

Synthesis and crystal structure of the chiral β -amino alcohol (S)- α,α -diphenyl-2-pyrrolidine methanol

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Optically pure (S)- α,α -diphenyl-2-pyrrolidine methanol was prepared from L-proline via protection of the amino group, reaction with the Grignard reagents and deprotection of the amino-protected groups in 54.4% yield. The synthetic conditions to prepare (S)- α,α -diphenyl-2-pyrrolidinemethanol were optimised. Single crystal X-ray diffraction analysis revealed that the molecular structure of the compound was enantiomerically pure. The crystals are orthorhombic, space group $P2(1)2(1)2(1)$, with unit cell parameters $a = 8.9000(18)$ Å, $b = 9.2405(18)$ Å, $c = 16.671(3)$ Å, $V = 1371.1(5)$ Å³, $D_x = 1.227$ g cm⁻³, $Z = 4$, $T = 113(2)$ K, $F(000) = 628$, $R^1 = 0.0335$ and $wR^2 = 0.0707$. The absolute structure parameter was $-1.6(17)$.

Keywords: (S)- α,α -diphenyl-2-pyrrolidine methanol, crystal structure, chirality

Many optically active β -amino alcohols and other amino acid derivatives are important chiral reagents and are important precursors of chiral catalysts.^{1,2} They have been widely used in many asymmetric catalysis reaction, for example, asymmetric reduction of ketones,^{3,4} addition reactions of diethyl zinc to aldehydes,⁵ and Diels-Alder reactions.⁶ (S)- α,α -diphenyl-2-pyrrolidine methanol **4** is a very important chiral β -amino alcohol catalyst precursor.⁷ To the best of our knowledge, the crystal structure of the title compound has not been reported.

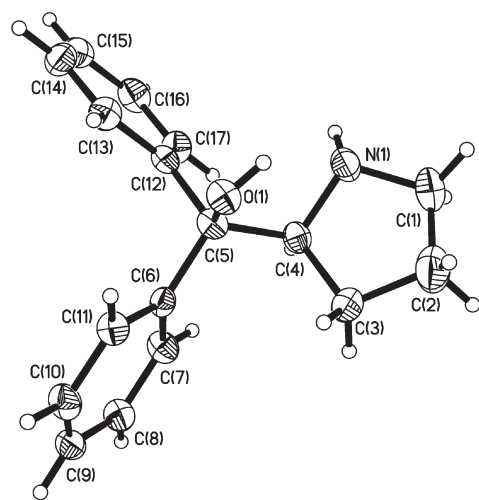
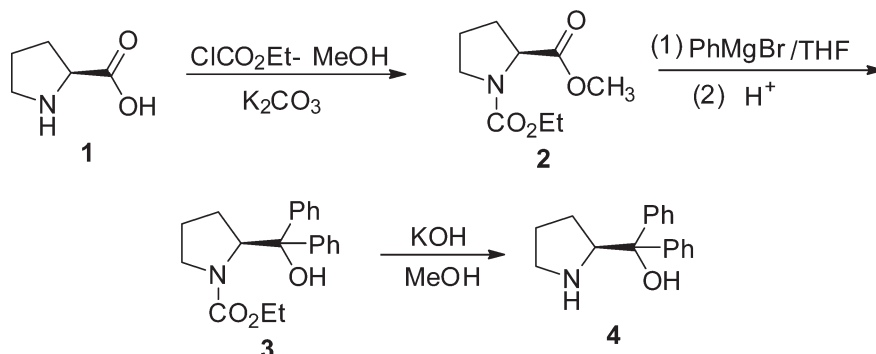


Fig. 1 ORTEP drawing of the structure of **6**, *n*-pentane as well as H atoms have been omitted for clarity except the H atoms on the OH. Thermal ellipsoids are drawn at 50% probability level.

