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(2*S*,3*S*)-2-(*N*,*N*-Dibenzylamino)-butane-1,3-diol refined using a multipolar atom model

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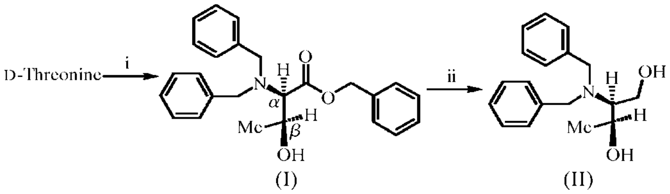
The crystal structure of the title compound, $C_{18}H_{23}NO_2$, was determined using the experimental library multipolar atom model. The refinement showed a significant improvement of crystallographic statistical indices when compared with a conventional spherical neutral atom refinement.

Comment

Enantiomerically pure amino acids and their derivatives play an important role as indispensable intermediates in the pharmaceutical industry and agrochemistry (Breuer *et al.*, 2004, and references therein). Among these optically active amino-alcohols, L- and/or D-threoninol have recently received much attention as chiral parts of promising drugs against chemokine-mediated diseases (Brough & McInally, 2004), for the synthesis of acridine–DNA conjugates for site-selective RNA scissors (Shi *et al.*, 2005), as linkers for Methyl Red incorporation into DNA (Kashida, Tanaka *et al.*, 2006), as asymmetric *cis*-platinum(II) complexes for cancer therapy (van Rijt *et al.*, 2006), as intercalators between pyrene moities and an oligodeoxyribonucleotide for the detection of deletion polymorphisms (Kashida, Asanuma *et al.*, 2006) or between 10–23 DNAzyme and a binding arm for RNA cleavage activity enhancement (Asanuma *et al.*, 2006), and for the synthesis of inhibitors of protein kinase C for the treatment of inflammation (Peng *et al.* 2006) or of a small combinatorial library of dihydroceramide analogs (Villorbina *et al.*, 2007).

As part of a programme for the evaluation of new asymmetric catalysts from the chiral pool (Waykole *et al.*, 2007) (*i.e.* amino acids, sugars, *etc.*), we have synthesized the new optically pure α-amino alcohol (II) in two steps from readily available D-threonine. Diol (II) is a convenient source of D-threoninol by catalytic hydrogenolysis under mild conditions with toluene as the sole by-product (Yoshida *et al.*, 1988). We report here the X-ray structure of (II), which was prepared in good yield by reduction of the intermediate ester, (I).



(i) Benzyl bromide, Na_2CO_3, EtOH, H_2O, ref.
(ii) $LiAlH_4$, THF

The molecular structure of (II) is depicted in Fig. 1. An intramolecular O1—HO1···N1 hydrogen bond (Table 2) forms a five-membered ring. Atom N1 lies about 0.407 Å out of the plane defined by the three neighbouring C atoms (C1, C5 and C12), towards atom HO1 (Fig. 1). The sum of the valence angles around the N atom is 338.9°, indicating sp^3-hybridization (328° for sp^3 and 360° for sp^2). The crystal structure of (II) is presented in Fig. 2. Chains along the *b* axis are formed by O2—HO2···O1^{i} hydrogen bonds [symmetry code: (i) x, $y + 1$, z; Table 2].

Initially, in the independent atom model (IAM) refinement, a conventional spherical neutral atom model was applied. Scale factors, atomic positions and displacement parameters for all atoms were refined using the *MoPro* program (Guillot *et al.*, 2001; Jelsch *et al.*, 2005) until convergence. In the experimental library multipolar atom model (ELMAM) refinement, the same parameters were varied but a multipolar charged atom model was applied. The electron-density parameters were transferred from the ELMAM library (Pichon-Pesme *et al.*, 2004; Zarychta *et al.*, 2007) and subsequently kept fixed. Riding restraints on H-atom *B* factors were applied similarly in both refinements, which were carried out with the same intensity data and cut-off criterion [$I/\sigma(I) \geq 0$]. The H—*X* distances were restricted to standard values in X-ray and

