoyl derivative

Wanda Wieczorek,[1] Maria Bukowska-Strzyżewska,*,[1] Mirosław T. Leplawy,*,[1] and Aleksandra Olma[1]

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α-Hydroxymethyltyrosine has been synthesized by a route involving α-hydroxymethylation. Dextrorotatory N-benzoyl-α-hydroxymethyltyrosine **4** crystallizes in space group $P2_12_12_1$ with cell parameters: a = 13.2266(9), b = 16.1099(9), c = 7.4475(5) Å, V = 15.86.9(2) Å^3, Z = 4. The structure was solved by direct methods and refined to R = 0.047 and R_w = 0.066 with 1549 independent and 956 $\overline{hkl}$ reflections. The absolute configuration of **1** was determined as *R* by the application of Hamilton test and by the estimation of the Bijvoet coefficient *B*. Just as in N-benzoyl-α-methylcysteine (Wieczorek *et al.*, 1989), the α-amino acid residue adopts the C_5 ring conformation similar to the fully extended form. The two side chains also adopt an extended conformation around the C^α atom.

Introduction

α-Hydroxymethyltyrosine belongs to the family of non-proteinogenic α,α-disubstituted amino acids which offer a useful addition to the arsenal of the peptide chemist, whether his major concern is stereochemistry of peptide chain, enzymatic resistance, or interesting biological effects. Interest in the research on α,α-disubstituted amino acids is stimulated by the usefulness of these residues to produce restraints on conformational freedom of peptide chain and by their potential to furnish highly specific enzyme inhibitors. The synthesis of α-hydroxymethyltyrosine as a valuable tool to investigate the antihypertensive properties of various amino acid analogues has been published in 1976 (Schnettler *et al.*, 1976). The authors were able to obtain the compound via azlacton only in 2.8% yield. Kollonitsch *et al.* (1978) obtained α-hydroxymethyltyrosine as a substrate in synthesis of α-fluoromethyltyrosine, potent-time dependent decarboxylase inhibitor. The authors have not given the details of synthesis and resolution. In this paper we describe the practical synthesis of α-hydroxymethyltyrosine via selective α-hydroxymethylation of tyrosine in 50% overall yield, enantiomeric separation, and absolute configuration solved by X-ray analysis of its (+)N-benzoyl derivative.

[1]Institute of General Chemistry and Institute of Organic Chemistry, Technical University, 90-924 Łódź, Poland.

Experimental

Synthesis

General. All solvents were purified by conventional methods. Evaporations were carried out under reduced pressure. Melting points were determinated on capillary melting point apparatus and are uncorrected. Optical rotations were measured in a 1 dcm cell on a Perkin–Elmer polarimeter (Model 241) at 589 nm. Elemental analyses were performed by our Analytical Laboratory. ^{1}H-nmr spectra were recorded on Tesla B5-487C 80 MHz spectrometer.

Synthesis scheme. α-Hydroxymethyltyrosine was prepared by our general procedure for the transformation of protein amino acid into α-hydroxymethylated

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analogs via selective α-hydroxymethylation. Racemic N-benzoyl-α-hydroxymethyltyrosine obtained after basic degradation of 4-oxo-1,3-dioxane **3** was resolved by crystallization of its salt with (−) quinine and (+) enantiomer was used for the measurements.

N,O-Dibenzoyltyrosine **1**. This starting material was prepared according to general procedure for Schotten-Bauman reaction. From 30 g of tyrosine and 42.2 ml of benzoyl chloride 45.6 g (71.2%) of **1** was obtained. *Mp* = 197–198°C.

5-Benzoylamino-5-p-benzoyloxobenzyl-4-oxo-1,3-dioxane **3**. N,O-Dibenzoyltyrosine (27 g, 69.6 mmol) in 135 ml of acetic anhydride was heated on a steam bath until a clear solution formed. The solution was cooled to room temperature and evaporated to dryness. The residue was re-evaporated twice with xylene. IR spectrum of the oily residue showed a strong absorption band at 1820 cm^{-1} characteristic for 5-oxo-4,5-dihydro-1,3-oxazoles. The resultant 2-phenyl-4-*p*-benzoyloxobenzyl-5-oxo-4,5-dihydro-1,3-oxazole **2** was dissolved in pyridine (10 ml) and 70 ml a solution of formaldehyde in isopropanol (40%) was added. The mixture was stirred for 3 h at r.t., then isopropanol was evaporated and crude product was recrystallized from ethanol-light petroleum. Yield 26.5 g (88.4%), mp 181–182°C. ^{1}H-nmr ($CDCl_3$) δ_H = 3.10;3.50 (2H,AB system, J = 14 Hz) 4.18 (s, 2H),5.40;5.65 (2H,AB system, J = 5.6 Hz); 6.80;7.80 (m, 14H). Elemental analysis for $C_{25}H_{21}O_6N$ (431.42) required C 69.5; H 4.9; N 3.2%. Found C 69.1; H 5.3; N 3.2%.