Table 1 Crystallographic data and structure refinement summary

CCDC deposit no.	741092
Empirical formula	C ₁₇ H ₁₉ NO
Formula weight	253.33
Temperature(K)	113(2)
Wavelength (Mo K α) (Å)	0.71073
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	
<i>a</i> (Å)	8.9000(18)
<i>b</i> (Å)	9.2405(18)
<i>c</i> (Å)	16.671(3)
Volume(Å ³)	1371.1(5)
<i>Z</i>	4
Crystal size	0.16 x 0.12 x 0.06
Calculated density (Mg m ⁻³)	1.227
Absorption coefficient (mm)	0.076
<i>F</i> (000)	544
Reflections collected/unique	9219/2405 [R(int) = 0.0334]
Completeness to theta = 24.98	99.5 %
Data/restraints/parameters	2405/1/178
Limiting indices	-9 <= <i>h</i> <= 10, -10 <= <i>k</i> <= 10, -18 <= <i>l</i> <= 19
Goodness of fit on <i>F</i> ²	1.054
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ¹ = 0.0405, <i>wR</i> ² = 0.1010
<i>R</i> indices (all data)	<i>R</i> ¹ = 0.0436, <i>wR</i> ² = 0.1040
Absolute structure parameter	-1.6(17)
Largest diff. peak and hole (e Å ⁻³)	0.371 and -0.252

We present here the crystal structure of (S)- α,α -diphenyl-2-pyrrolidine methanol **4** and its preparation, which may give a better understanding of the mechanism of the catalytic reactions.



Scheme 1 Preparation of (S)- α,α -diphenyl-2-pyrrolidine methanol **4**.

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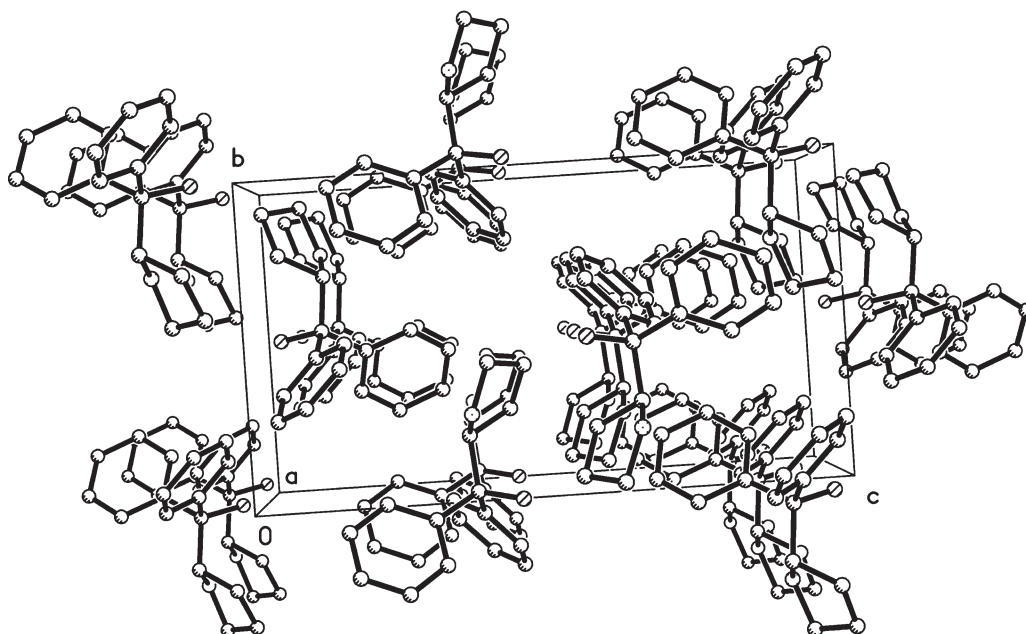


Fig. 2 Three-dimensional molecular-packing diagram of the title compound.

Results and discussion

Optically pure (*S*)- α , α -diphenyl-2-pyrrolidinemethanol was prepared from *L*-proline in three steps involving protection of the amino protection, reaction with the Grignard reagents and deprotection of the amino-protected groups.

N-Ethoxy carbonyl was chosen as a protecting group as it is introduced under mild alkaline conditions ($K_2CO_3/MeOH$). Although the total yield was slightly lower than other methods, the easy access to raw materials, easy operation and simple processing, made this synthetic method more suitable for large-scale production.