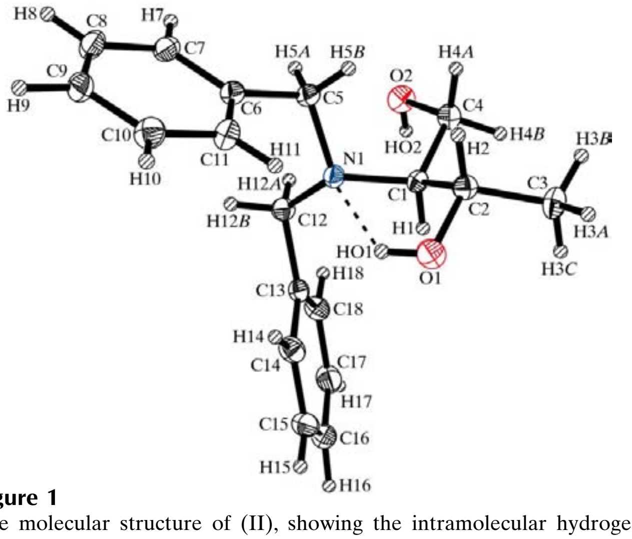


Figure 1
The molecular structure of (II), showing the intramolecular hydrogen bond (dashed line). Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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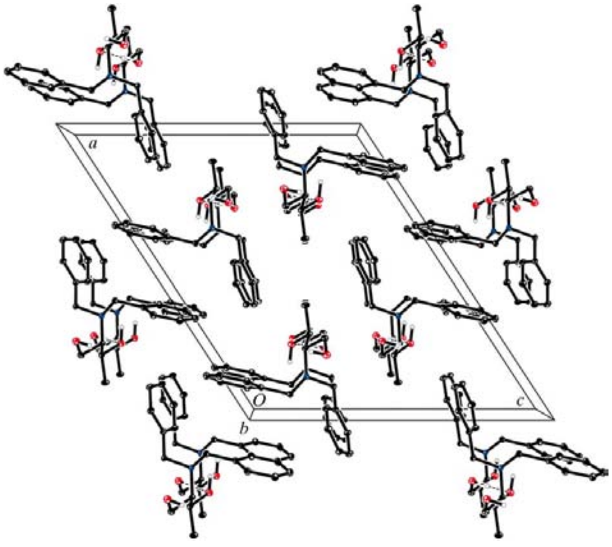

Figure 2
The packing of (II), showing the arrangement of the chains.

neutron diffraction studies (Allen, 1986) in the IAM and ELMAM refinements, respectively (0.002 Å distance σ). The ELMAM refinement shows a good improvement in statistical indexes when compared with the IAM refinement; the $R(F)$ factor is reduced from 4.22 to 3.02% and $wR(R)$ from 5.12 to 3.37%. The minimum and maximum peaks in the residual electron density are −0.036 and 0.056 e Å^{-3}, respectively, after the IAM refinement and −0.028 and 0.039 e Å^{-3} after the ELMAN refinement. The most significant differences in the geometry of compound (II) are, as expected, the bond distances involving H atoms, which had different targets in the ELMAN and IAM refinements. When H atoms are not considered, the r.m.s. deviation between the two structures is 0.0067 Å, while the r.m.s. discrepancy for the bond lengths is 0.0055 Å. The differences do not exceed 0.015 Å for bond distances and 0.5° for bond angles when H atoms are excluded. The H—C—H angles show the strongest (2.9°) r.m.s. discrepancy, the X—Y—H angles differ by 1.8°, while the X—Y—Z angles are less affected, with a low (0.2°) r.m.s. difference. The s.u. values of the bond distances and angles are smaller with the ELMAM refinement owing to better R factor values (Table 1).

The largest effect of the multipoles transfer on the crystallographic structure is observed in the atomic thermal motion. The r.m.s. difference over all the U^{ij} parameters reaches 16% between the two refinement models. The U^{ij} values derived from the IAM refinement have an r.m.s. value 10% larger on average than those derived from the ELMAM refinement. With the independent spherical atom model, the displacement parameters are incorrect as they incorporate some significant deformation electron density due to improper deconvolution between these two features (Jelsch *et al.*, 1998).