N-benzoyl-α-hydroxymethyltyrosine **4**. A solution of **3** (12.93 g, 30 mmol) in acetone (30 ml) and 2 N sodium hydroxide was stirred for 3 h at r.t. then the acetone was evaporated. The residue was acidified with 2 N hydrochloric acid and the aqueous layer was extracted with ethyl acetate. After evaporation of the dried extract the crude product was recrystallized from ethanol-light petroleum. Yield 8.55 g (90%) mp 176–177°C. ^{1}H-nmr ($NaOD/D_2O$) δ_H = 3.29;3.65 (2H,AB system, J = 13.6 Hz) 4.36;4.69 (2H,AB system, J = 10.2 Hz) 6.82;7.24 (4H AA'XX' system, $J_{A'X} = J_{AX'} = 0$; $J_{AX} = J_{A'X'}$ = 9.8 Hz); 7.71;8.15 (5H,m). Elemental analysis for $C_{17}H_{17}O_5N$ (315.31) required C 64.7; H 5.4; N 4.5%. Found: C 64.7; H 5.6; N 4.3%.

Resolution of racemic N-benzoyl-α-hydroxymethyltyrosine. A salt formed from equimolar amounts of racemic N-benzoyl derivative **4** and (−) quinine was separated by fractional crystallization from ethyl acetate into diastereoisomeric salts A and B. The less soluble salt A had constant mp 213–214°C and constant $[\alpha]_D^{20}$ = −34.4° (c = 1, MeOH). The more soluble salt (oil) had constant $[\alpha]_D^{20}$ = −138.0° (c = 1; MeOH). The less soluble salt A was suspended in 2 N HCl, shaken, and extracted with ethyl acetate. Evaporation of dried extract furnished (+)-N-benzoyl-α-hydroxymethyltyrosine. (+)**4** mp. 230–231°; $[\alpha]_D^{20}$ = +78.4° (c = 1; MeOH). The same procedure applied to salt B yielded (−)**4**, mp. 229–230°C; $[\alpha]_D^{20}$ = −82.0° (c = 1; MeOH).

(+) and (−)-α-Hydroxymethyltyrosine. A suspension of (+)**4** (1.58 g, 5 mmol) in 5 N hydrochloric acid (8 ml) was refluxed for 5 h. The resulting insoluble benzoic acid was filtered off, and the solution was evaporated to give crude, solid α-hydroxymethyltyrosine hydrochloride. This was dissolved in water and passed through an ion exchange column. The column was washed with water until the eluate became neutral, and then eluated with 2 N ammonia. The eluates which gave positive ninhydrin test were combined and evaporated to dryness. Crystallization of the solid residue from water–ethanol yielded (+)-α-hydroxymethyltyrosine, (+**5**), (0.87 g, 90%) mp. 284–285°C; $[\alpha]_D^{20}$ = +4.54° (c = 1,2 N HCl). The enantiomeric purity was 97% as determinated with HPLC using Marfey reagent. ^{1}H-nmr ($NaOD/D_2O$), δ_H = 2.82;3.27 (2H,AB system J = 13.6 Hz) 3.85;4.24 (2H AB system δ = 11.4 Hz) 6.79;7.41 (4H, AA'XX' system, $J_{A'X} = J_{AX'} = 0$; $J_{AX} = J_{A'X'}$ = 8.2 Hz). Elemental analysis for $C_{10}H_{13}O_4N$ (195.20) required C,56.9; H,6.2; N,6.6%. Found C,56.6; H,6.2; N,6.4%.

The same procedure applied to (−)**4** gave (−)α-hydroxymethyltyrosine ((−)**5**), $[\alpha]_D^{20}$ = 4.38 (c = 1, 2 N HCl). The enantiomeric purity was 95% (determinated with Marfey reagent).

