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The Absolute Configuration of an Intermediate in the Asymmetric Synthesis of Unusual Amino Acids

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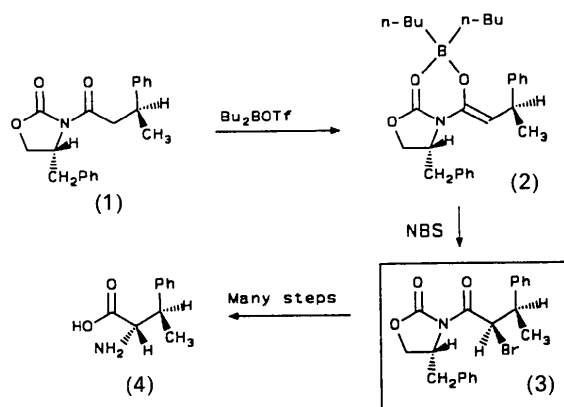
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Abstract. (4*R*)-3-[(2'*R*,3'*R*)-2'-Bromo-3'-(phenylbutanoyl)]-4-(phenylmethyl)-2-oxazolidinone, $C_{20}H_{20}BrNO_3$, $M_r = 402.30$, monoclinic, $P2_1$, $a = 11.542$ (2), $b = 7.625$ (1), $c = 11.667$ (1) Å, $\beta = 113.97$ (1)°, $V = 938.2$ (2) Å³, $Z = 2$, $D_x = 1.42$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.71073$ Å, $\mu = 21.8$ cm⁻¹, $F(000) = 412$, $T = 296 \pm 1$ K, final $R = 0.028$ for 2369 observed reflections. Since a D-chiral auxiliary was used the configuration at the α -carbon was *R* as expected. The two carbonyls are aligned in opposite directions to each other to overcome van der Waals repulsions.

Introduction. We have recently described our approach to the asymmetric synthesis of individual isomers of β -methylphenylalanines (Dharanipragada, Nicolas, Toth & Hruby, 1989) and β -methyltyrosines (Nicolas, Dharanipragada, Toth & Hruby, 1989). These compounds, by virtue of their biased side-chain rotamer populations, are very useful in controlling peptide topography (Hruby, Al-Obeidi & Kazmierski, 1990). The stereochemistry at the α -carbon for these compounds is controlled by utilizing chiral auxiliaries (Evans, Ellman & Dorow, 1987). Thus, face-selective halogenation of boron enolate (2) derived from (1) gave the crystalline bromide (3) as the major product, which was converted in several steps to the *threo*-L- β -methylphenylalanine (4). Determination of the absolute stereochemistry of (3) will support models for asymmetric induction (Evans, Ellman & Dorow, 1987; Evans, Britton, Ellman & Dorow, 1990). In the case reported here, since a D-chiral auxiliary was used, electrophilic bromination should give an *R* configuration at the 2' site. For the first time, an X-ray

structure determination is used to demonstrate directly that this occurs.



Experimental. Crystals of (3) were obtained from a solution of ethyl acetate and hexane. A colorless block crystal having approximate dimensions of $0.32 \times 0.38 \times 0.70$ mm was mounted on a glass fiber for data collection. Data were collected on a Syntex $P2_1$ diffractometer, with graphite-monochromated Mo $K\alpha$ radiation using the θ - 2θ scan mode. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $20 < 2\theta < 33^\circ$. Lorentz and polarization corrections were applied to the data. An empirical absorption correction based on a series of ψ scans was applied to the data. Relative transmission coefficients ranged from 0.760 to 0.998 with an average value of 0.889. Data were collected to a maximum 2θ of 50.0° , from the $+h+k \pm l$ and $-h-k \pm l$ quadrants. Three standard reflections were measured after every 97

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Table 1. *Positional parameters and their estimated standard deviations*

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(1/3)(U_{11} + U_{22} + U_{33})$.