Crystal structure

Single crystal X-ray diffraction analysis reveals that the molecular structure of compound **4** confirms the formulation of the compound (shown in Fig. 1). This compound is enantiomerically pure and crystallised in the noncentrosymmetric $P2_12_12_1$ space group (Table 1).

It can be seen from Figs 1 and 2, that in order to relieve strain, the four carbon atoms of the pyrrolidine ring nearly exists in a plane, as shown by the torsion angle of C(1)–C(2)–C(3)–C(4) is $-7.3(3)^\circ$ (Table 2), while its nitrogen atom is outside the plane. The ring exists as an envelope conformation. The N atom is located near the OH side. This facilitates the coordination atoms in complex formation. There are intra-

molecular hydrogen bond O1–H1...N1 in unit cell [H1...N1=2.25Å, O1–H1...N1 =116.3°] (Table 3).

Experimental

All reactions were carried out under argon and monitored by TLC. THF was dried using Na under reflux. Melting points (uncorrected) were measured with a XT4 melting point apparatus. 1H spectra were recorded on a Varian Mercury plus 300 MHz using $CDCl_3$ as solvent unless otherwise noted and TMS as the internal standard. All chemical shifts were reported in parts per million (ppm), Optical rotations were measured on a WZZ-3 polarimeter. The title compound was prepared according to Scheme 1.

*Synthesis of S(-)-N-ethoxycarbonyl proline methyl ester (2):*⁸ K_2CO_3 (2.8 g, 40 mmol) was added into a solution of *L*-proline **1** (2.3 g, 20 mmol) in CH_3OH (30 mL) in an ice bath. The heterogeneous mixture was stirred, and ethyl chloroformate (4.4 g, 40 mmol) was slowly added at $0^\circ C$. The reaction mixture was warmed to room temperature and stirred overnight. The methanol was removed under reduced pressure and 20 mL water was added, the mixture was extracted with CH_2Cl_2 (3 \times 30 mL) and the combined organic phases were washed with brine, dried (anhydrous $MgSO_4$) and evaporated

Table 3 Hydrogen-bonding geometry [Å, deg] for **4**

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(1)–H(1C)...N(1)	0.82	2.25	2.719(2)	116.3

Table 2 Selected bond lengths (Å) and angles (deg) for **4**

Bond	Distance	Bond angle	deg
O(1)–C(5)	1.430(2)	C(1)–N(1)–C(4)	106.85(17)
N(1)–C(1)	1.465(3)	N(1)–C(1)–C(2)	103.73(19)
N(1)–C(4)	1.473(2)	C(1)–C(2)–C(3)	106.4(2)
C(1)–C(2)	1.491(4)	N(1)–C(4)–C(3)	103.50(15)
C(2)–C(3)	1.515(3)	N(1)–C(4)–C(5)	108.20(15)
C(3)–C(4)	1.541(3)	C(3)–C(4)–C(5)	113.09(15)
C(4)–C(5)	1.550(3)	C(2)–C(3)–C(4)	105.60(18)
C(5)–C(6)	1.523(3)	C(2)–C(3)–C(4)–N(1)	-15.3(2)
C(5)–C(12)	1.543(3)	N(1)–C(1)–C(2)–C(3)	27.4(3)
C(6)–C(11)	1.382(3)	C(4)–N(1)–C(1)–C(2)	-38.4(2)
C(6)–C(7)	1.394(3)	C(1)–C(2)–C(3)–C(4)	-7.3(3)
C(7)–C(8)	1.386(3)	C(1)–N(1)–C(4)–C(3)	33.34(19)
C(8)–C(9)	1.381(3)	N(1)–C(4)–C(5)–O(1)	-52.69(18)

to give a brown oil. The crude product was purified by column chromatography (flash silica gel, eluent: EtOAc/*n*-hexane 1:4) to give a colourless liquid **2**. (3.5 g, 87.1%) $[\alpha]_D^{20} = -69.2^\circ$ ($c = 1.2$, CHCl_3). IR (cm^{-1}): 1710–1740 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3 , ppm): δ 1.18–1.23 (t, $J = 6.8$ Hz, 3H, CH_3), 1.83–2.26 (m, 4H, CH_2CH_2), 3.35–3.58 (m, 2H, NCH_2), 3.71 (s, 3H, OCH_3), 4.03–4.21 (q, 2H, OCH_2), 4.24–4.38 (m, 1H, NCH). CIMS(m/z): 201(M^+).