X-ray analysis of **4**

Clear colorless crystals of (+) N-benzoyl-α-hydroxymethyltyrosine were grown by slow evaporation of ethyl acetate solution. A crystal with approximate dimensions of 0.3, 0.3, 0.2 mm was used for the measurement of cell constants and intensity data collection. Accurate unit-cell dimensions were obtained by the least-squares fit to the θ values of 25 reflections measured on a SYNTEX $P2_1$ diffractometer.

Diffraction data were collected at 293 K using graphite-monochromated Cu $K\alpha$ radiation. After every 100 reflections three standard reflections were measured to check misorientation and radiation damage. No systematic intensity reduction was observed. The intensity data were corrected for Lorentz and polarization effects. Crystal and experimental details are listed in Table 1. The structure was solved by direct methods using the SHELXS-86 programs (Sheldrick, 1986) and refined by

Table 1. Crystal and experimental parameters

Formula	$C_{17}H_{17}NO_5$
M_r	315.325
a(Å)	13.2266(9)
b(Å)	16.1099(9)
c(Å)	7.4475(5)
V(Å^3)	1586.9(2)
Z	4
F(000)	664
Space group	$P2_12_12_1$
D_x (mg m^{-3})	1.320
D_m (mg m^{-3})	1.31(1)
μ(Cu $K\alpha$) mm^{-1}	0.775
λ (cu $K\alpha$) Å	1.54178
Reflections measured	2908
Unique reflections with $I > 2\sigma(I)$	1549
R	4.71
Rw	6.58

full-matrix least squares method using the program SHELX 76 (Sheldrick, 1976). During the refinement of the nonhydrogen atoms with anisotropic thermal parameters, the hydrogen atoms contributions (with exception of the hydroxyl hydrogens) were included in the structure factors, after calculating their positions on the basis of idealized geometry, and refined isotropically in the riding mode. The positions of the hydroxyl hydrogens were found from a difference map and refined with isotropic thermal parameters. The function minimized was $\Sigma w(|F_0| - |F_c|)^2$. A weighting scheme of the form $w^{-1} = \sigma^2(F_0) + gF_0^2$ was employed with a final g value of 0.008. An empirical isotropic extinction correction was introduced in the form: $F_c' = F_c(1 - xF_c^2/\sin\theta)$ and the parameter x was refined to the value of 0.021(3). Convergence was obtained at $R = 0.0471$ and $R_w = 0.0658$. The final difference Fourier map showed residual electron density between ± 0.3 e Å^{-3}. The absolute configuration of **4** was determined by Hamilton method (Hamilton, 1965; Rogers, 1981) and confirmed by the comparison of the Bijvoet's pairs. The model of the structure with the reversed signs of all the positional atom parameters was refined as described above. The resulting R^- and R_w^- values of 0.0473 and 0.0660 showed that the model with inverse configuration had to be rejected: the R-ratio $= R^-/R^+ = 0.0473/0.0471 = 1.005$, the R_w ratio $= R_w^-/R_w^+ = 0.0660/0.0658 = 1.003$, the number of independent parameters $N = 1549 - 226 = 1323$. According to the Pearson and Hartley tables of R_{ratio} values as the function of the significance level α, and number of independent parameters N, for a one-dimensional hypothesis (Pearson and Hartley, 1966), the significance level $\alpha = 5 \times 10^{-3}$.

Although Hamilton's method safely established the absolute configuration of **4**, we decided to confirm this assignment by a direct comparison of the Bijvoet's coefficient B (Beurskens *et al.*, 1980). The differences $\Delta F_0 = F_0(h) - F_0(\bar{h})$ and $\Delta F_c = F_c(h) - F_c(\bar{h})$ were calculated. The 36 Bijvoet pairs with $|\Delta F_0| > 5\sigma(\Delta F_0)$ and $|\Delta F_c| > 0.009\,[F_0(h) + F_c(\bar{h})]$ were selected and Bijvoet's coefficient $B = \Sigma(\Delta F_c \Delta F_0)/\Sigma|\Delta F_c \Delta F_0| = 0.78$ was computed. The positive value of this coefficient confirms the configuration determined by Hamilton test. The final atomic parameters are given in Tables 2, 3, and 4. Plots were made with PLUTO program (Motherwell, 1976), while geometrical calculations were performed using the program PARST (Nardelli, 1983). All calculations were performed on an AMSTRAD 1512 microcomputer.