	x	y	z	U_{eq} (Å ²)
Br	0.58838 (3)	0.754	0.32572 (3)	0.0719 (1)
O4	0.7011 (2)	0.5616 (4)	0.6059 (2)	0.0703 (8)
O8	1.0641 (2)	0.6003 (4)	0.5627 (2)	0.0893 (8)
O9	0.9012 (2)	0.6133 (4)	0.3778 (2)	0.0813 (8)
N5	0.8731 (2)	0.5830 (3)	0.5636 (2)	0.0497 (6)
C1	0.6187 (3)	0.2172 (4)	0.4383 (3)	0.070 (1)
C2	0.5589 (3)	0.3869 (4)	0.3692 (3)	0.0490 (8)
C3	0.6629 (3)	0.5242 (4)	0.3906 (3)	0.050 (1)
C4	0.7434 (3)	0.5592 (4)	0.5273 (3)	0.0507 (8)
C6	0.9586 (3)	0.6028 (4)	0.6967 (3)	0.0503 (8)
C7	1.0834 (3)	0.5562 (6)	0.6897 (4)	0.078 (1)
C9	0.9394 (3)	0.5988 (5)	0.4886 (3)	0.060 (1)
C21	0.4849 (3)	0.3567 (4)	0.2293 (3)	0.049 (1)
C22	0.3617 (3)	0.4128 (4)	0.1692 (3)	0.059 (1)
C23	0.2951 (3)	0.3907 (5)	0.0409 (3)	0.062 (1)
C24	0.3515 (3)	0.3103 (5)	-0.0288 (3)	0.063 (1)
C25	0.4744 (3)	0.2517 (7)	0.0296 (3)	0.0673 (8)
C26	0.5403 (3)	0.2753 (5)	0.1578 (3)	0.0613 (8)
C60	0.9542 (3)	0.7863 (4)	0.7468 (3)	0.0520 (8)
C61	1.0426 (3)	0.8007 (4)	0.8883 (3)	0.0493 (8)
C62	1.0122 (3)	0.7248 (4)	0.9745 (2)	0.0580 (8)
C63	1.0945 (3)	0.7348 (5)	1.1006 (3)	0.066 (1)
C64	1.2086 (3)	0.8191 (4)	1.1350 (3)	0.061 (1)
C65	1.2403 (3)	0.8962 (5)	1.0451 (3)	0.065 (1)
C66	1.1579 (3)	0.8883 (4)	0.9205 (3)	0.059 (1)

reflections. Intensities of these standards remained constant within experimental error throughout data collection. No decay correction was applied. A total of 3764 reflections were collected, of which 3303 were unique and not systematically absent. Intensities of equivalent reflections were averaged. Friedel-related reflections were not averaged. The agreement factors for the averaging of the 668 observed and accepted reflections was 1.2% based on intensity and 1.2% based on F_o . A total of 2369 reflections were considered observed, $I > 3\sigma(I)$. The structure was solved using the Patterson heavy-atom method which revealed the position of the Br atom. The remaining atoms were located in succeeding difference Fourier syntheses. H atoms were included in the refinements but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least squares where the function minimized was $\sum w(|F_o| - |F_c|)^2$. Weights were calculated using the counter weighting formula, $w = 4(F_o)^2/\sigma^2(F_o)^2$. The final cycle of refinement included 225 variable parameters and converged (largest parameter shift/e.s.d. ratio was 0.00) with unweighted and weighted agreement factors of $R = 0.028$, and $wR = 0.032$. The y coordinate of the Br was held fixed to define the origin and all non-H atoms were refined with anisotropic thermal parameters. The standard deviation of an observation of unit weight was $S = 1.11$. Refinement of the enantiomeric model gave significantly higher refinement indices, $R = 0.067$ and $wR = 0.0847$. For a refinement with 2369 observations and 255 param-

Table 2. *Bond distances (Å) and angles (°)*

Numbers in parentheses are estimated standard deviations in the least-significant digits.

Br—C3	1.962 (8)	C21—C22	1.37 (1)
O4—C4	1.20 (1)	C21—C26	1.39 (1)
O8—C7	1.45 (1)	C22—C23	1.39 (1)
O8—C9	1.34 (1)	C23—C24	1.37 (1)
O9—C9	1.19 (1)	C24—C25	1.38 (1)
N5—C4	1.39 (1)	C25—C26	1.39 (1)
N5—C6	1.47 (1)	C60—C61	1.51 (1)
N5—C9	1.38 (1)	C61—C62	1.38 (1)
C1—C2	1.53 (1)	C61—C66	1.39 (1)
C2—C3	1.53 (1)	C62—C63	1.39 (1)
C2—C21	1.52 (1)	C63—C64	1.37 (1)
C3—C4	1.51 (1)	C64—C65	1.37 (1)
C6—C7	1.52 (1)	C65—C66	1.38 (1)
C6—C60	1.53 (1)		
C7—O8—C9	109.6 (7)	O9—C9—N5	129.7 (8)
C4—N5—C6	120.8 (6)	C2—C21—C22	120.9 (7)
C4—N5—C9	128.5 (7)	C2—C21—C26	121.2 (7)
C6—N5—C9	110.7 (6)	C22—C21—C26	117.9 (8)
C1—C2—C3	109.6 (6)	C21—C22—C23	121.2 (8)
C1—C2—C21	111.9 (7)	C22—C23—C24	120.3 (8)
C3—C2—C21	109.8 (6)	C23—C24—C25	119.5 (8)
Br—C3—C2	110.8 (5)	C24—C25—C26	119.7 (9)
Br—C3—C4	103.6 (5)	C21—C26—C25	121.4 (8)
C2—C3—C4	113.4 (6)	C6—C60—C61	111.0 (7)
O4—C4—N5	119.1 (7)	C60—C61—C62	120.7 (7)
O4—C4—C3	122.9 (7)	C60—C61—C66	121.1 (7)
N5—C4—C3	117.9 (7)	C62—C61—C66	118.2 (8)
N5—C6—C7	99.4 (7)	C61—C62—C63	121.0 (8)
N5—C6—C60	112.7 (7)	C62—C63—C64	119.8 (8)
C7—C6—C60	114.5 (7)	C63—C64—C65	119.9 (8)
O8—C7—C6	104.3 (7)	C64—C65—C66	120.2 (9)
O8—C9—O9	121.7 (8)	C61—C66—C65	120.9 (8)
O8—C9—N5	108.5 (8)		