(*S*)-*N*-ethoxycarbonyl- α , α -diphenyl-2-pyrrolidinemethanol (**3**):^{8,9} Bromobenzene (10.0 g, 63.5 mmol) in THF (30 mL) was added portion-wise into a suspension of magnesium filings (1.5 g, 63.5 mmol) and a little iodine in THF (30 mL) at 0°C . The heterogeneous mixture was stirred for 0.5 h, and a solution of **2** 4.0 g (20.0 mmol) in THF (30 mL) was added. The mixture was stirred at 0°C for 4 h. Saturated ammonium chloride solution was added and the solution was filtered through Celite. The residue was extracted with CHCl_3 (3 \times 30 mL), the combined organic phase was washed with water, dried (anhydrous MgSO_4) and evaporated to give a yellow liquid **3**. The yellow liquid was dissolved in hot petroleum ether and cooled. A white solid was obtained which was filtered and recrystallised from anhydrous ethanol to afford **3** (4.9 g, 73.5%) as a white crystalline solid. m.p. 111–113 $^\circ\text{C}$, $[\alpha]_D^{25} = +56.8^\circ$ ($c = 4.11$, CH_3OH). $^1\text{H NMR}$ (300 MHz, CDCl_3 , ppm): δ 1.23–1.26 (t, $J = 7.2$ Hz, 3H, CH_3), 1.45–2.16 (m, 4H, CH_2CH_2), 3.01 (m, 2H, NCH_2), 3.38–3.46 (m, 1H), 4.05–4.19 (q, $J = 4.5$ Hz, 2H, OCH_2), 4.93 (m, 1H, NCH), 7.26–7.40 (m, 10H, ArH). IR (cm^{-1}): 3375, 1680 cm^{-1} . Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_3$: 73.82; H, 7.12; N, 4.30. Anal. Found: C, 73.66; H, 7.18; N, 4.28%. CIMS(m/z): 325(M^+).

(*S*)- α , α -diphenyl-2-pyrrolidinemethanol (**4**): KOH (5.6 g, 100 mmol) was dissolved in 50 mL methanol, and **3** (3.0 g, 10.1 mmol) was added. The mixture was stirred under reflux for 12 h, and then cooled to room temperature. The methanol was removed under reduced pressure and 30 mL water was added. The mixture was extracted with CH_2Cl_2 (3 \times 30 mL). The combined organic phases were washed with water, dried (MgSO_4) and evaporated to afford a yellow liquid. The yellow liquid was dissolved in hot petroleum ether

and cooled. A white solid was obtained and filtered to afford **4** (7.7 g, 85.0%), m.p. 74–76 $^\circ\text{C}$, $[\alpha]_D^{25} = -57.1^\circ$ ($c = 1.11$, CHCl_3), (lit.¹⁰ m.p. 74.0–74.8 $^\circ\text{C}$, $[\alpha]_D^{25} = -68^\circ$ ($c = 3$, CH_3OH)), $^1\text{H NMR}$ (300 MHz, CDCl_3 , ppm): δ 1.51–1.75 (m, 4H, CH_2CH_2), 2.92–3.23 (m, 4H, OH, NH, NCH_2), 4.23–4.28 (m, 1H, NCH), 7.13–7.60 (m, 10H, ArH). IR (cm^{-1}): 3344, 2957, 1490, 1393, 751, 706 cm^{-1} . Calcd for $\text{C}_{17}\text{H}_{18}\text{NO}$, 80.60; H, 7.56; N, 5.53. Anal. Found: C, 80.74; H, 7.63; N, 5.63%. CIMS(m/z): 253(M^+).

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications (no. CCDC-251130). Copies of available materials can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223-336033; or deposit@ccdc.cam.ac).

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