Results and discussion

Figure 1 shows a perspective view of (+)N-benzoyl-α-hydroxymethyltyrosine. The configuration at the $C^{\alpha}(8)$ atom is R according to the Cahn–Ingold–Prelog convention (1966). Selected bond lengths and angles are listed in Table 5. The backbone and side-chain conformations are similar to those in N-benzoyl-S-benzyl-α-

Table 2. Positional parameters ($\times 10^4$) for the nonhydrogen atoms

	x	y	z
N(1)	6013(2)	5161(1)	605(3)
O(1)	4416(2)	4460(1)	−676(3)
O(2)	4408(1)	3406(1)	1283(3)
O(3)	6632(1)	3441(1)	−578(2)
O(4)	2586(1)	6879(1)	5466(3)
O(5)	7368(1)	5515(1)	2281(3)
C(1)	4788(1)	5150(1)	4024(3)
C(2)	3764(2)	4953(2)	4019(5)
C(3)	3038(2)	5529(2)	4489(5)
C(4)	3332(2)	6322(1)	4983(4)
C(5)	4337(2)	6542(2)	4950(4)
C(6)	5061(2)	5943(2)	4481(4)
C(7)	5576(2)	4499(2)	3558(3)
C(8)	5756(2)	4380(1)	1508(3)
C(9)	4791(2)	4094(2)	557(4)
C(10)	6728(2)	5696(1)	1114(4)
C(11)	6699(2)	6538(2)	233(4)
C(12)	5864(3)	6837(2)	−640(5)
C(13)	5853(4)	7622(2)	−1398(5)
C(14)	6715(4)	8109(2)	−1278(5)
C(15)	7551(3)	7827(2)	−399(5)
C(16)	7557(3)	7036(2)	367(4)
C(17)	6575(2)	3717(1)	1228(4)

Table 3. Anisotropic thermal parameters ($\times 10^4$) for the nonhydrogen atoms

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	384(10)	391(10)	517(10)	−4(9)	−40(9)	−15(8)
O(1)	516(11)	726(14)	662(12)	114(11)	−185(10)	−112(9)
O(2)	418(9)	474(10)	791(12)	39(9)	−60(10)	−61(7)
O(3)	525(10)	374(8)	548(10)	−22(7)	109(8)	−16(7)
O(4)	450(10)	404(10)	864(14)	−77(9)	154(10)	18(7)
O(5)	499(10)	457(9)	684(11)	21(9)	−175(9)	−50(7)
C(1)	416(12)	434(12)	459(12)	12(10)	9(10)	35(10)
C(2)	489(14)	419(14)	795(19)	−34(13)	134(14)	−3(11)
C(3)	413(13)	459(14)	921(21)	−84(15)	156(14)	−42(11)
C(4)	420(13)	412(12)	582(14)	−5(11)	81(11)	−4(9)
C(5)	441(12)	460(13)	709(16)	−141(13)	38(13)	−24(11)
C(6)	401(13)	552(15)	717(17)	−104(13)	4(13)	−2(10)
C(7)	450(13)	461(13)	494(13)	3(10)	−15(11)	58(10)
C(8)	362(11)	373(12)	500(13)	3(9)	−15(10)	33(9)
C(9)	392(11)	419(12)	592(14)	−40(11)	−17(11)	33(10)
C(10)	432(12)	411(12)	475(12)	−20(10)	15(10)	−1(10)
C(11)	586(15)	385(11)	492(12)	−26(10)	44(11)	−37(11)
C(12)	783(21)	525(16)	822(21)	101(15)	−119(18)	15(15)
C(13)	1111(28)	497(16)	817(23)	46(17)	−183(22)	64(18)
C(14)	1281(32)	427(15)	637(17)	44(14)	4(21)	64(19)
C(15)	1029(27)	513(18)	645(17)	−9(14)	108(18)	−174(17)
C(16)	719(18)	475(14)	546(13)	−25(12)	57(13)	−108(13)
C(17)	396(12)	426(12)	560(13)	0(11)	−2(11)	64(9)

hydroxymethylcysteine (Wieczorek *et al*, 1989). The nearly coplanar disposition of the two dipoles N—H and C(9)=O permits to close α-carbon atom by N—H · · · O intramolecular hydrogen bond in a pentagonal ring, and thus the backbone of the α-amino acid residue adopts the extended C_5 ring conformation [ω(C11—C10—N1—C8) = 166.8(2), Φ(C10—N1—C8—C9) = 171.2(2), Ψ(N1—C8—C9—O2) = 176.3(2)°]. The four torsion angles on the C10—N1 bond