eters the inverted structure can be rejected at greater than the 0.005 level based on Hamilton's R -factor-ratio test (Hamilton, 1965). These higher refinement indices confirm the correctness of the enantiomer reported, which is in agreement with the expected structure. The maximum peak in the final difference Fourier map was $(\Delta\rho_{max}) = 0.34 (5) e \text{ \AA}^{-3}$, and the minimum peak $(\Delta\rho_{min}) = -0.27 (5) e \text{ \AA}^{-3}$. Scattering factors were taken from Cromer & Waber (1974). Anomalous-dispersion effects were included in F_c ; the values for f' and f'' were those of Cromer (1974). All calculations were performed on a VAX computer using *SDP/VAX* (Frenz, 1978). Table 1 gives the atomic parameters and Table 2 lists the non-H bond distances and angles.*

Discussion. Structural supports for models of asymmetric induction in the aldol reactions using chiral auxiliaries *via* the Evans route are known in the literature (Abdel-Magid, Pridgen, Eggleston & Lantos, 1986; Eggleston, Abdel-Magid, Pridgen &

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54883 (22 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

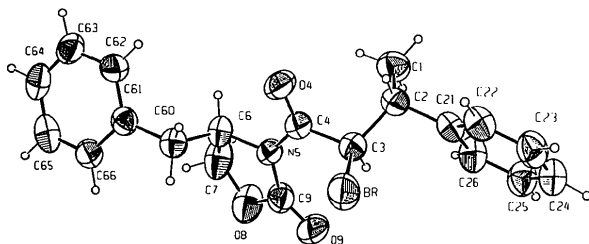


Fig. 1. X-ray structure of (4*R*)-3-[(2'*R*,3'*R*)-2'-bromo-3'-(phenylbutanoyl)]-4-(phenylmethyl)-2-oxazolidinone.

Lantos, 1986). However, X-ray structures of the intermediate bromide obtained from the electrophilic bromination methodology (Evans *et al.*, 1990) have not been reported to date. In our synthesis (Dharanipragada *et al.*, 1989) of optically pure isomers of β -methylphenylalanine, the stereochemistry at the β -carbon is preset by the choice of starting material, *i.e.* (+)- or (–)-3-phenylbutyric acid, the absolute configuration of which is known (Weidler & Bergson, 1964). Hence, determination of stereochemistry at the α -carbon will support models for asymmetric induction (Evans *et al.*, 1987, 1990). In the present case, since a D-chiral auxiliary was used, one would expect to obtain an *R* configuration at all of the three chiral centers in (3). The X-ray structure supported this expectation (Fig. 1), and the optical rotation, $[\alpha]_D^{23} = -38^\circ$ (c 1.1 g dm⁻³, CHCl₃) (Dharanipragada, VanHulle, Bannister, Bear, Kennedy & Hruby, 1992), was also consistent with this stereochemistry. Interestingly, in the solid state, the carbonyls in (3) are aligned opposite to each other presumably to overcome the dipole–dipole interactions and/or van der Waals repulsions. In the enolate (2), however, one would expect them to be parallel to each other due to cyclization by boron. The torsional angle C₂₁—C₂—C₃—Br is 65.4 (3)°. If the inversion

of configuration during displacement of bromide by azide *via* an S_N2 reaction (Dharanipragada *et al.*, 1989) is taken into account, the resulting amino acid (4) would have $\chi_1 = -65^\circ$, suggesting a *gauche*(–) conformation. The absolute configuration found here is completely consistent with the proposed asymmetric induction.

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Structure of *N*-Benzyl-3-benzylidene-4-methyl-4-nitro-5-phenyl-2-pyrrolidinone

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Abstract. C₂₅H₂₂N₂O₃, $M_r = 398.47$, orthorhombic, *Pbn*2₁, $a = 9.385$ (4), $b = 12.314$ (4), $c = 18.573$ (6) Å, $V = 2146.42$ Å³, $Z = 4$, $D_m = 1.237$, $D_x =$

1.233 g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 0.47$ cm⁻¹, $F(000) = 840$, $T = 298$ K, final $R = 0.039$ for 1518 observed reflections. Results of X-ray analysis reveal