Experimental

For the preparation of (2*S*,3*S*)-benzyl 2-(*N*,*N*-dibenzylamino)-3-hydroxybutanoate, (I), benzyl bromide (6.6 ml, 55 mmol, 3.3 equivalents) was dropped over a period of 30 min on to a magnetically stirred dispersion of 98% D-threonine (2.02 g, 16.6 mmol) and Na_2CO_3 (3.875 g, 19.5 mmol, ∼2.2 equivalents) in 75% aqueous EtOH (50 ml) at room temperature. The resulting mixture was refluxed for 2.5 h [the formation of (I) being monitored by SiO_2 thin-layer chromatography (TLC); R_F = 0.43; AcOEt–cyclohexane 1:4], cooled to room temperature, concentrated under reduced pressure, and partitioned between dichloromethane and water (2 × 50 ml). The aqueous phase was extracted with dichloromethane (3 × 50 ml). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 ml) and water (3 × 50 ml), dried over $MgSO_4$, and finally concentrated *in vacuo* to afford the crude ester (I) as a pale-yellow syrup, which was used for the next step without further purification (yield 5.8 g, 14.9 mmol, ∼90%). An analytical sample was isolated by TLC (SiO_2, AcOEt–hexane 1:9) as a colourless gum. $[\alpha]_D$ = +148.9° (c = 2.6, $CHCl_3$). MS (70 eV, EI$^+$) calculated for $C_{25}H_{27}NO_3$ = 389; found m/z (%) = 390 (23) $[M + H]^+$, 344 (32) $[M - C_2H_5O]^+$. IR (film): 1730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$, 298 K): δ 7.15–7.55 (15H, *m*, aromatic), 5.35 (1H, *d*, J = 12.4 Hz, CHHPh), 5.22 (1H, *d*, CHHPh), 4.07 (1H, *m*, H-β), 4.07 (2H, *d*, J = 13.2 Hz, NCHHPh), 3.5 (1H, *s*, OH), 3.39 (2H, *d*, NCHHPh), 3.11 (1H, *d*, J = 9.5 Hz, H-α), 1.1 (3H, *d*, J = 5.8 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.45 (C aromatic), 135.7 (C aromatic), 129.1, 128.7, 128.6, 128.5, 127.4 (CH aromatic), 67.2 (C-β), 66.3 ($PhCH_2O$), 63.2 (C-α), 54.8 ($PhCH_2N$), 19.2 (CH_3). Elemental analysis calculated for $C_{25}H_{27}NO_3$: C 77.09, H 6.99, N 3.60%; found: C 76.91, H 6.81, N 3.67%.

For the preparation of (II), a solution of crude ester (I) (5.453 g, 14.0 mmol) in absolute ether (50 ml) was dropped over a period of 30 mm on to a magnetically stirred suspension of 95% $LiAlH_4$ (0.78 g, ∼19.5 mmol, 1.15 equivalents) in absolute tetrahydrofuran (THF, 50 ml) under argon cooled below 277 K. The mixture was stirred for 25 h at room temperature and refluxed for an additional hour. After completion of the reaction (checked by SiO_2 TLC; ethyl acetate–*n*-hexane 1:1; $R_F \simeq 0.29$), the mixture was cooled to room temperature, quenched by slow addition of ethyl acetate (5 ml) and saturated aqueous Na_2SO_4 (5 ml), and stirred overnight in air. The suspension was filtered through sintered glass and the remaining salts thoroughly washed with a dichloromethane–ethanol mixture (1:1, 100 ml). The filtrates were concentrated under reduced pressure and the residue partitioned in dichloromethane–water (2 × 50 ml), washed with water (2× 20 ml), dried over $MgSO_4$, concentrated under reduced pressure, and finally stored at 277 K. The resulting solids were isolated by filtration and crystallized twice from ethyl acetate–hexanes (1:19) to yield pure alcohol (II) (3.2 g, ∼73%) as white crystals suitable for X-ray diffraction (m.p. 363–364 K). $[\alpha]_D$ = +54.0° (c = 1, $CHCl_3$). MS (70 eV, EI$^+$): m/z 286.1 $[M + H]^+$. ^1H NMR (250 MHz, $CDCl_3/\varepsilon$ D_2O): δ 7.2–7.42 (*m*, 10H, aromatic), 3.99 (2H, *d*, J = 13.2 Hz, NCHHPh), 3.85 (1H, *m*, H-β), 3.8 (2H, *d*, J = 13.2 Hz, J = 5.8 Hz, CH_2OD), 3.72 (2H, *d*, NCHHPh), 2.61 (1H, *d*, J = 8.8 Hz, H-α), 1.15 (3H, *d*, J = 5.8 Hz, CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ 139.5 (C aromatic), 129.4, 128.7, 127.5 (CH aromatic), 65.5 (C-β), 64.8 (C-α), 59.1 ($PhCH_2$), 54.7 (CH_2—OH), 20.4 (CH_3). Elemental analysis calculated for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91%; found: C 75.79, H 8.09, N 4.90%.