Table 4. Positional parameters ($\times 10^4$) and U_{iso} ($\times 10^3$) for hydrogen atoms

	x	y	z	U
H(1)	5590	5253	−439	85(12)
H(2)	3812	3260	757	122(18)
H(3)	6980	3840	−1169	75(11)
H(4)	2746	7379	5679	84(13)
H(21)	3534	4346	3612	51(8)
H(31)	2257	5360	4500	47(7)
H(51)	4569	7153	5333	83(11)
H(61)	5842	6113	4447	66(10)
H(71)	6277	4669	4174	44(7)
H(72)	5327	3916	4090	54(8)
H(121)	5205	6456	−753	88(12)
H(131)	5189	7860	−2038	170(23)
H(141)	6732	8704	−1921	134(20)
H(151)	8200	8220	−280	103(15)
H(161)	8214	6817	1058	60(9)
H(171)	7292	3965	1621	58(9)
H(172)	6395	3195	2060	81(11)

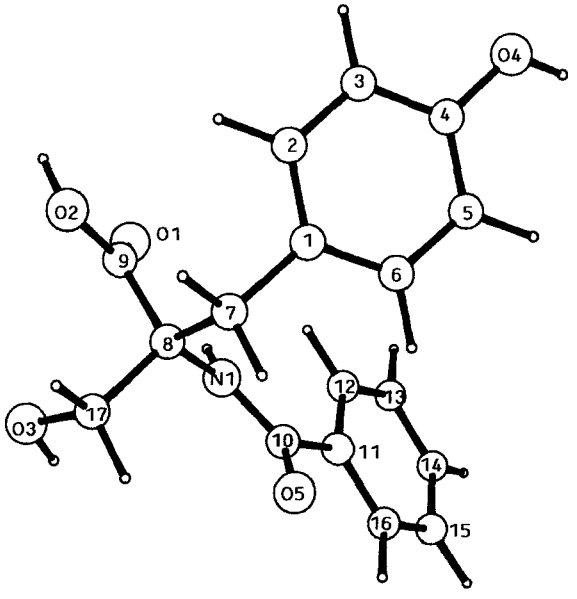


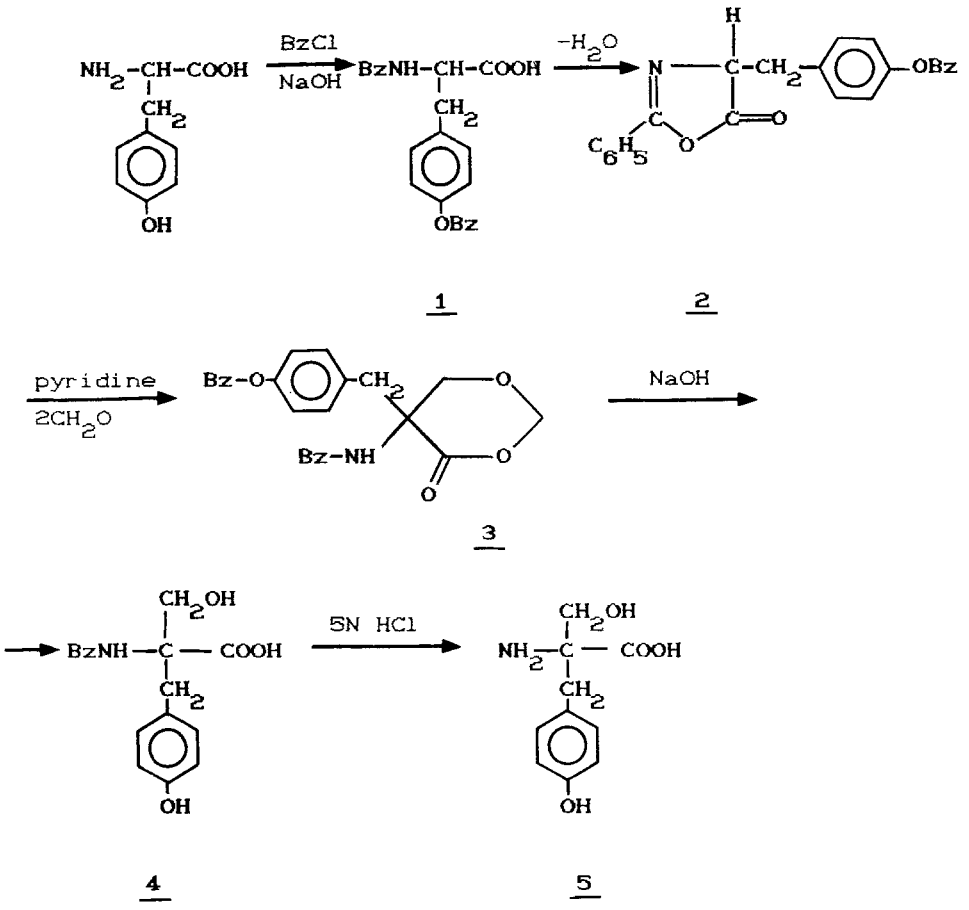
Fig. 1. View of the molecule, showing atomic numbering.

Table 5. Bond lengths (Å) and bond angles (°)

C(8)—N(1)	1.468(3)	C(10)—N(1)	1.335(3)
C(9)—O(1)	1.199(4)	C(9)—O(2)	1.333(3)
C(17)—O(3)	1.418(3)	C(4)—O(4)	1.381(3)
C(10)—O(5)	1.248(3)	C(2)—C(1)	1.391(4)
C(6)—C(1)	1.371(4)	C(7)—C(1)	1.519(4)
C(3)—C(2)	1.380(4)	C(4)—C(3)	1.385(4)
C(5)—C(4)	1.376(4)	C(6)—C(5)	1.404(4)
C(8)—C(7)	1.557(3)	C(9)—C(8)	1.530(4)
C(17)—C(8)	1.536(3)	C(11)—C(10)	1.507(4)
C(12)—C(11)	1.369(5)	C(16)—C(11)	1.393(5)
C(13)—C(12)	1.385(5)	C(14)—C(13)	1.387(7)
C(15)—C(14)	1.363(6)	C(16)—C(15)	1.396(5)
C(10)—N(1)—C(8)	126.0(2)	C(6)—C(1)—C(2)	118.0(2)
C(7)—C(1)—C(2)	120.7(2)	C(7)—C(1)—C(6)	121.3(2)
C(3)—C(2)—C(1)	121.6(3)	C(4)—C(3)—C(2)	119.5(2)
C(3)—C(4)—O(4)	117.9(2)	C(5)—C(4)—O(4)	121.8(2)
C(5)—C(4)—C(3)	120.3(2)	C(6)—C(5)—C(4)	119.1(2)
C(5)—C(6)—C(1)	121.5(3)	C(8)—C(7)—C(1)	114.5(2)
C(7)—C(8)—N(1)	112.2(2)	C(9)—C(8)—N(1)	103.8(2)
C(9)—C(8)—C(7)	111.3(2)	C(17)—C(8)—N(1)	111.8(2)
C(17)—C(8)—C(7)	109.1(2)	C(17)—C(8)—C(9)	108.5(2)
O(2)—C(9)—O(1)	124.2(2)	C(8)—C(9)—O(1)	123.5(2)
C(8)—C(9)—O(2)	112.3(2)	O(5)—C(10)—N(1)	121.8(2)
C(11)—C(10)—N(1)	116.1(2)	C(11)—C(10)—O(5)	122.1(2)
C(12)—C(11)—C(10)	123.0(3)	C(16)—C(11)—C(10)	117.8(3)
C(16)—C(11)—C(12)	119.2(3)	C(13)—C(12)—C(11)	121.5(4)
C(14)—C(13)—C(12)	118.8(4)	C(15)—C(14)—C(13)	120.6(3)
C(16)—C(15)—C(14)	120.3(3)	C(15)—C(16)—C(11)	119.5(3)
C(8)—C(17)—O(3)	112.6(2)		