Crystal data

$C_{18}H_{23}NO_2$
M_r = 285.37
Monoclinic, $C2$
a = 18.6701 (4) Å
b = 6.652 (1) Å
c = 16.060 (2) Å
β = 123.126 (8)°
V = 1670.4 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 100 (2) K
0.35 × 0.25 × 0.20 mm

Data collection

Oxford Diffraction Xcalibur2 diffractometer
8273 measured reflections
2016 independent reflections
1966 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.022$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.030$
$wR(F^2) = 0.034$
$S = 1.04$
2016 reflections
199 parameters
46 restraints
H-atom parameters constrained
$\Delta\rho_{\rm max} = 0.05$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.03$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O1—HO1···N1	0.97	2.06	2.729 (3)	125
O2—HO2···O1$^{\rm i}$	0.97	1.87	2.789 (2)	158

Symmetry code: (i) $x, y+1, z$.

Table 2
Selected geometric data for (II) (Å, °).

ELMAM is the experimental library multipolar atom model and IAM is the independent atom model.

Distance/angle	ELMAM	IAM
O1—C2	1.465 (2)	1.461 (3)
O2—C4	1.436 (2)	1.435 (3)
N1—C1	1.502 (2)	1.502 (3)
N1—C5	1.506 (1)	1.504 (1)
N1—C12	1.496 (2)	1.500 (4)
O1—C2—C1	107.3 (2)	107.3 (4)
O1—C2—C3	108.2 (2)	108.4 (4)
O2—C4—C1	112.5 (3)	112.5 (5)
C1—N1—C5	112.6 (3)	112.8 (5)
C1—N1—C12	115.8 (3)	115.7 (4)
C5—N1—C12	110.5 (3)	110.4 (5)

At first, a least-squares refinement, based on $|F^2|$, was carried out using the program *SHELXL97* (Sheldrick, 1997), the H atoms being constrained according to standard crystallography stereochemistry. A least-squares refinement, based on $|F|$, was then carried out with the program *MoPro* (Guillot *et al.*, 2001; Jelsch *et al.*, 2005) using the ELMAM approach (Zarychta *et al.*, 2007). The reflection weights were set equal to $1/\sigma^2(F_{\rm o})$. The $U_{\rm iso}$(H) values were restrained to be $1.2U_{\rm eq}$ of the attached atom, with a standard deviation of 0.01 Å. In the absence of suitable anomalous scattering, the refinement of the Flack (1983) parameter led to inconclusive values; therefore Friedel equivalent reflections were merged prior to the final refinements. The absolute structure was set by reference to the known chirality of the enantiomerically pure D-threonine used in the chemical synthesis.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2006); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2006); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *MoPro* (Guillot *et al.*, 2001; Jelsch *et al.*, 2005); molecular graphics: *SHELXTL* (Sheldrick, 1990); software used to prepare material for publication: *publCIF* (Westrip, 2007).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3056). Services for accessing these data are described at the back of the journal.

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