[ω_1(C11—C10—N1—C8) = 166.8(2), ω_2(O5—C10—N1—H1) = −169(3), ω_3(O5—C10—N1—C8) = 11.6(4), ω_4(C11—C10—N1—H1) = 13(3)°] indicate that the deviations from planarity of the six atoms C11,O5,C10,N1,C8,H1 are caused only by twist around the C10—N1 bond [τ(C10) = 168°]. Out-of-plane bendings at N1 and C10 atoms are less than 1.6°. This fact is inconsistent with the statement that it is always easier in energy to achieve a given torsion angle by a combination of out-of-plane bending and twisting distortion, than by a pure twisting distortion (Dunitz, 1976). The side chains conformations (χ) on the C7—C8 and C8—C17 bonds indicate the extended conformation of the two side chains around the C^{α} atom [χ(C1—C7—C8—C17) = 179.3(2) and χ(C7—C8—C17—O3) = 167.3(2)]. Observed bond lengths and angles are similar as in many aminoacid structures (Ashida *et al.*, 1987). Only the backbone angle at C^{α} atom [N1—C8—C9 = 103.8(2)°] is smaller than the usual value of 111°. This is a consequence of the before mentioned intramolecular N1—H1 · · · O1 hydrogen bonding. Hydrogen bonds in five-membered rings are rather weak (Paterson *et al.*, 1981), because the lone pairs of the acceptor atoms occupy unfavorable positions, and the distances of the hydrogen atoms to these atoms are longer, than in the more favorable six-membered ring system. The distance H1 · · · O1 of 2.02 Å and the angle N1—H1 · · · O1 of 115° indicate a weak nonlinear hydrogen bond. Figure 2 shows a stereoscopic view of the molecular packing in the unit cell. The three intermolecular O—H · · · O hydrogen bonds link molecules in the three-dimensional system. The hydrogen bonds O2—H2 · · · O4′, O3—H3 · · · O5′ and O4—H4 · · · O3′ are: 1.87, 1.78, and 1.90 Å with the angles O2—H2 · · · O4′, O3—H3 · · · O5′ and O4—H4 · · · O3′ of 159, 168, and 163°; distances O2 · · · O4′, O3 · · · O5′ and O4 · · · O3′ are 2.745(2), 2.668(2), and 2.722(2) Å. Atoms O3 and O4 of the hydroxy groups are the donor and acceptor of the hydrogen bonds.

Hydrolysis of (+)N-benzoyl-α-hydroxymethyltyrosine **4** leads to dextrorotatory α-hydroxymethyltyro-



Scheme 1

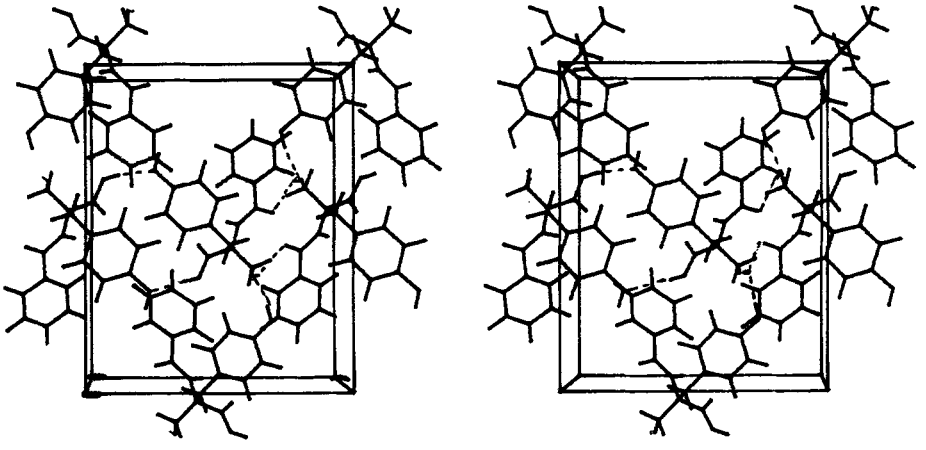


Fig. 2. A stereoview of the unit cell; a-axis to the right and the b-axis to the top.

sine, $[\alpha]_D^{20} = +4.54°$ (c = 1, 2 N HCl). This result proves *R*-configuration for dextrorotatory enantiomer of α-hydroxymethyltyrosine.

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Structure factor data have been deposited with the British Library, Boston Spa, Wetherby, West Yorkshire, UK as supplementary publication No. 60710 (24 pages).